Yield of Genetic Screening in Inherited Cardiac Channelopathies
How to Prioritize Access to Genetic Testing

Rong Bai, MD; Carlo Napolitano, MD, PhD; Raffaella Bloise, MD; Nicola Monteforte, MD; Silvia G. Priori, MD, PhD

Background—Identification of mutations in cardiac ion channel genes concurs to the diagnosis of long-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. However, because availability of genetic screening is still limited and reimbursement policies are lacking, there is a need of evidence-based criteria to prioritize access to genetic testing for these diseases.

Methods and Results—We determined the yield of genetic testing and cost per positive genotyping in 1394 consecutive probands. Among the 546 patients referred for long-QT syndrome-genes screening, those with clinical diagnosis of long-QT syndrome had the highest yield (64%) and lowest cost (US $8418) for each positive genotyping. Among 798 individuals screened for mutation on the SCN5A gene, the highest yield was obtained in patients with type 1 Brugada syndrome ECG pattern (51 of 405; 13%) corresponding to a cost of US $21 441 per positive genotyping. In conclusive Brugada syndrome patients the presence of atrioventricular block (odds ratio: 3.3, CI: 1.8 to 6.1; \( P = 0.0001 \)) increases the yield (23%) of genotyping and reduces its cost (US $ 11 700). Among 175 patients screened on RyR2 gene, those with documented bidirectional ventricular tachycardia had the highest incidence (62%) of mutations and the lowest cost (US $5263) per positive genotyping. Genetic screening of unselected family members of sudden cardiac death victims and idiopathic ventricular fibrillation survivors is largely ineffective (yield of 9%) and costly (US $71 430 per 1 positive genotyping).

Conclusions—Genotyping can be performed at reasonable cost in individuals with conclusive diagnosis of long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia, and in patients with type I Brugada syndrome ECG with atrioventricular block. These patients should be given priority to access genetic testing. (Circ Arrhythmia Electrophysiol. 2009;2:6-15.)

Key Words: genetics ■ long-QT syndrome ■ catecholaminergic VT ■ Brugada syndrome

Long-QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) are the 3 most prevalent inherited cardiac channelopathies that cause sudden cardiac death (SCD) in young patients with structurally intact heart. In the last decade, several disease genes were discovered and genotype-phenotype studies demonstrated that management of affected individuals and family members can be tailored to the genetic substrate.1–6 Unfortunately, so far there has been a slow introduction of genetic testing into clinical practice: only few research laboratories accept samples for genetic analysis and commercial genotyping is not widely available besides being expensive. The lack of reimbursement policies further discourages the development of genetic assays for cardiac channelopathies.
LQTS, BrS, or CPVT or with a personal or family history of idiopathic ventricular fibrillation (IVF)/cardiac arrest (CA)/SCD referred to our center for molecular diagnosis entered the present study. Clinical profiles and results of genetic analysis were input in a searchable custom-made database; each patient was coded with a unique string of letters and numbers so that patient’s identity was unknown to the investigators. Among the 1394 probands, 1219 met criteria for either a “conclusive diagnosis (CD)” or a “possible diagnosis (PD)” (as defined later) of LQTS, BrS, and CPVT; the remaining 175 cases were either survivors of IVF or family member of premature SCD victim (IVF-FMSCD). In these 175 cases, structural heart disease was unable to indentify despite of intensive clinical investigations including coronary artery angiogram.

Protocol of Genetic Screening and Grouping of Patients

**KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2** genes were analyzed when screening for LQTS using the DHPLC/sequencing method as previously reported,1 SCN5A was the only gene analyzed in BrS screening and **RyR2** was the gene analyzed in CPVT screening.7,8

Patients with CD or PD of LQTS, BrS or CPVT were tested for the corresponding genes. Subjects in the IVF-FMSCD group were screened on the **SCN5A** when IVF/SCD occurred at rest or during sleep, or on LQTS-related and **RyR2** genes whereas the event occurred during stress and emotion. Whenever the amount of DNA available was insufficient to perform a full screening on both LQTS-related genes and the **RyR2** gene, samples were screened for LQTS genes.

