

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

Michael J. Ackerman, MD, PhD,¹ Silvia G. Priori, MD, PhD,² Stephan Willems, MD, PhD,³ Charles Berul, MD, FHRS, CCDS,⁴ Ramon Brugada, MD, PhD,⁵ Hugh Calkins, MD, FHRS, CCDS,⁶ A. John Camm, MD, FHRS,⁷ Patrick T. Ellinor, MD, PhD,⁸ Michael Gollob, MD,⁹ Robert Hamilton, MD, CCDS,¹⁰ Ray E. Hershberger, MD,¹¹ Daniel P. Judge, MD,^{6,12} Hervé Le Marec, MD,¹³ William J. McKenna, MD,¹⁴ Eric Schulze-Bahr, MD, PhD,¹⁵ Chris Semsarian, MBBS, PhD,¹⁶ Jeffrey A. Towbin, MD,¹⁷ Hugh Watkins, MD, PhD,¹⁸ Arthur Wilde, MD, PhD,¹⁹ Christian Wolpert, MD,²⁰ Douglas P. Zipes, MD, FHRS²¹

¹From Mayo Clinic, Rochester, Minnesota, ²Fondazione Salvatore Maugeri University of Pavia, Pavia, Italy and New York University, New York, New York, ³University Hospital Hamburg-Eppendorf, Hamburg, Germany, ⁴Children's National Medical Center and George Washington School of Medicine, Washington, District of Columbia, ⁵Girona Institute of Biomedical Research and University of Girona School of Medicine, Girona, Spain, ⁶Johns Hopkins University, Baltimore, Maryland, ⁷St. George's University of London, London, United Kingdom, ⁸Massachusetts General Hospital, Cardiac Arrhythmia Service, Boston, Massachusetts, ⁹University of Ottawa Heart Institute, Ottawa, Canada, ¹⁰Hospital for Sick Children, Toronto, Canada, ¹¹University of Miami Miller School of Medicine, Miami, Florida, ¹²Université Paris Descartes, Paris, France, ¹³l'Institut du thorax, Nantes Cedex, Nantes, France, ¹⁴Institute of Cardiovascular Science, University College London, London, United Kingdom, ¹⁵University Hospital Muenster, Muenster, Germany, ¹⁶University of Sydney, Sydney, Australia, ¹⁷Cincinnati Children's Hospital, Cincinnati, Ohio, ¹⁸University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom, ¹⁹University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands, ²⁰Ludwigsburg Clinic, Ludwigsburg, Germany, and ²¹Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana.

Preamble

This international consensus statement provides the state of genetic testing for the channelopathies and cardiomyopathies. It summarizes the opinion of the international writing group members based on their own experience and on a general review of the literature with respect to the use and role of genetic testing for these potentially heritable cardiac conditions. This document focuses primarily on the state of genetic testing for the 13 distinct entities detailed and the relative diagnostic, prognostic, and therapeutic impact of the genetic test result for each entity. It does not focus on the therapeutic management of the various channelopathies and cardiomyopathies. Treatment/management issues are only discussed for those diseases (i.e., LQTS, HCM, DCM + CCD, RCM)

in which the genetic test result could potentially influence treatment considerations.

Writing recommendations for genetic diseases require adaptation of the methodology normally adopted to prepare guidelines for clinical practice. Documents produced by other scientific societies have acknowledged the need to define the criteria used to rank the strength of recommendation for genetic diseases.¹

The most obvious difference is that randomized and/or blinded studies do not exist. Instead, most of the available data are derived from registries that have followed patients and recorded outcome information. The authors of this statement have therefore defined specific criteria for Class I, Class IIa or b, and Class III recommendations and have used the conventional language adopted by AHA/ACC/ESC Guidelines to express each class. All recommendations are level of evidence (LOE) C (i.e., based on experts' opinions).

A Class I recommendation (“**is recommended**”) was applied for genetic testing in index cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of a genetic test is high (likelihood of positive result >40% and

KEYWORDS Genetics; Cardiomyopathies; Channelopathies (Heart Rhythm 2011; 8:1308–1339)

The Heart Rhythm Society and European Heart Rhythm Association endorsed the document in April of 2011. The American Heart Association endorsed the document in June of 2011. **Correspondence and reprint requests:** Sonja Olson, Heart Rhythm Society, 1400 K Street NW, Washington, DC 20005. E-mail address: solson@hrsonline.org.

signal/noise ratio >10; Table 3), AND/OR when the genetic test result provides either diagnostic or prognostic information, or when the genetic test result influences therapeutic choices according to data in Figure 1 and in Table 3. In all the remaining situations, the authors have used either “can be useful” to articulate either a Class IIa recommendation or “may be considered” to signify a Class IIb recommendation. A Class III (“should not” or “is not recommended”) recommendation was applied in cases in which it was agreed that the genetic test result failed to provide any additional benefit or could be harmful in the diagnostic evaluation of patients with possible inherited heart disease.

Screening of family members for the mutation identified in the proband of the family is recommended as a Class I when genetic testing leads to the adoption of therapy/protective measures/lifestyle adaptations. Conversely, the authors have assigned a Class IIa recommendation when results of genetic testing are not associated with the use of therapeutic or protective measures but the results may be useful for reproductive counseling or instances in which genetic testing is requested by the patient who wants to know his/her mutation status.

When using or considering the guidance from this document, it is important to remember that there are no absolutes governing many clinical situations. The final judgment regarding care of a particular patient must be made by the health care provider and the patient in light of all relevant circumstances. Recommendations are based on consensus of the writing group following the Heart Rhythm Society’s established consensus process. It is recognized that consensus does not mean unanimous agreement among all writing group members. We identified those aspects of genetic testing for which a true consensus could be found. Surveys of the entire writing group were used. The authors received an agreement that was equal to or greater than 84% on all recommendations; most recommendations received agreement of 94% or higher. This statement is directed to all healthcare professionals who are involved with genetic testing for the channelopathies and cardiomyopathies. All members of this document-writing group provided disclosure statements of all relationships that might present real or perceptible conflicts of interest. Disclosures for the members of the task force are published in the Appendix section.

TABLE OF CONTENTS

Introduction and Summary of Expert Consensus Recommendations (see Table 1)

Table 1. Expert Consensus Recommendations

Table 2. Summary of Common Cardiac Channelopathy/ Cardiomyopathy-Associated Genes (>5% of Disease)

Table 3. Yield and Signal-to-Noise Associated with Disease-Specific Genetic Testing

I. State of Genetic Testing for Long QT Syndrome (LQTS)

a. Expert Consensus Recommendations

- b. Diagnostic Implications of LQTS Genetic Testing
 - i. Summary of the Common LQTS Genes (see Table 2)
 - ii. Index Cases
 - iii. Family Screening
- c. Prognostic Implications of LQTS Genetic Testing
- d. Therapeutic Implications of LQTS Genetic Testing

II. State of Genetic Testing for CPVT

- a. Expert Consensus Recommendations
- b. Diagnostic Implications of CPVT Genetic Testing
 - i. Summary of the Common CPVT Genes (Table 2)
 - ii. Index Cases
 - iii. Family Screening
- c. Prognostic and Therapeutic Implications of CPVT Genetic Testing

III. State of Genetic Testing for Brugada Syndrome (BrS)

- a. Expert Consensus Recommendations
- b. Diagnostic Implications of BrS Genetic Testing
 - i. Summary of Common BrS Genes (Table 2)
 - ii. Index Cases
 - iii. Family Screening
- c. Prognostic and Therapeutic Implications of BrS Genetic Testing

IV. State of Genetic Testing for Progressive Cardiac Conduction Disease (CCD)

- a. Expert Consensus Recommendations
- b. Diagnostic Implications of CCD Genetic Testing
 - i. Index Cases
 - ii. Family Screening
- c. Prognostic and Therapeutic Implications of CCD Genetic Testing

V. State of Genetic Testing for Short QT Syndrome (SQTS)

- a. Expert Consensus Recommendations
- b. Diagnostic Implications of SQTS Genetic Testing
- c. Prognostic and Therapeutic Implications of SQTS Genetic Testing

VI. State of Genetic Testing for Atrial Fibrillation

- a. Expert Consensus Recommendations
- b. Diagnostic Implications of AF Genetic Testing
- c. Prognostic and Therapeutic Implications of AF Genetic Testing

VII. State of Genetic Testing for Hypertrophic Cardiomyopathy (HCM)

- a. Expert Consensus Recommendations
- b. Diagnostic Implications of HCM Genetic Testing
 - i. Summary of Common HCM Genes (Table 2)
 - ii. Index Cases
 - iii. Family Screening

- c. Prognostic Implications of HCM Genetic Testing
 - d. Therapeutic Implications of HCM Genetic Testing
- VIII. State of Genetic Testing for Arrhythmogenic Cardiomyopathy (ACM)/Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)
- a. Expert Consensus Recommendations
 - b. Diagnostic Implications of ACM/ARVC Genetic Testing
 - i. Summary of the Common ACM/ARVC Genes (see Table 2)
 - ii. Index Cases
 - iii. Family Screening
 - c. Prognostic and Therapeutic Implications of ACM/ARVC Gene Testing
- IX. State of Genetic Testing for Dilated Cardiomyopathy (DCM)
- a. Expert Consensus Recommendations
 - b. Diagnostic Implications of DCM Genetic Testing
 - i. Index Case
 - ii. Family Screening
 - c. Prognostic Implications of DCM Genetic Testing
 - d. Therapeutic Implications of DCM Genetic Testing
- X. State of Genetic Testing for Left Ventricular Noncompaction (LVNC)
- a. Expert Consensus Recommendations
 - b. Diagnostic Implications of LVNC Genetic Testing
 - i. Index Cases
 - ii. Family Screening
 - c. Prognostic and Therapeutic Implications of LVNC Genetic Testing
- XI. State of Genetic Testing for Restrictive Cardiomyopathy (RCM)
- a. Expert Consensus Recommendations
 - b. Diagnostic Implications of RCM Genetic Testing
 - i. Summary of Common RCM Genes (Table 2)
 - ii. Index Case
 - iii. Family Screening
 - c. Prognostic Implications of RCM Genetic Testing
 - d. Therapeutic Implications of RCM Genetic Testing
- XII. State of Genetic Testing for Out-of-Hospital Cardiac Arrest Survivors
- a. Expert Consensus Recommendations
 - b. Clinical Evaluation
 - c. Role of Genetic Testing in OHCA
- XIII. State of Post-Mortem Genetic Testing in Sudden Unexpected Death Cases (SUD/SIDS)
- a. Expert Consensus Recommendations
 - b. Diagnostic Implications of SUDS/SIDS Genetic Testing
 - i. Family Screening
 - c. Prognostic and Therapeutic Implications of SUDS/SIDS Genetic Testing

Appendix 1. Glossary of Terms Related to Genetic Testing

Appendix 2. Author Disclosures

Appendix 3. Peer Review Disclosures

Introduction

Expert Consensus Recommendations

- Genetic counseling **is recommended** for all patients and relatives with the familial heart diseases detailed in this document and should include discussion of the risks, benefits, and options available for clinical testing and/or genetic testing.
- Treatment decisions **should not** rely solely on his/her genetic test result but **should be** based on an individual's comprehensive clinical evaluation.
- It **can be useful** for pre-genetic test counseling, genetic testing, and the interpretation of genetic test results to be performed in centers experienced in the genetic evaluation and family-based management of the heritable arrhythmia syndromes and cardiomyopathies described in this document.

See Table 1: Summary of Expert Consensus Recommendations

Since the discovery of the first cardiomyopathy-causative gene in 1990 and the sentinel channelopathy-causative genes in 1995, genetic testing for potentially heritable channelopathies and cardiomyopathies has advanced from basic scientific discovery to clinical application. Today, the majority of channelopathy/cardiomyopathy genetic tests are clinically available diagnostic tests. This maturation requires cardiologists and heart rhythm specialists to acquire a new vocabulary, the language of genomic medicine.

There is a substantial knowledge gradient among cardiologists regarding heritable channelopathies and cardiomyopathies. Among heart rhythm specialists, it is estimated that less than 20% of a pediatric electrophysiologist's training and less than 10% of an adult electrophysiologist's training pertains to the heritable channelopathies such as long QT syndrome. With the complexities of genetic testing, it will be essential for training programs to address and bridge these knowledge gaps. Genetic counseling is recommended for all patients and relatives with the familial heart diseases detailed in this statement. Counseling should include a thorough discussion of the risks, benefits, and options available for clinical genetic testing.

The broader ethical, legal, and societal implications (ELSI) of genetic testing are beyond the scope of this document and a variety of national regulations and specifications exist.^{2,3} Questions regarding the possibility of and role for pre-implantation genetic testing of embryos generated with assisted reproductive technologies are emerging. If the electrophysiologist or cardiologist is not equipped to discuss these issues, genetic counseling should be done in partnership with genetic counselors, nurse-geneticists, and/or geneticists.^{4,5} Such a multidisciplinary approach may help serve the needs of the index

Table 1 Summary of Expert Consensus Recommendations**STATE OF GENETIC TESTING FOR LONG QT SYNDROME (LQTS)****Class I (is recommended)**

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.

Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing **is recommended** 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 IIb (may be considered)

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.

STATE OF GENETIC TESTING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)**Class I (is recommended)**

Comprehensive or CPVT1 and CPVT2 (*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.

STATE OF GENETIC TESTING FOR BRUGADA SYNDROME (BrS)**Class I (is recommended)**

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 IIa (can be useful)

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.

Class III (is not indicated/recommended)

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

STATE OF GENETIC TESTING FOR PROGRESSIVE CARDIAC CONDUCTION DISEASE (CCD)**Class I (is recommended)**

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

Class IIb (may be considered)

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.

STATE OF GENETIC TESTING FOR SHORT QT SYNDROME (SQTS)**Class I (is recommended)**

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 IIb (may be considered)

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.

STATE OF GENETIC TESTING FOR ATRIAL FIBRILLATION**Class III (is not indicated/recommended)**

Genetic testing **is not indicated** for atrial fibrillation at this time.

SNP genotyping in general and SNP rs2200733 genotyping at the 4q25 locus in particular for AF **is not indicated** at this time based on the limited outcome data currently available.

STATE OF GENETIC TESTING FOR HYPERTROPHIC CARDIOMYOPATHY (HCM)**Class I (is recommended)**

Comprehensive or targeted (*MYBPC3*, *MYH7*, *TNNI3*, *TNNI2*, *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.

STATE OF GENETIC TESTING FOR ARRHYTHMOGENIC CARDIOMYOPATHY (ACM)/ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)**Class I (is recommended)**

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 IIa (can be useful)

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.

Class IIb (may be considered)

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).

Class III (is not indicated/recommended)

Genetic testing **is not recommended** for patients with only a single minor criterion according to the 2010 task force criteria.

Table 1 Continued

STATE OF GENETIC TESTING FOR DILATED CARDIOMYOPATHY (DCM)	
Class I (is recommended)	
Comprehensive or targeted (<i>LMNA</i> and <i>SCN5A</i>) 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 a family history of premature unexpected sudden death.	
Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.	
Class IIa (can be useful)	
Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.	
STATE OF GENETIC TESTING FOR LEFT VENTRICULAR NONCOMPACTION (LVNC)	
Class I (is recommended)	
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 IIa (can be useful)	
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.	
STATE OF GENETIC TESTING FOR RESTRICTIVE CARDIOMYOPATHY (RCM)	
Class I (is recommended)	
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 IIb (may be considered)	
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.	
STATE OF GENETIC TESTING FOR OUT-OF-HOSPITAL CARDIAC ARREST SURVIVORS	
Class I (is recommended)	
In the survivor of an Unexplained Out-of-Hospital Cardiac Arrest, genetic testing should be guided by the results of medical evaluation and is used for the primary purpose of screening at-risk family members for subclinical disease.	
Class III (is not indicated/recommended)	
Routine genetic testing, in the absence of a clinical index of suspicion for a specific cardiomyopathy or channelopathy, is not indicated for the survivor of an Unexplained Out-of-Hospital Cardiac Arrest.	
STATE OF POST-MORTEM GENETIC TESTING IN SUDDEN UNEXPECTED DEATH CASES (SUD/SIDS)	
Class I (is recommended)	
For all SUDS and SIDS cases, collection of a tissue sample is recommended (5–10 mL whole blood in EDTA tube, blood spot card, or a frozen sample of heart, liver, or spleen) for subsequent DNA analysis/genetic testing.	
Mutation-specific genetic testing is recommended for family members and other appropriate relatives following the identification of a SUDS-causative mutation in the decedent.	
Class IIb (may be considered)	
In the setting of autopsy negative SUDS, comprehensive or targeted (<i>RYR2</i> , <i>KCNQ1</i> , <i>KCNH2</i> , and <i>SCN5A</i>) 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).	

cases and their families more fully. In addition, it can be helpful for pre-genetic test counseling, genetic testing, and the interpretation of genetic test results to be performed in centers experienced in the genetic evaluation and family-based management of the heritable arrhythmia syndromes and cardiomyopathies described in this statement.

Genetic testing must not be viewed as a one-size-fits-all solution. There are more than 50 distinct channelopathy/cardiomyopathy-associated genes with hundreds of discrete missense, nonsense, insertion/deletion, frameshift, and splice site mutations.⁶ Table 2 summarizes only the common disease-associated genes responsible for $\geq 5\%$ of a given disease that is detailed in this consensus statement. In addition, the yield of genetic testing is disease dependent ranging among the channelopathies from $<20\%$ for short QT syndrome to 75% for the current generation long QT syndrome genetic test. Among the cardiomyopathies, the yields range from $<20\%$ for restrictive cardiomyopathy to 60% for familial hypertrophic cardiomyopathy (Table 3). Consequently, a negative genetic test can never, by itself, rule out the presence of any of the diseases under

consideration for the index case. When caring for a patient with an unequivocal disease phenotype but a negative genetic test, non-genetic cardiologists from this writing group without a direct or potential conflict of interest (Drs. A.J. Camm and D. Zipes) encourage physicians to seek out research laboratories that look for novel disease-causing genes for the patient's particular disease.

In addition, the diagnostic, prognostic, and therapeutic contribution of a genetic test result also is disease dependent for the index case (Figure 1). The impact of each disease-specific genetic test in each of these three areas is detailed in each section of this document. This triad is satisfied most fully for long QT syndrome.^{6–8} Regardless of the disease in question or the specific genetic test pursued, treatment decisions should not rely solely on the patient's genetic test result but should be based on results from his/her comprehensive clinical evaluation.

