Society Position Statement

Recommendations for the Use of Genetic Testing in the Clinical Evaluation of Inherited Cardiac Arrhythmias Associated with Sudden Cardiac Death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society Joint Position Paper

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ABSTRACT

The era of gene discovery and molecular medicine has had a significant impact on clinical practice. Knowledge of specific genetic findings causative for or associated with human disease may enhance diagnostic accuracy and influence treatment decisions. In cardiovascular disease, gene discovery for inherited arrhythmia
Genetic Testing in Arrhythmia Syndromes

Introduction

The evolution of knowledge in cardiovascular genetics over the past 15 years has refined our mechanistic understanding of inherited cardiac syndromes associated with sudden cardiac death (SCD) and has led to changes in our approach to clinical diagnosis and management of patients and their families.

Clinical training does not routinely emphasize the appropriate use of genetic testing as a clinical tool. Yet, with the advent of commercial, for-profit genetic testing facilities, the availability of this option is well known to physicians. This novel testing has been embraced with marked enthusiasm, often with little regard for the utility of genetic testing or the role of patient counseling and education.

This paper presents the consensus of a panel of Canadian arrhythmia specialists, geneticists, genetic counsellors, and a medical ethicist. The mandate of the panel was to formulate disease-specific recommendations for the use of genetic testing in the care of patients and families with documented or suspected genetic conditions associated with SCD. In the context of contemporary knowledge, the panel deliberated on the clinical value of genetic testing with reference to the potential yield of positive and interpretable genetic findings.

In formulating recommendations, the committee recognized that there exists a paucity of double-blind, randomized trials that form the basis for most guideline documents. Thus, the panel endeavored to reach consensus based on their collective experience. Not all regions of Canada have available the resources to provide care according to all the recommendations of this document. In such circumstances, physicians are encouraged to consult with expert colleagues elsewhere while attempting to develop the necessary resources locally.

Decision making for genetic testing

Decisions regarding the need to proceed with genetic testing should be based primarily on the clinical value the genetic information may provide in the care of patients or their families. For many diseases, genetic testing is not necessary in establishing a diagnosis, but serves as a tool to screen family members to reconcile concerns of subclinical disease and the need for medical surveillance. In other instances, genetic testing may help to establish a diagnosis in equivocal clinical presentations, understanding that the genetic information may require cautious interpretation, similar to other clinical tests (eg, cardiac magnetic resonance imaging) that provide helpful but often inconclusive diagnostic results.

In light of the low prevalence of inherited arrhythmia syndromes, clinical evaluation and decisions regarding the utility of genetic testing should be made by physicians with a dedicated practice. The physician expert should have knowledge in the interpretation of genetic data. Specialized arrhythmia clinics with the involvement of trained genetic counsellors focused on inherited arrhythmias are strongly encouraged. Inherited arrhythmia syndromes are often challenging to diagnose and are potentially lethal, and the implications of a wrong diagnosis may be fatal or have lifelong consequences. Discordance in diagnostic accuracy between nonspecialty clinics and specialized clinics exists. For the long QT syndrome (LQTS), 40% of patients labelled with LQTS were considered inappropriately diagnosed after evaluation in a dedicated inherited arrhythmia clinic. Specialized clinics also serve to improve cost-effectiveness and yield from genetic testing.

Ethical issues in genetic testing

Genetic testing for SCD susceptibility raises issues such as stigma, privacy, and insurance and employment discrimination. Novel issues include possible child protection obligations under provincial statutes and the possibility of public protection or “duty to warn” scenarios. Whereas genetic testing for susceptibility for later-onset conditions (eg, breast cancer) has typically been deferred until patients attain capacity to make their own decisions, the availability of effective prophylaxis treatment in genetic arrhythmia syndromes may mandate the testing of at-risk children. When a first-degree relative, if affected, might imperil public safety (eg, an airline pilot), duty-to-warn obligations may exist when assessment is refused. These emerging issues are now being explored, and the ethical, legal, and social contexts are complex. A thorough discussion of
these issues is available in the on-line supplement (see Supplementary Material).

**Disease-Specific Recommendations for Clinical Genetic Testing**

**The role of genetic testing in LQTS**

LQTS (incidence, 1 per 3000)\(^3\) is characterized by electrocardiographic prolongation of the QT interval, syncope, and sudden death. LQTS causes 3000 to 4000 sudden deaths per year in the United States.\(^4\) The risk of cardiac arrhythmias is directly proportional to the duration of the corrected QT interval (QTc) duration.\(^5,7\)

**Diagnosis.** Most patients with LQTS have a QTc > 460 milliseconds, but up to 40% of gene carriers will have a normal QTc, reflecting variable disease penetrance.\(^8,9\) The Schwartz milliseconds, but up to 40% of gene carriers will have a normal QTc duration likely reflecting differences in the clinical expertise of ordering physicians. The majority of genetically confirmed cases are the result of mutations in 3 genes. In 90% of cases, LQTS is not recommended. Given the small number of variants described in these genes, results are more likely to be of unknown significance and of limited clinical value if a clear familial pattern of disease is not recognized. In patients with negative genetic testing but clinically robust phenotype, consideration may be given to assessing rare genes on a case-by-case basis.

