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Cost-Effectiveness Analysis of Genetic Testing for Familial Long QT Syndrome In Symptomatic Index Cases

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Short Title: Cost-Effectiveness Analysis of Genetic Testing for LQTS

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ABSTRACT

Objective: To conduct a cost-effectiveness analysis of genetic testing in the management of patients who have or are suspected to have familial long QT syndrome (LQTS).

Background: Genetic testing for LQTS has been available in a research setting for the past decade, and a commercial test has recently become available. However, the costs and effectiveness of genetic testing has not been estimated.

Methods: We examined the incremental cost-effectiveness of genetic testing compared to no genetic testing for symptomatic index cases and how this varied according to changes in assumptions and data inputs. Data were obtained from the published literature and a clinical cohort.

Results: We found that genetic testing is more cost-effective than not testing for symptomatic index cases at an estimated cost of $2500 per year of life saved. These results were generally robust although they were sensitive to some data inputs such as the cost of testing and the mortality rate among untreated individuals with LQTS.

Conclusions: A genetic test for familial LQTS is cost-effective relative to no testing, given our assumptions about the population to be tested and the relevant probabilities and costs. The primary benefit of testing is to more accurately diagnose and treat individuals based on a combination of clinical scores and test results. Future economic analyses of testing for familial LQTS should consider the potential benefits of genetic testing of broader populations, including family members.

Key Words: cost-effectiveness analysis, familial long QT syndrome, genetic testing

Abbreviations: Familial long QT syndrome (LQTS), implantable cardioverter defibrillators (ICDs)

INTRODUCTION

Familial long QT syndrome (LQTS) is a genetic disorder characterized by prolonged ventricular repolarization (QT interval prolongation) and an increased propensity for syncope, seizures, and sudden death secondary to its stereotypical arrhythmia of *torsade de pointes* (TdP).[1] It has been estimated that 2,000 to 3,000 children and young adults may die each year in the United States due to LQTS. Studies have demonstrated that LQTS genotypes influence both the probability and the lethality of cardiac events, e.g.,[2-4]. Genetic testing for LQTS has been available in a research setting for the past decade, and a commercial test (FAMILION) performed in a CLIA-approved laboratory has recently become available.[5] This test may be useful for providers who evaluate patients with suspected LQTS, as well as in the drug discovery process.

The objective of this study was to conduct a cost-effectiveness analysis of genetic testing for familial LQTS among symptomatic index cases. To date, there have not been any published economic analyses pertaining to genetic testing for this or any other heritable arrhythmia syndrome. Cost-effectiveness analysis is a widely used, quantitative method for systematically comparing the costs and health outcomes of competing health interventions or technologies.[6] LQTS is a complex disease and there are many uncertainties about its clinical course and treatment. However, patients and their providers must make treatment decisions and reimbursement and health care policies must be developed despite these uncertainties. Cost-effectiveness analysis is particularly useful when decisions are uncertain, as it provides information on the relative costs and benefits and how these might change under different scenarios. We believe that our results provide data that can be used to inform decision-making and to lay the groundwork for future, more definitive studies as more data become available.

METHODS

Cost-Effectiveness Analysis Approach

We examined the incremental cost-effectiveness of genetic testing compared to no genetic testing and how this varied according to changes in our assumptions and data inputs. We used standard procedures for conducting cost-effectiveness analyses,[6] as we have used or discussed in other analyses. [7-11] We provide here a summary of methods and data used; more details are available from the first author on request.

We used a decision analytic tree to model the relevant clinical pathways and their costs and outcomes.[12] A simplified picture of the tree is shown in Figure 1. We estimated a "typical pathway" for LQTS diagnosis and treatment; although there is variability in the pathways for LQTS patients, analyses must be simplified in order to be tractable. The tree shows that the initial decision is whether to test or not among a population that either has definite or inconclusive clinical scores suggesting the diagnosis of LQTS. Individuals who are tested will be found to either have a mutation or no mutation; if they have a mutation they may have different types. Individuals are treated with beta-blockers and/or implantable cardioverter defibrillators (ICDs). Individuals may experience no additional symptoms, have a syncopal event, or experience sudden cardiac death from which they may or may not survive.