The correct identification of the definitive disease-causing mutation in an index case potentially affords a gold standard diagnostic marker for the presence or absence of the patho-

Table 2 Summary of Common Cardiac Channelopathy/Cardiomyopathy-Associated Genes (>5% of Disease)

Gene	Locus	Protein	% of Disease
Section I – Long QT Syndrome (LQTS)			
<i>KCNQ1</i> (LQT1)	11p15.5	I _{Ks} potassium channel alpha subunit (Kv7.1)	30%–35%
<i>KCNH2</i> (LQT2)	7q35-q36	I _{Kr} potassium channel alpha subunit (Kv11.1 or hERG)	25%–40%
<i>SCN5A</i> (LQT3)	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	5%–10%
Section II – Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)			
<i>RYR2</i> (CPVT1)	1q42.1-q43	Ryanodine receptor 2	60%
Section III – Brugada Syndrome (BrS)			
<i>SCN5A</i>	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	20%–30%
Section IV – Cardiac Conduction Disease (CCD)			
<i>SCN5A</i>	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	5%
Section V – Short QT Syndrome (SQTs)			
<i>None of the three known disease-associated genes has been shown to account for ≥5% of this disease</i>			
Section VI – Atrial Fibrillation (AF)			
<i>None of the known disease-associated genes has been shown to account for ≥5% of this disease</i>			
Section VII – Hypertrophic Cardiomyopathy (HCM)			
<i>MYBPC3</i>	11p11.2	Cardiac myosin-binding protein C	20%–45%
<i>MYH7</i>	14q11.2-q12	β-Myosin heavy chain	15%–20%
<i>TNNT2</i>	1q32	Cardiac troponin T type 2	1%–7%
<i>TNNI3</i>	19q13.4	Cardiac troponin I type 3	1%–7%
Section VIII – Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)			
<i>PKP2</i>	12p11	Plakophilin 2	25%–40%
<i>DSG2</i>	18q12.1	Desmoglein 2	5%–10%
<i>DSP</i>	6p24	Desmoplakin	2%–12%
<i>DSC2</i>	18q12.1	Desmocollin 2	2%–7%
Section IX – Dilated Cardiomyopathy (DCM)			
<i>None of the >25 known disease-associated genes has been shown to account for ≥5% of this disease</i>			
Section IX – Dilated Cardiomyopathy with Cardiac Conduction Defect (DCM + CCD)			
<i>SCN5A</i>	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	5%–10%
<i>LMNA</i>	1q22	Lamin A/C	5%–10%
Section X – Left Ventricular Non-Compaction (LVNC)			
<i>LBD3</i>	10q22.2-q23.3	LIM binding domain 3	~5%
Section XI – Restrictive Cardiomyopathy (RCM)			
<i>MYH7</i>	14q11.2-q12	β-Myosin heavy chain	~5%
<i>TNNI3</i>	19q13.4	Cardiac troponin I type 3	~5%
Section XIII – Sudden Unexplained Death Syndrome (SUDS)			
<i>RYR2</i>	1q42.1-q43	Ryanodine Receptor 2	10%–15%
<i>KCNQ1</i>	11p15.5	I _{Ks} potassium channel alpha subunit (Kv7.1)	5%–10%
<i>KCNH2</i>	7q35-q36	I _{Kr} potassium channel alpha subunit (Kv11.1 or hERG)	~5%
Section XIII – Sudden Infant Death Syndrome (SIDS)			
<i>SCN5A</i>	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	3%–5%

genic substrate among relatives. Accordingly, genetic testing in individuals with the familial diseases outlined in this document may be useful to identify at-risk family members, to identify the cause of their condition, to determine their likelihood of syndromic disease manifestations, and to assist with family planning. Consequently, mutation-specific genetic testing among the family members has diagnostic, prognostic, and therapeutic implications ranging from a negative genetic test

and potential dismissal from cardiology to a positive genetic test in a relative without clinical evidence for the disease in question that results in prophylactic treatment.⁸ However, the age at genetic testing and use of genetic testing for asymptomatic family members and other relatives without a manifest diagnosis are disease dependent. For diseases such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, in which preventive measures or prophylactic

Table 3 Yield and Signal-to-Noise Associated with Disease-Specific Genetic Testing

Section – Disease	Yield of Genetic Test*	% of Controls with a Rare VUS#	Signal-to-Noise (S:N) Ratio+
Section I – LQTS	75% (80%)	4%	19:1
Section II – CPVT	60% (70%)	3%	20:1
Section III – BrS	20% (30%)	2% (just <i>SCN5A</i>)	10:1
Section IV – CCD	Unknown	Unknown	Unknown
Section V – SQTS	Unknown	3%	Unknown
Section VI – AF	Unknown	Unknown	Unknown
Section VII – HCM	60% (70%)	~5% (unpublished data)	12:1
Section VIII – ACM/ARVC	60%	16%	4:1
Section IX – DCM	30%	Unknown	Unknown
Section IX – DCM + CCD	Unknown	4% (for <i>SCN5A</i> and <i>LMNA</i>)	Unknown
Section X – LVNC	17%–41%	Unknown	Unknown
Section XI – RCM	Unknown	Unknown	Unknown

*Yield of Genetic Test is a published/unpublished estimate derived from unrelated cases with unequivocal disease phenotype. First number is the yield associated with the targeted major gene scan. The number in parentheses is the total yield when including all known disease-associated genes that have been included in commercial disease gene panels. When only a single percentage is provided, this represents the estimate from a comprehensive disease gene panel. These yield values represent estimates for whites with the particular disease phenotype. Evidence is lacking to establish point estimates for minority populations.

#% of Controls with a Rare Variant of Uncertain Significance (VUS) represents a frequency of rare amino acid substitutions found in whites in the major disease-associated genes that, had it been found in a case, would have been reported as a “possible disease-associated mutation.” This number does not include the frequency of rare genetic variants present in the minor disease-associated genes. Thus, it represents a lower point estimate for the potential false positive rate. A question mark indicates that an otherwise healthy control population has not been systematically examined for the genes of interest. As with the Yield of Genetic Test, these estimates are derived for whites.

+The signal-to-noise (S:N) ratio is derived by dividing the yield by the background rate of VUS in controls. This provides a sense of the positive predictive value of a “positive” genetic test result.

therapy is advised for the asymptomatic host with a non-diagnostic clinical phenotype, mutation-specific genetic testing should be performed as early as infancy, independent of age. For other diseases, it is reasonable to discuss monitoring for onset of clinical manifestations rather than identification of a mutation-positive relative during childhood for a disease that may never appear or may appear later in life. These issues regarding timing of genetic testing must be discussed carefully with the family.

Because of the genetic test result’s potential to influence clinical decisions, it is critical to scrutinize and communicate the test result carefully. Contrary to common misperception,

genetic tests are probabilistic tests, not deterministic tests. Many positive test results contain the index case’s and his/her family’s definitive disease-causing mutation, the proverbial pathogenic “smoking gun.” However, many so-called “positive” test results are represented by less informative DNA variants currently annotated with the expression “Variants of Uncertain Significance” (VUS). Only recently is the frequency of rare VUS among otherwise healthy volunteers across the exomes of various disease-causing genes being identified.^{9–12}

Table 3 summarizes the known background frequency of rare VUS for the common disease-associated genes, which enables an initial estimate of the “signal-to-noise” ratio for the various genetic tests. As commercialized disease-specific gene panels increase to include the minor disease-associated genes in which each gene is responsible for <1% of the disease in question, this “signal-to-noise” ratio potentially declines because many of these minor genes are often paradoxically accompanied with a measurable frequency of VUS.

This VUS issue and its associated possibility of a false positive genetic test results are also disease dependent, ranging from a relatively low rate of false positives for CPVT testing to an alarmingly high rate of possible false positives associated with the ACM/ARVC test. A false positive involves the identification of a rare but otherwise non-pathogenic mutation. For many disease-specific genetic tests, the false positive rate is unknown. The potential for false positive genetic test results rises significantly when genetic testing is pursued in settings in which the phenotype is ambiguous or absent, such as in screening. Consequently, there is no role for universal genetic testing for any of the diseases detailed in this statement. Instead,

Section # – Disease	Diagnostic	Prognostic	Therapeutic
Section I – LQTS	+++	+++	++
Section II – CPVT	+++	+	-
Section III – BrS	+	+	-
Section IV – CCD	+	+	+
Section V – SQTS	+/-	-	-
Section VI – AF	-	-	-
Section VII – HCM	+++	++	+
Section VIII – ACM/ARVC	+	+/-	-
Section IX – DCM	+/-	-	-
Section IX – DCM + CCD	++	++	+
Section X – LVNC	+	-	-
Section XI – RCM	+	+	+

Figure 1 Impact of genetic testing for the index case. The relative strength (– = negligible to +++ = strong) regarding the contribution/impact of the genetic test result for the index case for each disease in each of the three categories (diagnostic, prognostic, and therapeutic) was voted upon by each writing member and >90% consensus was achieved for each “cell.” The level of evidence for each cell’s designation is the same as for the entire document, Level of Evidence C.

genetic testing must be phenotype directed. If the clinical diagnosis is in question, it may be prudent first to refer the patient to a center specializing in that particular disease rather than proceeding directly with genetic testing.

Genetic testing must not be viewed as a simple blood test. Genetic testing for the diseases outlined in this document need to be approached as one component of a comprehensive cardio-genetic evaluation in which all the aforementioned issues, including (a) the certainty and expertise of proband diagnosis, (b) the probabilistic nature of genetic testing and the need for pre-test counseling to inform the patient of the intrinsic uncertainties of genetic testing, and (c) the need to obtain a family history to get a sense of disease penetrance and expressivity, are addressed with care.

I. STATE OF GENETIC TESTING FOR LONG QT SYNDROME (LQTS)

Expert Consensus Recommendations

1. 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.
2. Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing **is recommended** 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).
3. 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.
4. 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.

Congenital long QT syndrome (LQTS) is a genetic disease characterized by its hallmark electrocardiographic feature of QT prolongation and T wave abnormalities, its trademark arrhythmia of *torsades de pointes* (TdP), and its predisposition for syncope, "seizures," and sudden cardiac death (SCD) in young individuals with structurally normal hearts.¹³ The majority of LQTS index cases manifest diagnostic QT prolongation on their resting 12-lead ECG, while approximately 10 to 40% of LQTS patients (index cases and relatives) have non-diagnostic QT intervals at rest and are referred to as "normal QT interval" or "concealed" LQTS.^{14–17} Besides needing to verify the computer derived QTc value manually, careful inspection of T wave and U

wave morphology is necessary to detect subtle clues regarding the possible presence of LQTS. Exercise testing, catecholamine stress testing, and Holter monitoring may increase diagnostic sensitivity in some patients.^{18–22} A clinical diagnostic score, developed before genetics entered the field of LQTS, still is used in clinics to help in establishing the diagnosis.²³ Secondary causes have to be excluded as the cause for repolarization changes.

With an estimated incidence of at least 1 in 2,500 people,²⁴ LQTS is underscored by marked clinical heterogeneity ranging from a lifelong asymptomatic state to sudden death during infancy. LQTS is more likely to express itself before puberty in males and after puberty in females.^{17,25,26} Besides age and sex, the degree of QTc prolongation is associated with likelihood of a first LQT-triggered cardiac event (syncope or aborted cardiac arrest) while occurrence of such cardiac events, particularly while on therapy, is a strong predictor of recurrences.^{27–29} Among symptomatic index cases, the untreated 10-year mortality is approximately 50%.^{28–31}

Diagnostic Implications of LQTS Genetic Testing

Summary of the Common LQTS Genes (see Table 2)

Since the sentinel discovery of the primary LQTS-causative genes in 1995^{30,32} and 1996,³³ at least 13 LQTS genes have been reported.^{34–40} Comprehensive open reading frame analysis of the three canonical LQTS-causative genes—*KCNQ1*-encoded Kv7.1 channel subunit (LQT1), *KCNH2*-encoded Kv11.1 (LQT2), and *SCN5A*-encoded Nav1.5 (LQT3)—yields putative LQTS-associated mutations in 75% of clinically definite LQTS (Table 2).^{15,41} This yield may increase to 80% with inclusion of copy number variant (CNV)/genomic rearrangement testing of *KCNQ1* and *KCNH2*.^{42,43} Thus, nearly 70% of all LQTS stems from loss-of-function mutations involving either the Kv7.1 (IKs) potassium channel (LQT1) or the Kv11.1 (IKr) potassium channel (LQT2) while approximately 5%–10% is secondary to "gain-of-function" mutations in the Nav1.5 (INa) sodium channel (LQT3). The 10 additional minor LQTS genes comprise <5% of LQTS cases.

As such, approximately 15% to 20% of LQTS remains genetically elusive following comprehensive genetic testing of the currently known genes. The majority of LQTS is inherited as an autosomal dominant trait, the Romano-Ward syndrome. Sporadic (or *de novo*) alterations occur <5%–10% of the time. Extrapolating from the established prevalence of LQTS in general, the autosomal recessive form of LQTS, also known as Jervell and Lange-Nielsen syndrome, probably affects less than 1 in a million people and results from complete loss of Kv7.1 channel function, which precipitates sensorineural deafness in addition to LQT1 or LQT5 substrates associated with increased cardiac risk.^{44,45}

In addition to autosomal dominant and autosomal recessive LQTS, Andersen-Tawil syndrome (ATS) and Timothy syndrome (TS) have been classified in the past as LQT7 and LQT8, respectively. The cardiac phenotype of ATS includes

abnormal TU waves and QTU prolongation. ATS1 (LQT7) stems from mutations in the *KCNJ2*-encoded Kir2.1 potassium channel and accounts for approximately 50% to 60% of ATS. TS involves marked QT prolongation and syndactyly. TS1 (LQT8) is the result of gain-of-function mutations in the *CACNA1C*-encoded L-type calcium channel subunit.

Index Cases

Following the era of research-based genetic testing, LQTS genetic testing has been a clinically available, fee-for-service diagnostic test for the past 5–10 years.⁴⁶ Genetic analysis of *KCNQ1*, *KCNH2*, and *SCN5A* including CNV testing for *KCNQ1* and *KCNH2* genomic rearrangements will yield possible LQT1-, LQT2-, and LQT3-causative mutation(s) for 75% to 80% of patients with a robust LQTS phenotype. While addition of the 10 minor LQTS genes increases the yield by <5%, it significantly increases the chances of a false positive. Accordingly, either comprehensive genetic testing of all known LQTS genes or targeting the three major LQTS genotypes are acceptable strategies. As with every condition in this statement, a negative genetic test cannot exclude unequivocally the diagnosis of LQTS by itself.

Clinical LQTS genetic testing **is recommended** for any index case in which LQTS is suspected by a cardiologist based on the patient's clinical history, family history, QT interval duration, inspection of T-wave morphology, and/or response to either cycle/treadmill or catecholamine stress testing.⁴⁷ If that patient was tested previously in a research laboratory, testing should be repeated with an LQTS genetic test.^{48,49} The sensitivity of current clinical LQTS genetic tests is superior to the research-based genetic tests that were available in the 1990s and early 2000s. If a patient has exercise-triggered cardiac events, a mildly prolonged or normal resting QTc (usually <460 ms) and exercise-induced multiform PVCs, the diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) or Andersen-Tawil syndrome (ATS1/LQT7) in combination with other clinical signs also should be considered (see Section II on CPVT).^{50,51}

LQTS genetic testing should not be performed solely in response to a past history of fainting without cardiology consultation. It must not be performed as part of pre-sports participation or as a universal screening protocol. The significant rate of rare variants of uncertain significance (i.e., non-synonymous genetic variation: 4% in whites and 6% to 8% in non-whites) in the LQT1–3 genes complicates correct mutation assignment and mandates that LQTS genetic testing be sought based upon clinical suspicion rather than ordered indiscriminately.⁵² In some countries, there are strict legal restrictions against performing genetic testing in the absence of evident/suspected disease or of a proven gene mutation in a close family relative.

Even in the absence of symptoms, LQTS genetic testing **is recommended** for patients with unequivocal and otherwise idiopathic, serial QT prolongation (QTc $\geq$ 480 ms in prepubertal children and $\geq$ 500 ms in adults). Otherwise idiopathic implies that the QT prolongation cannot be attributed to disease states/conditions (e.g., electrolyte abnor-

malities, cardiac hypertrophy, bundle branch block, diabetes) associated with true or apparent QT prolongation. LQTS genetic testing **may be considered** for serial QTc values, on 12-lead ECG (not 24-hour QTc maximum values), $\geq$ 460 ms in prepubertal children and $\geq$ 480 ms in adults. These proposed QTc/genetic testing cut-off values found in an asymptomatic host during screening are intentionally set higher than the most recent AHA/ACCF/HRS guidelines-based designations of a QTc $\geq$ 450 ms in adult males and $\geq$ 460 ms in adult females as “Prolonged QTc.”⁵³ The only data regarding the possible yield of LQTS genetic testing based upon a particular QTc value involve genetic testing of 2- to 4-week-old infants with QTc $\geq$ 470 ms and a yield approaching 50%.⁵⁴

The role of LQTS genetic testing in the isolated setting of drug-induced LQTS requires individualized consideration. Approximately 10% to 20% of examined drug-induced LQT cases have LQTS-associated mutations compared to the VUS rate of 4% in controls.^{55–57} While LQTS genetic testing in the setting of drug-induced TdP **should be considered** for that index case, a 12-lead ECG **is recommended** for his/her first-degree relatives. The role of LQTS-focused postmortem genetic testing for the evaluation of sudden infant death syndrome (SIDS) and autopsy-negative sudden unexplained deaths (SUDS) is examined in the section on Postmortem Genetic Testing (Section XIII).

Finally, the genetic test result must be scrutinized with great caution, as all genetic tests are probabilistic tests rather than deterministic/binary ones.⁵² This issue of genetic test result interpretation applies to all the diseases detailed in this document.

Family Screening

When a causative mutation is identified in clinically affected index cases, mutation-specific genetic testing of all first-degree relatives (i.e., parents, siblings, offspring) is indicated.^{7,8} Genetic testing should be performed in individuals even with a negative clinical and electrocardiographic phenotype. The only way to rule out LQTS in such a family member in cases in which a probable LQTS-associated mutation has been established is a negative genetic test. A normal resting ECG with a “normal” QTc is not sufficient to rule out LQTS. If the genetic test, history, and 12-lead ECG are negative, LQTS is ruled out. However, if the mutation-specific genetic test is negative but prolonged QTc intervals are present, a genetic re-evaluation that could include repeat testing or proceeding with independent comprehensive LQTS genetic testing should be considered. Ideally, clinical and genetic evaluation of distant relatives should extend in concentric circles of first-degree relatives depending on where the LQTS-associated mutation tracks. It may be necessary to include second- and third-degree relatives in the initial genetic screen of relatives.