The LQTS group included all patients tested for LQTS-related genes and it was divided into 3 subgroups: (1) patients with QTc ≥470 ms were defined as “CD of LQTS (CD-LQTS)”; (2) patients with 440≤QTc<470 ms were defined as “PD of LQTS (PD-LQTS)”; and (3) “IVF-FMSCD” were either family members of victims of premature SCD or survivors of IVF/CA occurring during physical stress or emotion (Figure 1).

The BrS group included patients tested for the **SCN5A** gene and it was divided into 3 subgroups: (1) patients with spontaneous or flecainide/ajmaline induced type 1 BrS ECG configuration4 were defined as “CD of BrS (CD-BrS)”; (2) patients presenting with type 2 or type 3 BrS ECG pattern4 were defined as PD of BrS (PD-BrS); and (3) IVF-FMSCD were either family members of victims of premature SCD or survivors of IVF/CA occurring at rest or during sleep (Figure 2).

CPVT group included patients screened for **RyR2** mutation and were divided into 3 subgroups: (1) patients with documented bidirectional or polymorphic ventricular tachycardia (VT) induced by exercise/emotion were defined as “CD of CPVT (CD-CPVT)”; (2) patients with stress or emotion induced syncopal episodes but no documented bidirectional/polymorphic VT were defined as PD of CPVT (PD-CPVT); and (3) IVF-FMSCD were individuals with normal ECG who were either family members of victims of premature SCD or survivors of IVF/CA occurring during physical stress or emotion (Figure 3).

Definitions and Terms

**Index Case or Proband**

All patients in this study are index cases defined as the first member of each family referred to our center. The term “proband” is used as alternative to “index case” with the same meaning.

**Sudden Cardiac Death**

SCD is defined as an unexpected, unexplained death occurring within 1 hour from the onset of symptoms and manifesting as an abrupt change in a patient’s stable clinical state. “premature SCD” is defined as SCD occurring before age 40.1

**QTc**

QT interval was measured on lead II of standard 12-lead ECG (on lead I or III whenever measurement on lead II was technically difficult or not available) and corrected for heart rate (Bazett’s formula).9

**ECG Configuration and Diagnosis**

An ECG recording showing a J point elevation with coved ST segment elevation ≥2 mm and negative T wave in the right precordial leads is defined a type 1 ECG4 and is diagnostic for BrS. An ECG recording characterized by a saddle-back ST segment elevation ≥2 mm and positive/biphasic T wave (type 2 ECG) or by a saddle-back ST segment elevation ≤1 mm and positive T wave (type 3 ECG) is nondiagnostic4 and indicative of possible presence of BrS.

**Atrioventricular Block**

In the present study, the term atrioventricular block (AVB) refers to a first degree AVB (PR interval >200 ms).
**Mutation**

A mutation is defined as a DNA change that is not present in any of the 300 reference samples (600 alleles) and results in a modification of the protein.

**Positive Genotyping**

Genotyping or genetic testing is considered “positive” when a mutation considered with high probability causative of the inherited cardiac channelopathies was identified.

**Yield of Genetic Testing and Parameters Used for Cost Assessment**

The yield of LQTS, BrS, or CPVT genetic testing, defined as the percentage of patients with positive genotyping, was determined. To estimate the cost of genetic testing, we used the pricing currently adopted by the commercial genotyping company Familion (PGx Health, Clinical Data, Inc, Newton, Mass) corresponding to: US $5400.00 for LQTS screening that includes analysis of KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2 genes; US $4500.00 for BrS and CPVT.
S$2700.00 for BrS (screening of the SCN5A gene); and US $3248.73 for CPVT (screening of the RyR2 gene).10,11