**Recommendations for genetic testing in LQTS (Table 1)**

Genetic testing should include analysis of the KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 genes. Routine clinical genetic testing of rare genes (<1% detection rate) associated with LQTS is not recommended. Given the small number of variants described in these genes, results are more likely to be of unknown significance and of limited clinical value if a clear familial pattern of disease is not recognized. In patients with negative genetic testing but clinically robust phenotype, consideration may be given to assessing rare genes on a case-by-case basis.

**RECOMMENDATION**

Cardiac Arrest Survivor: Genetic testing is recommended in the cardiac arrest survivor with LQTS for the primary purpose of screening first-degree relatives.
All first-degree relatives of a genetically confirmed case of LQTS should be offered genetic testing regardless of symptom status or baseline ECG to determine whether they are gene carriers.

**RECOMMENDATION**

**Syncope with QTc prolongation:** Genetic testing is recommended in the patient with syncope and QTc prolongation that is attributed to LQTS.

Patients with syncope and QTc prolongation (>480 milliseconds) with characteristic T-wave abnormalities do not need genetic testing for a diagnosis of LQTS. However, genetic testing plays a role in assessing risk of sudden death in combination with the corrected QT interval, as well as predicting efficacy of beta blockade, and is therefore recommended. In patients with a borderline QTc interval (450-460 milliseconds), genetic testing is not recommended unless there are characteristic T-wave morphologies consistent with LQTS and/or a family history of premature SCD (age <40 years). Asymptomatic individuals with borderline QTc prolongation (460-480 milliseconds) warrant evaluation by a clinical expert prior to receiving genetic testing.

**RECOMMENDATION**

**Asymptomatic patient with QTc prolongation:** Genetic testing is recommended in the asymptomatic patient with consistent QTc prolongation that is clinically suspected to represent LQTS.

Genetic testing is recommended in asymptomatic individuals with a consistent QTc > 480 milliseconds (Schwartz score ≥ 3), in the absence of provoking medications, metabolic abnormalities, or structural heart disease. The role of genetic testing to confirm the diagnosis of LQTS in these patients is unclear, although genetic confirmation may be helpful for risk stratification and family screening. Given the low yield of genetic testing in asymptomatic patients with borderline QTc prolongation (450-460 milliseconds), routine genetic testing is not recommended. Genetic testing for asymptomatic individuals with QTc intervals in the 460-to-480-millisecond range should be considered only in the setting of a specialized inherited arrhythmia clinic.

**The role of genetic testing in Brugada syndrome**

Brugada syndrome is characterized by anterior precordial ST elevation on ECG and risk of ventricular fibrillation, most commonly at rest or during sleep. ECG findings without cardiac events is termed “Brugada pattern.” The Brugada ECG pattern is present in 1 per 4000 to 1/10,000 patients, influenced by ethnicity. 

**Diagnosis.** The diagnosis of Brugada syndrome follows an index event of syncope or cardiac arrest and ECG recognition of ST elevation of a coved-shaped pattern (type 1 ECG pattern) in leads V1 and V2. Type 2 and type 3 Brugada ECG patterns are characterized by a saddleback pattern in V1 and V2, with or without ST elevation, respectively. These additional ECG patterns are not considered diagnostic of the Brugada syndrome. The various Brugada ECG patterns may be intermittent. Patients with a type 2 or 3 pattern with unheralded syncope should undergo evaluation for Brugada syndrome. Intravenous administration of a sodium channel blocker may convert a type 2 or 3 ECG pattern into a type I pattern, raising the suspicion of Brugada syndrome. The type 1 Brugada ECG pattern may be provoked by fever or medications with sodium channel blocking properties. In some patients, conduction system disease coincides with the Brugada ECG pattern or may be the only ECG abnormality observed in family members.

**Management.** Patients with resuscitated cardiac arrest are managed with an ICD, which is also recommended for those with a history of syncope suspicious for arrhythmia. Drug therapy with β-blockers or amiodarone has not been useful. Quinidine has shown promise in one series, although efficacy based on data from randomized controls does not exist. Patients should avoid drugs with sodium channel blocking effects, comprehensively listed at www.brugadadrugs.org. Aggressive temperature lowering during febrile illnesses is necessary. There is considerable controversy regarding SCD risk in asymptomatic patients with type I Brugada ECG pattern. Data from a large cohort of patients suggest that asymptomatic individuals have a low event rate (<1%/y). The value of electrophysiological testing for risk stratification is not clearly established. A positive family history of Brugada syndrome–related SCD does not appear to confer a worse prognosis.

**Genetics.** The most commonly identified genetic defects are in the SCNS5A gene, accounting for approximately 20% of cases. However, sporadic cases without evident family history have a much lower yield. Five additional genes (SCNB1, SCNB3, KCNE3, CACNA1C, and CACNB2b) encoding subunits of sodium, potassium, and calcium channels have been implicated in Brugada syndrome but collectively account for a small proportion of cases (<3%). In a single family of Italian descent, a mutation in the glycerol-3-phosphate dehydrogenase 1–like gene (GPD1L) was identified and found to segregate with affected members.