Prognostic Implications of LQTS Genetic Testing

Numerous genotype–phenotype relationships in LQTS have been discovered in the past 15 years, including genotype–

suggestive ECG patterns, genotype-suggestive arrhythmogenic triggers, genotype-based natural histories, and genotype-specific responses to pharmacotherapy.^{58–61} The majority of these relationships pertain to the major LQTS genotypes: LQT1, LQT2, and LQT3. The genetic test result has joined traditional risk factors (i.e., gender, age at onset, QTc at rest, syncope) as independent prognostic risk factors.²⁴ Compared with the more common potassium channel loss-of-function subtypes (LQT1 and LQT2), patients with LQT3 appear to have the highest mortality per event.⁵⁹ In addition, within each of the two major LQTS genotypes (LQT1 and LQT2), the mutation's location within the protein and its functional sequelae have been proposed as independent risk factors with hazards ratios similar to the QTc >500 ms risk factor.^{62,63} Besides an observed risk stratifying class effect based on mutation type, mutation location, and mutation's impact on cellular function, mutation-specific risk stratification has emerged for a few discrete LQTS-causative mutations (e.g., A341V-KCNQ1, E1784K-SCN5A).^{64,65}

Therapeutic Implications of LQTS Genetic Testing

Beta blocker pharmacotherapy is the primary treatment for the management of most patients with LQTS.^{66–69} Among the three most common genotypes, beta blockers are extremely protective in LQT1 patients and moderately protective in LQT2.⁷⁰ In contrast, targeting of the pathologic, LQT3-associated late sodium current with propranolol (as the preferred beta blocker) and the possible addition of mexiletine, flecainide, or ranolazine represents the preferred pharmacotherapeutic option for LQT3.^{71–73}

Although genotype and mutation data must be incorporated with all of other non-genetic risk factors in assessing the patient's risk and personalizing the patient's treatment plan, no treatment decision should be influenced solely by either the genotype (LQT1-3) or the specific LQTS-causative mutation that was identified. In particular, a decision to implant an ICD prophylactically in an asymptomatic LQT3 host must include risk factors besides LQT3 genotype status.^{68,69}

II. STATE OF GENETIC TESTING FOR CPVT

Expert Consensus Recommendations

1. Comprehensive or CPVT1 and CPVT2 (*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.
2. Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic disease characterized by adrenergically

mediated ventricular arrhythmias causing syncope, cardiac arrest, and sudden cardiac death (SCD) in young individuals with structurally normal hearts.^{74,75} Symptoms typically occur with exertion or emotional stress. CPVT patients manifest with a normal resting ECG but exercise stress testing can elicit the typical bi-directional or polymorphic ventricular tachycardia. However, exercise-induced, single premature ventricular contractions (PVCs) or PVCs in bigeminy may be the only expression of the CPVT substrate. Ventricular fibrillation occurring during stress or emotion is the first manifestation of the disease in a minority of individuals. Holter monitoring may be useful in some patients to document catecholamine-related arrhythmias.

Supraventricular arrhythmias, ranging from isolated premature atrial contractions to runs of supraventricular tachycardia and bursts of atrial fibrillation, also are common in CPVT, stereotypically elicited by exercise or emotions. The concomitant presence of supraventricular arrhythmias also has been seen in LQTS, BrS, and HCM.

The mean age of onset of symptoms is 8 years old, but the first syncopal event may not occur until adulthood in some instances. Approximately 30% of affected individuals have symptoms before age 10 and nearly 60% of patients have at least one syncopal episode before age 40.⁷⁶

Diagnostic Implications of CPVT Genetic Testing

Summary of the Common CPVT Genes (Table 2)

Two CPVT genetic variants have been identified: an autosomal dominant form, due to mutations in the gene encoding for the cardiac ryanodine receptor (*RyR2*), and a less common autosomal recessive form, resulting from mutations in the gene for cardiac calsequestrin (*CASQ2*).^{77,78}

Index Cases

Approximately 65% of CPVT index cases have a *RYR2* mutation while the prevalence of *CASQ2* mutations is low, estimated at approximately 3% to 5%. Genetic screening allows the identification of mutations in up to 65% of patients with a clinical diagnosis.^{76,79}

More than 100 *RyR2* mutations have been reported as causative for the dominant form of CPVT (CPVT1). They tend to affect specific clusters/regions of the protein,^{50,80} primarily the FKBP12.6 binding domain, codons 2200–2500, and the transmembrane segments and C-terminus, starting from codon 3700. Therefore, because of the very large size of the *RYR2* gene, some laboratories only provide screening of selected exons encompassing these critical regions. Tiered screening has been proposed with subsequent screens encompassing the majority of *RYR2*.⁵⁰ Given the evidence that mutations outside the “clusters” have been identified, a CPVT genetic test that targets only a specific set of *RYR2*'s 105 translated exons may be suboptimal.

CASQ2 maps on chromosome 1p13.3-p11 and is the gene that causes the autosomal recessive form of CPVT (CPVT2). *CASQ2* is rare; as a consequence, only 12 CPVT-associated mutations and three non-synonymous polymorphisms (cSNP) have been shown to affect this gene (www.fsm.it/cardmoc/).

Because it is unclear whether *CASQ2* mutations may also cause autosomal dominant transmission of the phenotype and cases of double heterozygosity in non-consanguineous families have been reported,⁸¹ it is rational to screen *CASQ2* in sporadic *RYR2*-negative index cases.

Sudden cardiac arrest can be the first clinical presentation in up to 30% of cases.⁷⁶ Therefore, *RYR2* mutations may be regarded as a cause of adrenergically mediated idiopathic ventricular fibrillation (IVF), which may justify genetic testing in such instances. The yield of genetic testing in CPVT is the highest (65%) and most cost-effective among patients with typical bi-directional VT while for patients with non-typical clinical presentation (adrenergically induced syncope or IVF) the yield is much lower (<15%).⁷⁹ Of note, instances of SIDS have been associated with mutations in *RYR2*,⁸² but it is still unclear whether systematic *RYR2* screening is indicated and cost-effective for this population.

More recently, it has been proposed that mutations in two other genes may cause an arrhythmogenic disorder that resembles the classic description of CPVT (phenocopies): *KCNJ2*-encoding the Kir2.1 potassium channel that conducts I_{K1} and *ANKB* encoding for ankyrin B, a cytoskeletal protein.^{83,84} There is no definitive indication for a systematic screening of these genes in CPVT patients. However, if the primary *RYR2* genetic test is negative, careful consideration for a CPVT phenocopy should be given. If there is an abundance of ectopy present on 24-hour ambulatory monitoring, and prominent U wave, consider *KCNJ2* testing.

Family Screening

When a likely pathogenetic mutation is identified in clinically affected index cases, screening of all first-degree relatives is indicated. In addition, both first- and second-degree relatives should undergo clinical and genetic evaluation, including exercise stress testing when possible. Genetic testing for *RyR2* and *CASQ2* mutations should also be considered in first-degree relatives, even with a negative clinical phenotype.

Prognostic and Therapeutic Implications of CPVT Genetic Testing

There is no straightforward genotype-based risk stratification in CPVT. There also is no differential treatment approach presently for a CPVT1-positive index case compared to the CPVT index case with a negative genetic test. However, because CPVT may cause sudden death as first manifestation, genetic testing has relevance for clinical management and therapeutic decisions involving family members. Early CPVT genetic evaluation is important for all family members of CPVT index cases, facilitating pre-symptomatic diagnosis, appropriate counseling, and initiation of prophylactic beta blocker therapy. Considering the early age of manifestation of CPVT and its association with SIDS, it is reasonable that in families with a known CPVT-associated mutation, confirmatory genetic testing should be performed at birth to allow prompt initiation of beta blocker therapy in mutation-positive subjects.

III. STATE OF GENETIC TESTING FOR BRUGADA SYNDROME (BrS)

Expert Consensus Recommendations

1. 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.
2. Genetic testing **is not indicated** in the setting of an isolated type 2 or type 3 Brugada ECG pattern.
3. Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

Brugada syndrome (BrS) is characterized by right precordial ST elevation, frequently associated with conduction delays at different cardiac levels, potentially lethal arrhythmias, and a positive family history for sudden premature death.^{85,86} BrS typically expresses in males in their third to fourth decade of life and is responsible for a significant subset of sudden death in young individuals. The prevalence of the disease manifesting with clinical symptoms is estimated to be 1 in 5,000 to 10,000 in Western countries and may be more prevalent in South Asia. On the other side, the prevalence of clinically silent type 1 Brugada ECG pattern is likely much higher.⁸⁷ Phenotypic expression of BrS is rare in children.

Risk stratification is based on clinical parameters, particularly symptoms. Previous cardiac arrest and syncope put affected individuals at risk for recurrent (lethal) events.^{86,88} The role of other parameters, including the outcome of invasive electrophysiological studies, is disputed.⁸⁶⁻⁹² Treatment of high-risk patients consists of ICD implantation. Some researchers advocate a role for quinidine, particularly for low- to intermediate-risk patients.⁹³

Diagnostic Implications of BrS Genetic Testing

Summary of Common BrS Genes (Table 2)

At least eight genes may be causally involved. *SCN5A*, the gene encoding the cardiac sodium channel, accounts for the vast majority (>75%) of BrS genotype positive cases (Table 2). However, the yield of *SCN5A* genetic testing for robust clinical cases of BrS is approximately 25%.⁹⁴ Thus, the majority (>65%) of BrS cases remain genetically elusive.

Index Cases

The diagnosis of BrS is a clinical diagnosis and requires the signature type 1 Brugada ECG pattern in combination with one or more clinical variables such as unexplained syncope and family history of premature unexplained sudden death.⁸⁶ Genetic testing is not involved in the diagnosis, but the identification of a causative mutation may help confirm

a clinically uncertain diagnosis. The involvement of loss-of-function sodium channel mutations, the predominant genetic cause of BrS, may be recognized by more or less discrete conduction disorders at different levels of the heart.⁹⁵ Involvement of the calcium channel genes in patients with Brugada syndrome seems to be associated with relatively short QT intervals.⁹⁶

Family Screening

Genetic testing in families with an underlying causal gene defect may play a decisive role in who should take precautions in appropriate conditions (see below) and who should be followed.

Prognostic and Therapeutic Implications of BrS Genetic Testing

Data coupling genetic status to prognosis are scarce. Different outcomes as a function of the underlying gene defect have not been reported, and in a meta-analysis there seems to be no difference whether *SCN5A* is involved (BrS1).⁸⁸ However, in a subset analysis of patients with *SCN5A*-mediated BrS (i.e., BrS1), there may be a slightly better prognosis in cases of a *SCN5A* missense mutation compared with those leading to a truncated protein.⁹⁷ The latter also associates with more conduction delay (at different levels in the heart) than the former.

As there is no prognostic value of a genetic diagnosis, the presence of a BrS-associated mutation does not impact the treatment of an index case with BrS. However, asymptomatic *SCN5A* mutation-positive subjects also are advised to avoid or prevent fever and, if body temperature rises, to use antipyretic treatment liberally. Drugs that decrease sodium channel availability/functionality should be avoided by patients with BrS regardless of symptom status or electrocardiographic manifestation.⁹⁸ Both precautions are probably relevant for all patients with clinically diagnosed BrS independent of their genetic status.

IV. STATE OF GENETIC TESTING FOR PROGRESSIVE CARDIAC CONDUCTION DISEASE (CCD)

Expert Consensus Recommendations

1. 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.
2. Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the CCD-causative mutation in an index case.

This section pertains to familial forms of conduction disease, not to (common) non-familial forms secondary to structural heart disease. Cardiac conduction disorders (CCDs) typically are characterized by a delay in electrical impulse conduction at the atrial, nodal, and ventricular levels. In the

surface ECG, CCDs can be seen by a prolonged P-wave duration, PQ interval and QRS widening with axis deviation. Often, not all ECG changes initially are present and progressively develop an age-dependent penetrance.^{99,100}

In isolated forms of CCD, there are no extracardiac manifestations. The heart is structurally normal. ECG signs may include atrial inexcitability (atrial standstill), sinus node dysfunction, sino-atrial block, and features of Brugada syndrome (see Section III) that occur concomitantly or in isolation in a single patient and family members even in the presence of an identical genetic cause.^{101,102} In non-isolated forms of CCD, congenital heart disease (e.g., atrial septal defect, congenital AV block),¹⁰³ cardiomyopathy (e.g., dilated cardiomyopathy, as a lamin or cytoskeleton disorder; see Section IX), or extra-cardiac manifestation is present.¹⁰⁴

No systematic clinical data are available on the age of onset and course of symptoms in genetically affected individuals. Based on long-term observations in large CCD families, unaffected individuals beyond the age of 40 years can be differentiated from *SCN5A*-CCD mutation-positive subjects based upon ECG criteria as most older mutation-positive subjects exhibit prolonged PR and QRS intervals.⁹⁹

Diagnostic Implications of CCD Genetic Testing

When genetically mediated, the majority of CCD patients have an autosomal dominant mode of inheritance. Recessive or sporadic forms are rare.^{102,105,106} In isolated CCD, mutations in the gene encoding for the cardiac sodium channel (*SCN5A*) cause the majority of familial CCD,^{107,108} while mutations in the gene for the beta subunit (*SCN1B*) are single reports.¹⁰⁹ Recently, mutations in the transient receptor potential cation channel, subfamily M, member 4 (*TRPM4*) Ca^{2+} -activated cation channel gene were reported in patients with progressive CCD.^{110,111} These are estimated to account for a significant portion of inherited forms of RBBB (25%) or AV block (10%). Taken together, tiered genetic testing in patients with isolated CCD should comprise the *SCN5A* and *TRPM4* genes.

The relative portion of the identified genes within CCD families is not known. In idiopathic sinus node dysfunction (SND), mutations in the cardiac pacemaker channel gene *HCN4*^{112,113} 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.

When CCD is accompanied by the presence of concomitant congenital heart disease like atrial septal defects, mutations in cardiac transcription factor genes (*NKX2.5* or *GATA4*) are more likely.^{103,114} In absence of congenital heart disease, CCD also may precede left ventricular contractile dysfunction and development of dilated cardiomyopathy. This constellation typically is found in patients with laminopathies (*LMNA* gene), desmin-related myopathies (*DES* gene), or muscular dystrophies (e.g., *EMD* gene), and musculoskeletal and other abnormalities also can be found. Pleiotropic (tissue-spe-

cific) phenotypic expression of mutations may have an individual and age-dependent onset. Within larger sets, 74% of *DES* mutation-positive subjects have cardiologic signs (in 22% isolated), in the majority a dilated cardiomyopathy and atrioventricular conduction delay (60%).¹¹⁵ *LMNA* mutation-positive subjects share a similar pattern.^{116,117} In a few CCD families, *SCN5A* gene mutations or a reduced *SCN5A* protein expression may be associated with the development of heart failure and dilated cardiomyopathy.^{118–121} 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.

Index Cases

The diagnosis of a CCD in an index patient is a clinical one that requires an appropriate, ideally 12-lead ECG recording. In the majority of index cases, presence of congenital heart disease and cardiomyopathy must be investigated by echocardiography. Additional imaging studies including cardiac MRI may be considered. Early-onset CCD in the absence of structural heart disease should prompt consideration of CCD genetic testing, especially if a positive family history of conduction abnormalities and pacemaker implants is identified.

For the major genes associated with CCD, specialized cardiogenetic services have established a comprehensive testing panel. More than 20 *SCN5A* mutations are known, among them 75% missense mutations with a predicted full-length protein (see www.fsm.it/cardmoc/) and a randomly appearing distribution of the mutant site within the sodium channel protein. Despite the evidence that a loss of function is the key mechanism in sodium channel-related CCD, non-sense mutations are not as frequent as missense mutations. In addition, non-synonymous *SCN5A* gene variation is a frequent and ethnic-specific observation¹²² without impact on CCD. It is unclear as to whether a mutation in *SCN5A* resulting in Nav1.5 loss-of-function will yield a phenotype of BrS or CCD or an overlap syndrome with elements of both. Taken together, the identification of a CCD mutation confirms not only a clinical or suspected diagnosis of CCD but also allows its classification as a genetic (and potentially heritable) disease.

Family Screening

Cascade family screening is useful in families with mutation-positive CCD. When a clinical diagnosis of CCD is established in an index case, whether isolated or in conjunction with congenital heart disease, a careful clinical investigation of first-degree family members, even of those appearing unaffected, is necessary. Genotyping of family relatives is done after mutation identification in the index cases and may be useful to exclude presence or development of CCD. Due to the age-dependent disease manifestation, asymptomatic children in the first decade of life may

not be genetically investigated with the same impetus as family members in higher decades. Taken together, a clinical and genetic evaluation of family members is generally recommended to detect inherited forms of CCD disease and of associated, other cardiac and non-cardiac disease features.

Prognostic and Therapeutic Implications of CCD Genetic Testing

There is no genotype-based risk stratification for patients with CCD. Some mutations may be associated with development of heart failure and/or extracardiac features, such as myopathic features, that can be followed and treated after having CCD classified as a genetic entity.

Asymptomatic family members who are positive for the family's CCD-associated mutation should be regularly and prospectively followed for development of CCD-related symptoms, deterioration of cardiac conduction, and beginning of heart failure. In addition, medications with conduction slowing properties (e.g., antidepressants, antiarrhythmics) should be restricted, and fever, an aggravating trigger in individuals with sodium channel gene mutations, should be preemptively and symptomatically treated. Because there is no direct prognostic impact of a gene mutation, pacemaker implantations follow the national or internationally accepted indications¹²³ independent of genetic status.

V. STATE OF GENETIC TESTING FOR SHORT QT SYNDROME (SQTS)

Expert Consensus Recommendations

1. 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.
2. Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.

The short QT syndrome (SQTS) was described originally in 2000¹²⁴ as a new electrocardiographic pattern associated with atrial fibrillation and/or sudden cardiac death in the structurally normal heart. The characteristic sign for the disease is the presence of a very short QT interval on ECG, which may be accompanied by peaked T waves especially in the precordial leads. The age at onset of clinical manifestations may be extremely young, with reports of malignant forms being responsible for even neonatal sudden cardiac death, sometimes attributed to SIDS.^{125,126} The severity of the clinical manifestations of SQTS is highly variable, ranging from asymptomatic to atrial fibrillation, from recurrent syncope to sudden death.

The clinical diagnosis of SQTS remains a challenge, especially due to the difficulty of defining a newly described disease and the tendency of early reports to emphasize the

most extreme of disease phenotype. An absolute cut-off of abbreviated QTc interval for diagnostic consideration of SQTS has not been clearly defined. Epidemiologic data from a middle-aged Finnish population involving 10,822 men and women indicated that 97.5% of males had a QTc greater than 348 ms, while a value of 364 ms was identified for females.¹²⁷ Other large studies involving American, Japanese, and Swiss subjects have produced similar findings with the mean QTc generally 400 to 410 ms and values 2 standard deviations below the mean approximating 350 ms in males and 365 ms in females.^{128–170} However, SQTS genetic testing should not be pursued only because the QTc value is less than the lower 2.5th percentile. Instead, QTc values less than the 0.1 percentile would be more appropriate before ever considering SQTS genetic testing in the absence of symptoms.

Similar to LQTS, QTc overlap between SQTS and healthy controls exists, requiring the need for further diagnostic criteria to clarify diagnosis. A diagnostic scorecard for identifying low probability, intermediate probability and high probability cases has been published recently.¹³¹

Therapeutic options include the implantation of a defibrillator in cases of SCD or unexplained syncope meeting criteria for SQTS.¹³² Management of asymptomatic individuals or those with atrial fibrillation without ventricular arrhythmias remains uncertain. When a defibrillator is not recommended, the use of quinidine as primary therapy has been advocated due to its effect in prolonging the QT interval. However, longer follow-up is required to reach conclusions regarding efficacy of this approach.^{133–135}

Diagnostic Implications of SQTS Genetic Testing

SQTS is an autosomal dominant disease and genetically heterogeneous. Three SQTS-susceptibility potassium channel genes have been identified: *KCNH2* (SQT1), *KCNQ1* (SQT2), and *KCNJ2* (SQT3).^{136–141} Mutations in these genes yield a gain-of-function to their encoded potassium channel. Clinical cases describing a type 1 Brugada ECG pattern and associated with short QT-intervals and genetic mutations within *CACNA1C* or *CACNB2b* have been rarely described and proposed to represent sub-types of SQTS.¹⁴² However, as these cases may be readily recognized as BrS, invoking a second or alternative diagnosis of SQTS does not seem practical. Collectively, mutations in the three potassium channel genes may account for up to 20% of reported index cases.

