Cost-Effectiveness of Genetic Testing in Family Members of Patients With Long-QT Syndrome

Marco V. Perez, MD; Narmadan A. Kumarasamy, MPH; Douglas K. Owens, MD, MS; Paul J. Wang, MD; Mark A. Hlatky, MD

**Background**—Family members of patients with established long-QT syndrome (LQTS) often lack definitive clinical findings, yet may have inherited an LQTS mutation and be at risk of sudden death. Genetic testing can identify mutations in 75% of patients with LQTS, but genetic testing of family members remains controversial.

**Methods and Results**—We used a Markov model to assess the cost-effectiveness of 3 strategies for treating an asymptomatic 10-year-old, first-degree relative of a patient with clinically evident LQTS. In the genetic testing strategy, relatives undergo genetic testing only for the mutation identified in the index patient, and relatives who test positive for β-blockers. This strategy was compared with (1) empirical treatment of relatives with β-blockers and (2) watchful waiting, with treatment only after development of symptoms. The genetic testing strategy resulted in better survival and quality-adjusted life years at higher cost, with a cost-effectiveness ratio of $67 400 per quality-adjusted life year gained compared with watchful waiting. The cost-effectiveness of the genetic testing strategy improved to less than $50 000 per quality-adjusted life year gained when applied selectively either to (1) relatives with higher clinical suspicion of LQTS (pretest probability 65% to 81%), or to (2) families with a higher than average risk of sudden death, or to (3) larger families (2 or more first-degree relatives tested).

**Conclusions**—Genetic testing of young first-degree relatives of patients with definite LQTS is moderately expensive, but can reach acceptable thresholds of cost-effectiveness when applied to selected patients. (Circ Cardiovasc Qual Outcomes. 2011;4:76-84.)

**Key Words:** long-QT syndrome ■ cost-benefit analysis ■ genetics

The congenital long-QT syndrome (LQTS), which is characterized by prolongation of the QT interval on a standard ECG, is associated with syncope and sudden cardiac death. Linkage and mutational analyses have documented >450 mutations in 10 genes that are associated with various forms of LQTS. Although LQTS is relatively uncommon (estimated prevalence of 1 in 2000), it remains an important cause of sudden death in children, adolescents, and young adults.

The diagnosis of LQTS can be difficult, because prolongation of the QT interval is neither a sensitive nor specific finding, and classic manifestations, such as torsade de pointes may be lacking. The Schwartz score has been used to classify the probability that an individual has LQTS; a Schwartz score of ≥4 in family members is highly specific, but not sensitive for the identification of LQTS. Identification of the 3% to 4% of individuals who will die suddenly from LQTS can be even more challenging. Age, sex, degree of QT prolongation, and genetic subtype are associated with sudden cardiac death, but the risk of sudden death cannot be fully explained by these variables. Use of β-blockers and limitation of strenuous exercise significantly reduce sudden death in LQTS, and high-risk individuals may benefit from an implantable cardioverter-defibrillator (ICD).

In most cases, LQTS follows an autosomal dominant pattern of inheritance, and is not associated with other congenital abnormalities. The exclusion of LQTS in family members solely on clinical grounds has been difficult, and up to 6% of family members with normal QT intervals may ultimately have syncope or cardiac arrest. Recent studies have shown that one-third or more of family members who do not meet clinical criteria for LQTS nevertheless carry the apparently causal mutation.

Sequencing of the exons in 5 genes (KCNQ1, HERG, SCN5A, ANK2, and KCNE1) identifies a mutation in approximately 75% of individuals with definite LQTS by the Schwartz criteria. Although genotyping is a valuable research tool, its application in clinical practice remains uncertain. The use of genetic testing in relatives of patients with LQTS has become controversial, is expensive, and typically is not covered by health insurance.
Because clinical trials of LQTS and other rare conditions are difficult to perform, simulation studies and economic analysis can provide insight into optimal clinical treatment. A prior study of LQTS in symptomatic individuals suggested that determination of the genetic subtype might be cost-effective if it could identify the optimal treatment strategy, but this study did not assess genetic testing in asymptomatic relatives of patients with LQTS, and did not account for the effects of treatment on quality of life. We sought to determine whether genetic testing is cost-effective in first-degree relatives of patients with established LQTS.