**Recommendations for genetic testing in Brugada syndrome (Table 2)**

Since genetic testing identifies responsible genotypes in only 20% of patients, a negative genotype should not reassure physicians that symptoms are on the basis of a benign condition when a Brugada ECG pattern exists. Presently, genetic testing should be limited to analysis of the SCNS5A gene. Testing for mutations in SCNB1, SCNB3, KCNE3, CACNA1C, CACNB2b, CACNA1C, and GPD1L are not clinically indicated, because of their rarity, and should be considered only under special circumstances.

**RECOMMENDATION**

Cardiac arrest survivor: Genetic testing in the cardiac arrest survivor with a persistent or provokable type 1 Brugada ECG pattern is recommended for the primary purpose of screening of family members.

Cardiac arrest is often the first presentation of patients with Brugada syndrome. The purpose of testing in this scenario is to develop a screening tool for family members. While the clinical implications of a positive genotype in the absence of a phenotypic correlate in a family member is unknown, knowledge of gene-
carrier status provides the opportunity to counsel family members on issues related to fever and medication use. In cardiac arrest patients with an apparent type 2 or 3 ECG pattern but no provoca-
table type 1 pattern, genetic testing is not recommended as the
diagnosis of Brugada syndrome requires evidence of the character-
istic type 1 ECG pattern.

### RECOMMENDATION

Syncope and Brugada ECG pattern: Genetic testing in the
patient with syncope and a permanent or provokable type 1
Brugada ECG pattern is recommended for the primary pur-
pose of screening of family members.

The diagnosis of Brugada syndrome should be based on
clinical grounds, with genetic testing used only as a family
screening tool.

### RECOMMENDATION

Asymptomatic persistent or provokable type 1 Brugada
ECG pattern: Genetic testing in the asymptomatic patient
with persistent or provokable type 1 Brugada ECG pattern
is recommended for the primary purpose of screening fam-
ily members.

In asymptomatic patients, genetic testing should not be per-
fomed with the intent of risk stratification. At present, there is
no genotype that reliably determines prognosis in Brugada syn-
drome.

### Table 2. Summary recommendations for genetic testing in Brugada syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Testing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest survivor</td>
<td>++</td>
<td>Not for diagnostic or therapeutic purposes but plays a role in family screening</td>
</tr>
<tr>
<td>Persistent or provokable type 1 Brugada ECG pattern</td>
<td>++</td>
<td>Not for diagnostic or therapeutic purposes but plays a role in family screening</td>
</tr>
<tr>
<td>Apparent type 2 or 3 ECG pattern*</td>
<td>–</td>
<td>Genetic testing is not recommended as the diagnosis of Brugada syndrome requires evidence of the type 1 ECG pattern</td>
</tr>
<tr>
<td>with nonprovokable type 1 ECG pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>++</td>
<td>Principally for the purpose of family screening</td>
</tr>
<tr>
<td>Persistent or provokable type 1 Brugada ECG pattern</td>
<td>++</td>
<td>Principally for the purpose of family screening</td>
</tr>
<tr>
<td>Apparent type 2 or 3 ECG pattern*</td>
<td>–</td>
<td>Genetic testing is not recommended</td>
</tr>
<tr>
<td>with nonprovokable type 1 ECG pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent type 1 Brugada ECG pattern</td>
<td>++</td>
<td>Not useful for risk stratification; principally for the purpose of family screening</td>
</tr>
<tr>
<td>Apparent type 2 or 3 ECG pattern</td>
<td>–</td>
<td>Genetic testing is not recommended</td>
</tr>
<tr>
<td>with nonprovokable type 1 ECG pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relative</td>
<td>++</td>
<td>Clinical implications of an isolated positive genotype in the absence of a phenotype are unknown</td>
</tr>
<tr>
<td>Proband genotype positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proband genotype negative</td>
<td>–</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Recommendations: + + (strongly recommended), – (not recommended).

* Type 2 or 3 ECG patterns may resemble early repolarization or variations of normal ST segments.

### RECOMMENDATION

Type 2 or type 3 Brugada ECG pattern in symptomatic or asymptomatic individuals without evidence for intermit-
tent or provokable type 1 ECG pattern: Genetic testing is not recommended.

Genetic testing is not useful in patients with nonspecific ECG features suggestive of type 2 or 3 Brugada ECG pattern but without provokable type 1 pattern.