Prognostic and Therapeutic Implications of SQTS Genetic Testing

No genotype–phenotype correlation studies have been performed due to the few families available. However, it is clear that the identical SQT-associated mutation may yield a varied phenotype.^{136,139} This indicates that patient-oriented, not family-oriented, clinical decisions must be made. Treatment decisions in high probability cases of SQTS are not influenced by genetic findings.

VI. STATE OF GENETIC TESTING FOR ATRIAL FIBRILLATION

Expert Consensus Recommendations

1. Genetic testing **is not indicated** for atrial fibrillation at this time.
2. SNP genotyping in general and SNP rs2200733 genotyping at the 4q25 locus for AF **is not indicated** at this time based on the limited outcome data currently available.

Atrial fibrillation (AF) is the most common sustained arrhythmia and its prevalence is increasing. AF is associated with an increased risk of stroke, heart failure, dementia, and death.¹⁴³ Symptoms of AF include palpitations, fatigue, dyspnea on exertion, and chest pain, though many patients are found to have AF incidentally. Numerous risk factors for AF have been described, including hypertension, heart failure, and valve disease. AF has a genetic basis, as a family history of AF is associated with a two-fold risk of the disease.¹⁴⁴ If a family member is affected by AF before age 60, the relative risk increases to 4.7.¹⁴⁵

Diagnostic Implications of AF Genetic Testing

Mutations have been described in families with autosomal dominant AF including *KCNQ1*,^{146,147} *KCNJ2*,¹⁴⁸ *KCNE2*,¹⁴⁹ *SCN5A*,^{123,150} *KCNA5*,¹⁵¹ and *NPPA*.¹⁵² Numerous other ion channel genes have been implicated in sporadic forms of AF, most notably the cardiac connexin genes *GJA1* and *GJA5*, the genes encoding connexin 40 and connexin 43.¹⁵³ Despite the number of genes related to AF, the mutations identified appear to be unique to individual families and thus are rare causes of the arrhythmia.

Genome-wide association studies have identified common genetic variants or single nucleotide polymorphisms (SNPs) associated with AF. SNPs at three genetic loci may be associated with AF.^{154–157} Combinations of SNPs appear to be associated with a graduated risk of AF. However, little information links specific genetic variants to distinct clinical outcomes for AF. Because understanding of familial atrial fibrillation is in the early stages, it can be useful to refer individuals with an extensive history of familial AF to a research center.

Prognostic and Therapeutic Implications of AF Genetic Testing

There is no prognostic or therapeutic impact derived from an AF genetic test result.

VII. STATE OF GENETIC TESTING FOR HYPERTROPHIC CARDIOMYOPATHY (HCM)

Expert Consensus Recommendations

1. Comprehensive or targeted (*MYBPC3*, *MYH7*, *TNNI3*, *TNNI2*, *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.

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

Hypertrophic cardiomyopathy (HCM) is a common disorder (affecting 1 in 500 people) characterized by unexplained cardiac hypertrophy, myocyte disarray, and fibrosis.¹⁵⁸ HCM is inherited as an autosomal dominant trait in the majority of adult patients with typical features; *de novo* mutations are seen but are uncommon.¹⁵⁹ However, the proportion of familial disease is lower in older patients and/or those with non-classical features. As with other inherited cardiomyopathies, HCM shows marked phenotypic variability, even within families. Penetrance (i.e., the proportion of mutation-positive subjects who have clinically detectable disease) increases with age but remains incomplete. The risk of sudden death is low in patients with no clinical risk factors but is sufficient in those with one or more risk factors to justify consideration of ICD implantation.¹⁶⁰ Although the absolute risk of SCD may be lower in HCM than some other conditions considered in these guidelines, its high prevalence makes HCM one of the most frequently identified causes of SCD. As most individuals with HCM are asymptomatic and sudden death may be unheralded, cascade screening in families offers the best potential for prevention. Because clinical features can sometimes be mild or uncertain, genetic testing may provide the most effective means of identifying at-risk individuals.

Diagnostic Implications of HCM Genetic Testing

Summary of Common HCM Genes (Table 2)

HCM was termed a "disease of the sarcomere" when the first three disease genes identified were found to encode components of the contractile apparatus.¹⁶¹ Mutations in at least eight sarcomere protein genes have been shown to cause HCM. Disease-causing mutations in *MYH7*, encoding beta-myosin heavy chain, and *MYBPC3*, encoding cardiac myosin binding protein-C, are the most common, each accounting for one quarter to one third of all cases, with the remaining HCM genes each contributing 1% to 5% or less.¹⁶² Within each gene, most individual mutations are rare and indeed are frequently unique to single families. Some founder mutations are seen; as expected these are typically variants associated with less severe disease.¹⁶³

Further disease genes have been implicated in HCM, albeit with less robust evidence. Mutations in *CSRP3*, encoding muscle LIM protein,¹⁶⁴ are supported by good evidence including co-segregation and mutations in *ACTN2* (alpha-actinin 2) also showing some evidence of co-segregation.¹⁶⁵ Further rare variants have been described in candidate gene studies of *TCAP* (T-cap protein), *ANKRD1* (CARP), and *JPH2* (junctophilin).

A number of phenocopies of HCM present with apparently similar cardiac features in the setting of different inheritance patterns and/or systemic features. These include

the compound phenotype of HCM with Wolff-Parkinson-White syndrome and conduction abnormalities caused by mutations in *PRKAG2*, Fabry disease and Danon disease, mitochondrial DNA mutations and Noonan syndrome. In addition, there can be genetic overlap between HCM and left ventricular non-compaction (LVNC). These disorders should be considered in familial evaluation and, where appropriate, in genetic testing strategies.

Phenotypic correlations with the underlying HCM disease gene are of limited utility for managing patients; quantitative differences exist but there is substantial overlap between different disease gene groups, and exceptions are common. *MYH7* alleles usually are associated with relatively robust clinical disease expression. *MYBPC3* mutations have been associated with later onset disease, but once HCM is manifest the usual complication rates apply.¹⁶⁶ In a significant proportion of families with *TNNI2* mutations, the phenotype is of minor hypertrophy but substantial arrhythmia risk,¹⁶⁷ but not all *TNNI2* mutations behave this way. Allelic heterogeneity compounds the interpretation further, as the rarity of individual mutations usually means that insufficient clinical data are available to reliably characterize a given variant.

The diagnostic yield of sarcomere gene testing (e.g., comprising up to 9 genes) in clinical cases of familial HCM is typically approximately 60%¹⁶²; the yield depends upon patient selection, falling to approximately 30% in sporadic disease.^{168,169} Approximately 5% of cases have two or more variants (compound or double heterozygotes) though in many cases at least one of the variants is of uncertain significance.^{170,171} It is not known if index cases with a negative HCM genetic test have HCM-causing mutations in unexplored regions within the known HCM genes, in undiscovered genes or, instead, do not have a Mendelian cardiomyopathy. The absence of large families mapping to non-sarcomere loci favors the latter explanation.

Index Cases

Genetic testing **is recommended** for patients with a firm clinical diagnosis of HCM in which mutation-specific confirmatory testing would benefit family members and potentially other relatives. This will include (a) families with a history of SCD (where risk stratification will be skewed toward a higher risk profile with greater likelihood of active intervention in those found to be affected); (b) families in which multiple relatives are at risk who would otherwise need clinical evaluation; and (c) families in which clinical diagnosis is difficult, including those in which individuals have had clinical complications from HCM despite only mild hypertrophy. Similarly, genetic analysis of post mortem samples should be considered in instances of SCD where HCM was not previously known in the family.

Genetic testing **is not recommended** for diagnosis of HCM in patients with non-diagnostic clinical features outside the setting of expert clinical and detailed family assessment (e.g., to evaluate an athlete's heart). The absence of a sarcomere mutation cannot rule out familial HCM and variants of uncertain significance are a more frequent problem

in those with lower clinical pre-test probability of a pathogenic sarcomere mutation. For the same reason, population genetic screening for HCM is not advisable.

Family Screening

When a presumed pathogenetic mutation is identified in a clinically affected index case, testing **is recommended** for all first-degree relatives (i.e., offspring, siblings, parents). Such mutation-specific genetic testing of the relatives (i.e., cascade screening) may have particular advantages over clinical screening of family members for HCM, as EKG/ECG or echocardiographic abnormalities may be absent or subtle, or develop late in life. Genetic screening in families with a known mutation is cost-effective, allowing half of the relatives tested to be discharged without need for clinical investigations or long-term follow-up.¹⁷² Because HCM can confer significant risks even in young children, cascade genetic testing often involves children and must be undertaken with attention to counseling, education, and psychological assessment.

Prognostic Implications of HCM Genetic Testing

Knowledge of the underlying gene and mutation has a limited role in risk assessment and management of the individual patient, which instead is based largely on clinical risk factors.¹⁷³ However, validated clinical risk factors include a family history of SCD,¹⁷³ suggesting that with greater knowledge genotype–phenotype correlations ought to be useful in HCM. For example, patients with features of HCM but without pathogenic sarcomere mutations have a lower likelihood of a positive family history and, on average, a milder phenotype¹⁷⁴; thus, a negative genetic test may be of prognostic significance. There are only a few specific mutations that might carry a prognostic implication, and ordinarily a genetic test result in isolation will not constitute an indication for an ICD for primary prevention. Many families have a previously unrecorded mutation. Long-term efforts are needed to accumulate reliable evidence on genotype–phenotype correlations, especially those pertaining to specific mutations.¹⁷⁵

Therapeutic Implications of HCM Genetic Testing

Within typical, sarcomeric HCM, no HCM mutation-specific therapeutic implications exist, as therapy in HCM is not disease modifying and treatment response is not influenced by mutation type. However, experimental studies and small phase II clinical trials of interventions (including diltiazem and angiotensin receptor/aldosterone blockade) designed as disease modifying show promise^{176–179}; there is growing interest in efforts aimed at preventing the development of overt HCM in mutation-positive subjects.¹⁷⁵ Genotyping to identify such pre-clinical patients is expected to remain a research area for now but may enable genetically directed prophylactic pharmacotherapy in the future. However, for a small subset of patients with apparent HCM, genetic testing may reveal phenocopies of HCM (such as GLA-HCM or LAMP2-HCM) in individual patients and their families. Such genetic test results may have direct therapeutic implications including enzyme-replacement therapy in GLA-HCM (Fabry disease) and early transplantation in LAMP2-HCM (Danon disease).

VIII. STATE OF GENETIC TESTING FOR ARRHYTHMOGENIC CARDIOMYOPATHY (ACM)/ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

Expert Consensus Recommendations

1. 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.
2. Genetic testing **may be considered** for patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 task force criteria.
3. Genetic testing **is not recommended** for patients with only a single minor criterion according to the 2010 task force criteria.
4. 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.

Arrhythmogenic cardiomyopathy (ACM) is a progressive, heritable myocardial disorder that is a leading cause of ventricular arrhythmia and sudden cardiac death (SCD) in people age ≤ 35 years.^{180,181} The disease may involve either or both ventricles, but is most well recognized in its classic subtype with right-sided preponderance, arrhythmogenic right ventricular cardiomyopathy (ARVC).^{182,183} Clinical diagnosis is based on demonstration of characteristic ECG, arrhythmic, structural, and/or histological abnormalities.^{182,184} A confirmed family history and/or the presence of a definite or probable disease-causing mutation also contributes to diagnosis. Morphological abnormalities may resemble dilated cardiomyopathy, but the clinical presentation typically is with arrhythmia rather than heart failure manifestations. Classification of the disease bridges the gap between cardiomyopathies and inherited arrhythmia syndromes.¹⁸⁵ The early, “concealed” phase is characterized by propensity toward ventricular arrhythmia in the setting of preserved morphology, histology, and ventricular function. As the disease progresses, myocyte loss, inflammation, and fibroadiposis become evident. Structural abnormalities range from regional wall motion abnormalities, ventricular aneurysms, and increased trabeculation to global ventricular dilation and dysfunction.¹⁸⁶ Ventricular arrhythmia remains the most common clinical manifestation until the advanced stage of the disease, when a minority of individuals develop heart failure.^{187,188}

ACM/ARVC is most commonly transmitted as an autosomal dominant trait, although incomplete penetrance coupled with variable and age-dependent expression may obscure Mendelian inheritance patterns.^{189–191} Autosomal recessive forms are rare but recognized, most prominently in the cardiocutaneous syndromes of Naxos and Carvajal.^{192–196} Compound heterozygosity (co-inheritance of different disease alleles of a single gene) and digenic heterozygosity (co-inheritance of disease alleles for two different genes) frequently (up to 10% of the time) are identified,¹⁹⁷

and may contribute to the variable penetrance and complexity of disease inheritance in ACM.

Diagnostic Implications of ACM/ARVC Genetic Testing

Summary of the Common ACM/ARVC Genes (see Table 2)

Most of the genes implicated in ACM/ARVC encode desmosomal proteins (plakoglobin [JUP], desmoplakin [DSP], plakophilin-2 [PKP2], desmoglein-2 [DSG2], and desmocollin-2 [DSC2]).^{193,194,198–204} There are isolated reports of causal mutations in extra-desmosomal genes. The S358L mutation in *TMEM43* in the Newfoundland founder population causes a fully penetrant, nonclassic form of the disease associated with a high incidence of SCD and heart failure.²⁰⁴ Mutations in *TGFβ3* have been identified in a single family and unrelated index case, but not in other kindreds with linkage to the same chromosomal locus.²⁰⁵ The cardiac ryanodine receptor (*RyR2*) has been linked to a distinct clinical entity, ARVC2, which is characterized by juvenile SCD and effort-induced polymorphic ventricular tachycardia.²⁰⁶ ARVC2 is clinically and genetically similar to type 1 catecholaminergic polymorphic ventricular tachycardia (CPVT1) and likely represents a CPVT phenocopy rather than true ARVC.

Thirty percent to 70% of cases of ACM/ARVC harbor mutations in one of the implicated desmosomal genes, most of which show marked allelic heterogeneity.^{183,200,207–209} Estimates of the success rate of genotyping vary according to cohort location and ethnicity, selection criteria, and the stringency of the standards by which mutations are considered causal. Common haplotypes consistent with founder effects contribute to the 70% reported prevalence of *PKP2* mutations among ARVC families in the Netherlands.²⁰⁹ In other cohorts, recent studies suggest that many of the *PKP2* variants previously linked to ARVC actually are of uncertain pathogenicity. Three previously reported missense variants occur in 0.5% to 1.4% of healthy control subjects.²¹⁰ Furthermore, among a series of 38 index cases with *PKP2* defects, 9 were compound heterozygotes and 16 were double heterozygotes, with additional rare variants in other desmosomal genes.¹⁹⁷ This suggests that many *PKP2* variants are not sufficient *per se* for clinical disease. Doubt also has been cast on the pathogenicity of certain genetic variants in *DSG2*, which have been identified in healthy control subjects at frequencies of 0.5%–13.9%.²¹¹ Reports nevertheless indicate that many of the disputed desmosomal gene variants are selectively enriched in cases compared with controls, implying contribution to disease expression.^{210,212} The genetics of ACM/ARVC may therefore be more complex than previously appreciated, with frequent requirement for more than one “hit” for penetrant disease.^{197,213}

Arrhythmogenic cardiomyopathy behaves as a complex disease in many families, complicating definitive genetic diagnosis.¹⁹⁷ Integration of genetic testing into clinical practice is nonetheless proceeding, with the main applications being confirmatory testing in index cases and cascade screening of families.²⁰⁸ ACM genetic diagnosis is a moving target, with new

pathogenic mutations being discovered, and mutations previously considered pathogenic sometimes being reclassified/demoted to a status of benign or unknown clinical significance as new data emerge.¹² Given the approximate 50% yield of the current generation genetic test for a robust case of ACM and the 16% frequency of rare variants in these same genes among ostensibly healthy volunteers, it is possible that up to one-third of the rare missense variants identified during ACM genetic testing represent false positives.¹² Extreme caution is therefore necessary regarding both obtaining an ACM/ARVC genetic test and interpreting its significance. In particular, it may be prudent to refer a patient with a questionable diagnosis of ACM/ARVC to a specialty center rather than order the genetic test.

Index Cases

Confirmatory testing is defined as the use of genotyping to corroborate clinical diagnosis suspicion of disease in an index case.²⁰⁸ In ACM/ARVC, the appeal of confirmatory testing is strongest among populations with proven founder effects, such as the Netherlands and Newfoundland.^{204,209} Obstacles to this approach in other cohorts are numerous. Frequent “private” mutations necessitate *de novo* determination of causality, while variants with reduced penetrance and uncertain pathogenicity may nonetheless contribute.^{186,208} Because the diagnostic yield from screening the known causal genes is limited, failure to identify a mutation does not exclude the disease.

The early stage of ACM/ARVC is described as “concealed” because sentinel clinical abnormalities are lacking. Disease expression may be limited to a single feature common to other disorders, such as right precordial T-wave inversion or ventricular tachycardia of left bundle branch block morphology. Reliable and timely diagnosis is critical, however, because affected individuals may be at risk of SCD and management protocols must be tailored accordingly. In these cases, isolation of a radical variant in a desmosomal gene may be invaluable, while variants of unknown pathogenicity may suggest the need for close observation.²⁰⁸

Family Screening

The combination of variable penetrance, age-related expression, and unpredictable disease flare-ups complicates evaluation of relatives in ACM. An unremarkable clinical evaluation does not preclude transmission of the disease to children or onset of disease expression in later life, even beyond middle age. Referral centers specializing in familial disease have responded to this dilemma by offering periodic reassessment to first-, second-, and sometimes third-degree relatives. The burden on clinical resources is significant, as is the psychological impact on relatives, who must reconcile themselves to lifelong screening without major prospect of definitive reassurance. The less attractive alternative would entail presumption of gene-negative status among clinically unaffected adults, and accepting that a minority of them or their children may present catastrophically with an arrhythmic event.²⁰⁸

Definitive genetic diagnosis in an index case offers an attractive solution by enabling cascade screening of fami-

lies. In a typical family with an autosomal dominant inheritance pattern, approximately half of relatives will test gene-negative, affording them with permanent reassurance and obviating the need to screen their children. Resources then can be targeted to proven ACM mutation-positive subjects, who will require lifelong observation.²⁰⁸ This scenario, however, is feasible only when the identified mutation is an unequivocal, or at least high-probability, ACM-causative mutation. Given the complexity of the disease phenotype in many families and uncertainties in assessing pathogenicity of variants, caution is justified before discharging relatives with symptoms or borderline clinical abnormalities on the basis of a “negative” gene test.^{186,197}

Prognostic and Therapeutic Implications of ACM/ARVC Gene Testing

The spate of genotype–phenotype studies that followed the isolation of primary mutations in arrhythmogenic cardiomyopathy has identified few definitive patterns. Left ventricular involvement appears more marked in families with chain-termination mutations and/or desmoplakin disease, while individuals harboring *PKP2* variants may have earlier onset of both symptoms and ventricular arrhythmia.^{183,214,215} Intrafamilial phenotype diversity, however, is prominent.²¹⁶ In contrast to HCM, a family history of SCD does not appear to be a key indicator of adverse prognosis in ACM, suggesting that primary mutation analysis is of limited value in risk prediction. Variance component analysis suggests that both genetic and environmental modifiers contribute significantly to varying disease penetrance and phenotypic manifestations, including arrhythmic outcome, between family members who carry a gene mutation in arrhythmogenic cardiomyopathy.²¹⁶ Systematic investigation of genetic background ultimately may carve out a niche for comprehensive genetic profiling in prognostication and management, but attempts to do so are premature.