**WHAT IS KNOWN**

- Long-QT syndrome (LQTS) is an inherited disorder associated with mutations in one of several genes.
- Family members of a patient with LQTS may inherit a mutation, yet lack diagnostic symptoms or signs.
- The role of genetic testing for family members of LQTS patients remains controversial.

**WHAT THE STUDY ADDS**

- Compared with watchful waiting, genetic testing of first-degree family members of patients with LQTS may lead to better outcomes at a reasonable cost, particularly among family members with an “intermediate pretest probability” of LQTS.
- Empirical β-blocker therapy leads to lower mortality but worse quality of life than genetic testing. Genetic testing appears to be the most cost-effective approach.

**Methods**

**The Decision Model**

We developed a Markov decision model to assess the clinical outcomes and cost-effectiveness of genetic testing for a 10-year-old, first-degree family member of an index case (ie, proband) who has definite clinical evidence of the LQTS (Schwartz score ≥4). The model was designed to assess optimal treatment of the family members. We used the model to simulate the outcomes of a cohort of family members treated with 1 of 3 alternative strategies: (1) genetic testing, (2) empirical β-blocker treatment, and (3) watchful waiting with treatment only after development of symptoms (Figure 1).

In the watchful waiting strategy, family members were treated conservatively and monitored for development of symptoms suggestive of LQTS. Individuals who had minor symptoms (ie, palpitations, syncope, or dizziness) were started on β-blockers, whereas individuals with major symptoms (ie, torsade de pointes, resuscitated cardiac arrest) were treated with an ICD.

In the empirical β-blocker strategy, all first-degree family members were treated with β-blockers regardless of the degree of clinical suspicion for LQTS. Patients on β-blockers who had recurrent syncope or resuscitated cardiac arrest were given ICDs.

In the genetic testing strategy, the index case was first tested by exonic sequencing of 5 genes most often associated with LQTS. If no mutation was identified in the index case, first-degree relatives were treated with the “watchful waiting” strategy. If a presumably causal mutation was identified in the index case, the first-degree relatives then underwent genetic testing for that same mutation. Family members found to have this mutation on genetic testing were treated with β-blockers, whereas family members without this mutation were not treated further.

The model was based on several assumptions about the heritability of LQTS and the properties of the genetic test. The analysis was restricted to families with the Romano Ward Syndrome (ie, no deafness) and assumed that 50% of family members inherited the casual mutation, consistent with autosomal dominant transmission. We assumed that only individuals who inherited the causal mutation were at risk for LQTS-related symptoms and sudden death. On the basis of current data, we assumed that only 75% of probands with definite LQTS would have a presumably causal mutation identified. Importantly, we assumed that genetic testing had imperfect clinical predictive power, in that 10% of the putative mutations identified by sequencing were not the actual biological cause of LQTS.

We tested the effect on model results of variations in the pretest probability of the diagnosis, starting age, sex, annual risk of death due to LQTS, response to treatment based on genetic subtype, rates of compliance with treatment based on genetic results, and a decrease in risk of sudden death with increasing patient age. We assumed 100% compliance of β-blocker use in the base case. To account for varying degrees of compliance with β-blocker therapy, we also created a model in which only a fraction of family members assigned to β-blocker use took the β-blockers.

**Event Rates**

In all 3 scenarios, the subsequent clinical course of family members was simulated using the Markov model, with transition probabilities for the development of symptoms, sudden death due to LQTS, or death from unrelated causes. To estimate the risks of developing minor symptoms (palpitations, dizziness or syncope), major symptoms (aborted sudden death) or LQTS-related mortality, we used previously published prospective cohort studies (Table 1). In the base case, we assumed that β-blockers would reduce rates of cardiovascular events by 50%, based on prior matched time period analysis. We estimated that ICDs would reduce the rate of sudden death by 90%. We assumed the risks of sudden death and symptoms due to LQTS remained constant over follow-up and that the rate of non-LQTS death equaled that of the age-matched US population. These parameters were varied in a series of sensitivity analyses.

**Costs**

We analyzed medical costs from a societal perspective, adjusted to 2008 dollars (Table 1). The costs of drug therapy were based on current retail costs of generic drugs. The cost of hospitalizations, ICD implantation, and clinic visits were based on Medicare reimbursement levels. The cost of genetic testing was assumed as that of the manufacturer of the commercially available test (FAMILION, PGxHealth, New Haven, Conn). All health benefits and costs were discounted at a 3% per annual discount rate, consistent with established recommendations.