### The role of genetic testing in arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC), with an estimated prevalence of ARVC 1 per 5000, is character-
zied by fibrofatty replacement of myocardium. It affects the right ventricle predominantly but may have left ventricular involve-
ment.43 ARVC can result in ventricular arrhythmias, SCD, and right or biventricular dysfunction. Often sporadic, the condition is familial in up to 50% of index cases.43-44

### Diagnosis

Task Force criteria for the diagnosis were originally proposed in 1994 and updated in 2010.45,46 Criteria are grouped into those involving right ventricular function, tissue characteristics of the myocardium, ECG repolarization abnor-
malities, ECG depolarization abnormalities, arrhythmias, family
history, and genetic testing. The Task Force criteria are considered to be specific but relatively insensitive. Other rare conditions, such as cardiac sarcoidosis, may affect right ventricu-
lar myocardium and mimic the clinical and imaging features of ARVC.47,48 As ARVC may be a progressive disease, patients suspected of having ARVC who have initial equivocal diagnos-
tic test results should undergo reevaluation at least annually.

### Management

Patients with proven or suspected ARVC are discouraged from participation in competitive sports or endur-
ance training, and activity should be modified according to
American Heart Association recommendations.19 Patients
with documented ventricular arrhythmias should receive an
ICD as first-line therapy. It is not known whether an ICD or pharmacologic treatment will affect outcome in asymptomatic or gene-positive patients without overt disease. However, close
cardiac surveillance for disease development is necessary.

### Genetics

A pathogenetic theme for ARVC is the presence of mutations in genes encoding desmosomal proteins.49 Desmo-
somes are a primary component of cell adhesion junctions, ensur-
ing the structural and functional integrity of cardiomyocytes. Mu-
tations have been identified in genes encoding for desmosomal
proteins plakophilin-2 (PKP2), desmoplakin (DSP), plakoglobin
(JUP), desmocollin (DSC2), and desmoglein (DSG2).49-54 A
mutation in the gene encoding a nondesmosomal protein
(TMEM43) has been identified as the cause in a large cohort
of related patients in Newfoundland, Canada.55 The cellular func-
tion of the TMEM43 protein is unknown.

Plakophilin-2 (PKP2) mutations occur in up to 45% of cases
meeting ARVC Task Force criteria.56,57 The yield of PKP2 testing
may approach 70% when familial ARVC is confirmed, in contrast
to a lower yield in sporadic cases. Variable disease penetrance
and expression in PKP2 mutation carriers is common. Desmoplakin
(DSP) mutations occur in 6% to 16% of ARVC cases.51,58 A rare
autosomal recessive syndrome related to desmoplakin mutations is...
Clinical ARVC in accordance with Task Force criteria: Genetic testing is recommended for the primary purpose of screening family members.

Recommendations for genetic testing in ARVC (Table 3)

In view of the differing yields for the known causative genes, stepwise or tiered genetic testing should be performed. Genetic testing of the PKP2 and DSP genes should be performed first, which may yield a positive test in up to 50% of Task Force positive cases. If negative, additional testing of the DSG2 and DSC2 genes may identify a mutation in an additional 5% to 10% of cases. In patients with ancestry linked to Newfoundland, genetic testing of TMEM43 should be considered. Lastly, it should be emphasized that given the relatively recent history of gene discovery in ARVC and the natural genetic variability that occurs in culprit genes in apparently healthy controls, interpretation of genetic testing results for this condition is complex, necessitating the involvement of a specialized clinic.

Satisfying Task Force criteria for ARVC may be challenging because of variations in clinical expression of the disease. Addition of genetic testing in the 2010 Task Force criteria indicates the utility of including genetic testing results in arriving at a diagnosis. Although the genetic test result may not provide the definitive answer for diagnosis, the information gained can be weighed in the context of other clinical tests in diagnostic decision making and potentially confirm a diagnosis if a known disease-causing mutation is identified.

The role of genetic testing in catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by emotion- or exercise-induced syncope or cardiac arrest in structurally normal hearts.

Diagnosis. The rhythm disturbance of CPVT is polymorphic ventricular tachycardia (VT) that is induced during high adrenaline states. Clinical presentation is most common in prepubertal or adolescent years. In contrast to other channelopathies, baseline ECGs are usually normal. Bidirectional VT with exercise is a diagnostic hallmark of CPVT, although Andersen-Tawil syndrome (LQTS type 7) caused by KCNJ2 mutations may also demonstrate bidirectional VT, usually with a resting ECG showing prominent U waves. CPVT should be considered in the differential diagnosis of all adrenergic-mediated syncopal or cardiac arrest events, particularly in young individuals (aged < 20 years). Diagnosis is supported by reproducing the typical bidirectional VT or polymorphic VT induced by exercise or infusion of an adrenergic agonist, while confirming no evidence of structural heart disease. However, many arrhythmogenic cardiac conditions may manifest exercise-induced polymorphic VT (eg, ischemia, ARVC), and therefore careful diagnostic workup is required before diagnosing CPVT.

Management. β-Blockers are highly effective in suppressing adrenergic-mediated arrhythmias in CPVT. Treadmill testing should be performed to titrate β-blocker dosage to ensure adequate suppression of exercise-induced ventricular arrhythmias. Typically, high-dose β-blockers are required (eg, atenolol ≥ 2 mg/kg), although complete absence of premature ventricular contractions on exercise is rare. In addition, affected patients should be advised to refrain from intense physical exercise. In patients with recurrent syncope despite high-dose β-blockers, flecainide, cardiac sympathectomy, or ICD placement should be considered.