Ongoing follow-up studies will shed light on disease evolution in the growing cohort of apparently silent mutation-positive subjects. The paucity of data precludes formulation of management guidelines excepting the need for periodic re-evaluation. Animal studies and anecdotal clinical reports suggest that prolonged and intense physical activity, particularly endurance training, may accelerate disease progression.^{183,217} In the absence of large-scale clinical validation, however, proscriptive counseling of mutation-positive/phenotype-negative subjects must be counter-balanced by recognition of individual lifestyle preferences and the benefits of exercise on general and psychological health.

IX. STATE OF GENETIC TESTING FOR DILATED CARDIOMYOPATHY (DCM)

Expert Consensus Recommendations

1. 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 a family history of premature unexpected sudden death.

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

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

Dilated cardiomyopathy (DCM) is characterized by systolic dysfunction and left ventricular enlargement (LVE). Although many different insults to myocardium may cause a phenotype of dilated cardiomyopathy, the term DCM here implies that resulting from genetic cause. Patients who have genetic DCM present as DCM of unknown etiology and are usually assigned a diagnosis of idiopathic dilated cardiomyopathy (IDC) after detectable causes have been excluded. In most cases, no particular phenotypic features differentiate genetic DCM from IDC. Patients presenting with IDC have been shown to have familial DCM (familial dilated cardiomyopathy [FDC]) in 20% to 35%^{218–220} of cases when first-degree relatives are screened clinically (history, exam, ECG, echocardiogram), and as high as 48% if LVE itself is taken as an early sign of DCM.²¹⁹ For this reason, clinical screening of family members of an index case presenting with DCM of unknown cause has been recommended.²²¹ Whether sporadic DCM is principally a genetic disease remains untested in large prospective studies, and the role of genetic testing in sporadic disease remains uncertain.

Diagnostic Implications of DCM Genetic Testing

One goal of genetic testing for DCM is to identify at-risk relatives who host a disease-causing mutation. It should always be integrated into information derived from clinical screening. A genetic test also can help identify the cause of the condition and identify patients who are at highest risk of extra-cardiac features. A negative analysis of a family member in the case of a clearly pathogenic mutation in the index case is reassuring that this disorder will not occur in this family member. It is particularly important in children, allowing them to live a normal life, especially during their youth.

Index Case

DCM arising from genetic cause results principally from rare non-synonymous variants, primarily missense, with occasional nonsense, splice site, or small insertion/deletion variants. Rare variant missense mutations in >30 genes have been implicated. However, none of these genes appears to account for >5% of familial DCM. Recent reviews provide comprehensive DCM gene lists and highlight the broad variety of encoded proteins implicated in the pathogenesis of DCM, including cytoskeletal proteins, myofibrillar proteins, proteins of the nuclear envelope, and ion channels.^{222–224} The prevalence of larger deletions, dupli-

cations, or rearrangements not discernible by the most common methods of genetic testing is not known.

Most genetic DCM inheritance follows an autosomal dominant pattern, although X-linked, recessive, and mitochondrial patterns of inheritance occur. The sensitivity of genetic testing is estimated at 15% to 25%. This varies regarding the number of genes that are tested and the phenotypic features of the person tested. Those with conduction disease, elevated creatine kinase, and similarly affected family members may have the highest yield of genetic testing (Table 2).

Genetic DCM shows age-dependent penetrance. This means that an individual who carries a disease-causing rare variant is more likely to show a disease phenotype with increasing age, and that a normal phenotypic assessment by echocardiogram and ECG does not exclude the possibility of later onset disease.

The age of onset ranges from early infancy through late adulthood. Variable age of onset within a family carrying the same genetic predisposition to DCM often occurs. DCM also shows variable penetrance—manifestations of the disease can vary by individual, even among family members who all have the same variant, from a very mild case (e.g., minimal systolic dysfunction, minimal LVE) to aggressive, fully developed disease.

In some families, infants present with more aggressive disease than their relatives. Disease onset in young children should be used in a positive manner by allowing the diagnosis to facilitate family clinical screening of first-degree relatives. Also notable, young children may have metabolic and mitochondrial forms of hereditary DCM.

DCM is associated with muscular dystrophy, and any patient with an unknown form of skeletal myopathy should be assessed for associated cardiomyopathy. DCM is most prominently involved in the dystrophinopathies, resulting from mutations in dystrophin, and can lead to Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and X-linked cardiomyopathy (XLCM). DCM also can occur with myotonic dystrophy, myofibrillar myopathy, and many of the limb girdle muscular dystrophies.

Conduction system disease and/or serious, life-threatening arrhythmias with muscular dystrophy, usually but not always associated with DCM, also are prominent with Emery-Dreifuss muscular dystrophy, caused by *LMNA* or *EMD* mutations, and in desmin-related myopathies (DRM) that result from *DES* mutations.²²⁵

Family Screening

As a key surrogate to genetic testing and in recognition of the potential heritability of idiopathic DCM, patients with idiopathic DCM should be assessed with at least a 3-generational family history. All first-degree relatives of a patient with idiopathic DCM should be evaluated echocardiographically. Inference regarding arrhythmia risk can be influenced by the results of genetic testing. Individuals with a mutation in *LMNA* and *DES* appear to have increased risk of sudden cardiac death.²²⁵ Decisions regarding the use of a prophylactic ICD should not depend only on the ejection fraction.²²¹

Prognostic Implications of DCM Genetic Testing

There is no prognostic role of genetic testing for DCM except for the increased risk of sudden cardiac death in *LMNA*- and *DES*-mediated disease.

Therapeutic Implications of DCM Genetic Testing

A therapeutic role for DCM genetic testing exists for patients with DCM and prominent cardiac conduction system disease (CCD, also see Section IV) that often stems from mutations in *LMNA* (Figure 1). Because CCD (e.g., first-, second-, or third-degree heart block) and supra-ventricular arrhythmias commonly precede life-threatening ventricular arrhythmias, early or pre-emptive use of an implantable cardiac defibrillator (rather than a pacemaker) has been advocated prior to the occurrence of life-threatening syncope or sudden cardiac death.²²¹ It is unknown whether early pharmacological treatment of mutation-positive, pre-clinical subjects can prevent or delay manifestation of the disease. Genetic testing also has a therapeutic role for syndromic disease (e.g., muscular dystrophy) with known arrhythmia and/or conduction system disease (e.g., *LMNA*, *DES* variants) in terms of possible consideration of a prophylactic PM and/or ICD.

X. STATE OF GENETIC TESTING FOR LEFT VENTRICULAR NONCOMPACTION (LVNC)

Expert Consensus Recommendations

1. 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.
2. Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of an LVNC-causative mutation in the index case.

Left ventricular noncompaction (LVNC) is a recently classified form of inherited cardiomyopathy that is characterized by excessive and unusual trabeculations within the mature left ventricle (LV). LVNC represents a developmental failure of the heart to form fully the compact myocardium during the later stages of cardiac development.²²⁶ Clinically and pathologically, LVNC is characterized by a spongy morphological appearance of the myocardium occurring primarily in the LV, with the abnormal trabeculations typically being most evident in the apical and midlateral/inferior portions of the LV.^{227,228} In addition to the regional presence of prominent trabeculae and intertrabecular recesses in the LV, thickening of the myocardium in two distinct layers composed of compacted and non-compacted myocardium also classically is noted. The ratio of non-compacted versus compacted myocardium is often larger than 2.0 but there is controversy regarding diagnostic imaging criteria.

Patients with LVNC may present with a broad clinical spectrum from asymptomatic to severe heart failure and/or arrhythmias, and may be associated with overlapping features of left ventricular hypertrophy, dilation, restrictive features, or with various forms of congenital heart disease. The myocar-

dium in LVNC may demonstrate normal or abnormal systolic or diastolic function and the size, thickness, or function may change unexpectedly (“undulating phenotype”).²²⁸ The disease appears to have a higher incidence of thromboembolism than other cardiomyopathies and appears to be associated with systemic disease, particularly resulting in neuromuscular and metabolic derangement. In some families, a consistent phenotype of LVNC is seen in affected relatives, but individuals with features of LVNC commonly are found in families in which other affected relatives have typical HCM (see Section VII), DCM (see Section IX), or restrictive cardiomyopathy (RCM, see Section XI).

Compared with HCM and DCM, LVNC is rare. Its exact incidence and prevalence are unknown. LVNC occurs in newborns, young children, and adults, with the worst reported outcomes seen in infants, particularly those with associated systemic disease and metabolic derangement.²²⁸

Diagnostic Implications of LVNC Genetic Testing

LVNC has been identified in families with X-linked inheritance, autosomal dominant and autosomal recessive inheritance, and maternally inherited (matrilineal) mitochondrial inheritance.^{228–230} In addition, sporadic cases are common, involved in approximately 60% to 70% of cases. Although several LVNC-susceptibility genes have been identified, none predominates, and systematic evaluations of large populations have not been reported. LVNC arising from these genetic causes typically is associated with rare non-synonymous variants, primarily missense, with occasional nonsense, splice site, or small insertion/deletion variants. Mutations in approximately 15 genes have been implicated, including cytoskeletal, sarcomeric, and ion channel genes,^{231–237} with sarcomere-encoding genes being most common. In addition, syndromal disorders such as Barth syndrome and muscular dystrophies are associated with LVNC as well.^{238,239} Recent reviews provide more comprehensive information regarding the LVNC-associated genes that each may account for $\geq 2\%$ of the disease.^{231,232} These genes include the sarcomere-encoding genes β -myosin heavy chain (*MYH7*), α -cardiac actin (*ACTC1*), cardiac troponin T (*TNNT2*), myosin binding protein-C (*MYBPC3*) and *ZASP* (also called LIM-domain binding protein 3, *LBD3*).^{233,237} In addition, mutations in the X-linked gene taffazin (*TAZ*), which encodes an acyltransferase, cause Barth syndrome in young males.^{235,238} More than any other form of cardiomyopathy, mitochondrial disease is a prominent feature of infants and young children with LVNC and therefore requires evaluation.^{230,240}

Index Cases

A relatively small percentage of patients with LVNC have known genetic mutations, approximately 15% to 20%, though larger panels of genes can increase the yield proportionately. For instance, Klaassen and colleagues²³³ reported a 17% rate of mutation detection when looking at 6 genes among 63 unrelated adult index cases. More recently, Hoedemaekers et al²³⁷ reported use of a 17-gene panel in which mutations were recognized in 23 of 56 index cases (41%).

The clinical diagnosis of LVNC depends on particular expertise and knowledge of disease and imaging modalities, particularly echocardiography and cardiac magnetic resonance imaging (CMR), and is supported by electrocardiographic findings.^{228,241,242} Due to the low rate of a positive genetic test in index cases, the utility of genetic testing for the definitive diagnosis and care of the index case is of limited use. However, fee-for-service clinical genetic testing is available and is likely to become more useful as the larger percent of disease-causing genes is identified and larger series of patients have been evaluated.

Family Screening

Due to possible X-linked inheritance in some patients, affected male family members may have a more pronounced disease expression and females may have slighter signs of LVNC (or none at all), and thus may serve as transmitters for following generations. Somatic mitochondrial alterations are, in general, not heritable to next generations and require a different clinical and genetic consultation. Due to LVNC's potential heritability, patients with LVNC should be assessed with at least a 3-generational family history, and all first-degree relatives of a patient with LVNC should be evaluated echocardiographically.

Prognostic and Therapeutic Implications of LVNC Genetic Testing

No genotype–phenotype correlations have been associated with LVNC. Therefore, no prognostic implications can be speculated. The only implication of genetic testing is confirmation of diagnosis and the potential development of disease in mutation-positive members of the family, if tested. Therapy therefore is based completely on phenotypic findings.

No definitive therapeutic role has been established for LVNC genetic testing. Because associated mitochondrial or metabolic disease or syndromes such as Barth syndrome frequently are associated with LVNC, especially in young children, definitive diagnosis can lead to improved symptomatic therapy and improved prognostication in affected patients and family members.

XI. STATE OF GENETIC TESTING FOR RESTRICTIVE CARDIOMYOPATHY (RCM) Expert Consensus Recommendations

1. 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.
2. Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of an RCM-causative mutation in the index case.

Restrictive cardiomyopathy (RCM) is rare. Little has been reported on its prevalence or natural history. This condition is defined by the presence of impaired ventricular filling and diminished diastolic volume with normal or

nearly normal LV wall thickness and ejection fraction.²⁴³ RCM often overlaps with dilated or hypertrophic cardiomyopathies, as its definition is more functional than structural.²⁴⁴ It may be classified as primary or infiltrative, and familial forms are commonly recognized in both categories. Primary RCM typically is genetic, though the absence of clearly affected family members may lead to a diagnosis of idiopathic disease. Advances in the recognition of the genetic basis for RCM have led some to call “idiopathic RCM” an anachronistic term.²⁴⁵

Affected family members help to assign a pattern of inheritance, because autosomal dominant, recessive, X-linked, and matrilineal inheritance all occur with RCM. Endomyocardial biopsies may be performed when there is suspicion of infiltrative or storage disease. Histopathology typically is notable for extensive interstitial fibrosis. Focal fibrosis of the cardiac conduction system may occur, resulting in heart block or conduction system disease.

The concurrent presence of skeletal myopathy should be investigated, as familial RCM often occurs with mild to severe concomitant skeletal muscle involvement.²⁴⁶ Even among asymptomatic affected individuals, mild elevation of the serum creatine kinase (CK) may help to identify involvement of the skeletal muscle and to target clinical genetic testing.

Diagnostic Implications of RCM Genetic Testing

Genetic evaluation in familial RCM can be useful to confirm a diagnosis, to anticipate syndromic features that may accompany RCM, to evaluate family members who are at risk of the condition, and for family planning. Syndromic disorders often accompany familial RCM, and clinical genetic testing may facilitate their recognition.

Summary of Common RCM Genes (Table 2)

As with other forms of cardiomyopathy, familial RCM is genetically heterogeneous. RCM-associated mutations have been reported in four genes that encode key sarcomeric proteins/myofilaments (*MYH7*, *TNNT2*, *TNNI3*, and *ACTC*) and *MYH7*- and *TNNI3*-mediated RCM may each account for approximately 5% of the disease (Table 2). Mutations in sarcomere genes tend to cause a cardiac-restricted phenotype without skeletal myopathy, though *MYH7* mutations altering the C-terminal portion of cardiac myosin heavy chain may involve Laing distal skeletal myopathy.²⁴⁷ Genes encoding the remaining elements of the cardiac sarcomere remain good candidates for familial RCM but have not yet been shown to cause this particular phenotype.

Index Cases

The likelihood of finding a mutation in RCM can be inferred from manuscripts with genetic characterization of small cohorts. In a series of 12 children with RCM (mean age 5.1 years) who had testing of 8 sarcomere genes and *DES*, heterozygous sarcomere mutations were reported in four of the children, two of which were *de novo*.²⁴⁸ No mutations were identified in *DES* among this cohort. In another series of 15 index cases with RCM who had testing of five sarcomere genes, mutations were found in eight of them.²⁴⁹

Inherited storage disorders, such as hemochromatosis or the glycogen storage diseases, can cause cardiomyopathy, and RCM is a common phenotypic manifestation.²⁴³ Familial amyloid is a disorder of misfolded protein with pathologic deposition in many organs, though the pathologic amyloid deposition sometimes is present only in the heart. Although there are several genes in which mutations have been reported to cause amyloidosis, familial cardiac amyloid is most commonly caused by mutations in *TTR*, which encodes transthyretin.²⁵⁰ Although transthyretin amyloidosis occurs without race or gender predilection, certain *TTR* mutations are more common among specific ethnicities. For instance, approximately 3.5% of African-Americans harbor the *TTR* mutation Val122Ile.²⁵¹

Noonan syndrome is a genetically and phenotypically heterogeneous disorder characterized by short stature, characteristic facial features, webbed neck, and hypertrophic or restrictive cardiomyopathy.²⁵² Approximately 50% of individuals diagnosed with Noonan syndrome have a mutation in *PTPN11*.²⁵³ However, Noonan syndrome with either HCM or RCM is seldom *PTPN11* positive.²⁵⁴ Other Noonan syndrome susceptibility genes include *SOS1*, *KRAS*, *RAF1*, *SHOC2*, and *NRAS*. In one study, mild abnormalities on the ECG were present among 42 of 84 (50%) affected individuals, including left axis deviation, small R waves in the left precordial leads, and abnormal Q waves.²⁵⁵ The reduced prevalence of cardiomyopathy among individuals with a *PTPN11* mutation (6%) is balanced by the increased likelihood of finding cardiomyopathy when a *RAF1* mutation is present (95%).²⁵⁶ Accordingly, testing with a comprehensive Noonan gene panel is optimal in the setting of Noonan syndrome with cardiomyopathy.

Family Screening

As compared with other forms of cardiomyopathy, RCM is difficult to recognize in early stages because the heart does not become structurally dilated or thickened, and mild Doppler abnormalities can occur with hypertension, coronary atherosclerosis, or age. Therefore, a clear pathogenic mutation in an unequivocally affected family member can help in screening family members who are at risk or those who have borderline features suggesting familial RCM. Although not as heritable/familial as DCM and LVNC, patients with idiopathic RCM should be assessed with at least a 3-generational family history, and all first-degree relatives of a patient with idiopathic RCM should be evaluated echocardiographically.

Prognostic Implications of RCM Genetic Testing

There is no prognostic role of the genetic test result for the patients with isolated RCM. However, a genetic test that indicates a predisposition to a syndromic disorder such as *TTR*-amyloidosis can be useful. The use of genetic testing to determine prognostic information is likely best established for family members who are at risk of familial RCM.

Therapeutic Implications of RCM Genetic Testing

While direct therapeutic application of a genetic test result for RCM has not been definitively demonstrated, such results may impact the assessment of arrhythmia. The increased likelihood for arrhythmia associated with mutations in *TNNT2*, *DES*, or *LMNA* may alter one's approach to phenotypic arrhythmia assessment, though specific genotype–phenotype correlations may not be discernible. For disorders with multi-system involvement, recognition of an underlying syndrome that results in restrictive cardiac physiology can lead to disease-specific therapy, such as transplantation for *TTR*-amyloidosis or replacement enzyme infusions for some storage diseases. Finally, mutations in non-sarcomere genes can cause RCM, often accompanied by skeletal myopathy and cardiac conduction disease. The combination of RCM with elevated serum creatine kinase suggests a mutation in genes encoding desmin (*DES*) or lamin A/C (*LMNA*). Because these are associated with relatively high rates of sudden cardiac death, RCM secondary to *DES* or *LMNA* should prompt consideration of a prophylactic ICD, particularly in the setting of AV block or bundle branch block.^{229,230}

XII. STATE OF GENETIC TESTING FOR OUT-OF-HOSPITAL CARDIAC ARREST SURVIVORS

Expert Consensus Recommendations

1. In the survivor of an Unexplained Out-of-Hospital Cardiac Arrest, genetic testing **should be** guided by the results of medical evaluation and is used for the primary purpose of screening at-risk family members for subclinical disease.
2. Routine genetic testing, in the absence of a clinical index of suspicion for a specific cardiomyopathy or channelopathy, **is not indicated** for the survivor of an Unexplained Out-of-Hospital Cardiac Arrest.