**Quality of Life**

The model included quality-of-life adjustments for treatment with β-blockers and with ICD implants. Patients on β-blockers were assigned a utility of 0.96 and patients with an ICD and β-blockers a utility of 0.94, whereas asymptomatic patients on neither treatment had a utility of 1.0.

**Cost-Effectiveness Calculation**

The cost-effectiveness of 2 alternative strategies was calculated as the difference in costs divided by the difference in either life-years or quality-adjusted life-years (QALY’s). Results were rounded to the nearest $100 per additional (quality-adjusted) life-year.

**Sensitivity Analysis**

We assessed the effect of uncertainties in model parameters by performing sensitivity analyses using a range of plausible values for event rates, costs, and utilities.
Results

Base Case Analysis

The preferred strategy depended on whether quality of life on treatment was included in the model (Table 2). When the effect of quality of life was ignored, the strategy of empirical β-blocker treatment led to the highest life expectancy and had a cost-effectiveness ratio of $19,900 compared with the watchful waiting strategy. When the effect of quality of life was included in the analysis, however, the genetic testing strategy led to the best outcomes, with higher QALYs and costs than either the watchful waiting strategy or the empirical β-blocker strategy (Table 2). The cost-effectiveness of the genetic testing strategy compared with the watchful waiting strategy was $67,400 per QALY. When quality of life was considered, the empirical β-blocker strategy led to higher costs and worse clinical outcomes (ie, lower QALYs) than the watchful waiting strategy, and was therefore “dominated.”

The end states of a hypothetical cohort followed for 60 years (Table 3) show that although the empirical β-blocker strategy was most effective in reducing sudden death caused by LQTS, it also led to treatment of the most patients with β-blockers and consequently led to a lower overall quality of life. The genetic testing strategy led to fewer sudden deaths caused by LQTS compared with the watchful waiting strategy and to treatment of only a few more patients with β-blockers or an ICD (Table 3). In all strategies, approximately one-third of patients were projected to receive an ICD implant over a 60-year follow-up period.

Sensitivity Analysis

The projected cost-effectiveness of the genetic testing strategy relative to watchful waiting was highly sensitive to both the annual risk of death and the pretest probability of LQTS in first-degree relatives of the index case (Figure 2). The model results were also sensitive to the probability of developing symptoms, the reduction in quality of life due to β-blockers, and the efficacy of drug therapy.

In the base case analysis, we assumed the pretest probability of LQTS was 50%, consistent with a pattern of autosomal dominant inheritance. In practice, this initial pretest probability estimate can be revised upward or downward, based on an individual’s clinical characteristics (symptoms, QT interval), and this variation had a strong effect on the cost-effectiveness of genetic testing (Figure 3A). In family members with a low pretest probability of LQTS (eg, Schwartz score of 1), watchful waiting was the most cost-effective strategy. By contrast, in family members with an intermediate pretest probability (eg, Schwartz score of 2 or 3), genetic testing was the most cost-effective strategy, with a cost-effectiveness ratio of $50,000 per QALY for a pretest probability between 65% and 81%. However, for patients with the highest pretest probability of LQTS (eg, Schwartz score ≥4), empirical β-blocker treatment was the most cost-effective strategy (Figure 3A).

The model results were also very sensitive to variations in the risk of death caused by LQTS. When the annual risk of death was increased to 0.48% per year or more (ie, >1.2 times the base case estimate of 0.4% per year), the cost-effectiveness of genetic testing improved to less than $50,000 per QALY for a pretest probability between 65% and 81%. However, for patients with the highest pretest probability of LQTS (eg, Schwartz score ≥4), empirical β-blocker treatment was the most cost-effective strategy (Figure 3A).

Figure 1. The clinical decision model: Clinical decision tree used to create the Markov model. Watchful waiting of the family member was compared with initial treatment of the family member with β-blockers and genetic testing in the family. Palpitations, dizziness, and syncope were considered minor symptoms. Aborted sudden cardiac death and ventricular arrhythmias were considered major symptoms. Patients with ICD therapy continued to take β-blockers.
if the risk of sudden death from LQTS was assumed to diminish by 2.5% per year over follow-up, the incremental cost-effectiveness of genetic testing worsened to $93,900.