Statistical Analysis
Continuous variables are presented as mean ± SD and were tested for normal distribution with 1-sample Kolmogorov-Smirnov test. Mann-Whitney test was used to compare continuous variables without a normal distribution. Cost per positive genotyping was calculated by the following formula:

Cost per positive genotyping = cost for 1 screening × number of screened patients/number of patients with positive genotyping

As the cost for a specific screening is identical per individual, the comparison of “cost per positive genotyping” was actually equivalent to the comparison of “yield of genetic testing.” These comparisons were performed by using Pearson χ² test. Unpaired t test for independent sample was used to compare continuous variables with normal distribution. Binary logistic regression models were used to identify the predictors of positive genotyping in different subgroups. Statistical analysis was performed using the SPSS software (SPSS 13.0, Chicago, Ill). Two-tailed P < 0.05 was defined as statistical significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Study Population

LQTS Group
Three hundred four of 546 patients (56%) had conclusive LQTS diagnosis (CD-LQTS) and 160 of 546 (29%) had a possible LQTS diagnosis (PD-LQTS). Eighty-two patients in the IVF-FMSCD group were screened for LQTS; half of them (41 of 82) were family members of premature SCD victims and half were IVF/CA survivors (Figure 1, Table 1).

BrS Group
Among 798 patients included in this group, 405 (51%) had a CD-BrS; 248 (31%) had a PD-BrS, and 145 (18%) were IVF-FMSCD; 71 IVF/CA survivors and 74 family members of premature SCD victims (Figure 2, Table 1).

CPVT Group
Of the 175 patients included in this group, 81 (46%) were CD-CPVT, 21 (12%) were PD-CPVT, and the remaining 73 (42%) individuals were classified as IVF-FMSCD: 44 IVF/CA survivors and 29 family members of premature SCD victims (Figure 3, Table 1).

Yield and Cost of Genetic Testing for LQTS, BrS, and CPVT

LQTS Group
Mutations in the 5 LQTS-related genes were identified in 220 of 546 patients (40%), leading to a cost per 1 positive genotyping was US $13 402 in the entire LQTS group (Figure 4). Most of the genotyped individuals (205 of 220; 93%) were heterozygous carriers of a single mutation. The remaining 15 of 220 individuals (7%) were carriers of 2 mutations. Mutations in the KCNQ1 or KCNH2 genes accounted for 85% of positive genotyping. Yield of LQTS genetic testing was much higher in the CD-LQTS patients (64% versus 14% in PD-LQTS and 2% in IVF-FMSCD subgroups). The cost per 1 positive genotyping was US $8418 in CD-LQTS (P = 0.0001 versus PD-LQTS or IVF-FMSCD), US $37 565 in PD-LQTS and US $221 400 in IVF-FMSCD (P = 0.008 versus PD-LQTS) (Figure 4).

BrS Group
Genetic screening of SCN5A in these patients identified a mutation in 65 of 798 subjects (8%) with a cost per 1 positive genotyping at US $33 148 (Figure 5): 51 of 405 patients (13%) with type1 BrS ECG configuration (CD-BrS) were genotyped on SCN5A, whereas only 11 of 248 patients with PD-BrS (4%) carried a mutation. Among individuals in the IVF-FMSCD subgroup, the yield of SCN5A screening was 2%. The cost per positive genotype in BrS was US $21 441 for CD-BrS, US $60 872 for PD-BrS (P = 0.001 versus