Genetics. Two genetic forms of CPVT have been described: an autosomal dominant form, due to mutations in the cardiac ryanodine receptor gene (RYR2), and a rare autosomal recessive form with mutations in casequestrin (CASQ2).

Table 3. Summary recommendations for genetic testing in arrhythmogenic right ventricular cardiomyopathy

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Testing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ARVC in accordance with Task Force criteria</td>
<td>++</td>
<td>Genetic testing plays a role in the screening of identified family members</td>
</tr>
<tr>
<td>Clinical ARVC in accordance with Task Force criteria</td>
<td>–</td>
<td>ARVC is often sporadic, and genetic results do not provide risk stratification assistance</td>
</tr>
<tr>
<td>First-degree relative of genotype-positive proband</td>
<td>++</td>
<td>Useful for decisions of medical surveillance and lifestyle modification</td>
</tr>
<tr>
<td>First-degree relative of genotype-negative proband</td>
<td>–</td>
<td>Genetic testing not indicated</td>
</tr>
</tbody>
</table>

Recommendations: ++ (strongly recommended), – (not recommended). ARVC, arrhythmogenic right ventricular cardiomyopathy.
cases.63 Traditionally, genetic screening of this gene has been limited to so-called hotspot exons, regions of the gene presumed to be rich in disease-causing mutations. Because of the very large size of the RYR2 gene, such limited screening has been considered cost-effective. However, disease-causing mutations have been identified outside hotspot regions.68

**Recommendations for genetic testing in CPVT (Table 4)**

The large size of the RYR2 gene, as well as the clustering of disease-causing mutations to hotspot exons, justifies an initial targeted genetic screening approach for this gene. When genetic screening of targeted exons is negative and clinical suspicion remains, screening of the remaining RYR2 exons is recommended. In RYR2-negative cases, or when autosomal recessive inheritance is noted, screening of the CASQ2 gene is warranted. Patients demonstrating prominent U waves and negative RYR2 testing should be considered for testing of the KCNJ2 gene. Overall yield of genetic testing for clinical CPVT is in the range of 50% to 60%.

**RECOMMENDATION**

Clinically suspected CPVT: Genetic testing is recommended for the primary purpose of screening family members.

Genetic diagnosis may lead to preventive therapy and exercise restriction in family members. Reassurance may be provided to genotype-negative family members.

**The role of genetic testing in hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is characterized by cardiac hypertrophy in the absence of another cardiac or systemic disease. HCM is relatively common, estimated to have a prevalence of 1 per 500, and is the most common cause of SCD in the young.69

**Diagnosis.** The evaluation of patients with suspected HCM includes a history and physical examination, ECG, and 2-dimensional echocardiography. The diagnosis is generally established by echocardiography. ECG abnormalities may occasionally precede the onset of left ventricular hypertrophy on the echocardiogram.70,71 In children, ECG and echocardiographic abnormalities may not develop until late adolescence or adulthood, requiring routine medical surveillance in offspring of affected adults.

It is important to distinguish patients with HCM from patients with physiological causes of hypertrophy (eg, athlete’s heart) or infiltrative disorders.72-74

**Management.** Risk stratification of patients is recommended to determine the risk for SCD.69,75 Major risk factors are a family history of premature SCD, unexplained syncope, nonsustained VT, an abnormal blood pressure response to exercise, and massive left ventricular hypertrophy (maximum left ventricular wall thickness ≥30 mm).69,75 In patients considered high risk for SCD, an ICD is indicated. Exercise restriction is recommended to minimize arrhythmia provocation in high-risk individuals.

**Genetics.** HCM arises from genetic defects in close to 20 different genes, although the most common forms of HCM result from mutations in genes encoding proteins of the cardiac sarcomeric apparatus (Table 5).76 Genetic testing may detect a gene defect in 40% to 60% of patients.76,77 Mutations of the MYH7 and MYBPC3 genes account for the majority of cases.76 Approximately 3% of patients with HCM may have more than one pathogenic mutation, which may be associated with a more severe phenotype.76

Infiltrative or storage diseases may show similar findings on cardiac imaging and incorrectly lead to a diagnosis of HCM. Fabry’s disease (caused by genetic defects in the GLA gene) was detected in 6% of male patients diagnosed with presumed HCM at age ≥40 years.78 The identification of patients with this condition is important since enzyme replacement therapy is effective.79,80 Other inherited storage diseases showing features of HCM commonly have the ECG finding of ventricular preexcitation. These conditions include the glycogen storage conditions of Danon’s disease (LAMP2 gene), and the PRKAG2 cardiac syndrome (PRKAG2 gene).75,81,82

**Recommendations for genetic testing in HCM (Table 6)**

Since HCM is diagnosed by imaging studies, the principal role of genetic testing is not to confirm a diagnosis but rather to

**Table 4. Summary recommendations for genetic testing in catecholaminergic polymorphic ventricular tachycardia**

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Testing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically suspected CPVT</td>
<td>++</td>
<td>Genetic testing useful for the primary purpose of identifying at-risk family members</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>++</td>
<td>Useful for decisions of medical surveillance and lifestyle modification</td>
</tr>
</tbody>
</table>

Recommendations: ++ (strongly recommended).