The base case model assumed that genetic testing provided no pharmacogenomic information, and thus would not change the choice of drug treatment or its efficacy. If the specific genotype predicted response to drug treatment, and if genetically guided drug treatment had a relative risk reduction of 60% rather than the base case estimate of 50%, the cost-effectiveness of genetic testing would improve to $42,700 per QALY (Figure 3C). If the efficacy of genotype-guided drug therapy were improved further to 80%, the cost-effectiveness of the genotyping strategy would be $13,600 per QALY.

The reduction in quality of life as the result of β-blocker therapy had a substantial impact on the cost-effectiveness of the genetic testing strategy (Figure 3D). In the base case analysis, we assumed patients treated with β-blockers would have a quality-of-life decrement of 0.04. If β-blockers had a minimal effect on quality of life (decrement of 0.01 or less), empirical β-blocker treatment would be the most cost-effective strategy. Similarly, if the quality-of-life effects of treatment were ignored completely (ie, utility decrement of 0), empirical β-blocker therapy would be the preferred strategy, with an incremental cost-effectiveness ratio of $19,900 per life-year added compared with the watchful waiting strategy.

### Table 1. Assumptions of the Model

<table>
<thead>
<tr>
<th>Clinical Events</th>
<th>Value</th>
<th>Sensitivity Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of minor symptoms</td>
<td>5%/y</td>
<td>0% to 10%</td>
<td>12,19,37</td>
</tr>
<tr>
<td>Risk of major symptoms</td>
<td>0.8%/y</td>
<td>0% to 1.6%</td>
<td>12,17,19,21,37</td>
</tr>
<tr>
<td>Risk of death</td>
<td>0.4%/y</td>
<td>0.3% to 0.5%</td>
<td>12,17,19,21,37</td>
</tr>
<tr>
<td>Risk reduction of death/symptoms on β-blockers</td>
<td>50%</td>
<td>30% to 70%</td>
<td>21,23</td>
</tr>
<tr>
<td>Reduction of risk of death by ICDs</td>
<td>90%</td>
<td>70% to 99%</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs, Item</th>
<th>Cost (US$)</th>
<th>Sensitivity Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers, yearly</td>
<td>300</td>
<td>0–600</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>15 000</td>
<td>0–30 000</td>
</tr>
<tr>
<td>ICD maintenance, yearly</td>
<td>2000</td>
<td>0–4000</td>
</tr>
<tr>
<td>Genetic testing, proband</td>
<td>5400</td>
<td>0–5400</td>
</tr>
<tr>
<td>Genetic testing, family</td>
<td>900</td>
<td>0–900</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of Life, State</th>
<th>Utility</th>
<th>Sensitivity Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>On β-blocker</td>
<td>0.96</td>
<td>0.94–0.99</td>
</tr>
<tr>
<td>ICD implanted</td>
<td>0.94</td>
<td>0.92–0.99</td>
</tr>
</tbody>
</table>

### Table 2. Results of Cost-Effectiveness Analysis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Efficacy (Life-Years)</th>
<th>Incremental Cost-Effectiveness (Cost/Life-Years)</th>
<th>Incremental Efficacy (QALY)</th>
<th>Incremental Cost-Effectiveness (Cost/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No initial treatment</td>
<td>$16 048</td>
<td>25.65</td>
<td>$19 900 (Dominated)</td>
<td>25.16</td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>$24 563</td>
<td>26.07</td>
<td>$19 900 (Dominated)</td>
<td>24.89 (Dominated)</td>
<td></td>
</tr>
<tr>
<td>Genetic testing</td>
<td>$25 467</td>
<td>25.94</td>
<td>$67 400</td>
<td>25.30</td>
<td></td>
</tr>
</tbody>
</table>

Results represent the analysis performed using base case values with subjects starting at age 10 and followed for 60 years. Efficacy is rounded to 4 significant figures and cost-effectiveness is rounded to 3 significant digits. Costs are presented in US dollars.

Minor symptoms include palpitations, dizziness, and syncope; major symptoms include aborted sudden cardiac death.

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The incremental cost-effectiveness of the genetic testing strategy improved as the number of first-degree family members to be tested increased. The cost-effectiveness ratio improved from $67,400 per QALY for testing 1 family member to $48,100 for testing 2 family members, to $41,700 for testing 3 family members, and to $38,400 per QALY for testing 4 family members, largely because the $5,400 fixed cost of genetic testing of the index case would be spread over more subjects.