<table>
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<th>Table 1. Demographics of Study Population</th>
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<tr>
<td>Long-QT syndrome (LQTS) (N = 546)</td>
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<tr>
<td>Male gender (%)</td>
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<tr>
<td>Age (y)</td>
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<tr>
<td>Grouping based on QTc interval</td>
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<td>CD-LQTS (%) ; QTc (ms)</td>
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<td>PD-LQTS (%) ; QTc (ms)</td>
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<tr>
<td>IVF-FMSCD (%) ; QTc (ms)</td>
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<tr>
<td>Family history of SCD (%)</td>
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<td>Syncope (%)</td>
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<td>Cardiac arrest (%)</td>
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<tr>
<td>Positive genotyping (%)</td>
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<tr>
<td>Brugada syndrome (N = 798)</td>
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<tr>
<td>Male gender (%)</td>
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<td>Age (y)</td>
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<td>Grouping based on ECG configuration</td>
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<tr>
<td>CD-BrS (%)</td>
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<td>PD-BrS (%)</td>
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<td>IVF-FMSCD (%)</td>
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<td>Family history of SCD (%)</td>
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<td>Cardiac arrest (%)</td>
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<td>Conduction abnormalities (%)†</td>
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<td>Positive genotyping (%)</td>
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<td>Catecholaminergic polymorphic VT (N = 175)</td>
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<td>Male gender (%)</td>
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<tr>
<td>Age (y)</td>
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<tr>
<td>Grouping based on clinical manifestation</td>
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<tr>
<td>CD-CPVT (%)</td>
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<td>PD-CPVT (%)</td>
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<td>IVF-FMSCD (%)</td>
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<td>Family history of SCD (%)</td>
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<tr>
<td>Cardiac arrest (%)</td>
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<td>Positive Genotyping (%)</td>
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CD indicates conclusive diagnosis; PD, possible diagnosis; CPVT, catecholaminergic polymorphic ventricular tachycardia; FMSCD, family members of sudden cardiac death victims; IVF, idiopathic ventricular fibrillation. *P = 0.0001 for the Mann-Whitney test for QTc. †Conduction abnormalities included atrioventricular block and/or right bundle-branch block.
CD-BrS) and US $130 500 for IVF-FMSCD (P = 0.0001 versus CD-BrS; P = 0.348 versus PD-BrS) (Figure 5).

**CPVT Group**

A RyR2 mutation was detected in 50 of 81 patients with CD-CPVT (62%), in 1 of 21 case with PD-CPVT (5%), and in 11 of 73 individuals (15%) from IVF-FMSCD subgroup. The estimated cost per 1 positive RyR2 genotyping was US $5263 in CD-CPVT group, US $68 223 in PD-CPVT (P = 0.0001 versus CD-CPVT), and US $21 560 in IVF-FMSCD group (P = 0.0001 versus CD-CPVT; P = 0.381 versus patients with PD-CPVT). For the entire CPVT group, the yield of genetic testing was 35% (62 of 175) and cost per 1 positive genotyping was US $9170 (Figure 6).

**IVF-FMSCD Category**

Of all 175 cases with IVF-FMSCD, mutation on either of LQTS-related genes, SCN5A or RyR2 was identified in 15 patients, one of whom was overlapped in both LQTS and BrS groups. Accordingly, the yield of genetic testing in this IVF-FMSCD entity was 9% (15 of 175) regardless of etiology and the cost per 1 positive genotyping was US $71 430 (Figure 7).

**Predictors of Positive LQTS, BrS, and CPVT Genetic Testing**

Binary logistic regression analysis was performed to identify indicators of positive genotyping in each disease (Table 2).

**LQTS Group**

Logistic analysis was conducted in CD-LQTS and PD-LQTS groups but not in IVF-FMSCD as too few mutation carriers were present in this group. We entered in the model the following variables: gender, family history of SCD, syncope, and occurrence of CA. However, none of these variables was associated with an increased rate of positive genotyping.