CPVT, catecholaminergic polymorphic ventricular tachycardia.

**Table 5. Genes associated with hypertrophic cardiomyopathy**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>β-Myosin heavy chain</td>
<td>15%-30%</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C</td>
<td>15%-30%</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Troponin T</td>
<td>5%-10%</td>
</tr>
<tr>
<td>TNNI3</td>
<td>Troponin I</td>
<td>2%-5%</td>
</tr>
<tr>
<td>TPM1</td>
<td>α-Tropomysin</td>
<td>2%-5%</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-Myosin heavy chain</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>MYL2</td>
<td>Ventricular regulatory myosin light chain</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>MYL3</td>
<td>Ventricular essential myosin light chain</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ACTC</td>
<td>α-Cardiac actin</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>TNNT1</td>
<td>Troponin C</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LBD3</td>
<td>Limb binding domain 3</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CSRP3</td>
<td>Muscle LIM protein</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>TCAP</td>
<td>Telethonin</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>VCL</td>
<td>Vinculin</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-Actinin 2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>MYOZ2</td>
<td>Myozin 2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>JPH2</td>
<td>Junctophilin-2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Table 6. Summary recommendations for genetic testing in hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Testing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically diagnosed HCM</td>
<td>++</td>
<td>Genetic testing is recommended for the primary purpose of screening family members</td>
</tr>
<tr>
<td>Tier I gene testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier II gene testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically diagnosed HCM</td>
<td>++</td>
<td>Genetic testing is recommended for the primary purpose of screening family members</td>
</tr>
<tr>
<td>with ECG features of ventricular preexcitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier I gene testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier II gene testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically diagnosed HCM</td>
<td>−</td>
<td>Genetic testing is NOT recommended for the purpose of diagnostic confirmation</td>
</tr>
<tr>
<td>Clinically diagnosed HCM</td>
<td>−</td>
<td>Genetic testing is NOT recommended for the purpose of risk stratification and treatment decisions</td>
</tr>
<tr>
<td>Clinically suspected HCM</td>
<td>−</td>
<td>Genetic testing is NOT recommended for the purpose of differentiating HCM from other causes of cardiac hypertrophy, including athletes heart, hypertensive heart disease, and cardiac amyloidosis</td>
</tr>
</tbody>
</table>

Recommendations: + + (strongly recommended), − (not recommended).

HCM, hypertrophic cardiomyopathy.

provide a clinical tool for screening family members at risk of developing the disease. In light of the large number of genes associated with HCM and their respective yields of mutation detection, a tiered genetic testing approach is recommended. Initial testing for the 2 most common genetic causes, MYH7 and MYBPC3, yields a positive result in 30% to 50% of cases. A second tiered approach with testing of TNNT2, TNNI3, and TPM1 may be considered if results are negative and succeeds in detecting 10% to 15% of cases. Genetic testing of rare genes (<1% detection rate) associated with HCM is not likely to be clinically useful or cost-effective. Given the small number of variants described in these genes, results are more likely to be of unknown significance if a clear familial pattern of disease is not recognized. Lastly, in apparent HCM in which ventricular preexcitation is evident, genetic testing for cardiac storage diseases should be considered as first tier, including the genes PRKAG2, LAMP2, and GLA.

**RECOMMENDATION**

Clinically diagnosed HCM: Genetic testing is not recommended for the purpose of diagnostic confirmation.

In the absence of known at-risk family members who may benefit from genetic screening, there exists no clinical utility in identifying the culprit genotype. In addition, genetic testing may not exclude the possibility that the patient has HCM, since genetic testing is not 100% sensitive.

**RECOMMENDATION**

Clinically diagnosed HCM: Genetic testing is not recommended for the purpose of risk stratification and treatment decisions.

The use of genetic information to predict clinical progression of disease or risk of fatal arrhythmia is not currently supported by the medical literature. Prediction of event risk should be guided by clinical testing.

**RECOMMENDATION**

Clinically suspected HCM: Genetic testing is not recommended for the purpose of differentiating HCM from other causes of cardiac hypertrophy, including athlete’s heart, hypertensive heart disease, and cardiac amyloidosis.

HCM can usually be differentiated from other causes of increased wall thickness on the basis of standard clinical history and objective tests.

The role of genetic testing in dilated cardiomyopathy

Dilated cardiomyopathy (DCM) has a prevalence of 1 per 2500 and is characterized by dilation and dysfunction of the left or both ventricles. Often, the etiology remains unknown. The potential causes are vast and include myocardial destruction by toxic, infectious, or metabolic causes, such as alcoholism, viruses, or endocrine or nutritional deficiencies. Other causes may include infiltrative and inflammatory diseases, such as hemochromatosis, amyloidosis, or sarcoidosis. Familial DCM is estimated to occur in 20% to 35% of cases and most commonly involves genes encoding components of the myocyte sarcomere or cytoskeleton.