The base case model assumed the patient considered for genetic testing was 10 years old and followed for 60 years to age 70. The cost-effectiveness of genetic testing became much less favorable if the family member was tested at a later age or followed for a shorter period of time (Table 4). The base case also assumed an average mortality rate of 0.4% per year when male and female patients were combined. There is evidence, however, that after age 20, the risk of sudden death in females rises, whereas that of the males falls. If the rate of death in female patients increases to 0.6% per year and that of males decreases to 0.2% per year after age 20, the cost-effectiveness ratio worsens for males ($91,200 per QALY) and improves for females ($54,400) (Table 4).

Model results were not greatly affected by assumptions about compliance. If patient compliance were reduced to 80% for all patients from the base case assumption of 100%, the incremental cost-effectiveness ratio was relatively unchanged (Table 4). If compliance with β-blockers were higher among those with a positive genetic test (90%) than among those treated empirically (80%), the cost-effectiveness of the genetic testing strategy would be improved only slightly, to $65,100 per QALY.

### Discussion

Our analysis suggests that genetic testing of young first-degree family members of patients with clinically established LQTS may be cost-effective, particularly if applied selectively. The overall cost-effectiveness of genetic testing was moderately expensive, at $67,400 per QALY, but improved to less than $50,000 per QALY when applied to patients with higher clinical suspicion of LQTS (ie, pretest probability between 65% and 81%). The cost-effectiveness of genetic testing was also less than $50,000 per QALY when used in individuals with a stronger family history of sudden death from LQTS or in larger families (2 or more first-degree relations to be tested).

The genetic testing strategy was cost-effective in this study primarily because it led to earlier drug treatment for family members who inherited an LQTS mutation, which reduced the number of sudden cardiac deaths compared with the watchful waiting strategy (Table 3). Furthermore, by targeting use of β-blockers to only those family members with the mutation, the genetic testing strategy minimized the adverse effects and costs of drug treatment compared with empirical treatment. Family members who have a negative genetic test would also not have lifestyle restrictions (eg, avoiding exercise or competitive sports), nor would they undergo medical

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**Table 3. End State of Hypothetical Cohort**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>No Interventions</th>
<th>β-Blockers</th>
<th>ICD and β-Blockers</th>
<th>LQTS Sudden Cardiac Death</th>
<th>Other Deaths</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>No initial treatment</td>
<td>38.4</td>
<td>1.9</td>
<td>31.4</td>
<td>6.5</td>
<td>21.7</td>
<td>28.3</td>
</tr>
<tr>
<td>β-blocker</td>
<td>0</td>
<td>39.8</td>
<td>33.7</td>
<td>4.2</td>
<td>22.2</td>
<td>26.5</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>35.5</td>
<td>4.4</td>
<td>33.0</td>
<td>5.0</td>
<td>22.1</td>
<td>27.1</td>
</tr>
</tbody>
</table>

Values are percentage of subjects in any given state who were hypothetically followed for 60 years starting at age 10.

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**Base Case (Range)**

- **Probability of Death**
  - Pretest probability
  - Efficacy of BB
  - Probability of Minor Sx
  - Utility of BB
- **Efficacy Targeted Therapy**
  - Cost of Genetic Test
  - Gender
- **Cost of ICD Maint**
- **Specificity of Genetic Test**
- **Number of Family Members**
- **Utility of ICD**
- **Probability of Major Sx**
- **Efficacy of ICDs**
- **Sensitivity of Genetic Test**
- **Cost of BB**
- **Cost of ICD**
- **BB Compliance**
- **Prob of Recurrent Sx on BB**

**Variable**

- **ICE ($/QALY)**

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**Figure 2. Tornado plot of sensitivity analyses comparing watchful waiting with the genetic testing strategy.** The Markov model was most sensitive to the pretest probability of the family member being affected as well as the probability of developing symptoms and efficacy of β-blockers over the range of values selected. The ranges selected were thought to be clinically relevant values and are denoted in the left to right configuration as depicted in the diagram. Vertical dashed line represents the base case values used in the model. Prob indicates probability; Sx, symptoms; BB, β-blockers; Maint, maintenance; ICE, incremental cost-effectiveness; QALY, quality-adjusted life-years; Spec, specificity; and Sens, sensitivity.
monitoring and repeated evaluations for minor symptoms suggestive of LQTS. Our analysis did not incorporate likely cost savings from avoiding these additional clinic visits, ECGs, and other tests as a result of a negative genetic test for LQTS, which would only have improved the estimated cost-effectiveness of the genetic testing strategy.