**BrS Group**

We ran logistic regression in patients with CD-BrS and PD-BrS by including the following variables: gender, family history of SCD, syncope, occurrence of CA, and presence of AVB at ECG. The only variable predicting the identification of a mutation in the SCN5A gene among patients with type 1 BrS ECG was the presence of AVB (odds ratio [OR], 3.3; CI, 1.8 to 6.1; P = 0.0001). When the analysis was conducted in patients with PD-BrS, results indicated that in addition to AVB (OR, 11.0; CI, 2.6 to 46.7; P = 0.001), a history of
syncope was associated with higher probability of carrying a mutation in the \textit{SCN5A} gene (OR, 7.8; CI, 1.5 to 40.9; \(P = 0.015\)). Twenty-seven of 117 CD-BrS (23%) with AVB patients carried a \textit{SCN5A} mutation lowering the cost per 1 positive genotyping to US $11,700; whereas only 24 of 288 CD-BrS (8%) without AVB cases were identified having \textit{SCN5A} mutation resulting in a cost per positive genotyping at US $32,400 (Figure 8). Interestingly, in the small group of patients with PD-BrS and AVB, the yield of genetic testing was as high as 27% (6 of 22), which was associated with a cost per 1 positive genotyping at US $9900; whereas only 5 of 226 individuals with PD-BrS (2%) without AVB were \textit{SCN5A} mutation carriers and the cost per 1 positive genotyping in this subgroup was US $12,2040 (\(P = 0.0001\) versus PD-BrS with AVB). Analysis was not performed in PD-CPVT and IVF-FMSCD individuals because too few mutation carriers were present in these subgroups.

\textbf{Discussion}

Screening for mutations in genes that encode cardiac ion channels associated with LQTS, BrS, and CPVT is primarily sought in clinically affected patients to tailor risk stratification and management and to further identify family members.\textsuperscript{1–7} The importance of knowing the molecular substrate in patients with inherited cardiac channelopathies is recognized and highlighted in the guidelines for the prevention of SCD developed by the American Heart Association, the American College of Cardiology, and the European Society of Cardiology.\textsuperscript{12} However, genetic analysis is not yet available at most clinical centers and it is still mainly performed in finite research laboratories. Furthermore, the development of diagnostic genotyping is limited by the fact that in most countries reimbursement policies have not been defined. Thereby, the few structures that provide genetic testing are
supposed to focus on screening patients with profiles indicating a higher probability to be positively genotyped. On the contrary, however, we have recently observed an increase in the number of requests of genetic testing to confirm uncertain clinical diagnosis of inherited cardiac channelopathies, to identify the cause of CA in individuals with a structurally intact heart and to screen family members of victims of premature SCD with negative autopsy. The yield of genotyping in these patients remains unknown.

Data derived from our large genotyping practice show that patients with a CD of a cardiac ion channelopathy represent only half of the population referred for genotyping although account for 80% to 90% of final positive molecular diagnosis (mutation identified). Although a mutation is identified in >60% of patients with CD-LQTS or CD-CPVT at an acceptable cost per positive genotyping (US $8418 and US $5263, respectively; Figures 4 and 6), patients with type I BrS ECG have a much lower yield of genetic testing (13% with a cost per positive genotyping of US $21 441; Figure 5). Nevertheless, if the screening was limited in patients with CD-BrS and AVB, the yield of genotyping was considerably improved to 23% and the cost per positive genotyping decreased to US $11 700 (Figure 8). This observation is in agreement with the report by Smits et al. who found that the SCN5A-related patients have greater defects in impulse propagation (longer PR and HV intervals at baseline and greater QRS prolongations on sodium channel blocker challenge) than non-SCN5A-related patients. Considering that mutation screening in BrS is important to identify affected family members and not for directing management, it seems reasonable to prioritize access to genotyping those patients with type 1 BrS ECG and AVB.