**Diagnosis.** The diagnosis may be readily made by cardiac imaging studies and the exclusion of significant coronary disease. Cardiac biopsy may be considered as a diagnostic tool.

**Management.** Medical therapy includes the use of angiotensin-converting enzyme inhibitors, β-blockers, and spironolactone to minimize disease progression, control symptoms, and decrease arrhythmic risk. Electrophysiological testing is not recommended for risk stratification. For a left ventricular ejection fraction <35% and impaired New York Heart Association functional class, consideration of an ICD for the prophylaxis of SCD should be considered. In patients with a sig-
Table 7. Summary recommendations for genetic testing in dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Testing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically diagnosed DCM</td>
<td>−</td>
<td>Genetic testing is NOT recommended in the absence of established or probable familial disease as determined by family history or clinical testing of first-degree relatives</td>
</tr>
<tr>
<td>Clinically diagnosed DCM with evidence of probable familial DCM</td>
<td>++</td>
<td>Genetic testing is recommended for the primary purpose of screening family members</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>MYH7, MYBPC, TNNT2, LMNA, SCN5A</td>
<td></td>
</tr>
<tr>
<td>Clinically diagnosed familial DCM with evidence of atrial arrhythmias and high-grade conduction disease</td>
<td>++</td>
<td>Genetic testing is recommended for the primary purpose of screening family members</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>LMNA, SCN5A</td>
<td></td>
</tr>
<tr>
<td>Clinically diagnosed familial DCM with evidence of X-linked inheritance</td>
<td>++</td>
<td>Genetic testing is recommended for the primary purpose of screening family members</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>DMD</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations: ++ (strongly recommended), − (not recommended).

DCM, dilated cardiomyopathy.

significantly widened QRS duration (>150 milliseconds) and impaired New York Heart Association functional class, biventricular pacing may improve heart failure symptoms.86

Genetics. Over 30 genes have been reported to cause DCM.87 The yield of genetic testing is significantly enhanced when a family history is evident.85,86 In familial disease, the most common causes include genetic defects in the MYBPC3, MYH7, TNNT2, LMNA, and SCN5A genes, which collectively account for 15% to 30% of familial DCM.85,88,89

Familial DCM with atrial arrhythmias and high-grade conduction disease is most commonly due to mutations of the LMNA gene.85 Familial DCM demonstrating an X-linked pattern of inheritance and skeletal muscle weakness raises the suspicion of dystrophin (DMD) gene mutations.85

Recommendations for genetic testing in DCM (Table 7)

Genetic determinants of sporadic DCM have not been routinely described. Thus, in the absence of a family history determined either by history or by clinical evaluation of relatives, genetic testing is likely of limited value.

Probands should be questioned about family members with cardiac devices, unexpected SCD (at age < 50 years), skeletal muscle disorders, or heart failure. The presence of family members with any of these characteristics increases the probability of familial disease. Since familial DCM has an autosomal dominant pattern of inheritance and is associated with incomplete penetrance and variable age of onset, genetic testing remains valuable in screening family members despite the absence of clinical features.

A comprehensive testing approach for all reported DCM genes is not cost-effective. Targeting of the genes with the most likely chance for a positive finding or interpretable test result in familial DCM is most reasonable and includes the following genes: MYH7, TNNT2, MYBPC, TNNT, LMNA, and SCN5A. Should evaluation of these genes be negative, consideration may be given to genetic testing of phospholamban (PLN) and alpha-myosin heavy chain (MYH6) genes. When atrial arrhythmia or conduction disease is present, testing of LMNA or SCN5A should be prioritized. In X-linked inheritance, the dystrophin gene (DMD) should be targeted.

RECOMMENDATION

Clinically diagnosed DCM: Genetic testing is not recommended in the absence of established or probable familial disease as determined by family history and clinical testing of first-degree relatives.

Genetic testing in DCM in the absence of any family history is not recommended, as reports of interpretable genetic findings in isolated cases are scarce, and unique patient results will most often fall under the category of “variant of unknown significance.”

RECOMMENDATION

Clinically diagnosed DCM with evidence of probable familial disease: Genetic testing is recommended for the primary purpose of screening family members.

The clinical penetrance of disease and age of onset may be variable in familial DCM, warranting genetic testing as a potential tool for screening family members.

The role of genetic testing in unexplained SCD, sudden cardiac arrest, and the sudden infant death syndrome

SCD is defined as unexpected cardiac death within 1 hour of the onset of symptoms in individuals without a prior known condition that would appear to be fatal.90-91 Despite a complete investigation, autopsy may fail to establish a diagnosis, and the event remains unexplained. The prevalence of these “autopsy negative” cases of SCD has been reported in between 3% of a general young population and 35% in young military recruits.92-94 When SCD occurs in infancy without predisposing or precipitating clinical conditions and with a negative autopsy, the diagnosis of sudden infant death syndrome (SIDS) is applied.95

Similarly, in the survivor of a sudden cardiac arrest (SCA), evaluation may determine that there is a structurally normal heart. This is the clinical equivalent of a negative autopsy and is found in about 5% of cases.