Importantly, we found that the cost-effectiveness of genetic testing was strongly influenced by the pretest probability of the family member having LQTS (Figure 3A). The Schwartz score and Keating criteria use ECG data and other demographic and clinical criteria to categorize the pretest probability that an individual has LQTS. Although the accuracy of the pretest probability values attached to these scores is not well established, these scores nevertheless provide a basis for selective genetic testing based on the level of clinical suspicion of LQTS. Individuals with no symptoms or signs of LQTS apart from a positive family history (ie, Schwartz score of 1) have a pretest probability below the average of 50%, and genetic testing does not appear to be cost-effective compared with watchful waiting in such individuals. Patients who have nonspecific symptoms or a mildly prolonged QT interval (ie, Schwartz score of 2 or 3) have an intermediate probability of LQTS, and genetic testing appears to be the optimal strategy in such patients. Our model suggests that genetic testing of patients with a pretest probability of LQTS between 65% and 81% has a cost-effectiveness ratio of <$50 000/QALY. However, for patients with very high clinical suspicion of LQTS (Schwartz score ≥4, equivalent to a pretest probability above 82%), β-blocker treatment without genetic testing appears to be the optimal strategy. Because clinical evaluation to assess the pretest probability of LQTS is readily performed, these results suggest that a strategy of targeted genetic screening of first-degree relatives will be more cost-effective than a strategy of routine genetic screening.

The prognosis of LQTS also varies among families, and our model suggests that this variation affects the value of genetic testing. Some families have a strong history of sudden cardiac death, presumably because they carry an LQTS mutation that is associated with a worse prognosis. Our base case model incorporated an “average” risk of death caused by LQTS (0.4% per year). In families with risk of death that is higher than this average by 1.2 times or more, our model suggests that genetic testing would be particularly cost-effective (Figure 3B and Table 4). Conversely, in families with a lower than average risk (who presumably carry a lower risk LQTS genetic variant), genetic testing appears to be less cost-effective than watchful waiting.

Our base case model assumed that identification of the specific mutation present in a patient would not affect the choice of drug therapy or improve the efficacy of treatment. The cost-effectiveness of genetic testing would be much more favorable if information about the specific genotype could improve treatment efficacy through “personalization” of the treatment.
have been reported as low as 84% in patients with established LQTS.52 Compliance in family members without established disease has not been as well studied and probably would be lower.

One caveat about the genetic testing strategy is that the identification of a mutation in 1 of the 5 genes associated with LQTS does not necessarily prove that the identified genetic variant is actually the cause of LQTS in the proband. Although genetic sequencing has high analytic validity in determining an individual’s DNA sequence, the clinical validity of classifying mutations as presumably causal is imperfect.36,50 Few of the 450 described mutations in LQTS subjects have been evaluated for their functional effects using in vitro tests. Consequently, it is possible that in some patients the genetic variant identified by DNA sequencing may be a benign polymorphism rather than the true causal mutation. Ten genes have been associated with LQTS, but the current genetic test sequences only the exonic regions of 5 of these genes. If the true causal mutation occurs in a noncoding region, or if the functional impact of a variant is not assessed correctly, the genetic test could yield false-positive results. In this regard, it is notable that some patients have 2 genetic variants in a LQTS associated gene, only 1 of which may actually be the causal mutation. Our model has assumed that in 10% of families, the identified variant is not the “causal mutation.” Consequently, the genetic testing strategy in our model has a slightly higher number of sudden deaths due to LQTS than the empirical β-blocker strategy. Despite the possibility of a false-negative result, the genetic testing strategy was still cost-effective because avoiding unnecessary β-blocker use in half of the tested population gains more QALYs than are lost by missing a small proportion of the population with LQTS. Nevertheless, it is important to emphasize that genetic testing is not a perfect diagnostic method in LQTS, even in the 75% of probands with a mutation identified by DNA sequencing.

In conclusion, genetic testing is moderately expensive, yet can reach the generally accepted threshold for cost-effectiveness when applied to selected first-degree relatives of a patient with clinically evident LQTS. Selective genetic testing of individuals who either have a higher pretest probability of LQTS or who come from high risk families may be particularly cost-effective. The cost-effectiveness of the genotyping strategy would be improved by the development of tailored therapies for specific genotypes that are more effective, by improved genotyping strategies,53 and by lower costs of genetic testing.

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**Disclosures**

Dr Owens is a consultant to Generation Health.

**References**


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