The results of genotyping in patients in whom the diagnosis of LQTS, BrS, or CPVT is suspected but cannot be conclusively established prompt several considerations. Obviously, in this setting the answer provided by genetic testing is clinically important despite the considerable costs that range between US $37 565 per 1 positive genotyping in LQTS, to US $60 872 in BrS and to US $68 223 in CPVT. Facing the decision of whether it is reasonable to apply genotyping in these patients, it is critical to remember that a negative result of genetic testing in any of the 3 arrhythmogenic syndromes does not exclude the presence of the disease and that, therefore, only a positive genetic diagnosis is informative. Furthermore, cost is not the only determinant of whether it is worth offering genetic screening: the signifi-
cance of a positive genotyping is in fact clearly different in BrS versus in LQTS. In the latter, identification of a mutation directs treatment strategy, and therefore it may be worth accepting a higher expenditure given the benefit derived from being able to implement gene-specific therapies. Based on these considerations, it seems appropriate to recommend that whenever a diagnosis to LQTS, BrS, or CPVT is suspected but unconfirmed, clinical evaluation of family members prior to genetic screening should be undertaken. Evaluation of family members may allow identifying clinically affected individuals who should be then referred for molecular testing as proband of that family and with a higher probably of being successfully genotyped. Whenever the screening of family members is not informative, the clinician should weight the cost of the analysis versus the value of a positive genotyping in the patient and his/her family.

Among survivors with IVF/CA and family members of SCD victims, genetic screening is often the “last hope” to establish the cause of IVF/CA or SCD. Unfortunately, our data show that yield of genetic analysis in this population is very low for both LQTS (2% associated with a cost per positive genotyping of US $221 400) and BrS (2% associated with a cost per positive genotyping of US $130 500) whereas it has a relative higher yield and more reasonable cost in CPVT (15% of genotyped individuals corresponding to a cost per positive genotyping of US $21 560). Putting together, the yield of genetic testing was only 9% in all 175 IVF-FMSCD cases with a cost per 1 detected-mutation at US $71 430. The reasons accounting for the higher yield of RyR2 screening in IVF-FMSCD may be related to the high lethality of CPVT and to the fact that SCD is often the first manifestation of the disease. It seems, therefore, reasonable to recommend screening RyR2 gene for mutation in IVF/CA survivors when the event occurred during exercise/emotion and in family members of SCD victim when the proband died during a high adrenergic state.

**Conclusion**

Our data suggest that genetic testing can be performed at reasonable cost in individuals with conclusive clinical diagnosis of LQTS and CPVT; and therefore these patients should have a priority to access genetic screening. Conversely, screening for SCN5A mutation in unselected patients with diagnosis of BrS is less cost effective; however, the yield of genotyping increases substantially in patients with type I BrS ECG and AVB suggesting that this subset of patients with
BrS should be screened. Finally, our data show that, unexpectedly, the screening of family members of SCD victim and of IVF/CA survivors on LQTS and BrS genes is largely ineffective and costly. On the contrary, the search for mutations on the \textit{RyR2} gene in the entity of family members of SCD victims and IVF survivors with effort/emotion-related events leads to an acceptable yield and cost per positive genotyping.

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**Disclosures**

None.

**References**

There is a rapid growth in the request of genetic screening for long-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. Genetic testing is often offered to all patients irrespective of whether they are “clearly” affected or “possibly” affected by one of such diseases, and even family members of unexplained sudden death victims and idiopathic ventricular fibrillation survivors are directed to genotyping in attempt to clarify the substrate of the arrhythmic event. To help clinicians and third party payers prioritize access to genotyping when resources are limited, it becomes critical to draw some cost/benefit considerations. We retrospectively analyzed data of 1394 consecutive probands to determine the yield of genetic screening and cost per positive genotyping in patients with either a conclusive or a possible diagnosis of long-QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia and in family members of unexplained sudden death victims and idiopathic ventricular fibrillation survivors. We demonstrated that genotyping has the highest cost efficacy in individuals with a clinical conclusive diagnosis of long-QT syndrome or catecholaminergic polymorphic ventricular tachycardia. The yield and cost of genotyping is also reasonable in patients with type I Brugada syndrome ECG and atrioventricular block. However, genotyping family members of unexplained sudden death victims and idiopathic ventricular fibrillation survivors had low yield. Family history evaluation might be useful to better target genetic screening.
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