Out-of-hospital cardiac arrest (OHCA) occurs most commonly in the context of underlying structural heart disease.^{257,258} In older individuals (age >40 years), pre-existing coronary disease remains the most common etiology, while in younger cases, HCM and ACM/ARVC frequently are detected.^{257,258} These common conditions may be readily diagnosed in survivors of OHCA by coronary angiography and cardiac imaging studies, and in the case of HCM and ACM/ARVC, appropriate genetic evaluation and screening of first-degree relatives pursued (see Sections VII and VIII).

In the absence of evident structural heart disease despite careful evaluation of previous medical records or based on autopsy data, a broad differential diagnosis exists. Evaluations should seek to detect subclinical structural disease, including ACM/ARVC or cardiac sarcoidosis.^{259,260} Primary electrical diseases secondary to cardiac ion channel disorders may account for up to 25% of cases, including LQTS, CPVT, BrS, SQTS, and early repolarization syndrome (ERS).^{257,261} The latter has been described recently

and may represent a previously unrecognized underlying condition in survivors of OHCA.²⁶²

Although most survivors of OHCA may reasonably receive an implantable cardioverter-defibrillator (ICD), arriving at a diagnosis for the event is necessary to minimize the risk of arrhythmia recurrences and enable appropriate evaluation of family members who may be at risk of an inheritable disorder. Determining a diagnosis begins with a systematic clinical evaluation. Subsequently, targeted genetic testing **may be considered** for the purpose of diagnostic confirmation and family screening.

Clinical Evaluation

A review of the circumstances of the event may provide insight into the etiology. Cardiac arrest during exercise or sympathetic activation may be consistent with either LQT1 or CPVT1, while events secondary to auditory stimuli might suggest LQT2. Previously recognized seizures or cardiac arrest during sleep may be characteristic of BrS or LQT3. Specific family details, including a family history of neuromuscular disease, early pacemaker implantation, or unexplained heart failure, may prioritize investigational pathways to examine and diagnoses to be excluded, e.g., muscular dystrophy, storage diseases, or laminopathies, all of which may be associated with risk of cardiac arrhythmias.

Clinical testing includes resting ECG (and potentially signal-averaged ECG), exercise testing, telemetry/Holter monitoring, echocardiography, and cardiac magnetic resonance imaging. Coronary angiography is usually performed in adults. Provocative adrenergic and sodium channel blocker infusion should be considered for the potential unmasking of latent LQTS and BrS, respectively.²⁵² Caution is advised in reaching precipitous conclusions of either LQTS, BrS, or ERS based on early post-arrest ECGs, which commonly demonstrate either prolonged QT interval secondary to a number of physiological factors or J wave/Brugada ECG pattern changes secondary to therapeutic hypothermia and often resolves over a number of days. Overall, comprehensive clinical testing performed in consultation with specialized arrhythmia clinics may yield a clinical diagnosis in more than 50% of apparent unexplained cardiac arrests.^{257,261}

Role of Genetic Testing in OHCA

When a diagnosis is evident or suspected, genetic testing of the proband generally is recommended to enable cascade screening of family members. In almost all forms of inheritable cardiomyopathies and primary electrical disorders, incomplete or provokable (e.g., medications) disease penetrance is common, necessitating genetic testing in addition to clinical assessment of family members. A “shotgun” genetic testing approach should be avoided in survivors of unexplained cardiac arrest to minimize costs and avoid issues when uncertain genetic findings must be interpreted for family members in the absence of a correlating disease phenotype. Among patients of Dutch ancestry who are clas-

sified with idiopathic ventricular fibrillation (IVF) after their thorough OHCA clinical evaluation, genetic testing of DPP6 haplotype should be considered.²⁶³

XIII. STATE OF POST-MORTEM GENETIC TESTING IN SUDDEN UNEXPECTED DEATH CASES (SUD/SIDS)

Expert Consensus Recommendations

1. For all SUDS and SIDS cases, collection of a tissue sample **is recommended** (5–10 mL whole blood in EDTA tube, blood spot card, or a frozen sample of heart, liver, or spleen) for subsequent DNA analysis/genetic testing.
2. 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).
3. Mutation-specific genetic testing **is recommended** for family members and other appropriate relatives following the identification of a SUDS-causative mutation in the decedent.

Sudden cardiac death is a tragic and devastating result of a number of cardiovascular diseases. Autopsy-negative sudden unexpected death (SUD) is defined as a sudden death occurring within an hour of the onset of symptoms, often affecting the young (aged ≤ 35 years), and where the autopsy fails to identify a cause of death.²⁶⁴ In up to one-third of young people who die suddenly from a cardiac origin, no identifiable cause of death is found at autopsy.²⁶⁵ Although coronary ischemic heart disease accounts for a majority of sudden deaths across all ages, many other etiologies contribute to this problem, including genetic heart disorders that affect both the integrity of the heart's muscle (cardiomyopathies) and the heart's conduction system (channelopathies).

Sudden infant death syndrome (SIDS) represents a subgroup of unexplained sudden deaths among infants under the age of 1. Typically, the cause of death remains unexplained after a thorough case investigation, including a negative autopsy. Genetic studies in SIDS cases collectively suggest that up to 15% of SIDS cases may stem from an underlying genetic channelopathy.^{266–269}

Diagnostic Implications of SUDS/SIDS Genetic Testing

A cardiac channel molecular autopsy, in which DNA is collected at autopsy and post-mortem genetic testing of the various cardiac channelopathy-associated genes is conducted to search for an underlying cause, has revealed a cause of death in up to 35% of these SUD cases.^{270,271} These causes include primary arrhythmogenic disorders

such as LQTS, CPVT, and BrS. Mutations are identified most commonly in the *RYR2* (CPVT) gene (15 to 20%), and in *KCNQ1*, *KCNH2* and *SCN5A* (LQTS1-3) genes (10 to 15%). Primary arrhythmogenic disorders can predispose to more overt causes of death. Consequently, young deaths attributed to events such as drowning and motor vehicle accidents may have been directly precipitated by a ventricular arrhythmia. Furthermore, up to 15% of SIDS cases may stem from mutations in the genes implicated in LQTS, CPVT, and BrS.^{272,273}

Thus, if postmortem genetic testing were performed routinely, it is estimated that 25% to 35% of SUD cases from age 1 to 35 years and up to 15% of SIDS cases may be due to mutation(s) in one of the known channelopathy-associated genes.^{270,271,273} Intense cardiac testing of the SUD decedent's living first-degree relatives provides a similar estimate of approximately 25% to 35% of those families being diagnosed with a heritable arrhythmia syndrome.^{274,275}

Family Screening

The identification of a cause of death in a SUD or SIDS case has important implications for the psychosocial welfare of relatives, as it may provide comfort for the family wondering why their young son or daughter has died. Second, there are implications for living relatives, who **may be** at risk of developing the same disease. Cascade genetic testing in at-risk relatives is an important next step, often performed concurrently with clinical evaluation, with the goal to diagnose other family members who may have the same disease.²⁷⁶ This forms the foundation for appropriate prevention strategies in family members who possess the gene mutation and/or have clinical features of the disease. For many of the cardiac channelopathies that are potentially diagnosed by postmortem genetic testing, the decedent's genetic test results may influence directly the treatment of his/her living relatives in the exact same manner detailed for relatives of a living, mutation-positive index case in Sections I to III.

It has not been determined whether it would be more cost-effective to commence the evaluation of SUD among the living members with a cardiac channelopathy-focused molecular autopsy/postmortem genetic test of the decedent, or by clinically examining all first-degree relatives. Appropriate cardiac evaluation is recommended for all first-degree relatives of a SUDS case. However, considering the litany of tests that usually are performed on the living first-degree family members following such a SUD, the estimated 35% yield of a channelopathic explanation in the decedent may make the cardiac channel molecular autopsy the prudent place to start. Nevertheless, impediments to postmortem genetic testing for SUD include lack of reimbursement among third-party payers and lack of uniform standard operating procedures for the retention of material that would permit a comprehensive postmortem genetic test, such as blood in EDTA, blood spot cards, or frozen tissue.²⁷⁷ Implementation of these procedures will require collaborative

efforts with organizations that represent medical examiners and forensic pathologists, such as the National Association of Medical Examiners in the United States, to ensure collection and retention of appropriate material that would permit a molecular autopsy if desired. Postmortem genetic testing of every SIDS case, with its estimated 10%–15% yield for LQTS, CPVT, and BrS, may be more difficult to justify from a cost-effectiveness perspective. Genetic testing may have a higher yield in certain age groups (e.g., infants age less than 2 months, infants 4 to 12 months).²⁷⁸ Instead, a screening 12-lead ECG of such an infant's parents and siblings may be appropriate.

Prognostic and Therapeutic Implications of SUDS/SIDS Genetic Testing

Clinical and genetic screening of relatives of a SUD case provide an important opportunity to identify new at-risk family members and initiate management strategies. These treatment strategies are based on the individual diseases outlined in accompanying guidelines.

Appendix 1 Glossary of Terms Related to Genetic Testing

Allele: Reciprocal forms of genetic information at a specific locus (location) along the genome. An allele can refer to a segment of DNA or even a single nucleotide. The normal version of genetic information is often considered the “wild-type” or “normal” allele. The vast majority of the human genome represents a single version of genetic information.

Autosomal Dominant: The situation in which the disease can be expressed even when just one chromosome harbors the mutation.

Autosomal Recessive: The situation in which the disease is expressed only when both chromosomes of a pair are abnormal.

Cascade Testing: Procedure whereby all first-degree relatives of a genotype-positive index case are tested in concentric circles of relatedness. If one of the family members is genotype positive, all his/her first-degree relatives should be tested continuing this process following each genotype-positive family member.

Compound Heterozygosity: An individual who has two different mutant alleles at a particular locus, one on each chromosome of a pair; usually refers to individuals affected with an autosomal recessive disorder (from GeneTests).

Copy Number Variation (CNV): The situation in which the number of copies of a gene or other DNA sequence differs between individuals.

Digenic Heterozygosity: An individual with two different mutations in two different disease-associated genes, a “second hit” contributing to disease phenotype.

Disease-causing Mutation: A DNA sequence variation that represents an abnormal allele and is not found in the normal healthy population but exists only in the disease population and produces a functionally abnormal product.

Expressivity: The level of expression of the phenotype, and when the manifestations of the phenotype in individuals

who have the same genotype are diverse, the phenotype is said to exhibit variable expressivity.

First-Degree Relative: A blood relative who is a person's parent, sibling, or child.

Founder Mutation: The occurrence of a particular gene mutation at increased frequencies within a given population due to its presence in a small isolated group of ancestors that directly gave rise to the current population.

Genotype: A person's genetic or DNA sequence composition at a particular location in the genome.

Index Case/Proband: The person or patient who first draws clinical attention to a particular family in a genetic or epidemiologic investigation.

Mutation: A change of the DNA sequence within the genome.

Mutation – Deletion/Insertion: The removal (deletion) or addition (insertion) of nucleotides to the transcript that can be as small as a single nucleotide insertion/deletion or as large as several hundreds to thousands of nucleotides in length.

Mutation – Disease Causing: A DNA sequence variation that represents an abnormal allele and is not found in the normal healthy population but exists only in the disease population and produces a functionally abnormal product.

Mutation – Frameshift: Insertions or deletions occurring in the exon that alter the “reading frame” of translation at the point of the insertion or deletion and produce a new sequence of amino acids in the finished product. Frameshift mutations often result in a different product length from the normal gene product by creating a new stop codon, which produces either a shorter or longer gene product depending on the location of the new stop codon.

Mutation – Germline: Heritable change in the genetic make-up of a germ cell (sperm or ovum) that when transmitted to an offspring is incorporated into every cell in the body.

Mutation – In-Frame Insertion/Deletion: In-frame insertions and deletions occur when a multiple of three nucleotides is affected and result in a single or multiple amino acids being removed or added without affecting the remainder of the transcript.

Mutation – Missense: A single nucleotide substitution that results in the exchange of a normal amino acid in the protein for a different one.

Mutation – Nonsense: A single nucleotide substitution resulting in a substitution of an amino acid for a stop codon. A nonsense mutation results in a truncated (shortened) gene product at the location of the new stop codon.

Mutation – Somatic: Variants/mutations are said to be somatic if they occur in cells other than gametes. Somatic mutations cannot be transmitted to offspring.

Penetrance: The likelihood that a gene mutation will have any expression at all. In the situation in which the frequency of phenotypic expression is less than 100%, the genetic defect is said to be associated with reduced or incomplete penetrance.

Phenocopy: An individual who manifests the same phenotype (trait) as other individuals of a particular genotype but does not possess this genotype himself/herself.

Phenotype: A person's observed clinical expression of disease in terms of a morphological, biochemical, or molecular trait.

Polymorphism: Normal variations at distinct loci in the DNA sequence. The vast majority of the human genome represents a single version of genetic information. The DNA from one person is mostly made up of the same exact nucleotide sequence as another person. However, there are many small sections of sequence or even single nucleotides that differ from one individual to another.

Single Nucleotide Polymorphism (SNP): A single nucleotide substitution that occurs with a measurable frequency (i.e., >0.5% allelic frequency) among a particular ethnic population(s).

SNP – Nonsynonymous: A single nucleotide substitution whereby the altered codon encodes for a different amino acid or terminates further protein assembly (i.e., introduces a premature stop codon).

SNP – Synonymous: A single nucleotide substitution occurring in the coding region (exon), whereby the new codon still specifies the same amino acid.

Variant of Uncertain Significance (VUS): A mutation or genetic variation with uncertain clinical significance.

Appendix 2 Author Disclosures

Authors	Consultant Fees/Honoraria	Speaker's Bureau	Research Grant	Fellowship Support	Board Mbr/Stock Options/Partner	Other
Michael Ackerman, MD, PhD	Biotronik Boston Scientific Medtronic St. Jude Medical Transgenomic (FAMILION)	None	None	None	None	Transgenomic (FAMILION)—Royalty
Charles Berul, MD	Johnson & Johnson Medtronic	None	None	None	None	None
Ramon Brugada, MD, PhD	Ferrer Incode	None	None	None	None	None
Hugh Calkins, MD	Biosense Webster, Inc. AtriCure, Inc. Sanofi-Aventis TASER International, Inc. Medtronic Corp.	None	Medtronic, Inc. Boston Scientific Corp. St. Jude Medical	None	iRhythm	None
A. John Camm, MD	Servier Boehringer Ingelheim Medtronic Xention Discovery Boston Scientific Corp. Sanofi-Aventis	Sanofi-Aventis Boehringer Ingelheim Bayer	Daiichi Servier Bristol Meyers Squibb Sanofi-Aventis Pfizer	None	None	British Heart Foundation—Salary
Patrick Ellinor, MD, PhD	Sanofi-Aventis	None	None	None	None	None
Michael Gollob, MD	None	None	Other	None	None	None
Robert Hamilton, MD	None	None	Other	None	None	None
Ray Hershberger, MD	None	None	None	None	None	None
Daniel Judge, MD	None	None	None	None	None	None
Hervé Le Marec, MD						
William McKenna, MD	None	None	None	None	None	None
Silvia Priori, MD, PhD	Medtronic Boston Scientific PGxHealth (now Transgenomic) GeneDx Biotronik Daiichi	None	None	None	None	None
Eric Schulze-Bahr, MD	None	None	None	None	None	None
Chris Semsarian, MBBS	None	None	None	None	None	None
Jeffrey Towbin, MD	Transgenomic (FAMILION)	None	None	None	None	None

Appendix 2 Continued

Authors	Consultant Fees/Honoraria	Speaker's Bureau	Research Grant	Fellowship Support	Board Mbr/Stock Options/Partner	Other
Hugh Watkins, MD, PhD	None	None	None	None	None	Harvard Medical School—Royalty
Arthur Wilde, MD, PhD	PGxHealth (now Transgenomic) Sorin	None	None	None	None	None
Stephen Willems, MD, PhD	St. Jude Medical Boston Scientific Corp. Boehringer Ingelheim	None	None	None	None	None
Christian Wolpert, MD	Sorin Boston Scientific St. Jude Medical Medtronic C.R. Bard Biosense Webster		None	None	None	None
Douglas Zipes, MD	None	None	None	None	None	None

Appendix 3 Peer Review Disclosures

Authors	Consultant Fees/Honoraria	Speaker's Bureau	Research Grant	Fellowship Support	Board Mbr/Stock Options/Partner	Other
Paulus Kirchhof, MD	3M Medica, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Boston Scientific, Omron, MEDA Pharma, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer/BMS, Sanofi-Aventis, Servier, Siemens, Takeda	None	3M Medica/MEDA Pharma, Cardiovascular Therapeutics, Medtronic, Omron, Sanofi-Aventis, St. Jude Medical, German Federal Ministry for Education and Research (BMBF), Fondation LeDucq, German Research Foundation (DFG), European Union	None	None	None
Peter J. Schwartz, MD	BioControl Medical (B.C.M) Ltd., Institut de Recherches Internationales, Servier	None	None	None	None	None
Vincent Probst, MD	None	None	None	None	None	None
Jennifer Cummings, MD	Boston Scientific, Corazon Consulting, Medtronic, Sanofi-Aventis, St. Jude Medical	Sanofi-Aventis	None	None	None	None
Steve Ommen, MD	None	None	None	None	None	None
Steven Markowitz, MD	Boston Scientific, Medtronic, St. Jude Medical	Medtronic, Sanofi-Aventis	None	None	None	None
Rachel Lampert, MD	Boston Scientific, Medtronic	None	Boston Scientific, Medtronic, St. Jude Medical	None	None	None
Fred Kusumoto, MD	Medtronic	None	None	None	None	None
Mina Chung, MD	American College of Cardiology Foundation, Biotronik, Boston Scientific, Inc., Medtronic, National Institutes of Health Nexcura, Sanofi-Aventis, St. Jude Medical, University of Texas Health Science, Zoll, Inc.	None	Biotronik, Boston Scientific, Medtronic, National Institutes of Health, St. Jude Medical, Reliant Pharmaceuticals/GlaxoSmithKline	Medtronic, St. Jude Medical	None	None
Raymond Yee, MD	Medtronic	Medtronic				