This section describes the background for considering genetic testing in (1) the autopsy negative unexpected SCD victim, (2) the individual with resuscitated SCA, and (3) the infant who experiences SIDS.

Clinical and molecular considerations in unexplained SCD (Table 8)

Recommendations describing the appropriate investigations that are required to establish that an autopsy is negative have been published.96 A thorough assessment to rule out a structural cause of SCD should include a rigorous cardiac
Table 8. The role of genetic testing in unexplained sudden cardiac death, resuscitated sudden cardiac death, and sudden infant death syndrome

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Testing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained sudden death (negative autopsy)</td>
<td>++</td>
<td>Targeted gene screening of retained tissue of the deceased based on evidence of specific genetic syndrome from medical history or evaluation of first-degree relatives</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>In the absence of guiding clinical information, empirical gene screening for multiple possible conditions is not recommended</td>
</tr>
<tr>
<td>Resuscitated sudden cardiac death</td>
<td>++</td>
<td>Targeted gene screening based on results of clinical evaluation of patient or first-degree relatives</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Comprehensive empirical gene screening in the absence of guiding clinical information is not recommended</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
<td>++</td>
<td>Targeted gene screening based on previous history or clinical evaluation of first-degree relatives</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>Gene screening of KCNQ1, KCNH2, and SCN5A may be considered at the discretion of a clinical expert</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Comprehensive empirical gene screening for all possible genetic arrhythmia syndromes is not recommended</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>++</td>
<td>Useful for diagnostic and therapeutic purposes</td>
</tr>
</tbody>
</table>

Recommendations: ++ (strongly recommended), + (recommended), – (not recommended).

Clinical evaluation in the patient with resuscitated SCA

Clinical workup includes resting and signal-averaged ECG, exercise testing, telemetry or Holter monitoring, echocardiography, and magnetic resonance imaging. Coronary angiography is usually performed in adults, with discretionary use of electrophysiological testing including endocardial voltage mapping, cardiac biopsy, and left and right ventricular angiography. Provocative adrenaline and sodium channel blocker infusion should be considered for the potential unmasking of LQTS, CPVT, and Brugada syndrome.

Clinical and molecular considerations in SIDS

SIDS is a multifactorial disorder that causes between 65 and 100 deaths per 100,000 live births. Environmental associations include parental smoking, cosleeping, and the prone sleeping position. International standards define the process and information required to classify an infant death as SIDS.

Routine biochemical analysis of SIDS victims is performed to diagnose metabolic abnormalities that are responsible for about 5% of cases. Mutations associated with LQTS can be found in 2% to 9.5% of victims of SIDS.

In the absence of a pathologic diagnosis, referral of siblings and parents to a physician expert for clinical assessment is warranted and may provide information leading to targeted genetic testing of the deceased and family members.

RECOMMENDATION

Autopsy-negative, unexpected SCD: Genetic testing of retained tissue is recommended only when there is evidence of a clinical phenotype in family members.

In the absence of guiding clinical information, comprehensive screening of all possible genes responsible for inherited arrhythmias is not recommended. Proceeding with genetic testing in the absence of any correlating clinical phenotype may raise significant issues in the management of family members when genetic results of “unknown significance” are identified. When clinical history or family evaluation provides evidence for a specific genetic condition, screening of the appropriate genes should be undertaken in both the proband and the identified affected family member to corroborate clinical suspicion.

RECOMMENDATION

Survivor of SCA: Genetic testing of the survivor should be directed by the results of the survivor’s medical evaluation or that of his or her first-degree relatives.

Comprehensive molecular screening for all possible genetic arrhythmias as part of the medical evaluation is not recom-
mended. Genetic testing should be performed only on the basis of clinical evidence supporting a specific diagnosis.

**RECOMMENDATION**

SIDS: Genetic testing of retained tissue should be directed by history and clinical investigation of any first-degree relatives.

Consideration may be given to screening KCNH2, KCNQ1, and SCN5A under the direction of a clinical expert.

**Conclusion**

The clinical care of patients and families with suspected genetic arrhythmia syndromes may warrant the use of genetic testing. The decision to perform genetic testing should be based on the clinical value of the genetic information and should be performed with consideration of ethical and psychosocial issues. This requires a multidisciplinary approach including qualified arrhythmia specialists and counsellors. Specialized clinics with a focused clinical care approach to inherited arrhythmia syndromes are encouraged, with the aim of discouraging random genetic testing after inadequate evaluation and absence of appropriate counseling. Implicit is the assumption that a specialized clinic approach will provide the most comprehensive and cost-effective management of patients and their families.

The present recommendations are based on contemporary knowledge. The field of cardiovascular genetics is rapidly evolving, and surveillance for future developments in the field by expert panels remains necessary. Health insurance providers and government funding agencies may require restructuring to allow for financial coverage of genetic testing to optimize patient care.

**Supplementary Material**

To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at doi:10.1016/j.cjca.2010.12.078.

**References**