References

- ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation* 2006; 114:e385–e484.
- Liebman J. Some legal, social, and ethical issues related to the genetic testing revolution, as exemplified in the long QT syndrome. *J Electrocardiol* 2001; 34(Suppl):183–188.
- Nelson RM, Botkjin JR, Kodish ED, et al. (Committee on Bioethics). Ethical issues with genetic testing in pediatrics. *Pediatrics* 2001;107:1451–1455.
- Hendriks KSWH, Hendriks MMWB, Birnie E, et al. Familial disease with a risk on sudden death: a longitudinal study of the psychological consequences of predictive testing for Long QT syndrome. *Heart Rhythm* 2008;5:719–724.
- Christiaans I, van Langen IM, Birnie E, et al. Quality of life and psychological distress in hypertrophic cardiomyopathy mutation carriers: a cross-sectional cohort study. *Am J Med Genet* 2009;149A:602–612.
- Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. *Circulation* 2011;123:1021–1037.
- Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *Jama* 2005;294:2975–2980.
- Hofman N, Tan HL, Alders M, et al. Active cascade screening in primary inherited arrhythmia syndromes: does it lead to prophylactic treatment? *J Am Coll Cardiol* 2010;55:2570–2576.
- Ackerman MJ, Tester DJ, Jones G, et al. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. *Mayo Clin Proc* 2003;78:1479–1487.
- Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among Black, White, Asian, Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/Long QT syndrome genetic testing. *Heart Rhythm* 2004;1:600–607.
- Kapa S, Tester DJ, Salisbury BA, et al. Genetic testing for long QT syndrome—distinguishing pathogenic mutations from benign variants. *Circulation* 2009; 120:1752–1760.
- Kapplinger JD, Landstrom AP, Salisbury BA, et al. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. *J Am Coll Cardiol* 2011;57:2317–27.
- Ackerman MJ, Khositseth A, Tester DJ, et al. Congenital long QT syndrome in electrical diseases of the heart; genetics mechanisms, treatment, prevention. New York: Springer Publishing, 2008, pp. 462–482.
- Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 1999;99:529–533.
- Tester DJ, Will ML, Haglund CM, et al. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol* 2006;47:764–768.
- Vincent GM, Timothy KW, Leppert M, et al. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. *N Engl J Med* 1992;327:846–852.
- Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866–1874.
- Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. *Circulation* 2006;113:1385–1392.
- Takenaka K, Ai T, Shimizu W, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. *Circulation* 2003;107:838–844.
- Shimizu W, Noda T, Takaki H, et al. Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome. *Heart Rhythm* 2004;1:276–283.
- Krahn AD, Gollob M, Yee R, et al. Diagnosis of unexplained cardiac arrest: role of adrenaline and procainamide infusion. *Circulation* 2005;112:2228–2234.
- Viskin S, Postema PG, Bhuiyan ZA, et al. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. *J Am Coll Cardiol* 2010;55:1955–1961.
- Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. *Circulation* 1993;88:782–784.
- Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long-QT syndrome. *Circulation* 2009;120:1761–1767.
- Goldenberg I, Moss AJ, Peterson DR, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation* 2008;117:2184–2191.
- Hobbs JB, Peterson DR, Moss AJ, et al. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. *Jama* 2006;296:1249–1254.
- Monnig G, Eckardt L, Wedekind H, et al. Electrocardiographic risk stratification in families with congenital long QT syndrome. *Eur Heart J* 2006;27:2074–2080.
- Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. *J Am Coll Cardiol* 2007;49:329–337.
- Jons C, Moss AJ, Goldenberg I, et al. Risk of fatal arrhythmic events in long QT syndrome patients after syncope. *J Am Coll Cardiol* 2010;55:783–788.
- Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;80:805–811.
- Schwartz PJ, et al. Idiopathic long QT syndrome: progress and questions. *Am Heart J* 1985;109:399–411.
- Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* 1995;80:795–798.
- Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996; 12:17–23.
- Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999;97:175–187.
- Plaster NM, Tawil R, Tristani-Firouzi M, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* 2001;105:511–519.
- Splawski I, Timothy KW, Sharpe LM, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 2004; 119:19–31.
- Vatta M, Ackerman MJ, Ye B, et al. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. *Circulation* 2006;114: 2104–2112.
- Medeiros-Domingo A, Kaku T, Tester DJ, et al. SCN4B-encoded sodium channel beta4 subunit in congenital long-QT syndrome. *Circulation* 2007;116:134–142.
- Ueda K, Valdivia C, Medeiros-Domingo A, et al. Syntrophin mutation associated with long QT syndrome through activation of the nNOS-SCN5A macromolecular complex. *Proc Natl Acad Sci U S A* 2008;105:9355–9360.
- Yang Y, Liang B, Liu J, et al. Identification of a Kir3.4 mutation in congenital long QT syndrome. *Am J Hum Genet* 2010;86:872–880.
- Priori SG, Barhanin J, Hauer RN, et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management part III. *Circulation* 1999;99:674–681.
- Eddy CA, MacCormick JM, Chung SK, et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. *Heart Rhythm* 2008;5:1275–1281.
- Tester DJ, Benton AJ, Train L, et al. Prevalence and spectrum of large deletions or duplications in the major long QT syndrome-susceptibility genes and implications for long QT syndrome genetic testing. *Am J Cardiol* 2006;106:1124–1128.
- Goldenberg I, Moss AJ, Zareba W, et al. Clinical course and risk stratification of patients affected with the Jervell and Lange-Nielsen syndrome. *J Cardiovasc Electrophysiol* 2006;17:1161–1168.
- Schwartz PJ, Spazzolini C, Crotti L, et al. The Jervell and Lange-Nielsen syndrome. Natural history, molecular basis, and clinical outcome. *Circulation* 2006;113:783–790.
- Kapplinger JD, Tester DJ, Salisbury BA, et al. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. *Heart Rhythm* 2009;6:1297–1303.
- Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. *J Intern Med* 2006;259:39–47.
- Taggart NW, Haglund CM, Tester DJ, et al. Diagnostic miscues in congenital long-QT syndrome. *Circulation* 2007;115:2613–2620.
- Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *Jama* 2005;294:2975–2980.
- Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. *J Am Coll Cardiol* 2009;54:2065–2074.
- Tester DJ, Kopplin LJ, Will ML, et al. Spectrum and prevalence of cardiac ryanodine receptor (RyR2) mutations in a cohort of unrelated patients referred explicitly for long QT syndrome genetic testing. *Heart Rhythm* 2005;2:1099–1105.
- Kapa S, Tester DJ, Salisbury BA, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. *Circulation* 2009; 120:1752–1760.
- Rautaharju P, Surawicz B, Gettes L. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval. *J Am Coll Cardiol* 2009;53:982–991.

54. Schwartz PJ, Stramba-Badiale M. Repolarization abnormalities in the newborn. *J Cardiovasc Pharmacol* 2010;55:539–543.
55. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. *Circulation* 2002;105:1943–1948.
56. Paulussen AD, Gilissen RA, Armstrong M, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J Mol Med* 2004;82:182–188.
57. Lehtonen A, Fodstad H, Laitinen-Forsblom P, et al. Further evidence of inherited long QT syndrome gene mutations in antiarrhythmic drug-associated torsades de pointes. *Heart Rhythm* 2007;4:603–607.
58. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation* 2000;102:2849–2855.
59. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95.
60. Ackerman MJ. The long QT syndrome. *Pediatr Rev* 1998;19:232–238.
61. Choi K, Kopplin LJ, Tester DJ, et al. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation* 2004;110:2119–2124.
62. Moss AJ, Shimizu W, Wilde AA, 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.
63. Shimizu W, Moss AJ, Wilde AA, et al. Genotype-phenotype aspects of type 2 long QT syndrome. *J Am Coll Cardiol* 2009;54:2052–2062.
64. Crotti L, Spazzolini C, Schwartz PJ, et al. The common long-QT syndrome mutation KCNQ1/A341V causes unusually severe clinical manifestations in patients with different ethnic backgrounds: toward a mutation-specific risk stratification. *Circulation* 2007;116:2366–2375.
65. Makita N, Behr E, Shimizu W, et al. The E1784K mutation in SCN5A is associated with mixed clinical phenotype of type 3 long QT syndrome. *J Clin Invest* 2008;118:2219–2229.
66. Villain E, Denjoy I, Lupoglazoff JM, et al. Low incidence of cardiac events with beta-blocking therapy in children with long QT syndrome. *Eur Heart J* 2004;25:1405–1411.
67. Monnig G, Kobe J, Lohr A, et al. Implantable cardioverter-defibrillator therapy in patients with congenital long-QT syndrome: a long-term follow-up. *Heart Rhythm* 2005;2:497–504.
68. Schwartz PJ, Spazzolini C, Priori SG, et al. Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them? Data from the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry. *Circulation* 2010;122:1272–1282.
69. Horner JM, Kinoshita M, Webster TL, et al. Implantable cardioverter defibrillator therapy for congenital long QT syndrome: a single-center experience. *Heart Rhythm* 2010;7:1616–1622.
70. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000;101:616–623.
71. Schwartz PJ, Priori SG, Locati EH, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na⁺ channel blockade and to increases in heart rate. Implications for gene-specific therapy. *Circulation* 1995;92:3381–3386.
72. Ruan Y, Liu N, Bloise R, et al. Gating properties of SCN5A mutations and the response to mexiletine in long-QT syndrome type 3 patients. *Circulation* 2007;116:1137–1144.
73. Moss AJ, Windle JR, Hall WJ, et al. Safety and efficacy of flecainide in subjects with Long QT-3 syndrome (DeltaKPQ mutation): a randomized, double-blind, placebo-controlled clinical trial. *Ann Noninvasive Electrocardiol* 2005;10:59–66.
74. Coumel P, Fidelle J, Lucet V, et al. Catecholaminergic-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. *Br Heart J* 1978;40:28–37.
75. Leenhardt A, Lucet V, Denjoy I, et al. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation* 1995;91:1512–1519.
76. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002;106:69–74.
77. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001;103:196–200.
78. Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet* 2001;69:1378–1384.
79. Bai R, Napolitano C, Bloise R, et al. Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing. *Circ Arrhythm Electrophysiol* 2009;2:6–15.
80. George CH, Jundi H, Thomas NL, et al. Ryanodine receptors and ventricular arrhythmias: emerging trends in mutations, mechanisms and therapies. *J Mol Cell Cardiol* 2007;42:34–50.
81. Raffaele di Barletta M, Viatchenko-Karpinski S, Nori A, et al. Clinical phenotype and functional characterization of CASQ2 mutations associated with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2006;114:1012–1019.
82. Tester DJ, Dura M, Carturan E, et al. A mechanism for sudden infant death syndrome (SIDS): stress-induced leak via ryanodine receptors. *Heart Rhythm* 2007;4:733–739.
83. Tristani-Firouzi M, Jensen JL, Donaldson MR, et al. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). *J Clin Invest* 2002;110(3):381–388.
84. Mohler PJ, Splawski I, Napolitano C, et al. A cardiac arrhythmia syndrome caused by loss of ankyrin-B function. *Proc Natl Acad Sci U S A* 2004;101:9137–9142.
85. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. *J Am Coll Cardiol* 1992;20:1391–1396.
86. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome. Report of the Second Consensus Conference. *Heart Rhythm* 2005;2:429–440.
87. Fowler S, Priori S. Clinical Spectrum of patients with a Brugada ECG. *Curr Opin Cardiol* 2009;24:74–81.
88. Gehi AK, Duong TD, Metz LD, et al. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol* 2006;17:577–583.
89. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation* 2002;105:1342–1347.
90. Paul M, Gerss J, Schulze-Bahr E, et al. Role of programmed ventricular stimulation in patients with Brugada syndrome—a meta-analysis of worldwide published data. *Eur Heart J* 2007;28:2126–2133.
91. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada syndrome registry. *Circulation* 2010;121:635–643.
92. Brugada P, Brugada R, Mont L, et al. Natural history of Brugada syndrome: the prognostic value of programmed electrical stimulation of the heart. *J Cardiovasc Electrophysiol* 2003;14:455–457.
93. Viskin S, Wilde AA, Tan HL, et al. Empiric quinidine therapy for asymptomatic Brugada syndrome: time for a prospective registry. *Heart Rhythm* 2009;6:401–404.
94. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutation in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm* 2010;1:33–46.
95. Smits JPP, Eckardt L, Probst V, et al. Genotype-phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non SCN5A related patients. *J Am Coll Cardiol* 2002;40:350–356.
96. 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;115:442–449.
97. Meregalli PG, Tan HL, Probst V, et al. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. *Heart Rhythm* 2009;6:341–348.
98. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations and an up-to-date website (www.brugadadrugs.org). *Heart Rhythm* 2009;6:1335–1341.
99. Probst V, Kyndt F, Potet F, et al. Haploinsufficiency in combination with aging causes SCN5A-linked hereditary Lenegre disease. *J Am Coll Cardiol* 2003;41:643–652.
100. Brink AJ, Torrington M. Progressive familial heart block—two types. *S Afr Med J* 1977;52:53–59.
101. Postema PG, Van den BM, van Tintelen JP, et al. Founder mutations in the Netherlands: SCN5a 1795insD, the first described arrhythmia overlap syndrome and one of the largest and best characterised families worldwide. *Neth Heart J* 2009;17:422–428.
102. Benson DW, Wang DW, Dyment M, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest* 2003;112:1019–1028.
103. Schott JJ, Benson DW, Basson CT, et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. *Science* 1998;281:108–111.

104. Paul M, Zumhagen S, Stallmeyer B, et al. Genes causing inherited forms of cardiomyopathies. A current compendium. *Herz* 2009;34:98–109.
105. Bezzina CR, Rook MB, Groenewegen WA, et al. Compound heterozygosity for mutations (W156X and R225W) in SCN5A associated with severe cardiac conduction disturbances and degenerative changes in the conduction system. *Circ Res* 2003;92:159–168.
106. Neu A, Eiselt M, Paul M, et al. A homozygous SCN5A mutation in a severe, recessive type of cardiac conduction disease. *Hum Mutat* 2010;31:E1609–E1621.
107. Schott JJ, Alshinawi C, Kyndt F, et al. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet* 1999;23:20–21.
108. Tan HL, Bink-Boelkens MT, Bezzina CR, et al. A sodium-channel mutation causes isolated cardiac conduction disease. *Nature* 2001;409:1043–1047.
109. 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;118:2260–2268.
110. Kruse M, Schulze-Bahr E, Corfield V, et al. Impaired endocytosis of the ion channel TRPM4 is associated with human progressive familial heart block type I. *J Clin Invest* 2009;119:2737–2744.
111. Liu H, El Zein L, Kruse M, et al. Gain-of-function mutations in TRPM4 cause autosomal dominant isolated cardiac conduction disease. *Circ Cardiovasc Genet* 2010;3:374–385.
112. Schulze-Bahr E, Isbrandt D, Neu A, et al. A mutation in the cardiac pacemaker channel gene hHCN4 is linked to human sinus node disease. *Am J Hum Genet* 2001;69:183.
113. Milanese R, Baruscotti M, Gnecci-Ruscone T, et al. Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. *N Engl J Med* 2006;354:151–157.
114. Garg V, Kathiriyi IS, Barnes R, et al. GATA4 mutations cause human congenital heart defects and reveal an interaction with TBX5. *Nature* 2003;424:443–447.
115. Spaendonck-Zwarts K, van Hessem L, Jongbloed JD, et al. Desmin-related myopathy: a review and meta-analysis. *Clin Genet* 2010;Jul 21[Epub ahead of print].
116. Perrot A, Hussein S, Ruppert V et al. Identification of mutational hot spots in LMNA encoding lamin A/C in patients with familial dilated cardiomyopathy. *Basic Res Cardiol* 2009;104:90–99.
117. van Tintelen JP, Hofstra RM, Katerberg H, et al. High yield of LMNA mutations in patients with dilated cardiomyopathy and/or conduction disease referred to cardiogenetics outpatient clinics. *Am Heart J* 2007;154:1130–1139.
118. McNair WP, Ku L, Taylor MR, et al. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. *Circulation* 2004;110:2163–2167.
119. Hesse M, Kondo CS, Clark RB, et al. Dilated cardiomyopathy is associated with reduced expression of the cardiac sodium channel Scn5a. *Cardiovasc Res* 2007;75:498–509.
120. Olson TM, Michels VV, Ballew JD, et al. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. *Jama* 2005;293:447–454.
121. Shi R, Zhang Y, Yang C, et al. The cardiac sodium channel mutation delQKP 1507-1509 is associated with the expanding phenotypic spectrum of LQT3, conduction disorder, dilated cardiomyopathy, and high incidence of youth sudden death. *Europace* 2008;10:1329–1335.
122. Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm* 2004;1:600–607.
123. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary. *Heart Rhythm* 2008;5:934–955.
124. Gussak I, et al. Idiopathic short QT interval: a new clinical syndrome? *Cardiology* 2000;94:99.
125. Gaita F, et al. Short QT syndrome: a familial cause of sudden death. *Circulation* 2003;108:965.
126. Rhodes TE, Abraham RL, Welch RC, et al. Cardiac potassium channel dysfunction in sudden infant death syndrome. *J Mol Cell Cardiol* 2008;44:571–581.
127. Anttonen O, Junttila MJ, Rissanen H, et al. Prevalence and prognostic significance of short QT-interval in a middle-aged Finnish population. *Circulation* 2007;116:714–720.
128. Funada A, Hayashi K, Hidekazu I, et al. Assessment of QT-intervals and prevalence of Short QT syndrome in Japan. *Clin Cardiol* 2008;31:270–274.
129. Mason JW, Ramseth DJ, Chanter DO, et al. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. *J Electrocardiol* 2007;40:228–234.
130. Kobza R, Roos M, Niggli B, et al. Prevalence of long and short QT in a young population of 41,767 predominantly male Swiss conscripts. *Heart Rhythm* 2009;6:652–657.
131. Gollob MH, Redpath C, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol* 2011;57:802–812.
132. Schimpf R, et al. Congenital Short QT syndrome and implantable cardioverter defibrillator treatment: inherent risk for inappropriate shock delivery. *J Cardiovasc Electrophysiol* 2003;14:1273.
133. Viskin S, et al. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. *Heart Rhythm* 2004;1:587.
134. Wolpert C, et al. Further insights into the effect of quinidine in short QT syndrome caused by a mutation in HERG. *J Cardiovasc Electrophysiol* 2005;16:54.
135. Gaita F, et al. Short QT syndrome: pharmacological treatment. *J Am Coll Cardiol* 2004;43:1494.
136. Brugada R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 2004;109:30.
137. Cordeiro JM, et al. Modulation of I_{Kr} inactivation by mutation N588K in KCNH2: a link to arrhythmogenesis in short QT syndrome. *Cardiovasc Res* 2005;67:498.
138. Bellocq C, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. *Circulation* 2004;109:2394.
139. Hong K, et al. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. *Cardiovasc Res* 2005;68:433.
140. Priori SG, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. *Circ Res* 2005;96:800.
141. Hong K, et al. Short QT syndrome et atrial fibrillation caused by mutation in KCNH2. *J Cardiovasc Electrophysiol* 2005;16:394.
142. 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;115:442–449.
143. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e257–354.
144. Lubitz SA, Yin X, Fontes JD, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *Jama* 2010;304:2263–2269.
145. Arnar DO, Thorvaldsson S, Manolio TA, et al. Familial aggregation of atrial fibrillation in Iceland. *Eur Heart J* 2006;27:708–712.
146. Chen YH, Xu SJ, Bendahhou S, et al. Kcnq1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003;299:251–254.
147. Das S, Makino S, Melman YF, et al. Mutation in the s3 segment of kcnq1 results in familial lone atrial fibrillation. *Heart Rhythm* 2009;6:1146–1153.
148. Xia M, Jin Q, Bendahhou S, et al. A kir2.1 gain-of-function mutation underlies familial atrial fibrillation. *Biochem Biophys Res Commun* 2005;332:1012–1019.
149. Yang Y, Xia M, Jin Q, et al. Identification of a kcnk2 gain-of-function mutation in patients with familial atrial fibrillation. *Am J Hum Genet* 2004;75:899–905.
150. Makiyama T, Akao M, Shizuta S, et al. A novel scn5a gain-of-function mutation m1875t associated with familial atrial fibrillation. *J Am Coll Cardiol* 2008;52:1326–1334.
151. Olson TM, Alekseev AE, Liu XK, et al. Kv1.5 channelopathy due to kcnk5 loss-of-function mutation causes human atrial fibrillation. *Hum Mol Genet* 2006;15:2185–2191.
152. Hodgson-Zingman DM, Karst ML, Zingman LV, Heublein DM, Darbar D, Herron KJ, Ballew JD, de Andrade M, Burnett JC Jr, Olson TM. Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. *N Engl J Med* 2008;359:158–165.
153. Gollob MH, Jones DL, Krahn AD, et al. Somatic mutations in the connexin 40 gene (gja5) in atrial fibrillation. *N Engl J Med* 2006;354:2677–2688.
154. Gudbjartsson DF, Arnar DO, Helgadóttir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature* 2007;448:353–357.
155. Ellinor PT, Lunetta KL, Glazer NL, et al. Common variants in kcnk3 are associated with lone atrial fibrillation. *Nat Genet* 2010;42:240–244.
156. Benjamin EJ, Rice KM, Arking DE, et al. Variants in zfx3 are associated with atrial fibrillation in individuals of European ancestry. *Nat Genet* 2009;41:879–881.
157. Gudbjartsson DF, Holm H, Gretarsdóttir S, et al. A sequence variant in zfx3 on 16q22 associates with atrial fibrillation and ischemic stroke. *Nat Genet* 2009;41:876–878.
158. Maron BJ, McKenna WJ, Danielson GK, et al; Task Force on Clinical Expert Consensus Documents. American College of Cardiology; Committee for Prac-

- tice Guidelines. European Society of Cardiology. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42:1687–1713.
159. Watkins H, Thierfelder L, Hwang DS, et al. Sporadic hypertrophic cardiomyopathy due to de novo myosin mutations. *J Clin Invest* 1992;90:1666–1671.
 160. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Jama* 2007;298:405–412. Erratum in *JAMA* 2007;298:1516.
 161. Thierfelder L, Watkins H, MacRae C, et al. Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere. *Cell* 1994;77:701–712.
 162. Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation* 2003;107:2227–2232.
 163. Jääskeläinen P, Miettinen R, Kärkkäinen P, et al. Genetics of hypertrophic cardiomyopathy in eastern Finland: few founder mutations with benign or intermediary phenotypes. *Ann Med* 2004;36:23–32.
 164. Geier C, Gehrmlich K, Ehler E, et al. Beyond the sarcomere: CSRP3 mutations cause hypertrophic cardiomyopathy. *Hum Mol Genet* 2008;17:2753–2765.
 165. Chiu C, Bagnall RD, Ingles J, et al. Mutations in α -actinin-2 cause hypertrophic cardiomyopathy: a genome-wide analysis. *J Am Coll Cardiol* 2010;55:1127–1135.
 166. Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. *N Engl J Med* 1998;338:1248–1257.
 167. Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 1995;332:1058–1064.
 168. Van Driest SL. Yield of genetic testing in hypertrophic cardiomyopathy. *Mayo Clin Proc* 2005;80:739–744.
 169. Andersen PS, Havndrup O, Hougs L, et al. Diagnostic yield, interpretation, and clinical utility of mutation screening of sarcomere encoding genes in Danish hypertrophic cardiomyopathy patients and relatives. *Hum Mutat* 2009;30:363–370.
 170. Girolami F, Ho CY, Semsarian C, et al. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. *J Am Coll Cardiol* 2010;55:1444–1453.
 171. Ingles J, Doolan A, Chiu C, et al. Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling. *J Med Genet* 2005;42:e59.
 172. Wordsworth S, Leal J, Blair E, et al. DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model. *Eur Heart J* 2010;31:926–935.
 173. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;36:2212–2218.
 174. Olivetto I, Girolami F, Ackerman MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc* 2008;83:630–638.
 175. Force T, Bonow RO, Houser SR, et al. Research priorities in hypertrophic cardiomyopathy: report of a Working Group of the National Heart, Lung, and Blood Institute. *Circulation* 2010;122:1130–1133.
 176. Abozguia K, Elliott P, McKenna WJ, et al. The metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. *Circulation* 2010;122:1562–1569.
 177. Penicka M, Gregor P, Kerekes R, et al. The effects of candesartan on left ventricular hypertrophy and function in nonobstructive hypertrophic cardiomyopathy: a pilot, randomized study. *J Mol Diagn* 2009;11:35–41.
 178. Semsarian C, Ahmad I, Giewat M, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. *J Clin Invest* 2002;109:1013–1020.
 179. Teekakirikul P, Eminaga S, Toka O, et al. Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-beta. *J Clin Invest* 2010;120:3520–3529.
 180. Basso C, Corrado D, Thiene G. Cardiovascular causes of sudden death in young individuals including athletes. *Cardiol Rev* 1999;7:127–135.
 181. Tabib A, Loire R, Chalabreysse L, et al. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. *Circulation* 2003;108:3000–3005.
 182. Sen-Chowdhry S, Syrris P, Prasad SK, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *J Am Coll Cardiol* 2008;52:2175–2187.
 183. Sen-Chowdhry S, Syrris P, Ward D, et al. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation* 2007;115:1710–1720.
 184. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation* 2010;121(13):1533–1541.
 185. Towbin JA. Arrhythmogenic right ventricular cardiomyopathy: a paradigm of overlapping disorders. *Ann Noninvasive Electrocardiol* 2008;13:325–326.
 186. Sen-Chowdhry S, Morgan RD, Chambers JC, et al. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. *Annu Rev Med* 2010;61:233–253.
 187. Dalal D, Nasir K, Bomma C, et al. Arrhythmogenic right ventricular dysplasia: a United States experience. *Circulation* 2005;112:3823–3832.
 188. Peters S, Trummel M, Meyners W. Prevalence of right ventricular dysplasia-cardiomyopathy in a non-referral hospital. *Int J Cardiol* 2004;97:499–501.
 189. Sen-Chowdhry S, Syrris P, McKenna WJ. Genetics of right ventricular cardiomyopathy. *J Cardiovasc Electrophysiol* 2005;16:927–935.
 190. Dalal D, James C, Devanagondi R, et al. Penetrance of mutations in plakophilin-2 among families with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol* 2006;48:1416–1424.
 191. Awad MM, Calkins H, Judge DP. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Nat Clin Pract Cardiovasc Med* 2008;5:258–267.
 192. Awad MM, Dalal D, Tichnell C, et al. Recessive arrhythmogenic right ventricular dysplasia due to novel cryptic splice mutation in PKP2. *Hum Mutat* 2006;27:1157.
 193. McKoy G, Protonotarios N, Crosby A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 2000;355:2119–2124.
 194. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet* 2000;9:2761–2766.
 195. Protonotarios N, Tsatsopoulou A. Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. *Cardiovasc Pathol* 2004;13:185–194.
 196. Simpson MA, Mansour S, Ahnood D, et al. Homozygous mutation of desmocolin-2 in arrhythmogenic right ventricular cardiomyopathy with mild palmoplantar keratoderma and woolly hair. *Cardiology* 2009;113:28–34.
 197. Xu T, Yang Z, Vatta M, et al. Compound and digenic heterozygosity contributes to arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol* 2010;55:587–597.
 198. Rampazzo A, Nava A, Malacrida S, et al. Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet* 2002;71:1200–1206.
 199. Gerull B, Heuser A, Wichter T, et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. *Nat Genet* 2004;36:1162–1164.
 200. Pilichou K, Nava A, Basso C, et al. Mutations in desmoglein-2 gene are associated with arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2006;113:1171–1179.
 201. Syrris P, Ward D, Evans A, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocolin-2. *Am J Hum Genet* 2006;79:978–984.
 202. Asimaki A, Syrris P, Wichter T, et al. A novel dominant mutation in plakoglobin causes arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet* 2007;81:964–973.
 203. Awad MM, Dalal D, Cho E, et al. DSG2 mutations contribute to arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Hum Genet* 2006;79:136–142.
 204. Merner ND, Hodgkinson KA, Haywood AF, et al. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *Am J Hum Genet* 2008;82:809–821.
 205. Beffagna G, Occhi G, Nava A, et al. Regulatory mutations in transforming growth factor-beta3 gene cause arrhythmogenic right ventricular cardiomyopathy type 1. *Cardiovasc Res* 2005;65:366–373.
 206. Tiso N, Stephan DA, Nava A, et al. Identification of mutations in the cardiac ryanodine receptor gene in families affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2). *Hum Mol Genet* 2001;10:189–194.
 207. Corrado D, Thiene G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: clinical impact of molecular genetic studies. *Circulation* 2006;113:1634–1637.
 208. 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.
 209. van Tintelen JP, Entius MM, Bhuiyan ZA, et al. Plakophilin-2 mutations are the

- major determinant of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation* 2006;113:1650–1658.
210. Christensen AH, Benn M, Tybjaerg-Hansen A, et al. Missense variants in plakophilin-2 in arrhythmogenic right ventricular cardiomyopathy patients—disease-causing or innocent bystanders? *Cardiology* 2010;115:148–154.
 211. Posch MG, Posch MJ, Perrot A, et al. Variations in DSG2: V56M, V158G and V920G are not pathogenic for arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Nat Clin Pract Cardiovasc Med* 2008;5:E1.
 212. Posch MG, Posch MJ, Geier C, et al. A missense variant in desmoglein-2 predisposes to dilated cardiomyopathy. *Mol Genet Metab* 2008;95(1–2):74–80.
 213. Baucé B, Nava A, Boffagna G, et al. Multiple mutations in desmosomal proteins encoding genes in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart Rhythm* 2010;7:22–29.
 214. Baucé B, Basso C, Rampazzo A, et al. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. *Eur Heart J* 2005;26:1666–1675.
 215. Dalal D, Molin LH, Piccini J, et al. Clinical features of arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in plakophilin-2. *Circulation* 2006;113:1641–1649.
 216. Sen-Chowdhry S, Syrris P, Pantazis A, et al. Mutational heterogeneity, modifier genes, and environmental influences contribute to phenotypic diversity of arrhythmogenic cardiomyopathy. *Circ Cardiovasc Genet* 2010;3:323–330.
 217. Kirchhof P, Fabritz L, Zwiener M, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. *Circulation* 2006;114:1799–1806.
 218. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. *N Engl J Med* 1992;326:77–82.
 219. Baig MK, Goldman JH, Caforio AP, et al. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. *J Am Coll Cardiol* 1998;31:195–201.
 220. Grunig E, Tasman JA, Kucherer H, et al. Frequency and phenotypes of familial dilated cardiomyopathy. *J Am Coll Cardiol* 1998;31:186–194.
 221. Hershberger RE, Lindenfeld J, Mestroni L, et al. Genetic evaluation of cardiomyopathy—a Heart Failure Society of America practice guideline. *J Card Fail* 2009;15:83–97.
 222. Judge DP, Johnson NM. Genetic evaluation of familial cardiomyopathy. *J Cardiovasc Trans Res* 2008;1:144–154.
 223. Jefferies JL, Towbin JA. Dilated cardiomyopathy. *Lancet* 2010;375:752–762.
 224. Hershberger RE, Morales A, Siegfried JD. Clinical and genetic issues in dilated cardiomyopathy: a review for genetics professionals. *Genet Med* 2010;12:655–667.
 225. Spaendonck-Zwarts K, van Hessem L, Jongbloed JD, et al. Desmin-related myopathy: a review and meta-analysis. *Clin Genet* 2010;Jul 21[Epub ahead of print].
 226. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;113:1807–1816.
 227. Engberding R, Yelbuz TM, Breithardt G. Isolated noncompaction of the left ventricular myocardium: a review of the literature two decades after the initial case description. *Clin Res Cardiol* 2007;96:481–488.
 228. Pignatelli RH, McMahon CJ, Dreyer WJ, et al. Clinical characterization of left ventricular noncompaction in children. A relatively common form of cardiomyopathy. *Circulation* 2003;108:2672–2678.
 229. Towbin JA, Bowles NE. The failing heart. *Nature* 2002;415:227–233.
 230. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. *Pediatrics* 2004;114:925–931.
 231. Towbin JA. Left ventricular noncompaction: a new form of heart failure. *Heart Fail Clin* 2010;6:453–469.
 232. Ichida F. Left ventricular noncompaction. *Circ J* 2009;73:19–26.
 233. Klaassen S, Probst S, Oechslin E, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. *Circulation* 2008;117:2893–2901.
 234. Vatta M, Mohapatra B, Jimenez S, et al. Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. *J Am Coll Cardiol* 2003;42:2014–2027.
 235. Ichida F, Tsubata S, Bowles KR, et al. Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. *Circulation* 2001;103:1256–1263.
 236. Shan L, Makita N, Xing Y, et al. SCN5A variants in Japanese patients with left ventricular noncompaction and arrhythmia. *Mol Genet Metab* 2008;93:468–474.
 237. Hoedemaekers YM, Caliskan K, Michels M, et al. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. *Circ Cardiovasc Genet* 2010;3:232–239.
 238. Bleyl SB, Mumford BR, Thompson V, et al. Neonatal lethal noncompaction of the ventricular myocardium is allelic with Barth syndrome. *Am J Hum Genet* 1997;61:868–872.
 239. Finsterer J, Stöllberger C. Primary myopathies and the heart. *Scand Cardiovasc J* 2008;42:9–24.
 240. Tang S, Batra A, Zhang Y, et al. Left ventricular noncompaction is associated with mutations in the mitochondrial genome. *Mitochondrion* 2010;10:350–357.
 241. Jacquier A, Thuny F, Jop B, et al. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. *Eur Heart J* 2010;31:1098–1104.
 242. Eidem BW. Noninvasive evaluation of left ventricular noncompaction: what's new in 2009? *Pediatr Cardiol* 2009;30:682–689.
 243. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *N Engl J Med* 1997;336:267–276.
 244. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;113:1807–1816.
 245. Sen-Chowdhry S, Syrris P, McKenna WJ. Genetics of restrictive cardiomyopathy. *Heart Fail Clin* 2010;6:179–186.
 246. Stollberger C, Finsterer J. Extracardiac medical and neuromuscular implications in restrictive cardiomyopathy. *Clin Cardiol* 2007;30:375–380.
 247. Meredith C, Herrmann R, Parry C, et al. Mutations in the slow skeletal muscle fiber myosin heavy chain gene (MYH7) cause Laing early-onset distal myopathy (MPD1). *Am J Hum Genet* 2004;75:703–708.
 248. Kaski JP, Syrris P, Burch M, et al. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. *Heart* 2008;94:1478–1484.
 249. Kubo T, Gimeno JR, Bahl A, et al. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. *J Am Coll Cardiol* 2007;49:2419–2426.
 250. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 2005;112:2047–2060.
 251. Jacobson DR, Pastore RD, Yaghubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N Engl J Med* 1997;336(7):466–473.
 252. Tartaglia M, Gelb BD. Noonan syndrome and related disorders: genetics and pathogenesis. *Annu Rev Genomics Hum Genet* 2005;6:45–68.
 253. Tartaglia M, Mehler EL, Goldberg R, et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001;29:465–468.
 254. Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet* 2002;70:1555–1563.
 255. Croonen EA, van der Burgt I, Kapusta L, et al. Electrocardiography in Noonan syndrome PTPN11 gene mutation—phenotype characterization. *Am J Med Genet A* 2008;146:350–353.
 256. Pandit B, Sarkozy A, Pennacchio LA, et al. Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. *Nat Genet* 2007;39:1007–1012.
 257. van der Werf C, Hofman N, Tan HL, et al. Diagnostic yield in sudden unexplained death and aborted ventricular arrest in the young: the experience of a tertiary referral center in The Netherlands. *Heart Rhythm* 2010;7:1383–1389.
 258. Folke F, Gislason GH, Lippert FK, et al. Differences between out-of-hospital cardiac arrest in residential and public locations and implications for public-access defibrillation. *Circulation* 2010;122:623–630.
 259. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation* 2010;121:1533–1541.
 260. Vasaiwala SC, Finn C, Delpriori J, et al. Prospective study of cardiac sarcoid mimicking arrhythmogenic right ventricular dysplasia. *J Cardiovasc Electro-physiol* 2009;20:479–483.
 261. Krahn AD, Healey JS, Chauhan V, et al. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER). *Circulation* 2009;120:278–285.
 262. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016–2023.
 263. Alders M, Koopmann TT, Christiaans I, et al. Haplotype Sharing analysis implicates chromosome 7q36 harboring DPP6 in familial idiopathic ventricular fibrillation. *Am J Hum Genet* 2009;84:468–476.

264. Ackerman MJ, Tester DJ, Driscoll DJ. Molecular autopsy of sudden unexplained death in the young. *Am J Forensic Med Pathol* 2001;22:105–111.
265. Doolan A, Langlois N, Semsarian C. Causes of sudden cardiac death in young Australians. *Med J Aust* 2004;180:110–112.
266. Ackerman MJ, Siu BL, Sturner WQ, et al. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. *Jama* 2001;286:2264–2269.
267. Van Norstrand DW, Valdivia CR, Tester DJ, et al. Molecular and functional characterization of novel glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) mutations in sudden infant death syndrome. *Circulation* 2007;116:2253–2259.
268. Wang DW, Desai RR, Crotti L, et al. Cardiac sodium channel dysfunction in sudden infant death syndrome. *Circulation* 2007;115:368–376.
269. Arnestad M, Crotti L, Rognum TO, et al. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation* 2007;115:361–367.
270. Tester DJ, Spoon DB, Valdivia HH, et al. Targeted mutational analysis of the RyR2-encoded cardiac ryanodine receptor in sudden unexplained death: a molecular autopsy of 49 medical examiner/coroner's cases. *Mayo Clin Proc* 2004;79:1380–1384.
271. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. *J Am Coll Cardiol* 2007;49:240–246.
272. Schwartz PJ, Stramba-Badiale M, Segantini A, et al. Prolongation of the QT interval and the sudden infant death syndrome. *N Engl J Med* 1998;338:1709–1714.
273. Schwartz PJ, Priori SG, Dumaine R, et al. A molecular link between the sudden infant death syndrome and the long-QT syndrome. *N Engl J Med* 2000;343:262–267.
274. Tan HL, Hofman N, van Langen IM, et al. Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. *Circulation* 2005;112:207–213.
275. Behr E, Wood DA, Wright M, et al. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. *Lancet* 2003;362:1457–1459.
276. Ingles J, Semsarian C. Sudden cardiac death in the young: a clinical genetic approach. *Intern Med J* 2007;37:32–37.
277. Carturan E, Tester DJ, Brost BC, et al. Postmortem genetic testing for conventional autopsy-negative sudden unexplained death: an evaluation of different DNA extraction protocols and the feasibility of mutational analysis from archival paraffin-embedded heart tissue. *Am J Clin Pathol* 2008;129:391–397.
278. Beckwith JB. Defining the sudden infant death syndrome. *Arch Pediatr Adolesc Med* 2003;157:286–290.