Population

We included individuals aged 15-40 years in our analyses. We ended our analyses at age 40 because less is known about LQTS after this age. We assumed that the population to be tested represents symptomatic index cases, i.e. individuals with a compatible family history and clinical presentation consistent with the diagnosis of familial LQTS.[13, 14] The expected cost-effectiveness of confirmatory genetic testing involving either first-degree relatives (offspring, siblings,

parents) or more distant relatives was not included in this analysis. We modeled current practice by a heart rhythm specialist who is evaluating a putative proband or index case rather than potentially affected family members. These patients would include those achieving either a "definite" or "inconclusive" diagnostic clinical score for LQTS.[14] "Inconclusive" LQTS can be defined as a diagnostic cumulative score or “Schwartz and Moss” score between 1 and 4 and usually indicates a patient with a non-diagnostic ECG (QTc < 470 ms) who nonetheless may have compatible symptoms (exertional or auditory-triggered syncope, idiopathic ventricular arrhythmia without structural heart disease, "epilepsy" or history of unexplained near drowning, unexplained accidents, and/or family history of unexplained sudden death or drug-induced TdP/cardiac arrest). "Definite" LQTS usually denotes an individual with a clinical score $\geq$ 4 who shares clinical criteria with "inconclusives" but typically manifests diagnostic QT prolongation (QTc > 470 ms). We considered the three most commonly identified genotypes of LQTS: LQT1 due to mutations involving the *KCNQ1*-encoded potassium channel, LQT2 due to mutations involving the *KCNH2*-encoded potassium channel, and LQT3 due to mutations involving the *SCN5A*-encoded sodium channel.[15, 16]

We used data from the published literature and from an extensive Mayo Clinic cohort. From the range of values seen in these sources, we were able to make our choices for baseline inputs, as well as for the inputs for sensitivity analyses. The use of multiple sources allowed us to use more generalizable data from the literature but also to enhance the validity of our analyses by drawing on actual clinical data.

Key variables are shown in Table 1. The values for these variables were obtained from multiple articles (see below) and reviewed by two authors who are clinical experts (Ackerman and Berul). We also drew on data derived from 541 consecutive, unrelated patients who were

referred to Mayo Clinic's Sudden Death Genomics Laboratory at the Mayo College of Medicine between August 1997 and July 2004 for LQTS molecular genetic testing because of a clinical diagnosis of suspected familial LQTS regardless of the clinical diagnostic score for LQTS.[16] Since many of the data inputs are uncertain, we tested key assumptions and variables in sensitivity analyses by varying the values across wide ranges to assess whether the results changed. We attempted to use conservative estimates for our baseline data inputs and to use sensitivity analyses to test more liberal assumptions, e.g., that not all individuals diagnosed with LQTS would receive ICDs, that there was only a one-time cost for ICDs, and that ongoing work-up costs for individuals with inconclusive diagnoses are low.

Several assumptions were necessary in order to obtain usable results. We assumed that all individuals with a definite clinical score ($\geq$ 4) would be treated, regardless of the genetic test results, and that the majority of individuals with an inconclusive clinical score and a negative genetic test would in fact not have LQTS. We assumed that all previously symptomatic individuals failing beta-blocker therapy (estimated to be 25%) would receive ICDs[17, 18] and that 20 years of life were saved for each death averted (based on diagnosis at age 20 and that our study timeframe ends at age 40. Data were not available to estimate quality-adjusted life years saved, although it is highly unlikely these results would have been different). We assumed that treatment and mortality would vary by clinical diagnosis and, for those tested, LQTS mutation.

RESULTS

We compared the cost-effectiveness of genetic testing vs. no testing (Table 2). We found that genetic testing is more cost-effective than not testing at a cost per year of life saved of $2500. The cost per year of life saved is well below the standard threshold of $50,000 per life year saved that is often used to define a cost-effective intervention.[6] Although testing will cost

more because of the costs of testing and more people being treated, the number of deaths will be reduced because of better ability to diagnose and triage individuals into or away from treatment.

We describe the results in more detail to place them into context. We found that the primary benefit of testing is to more accurately diagnose and treat individuals. Among the 40% of index cases that will have *definite* LQTS clinical scores, the primary benefit is that the use of ICDs can be more appropriately targeted. Without genetic testing, 10% of individuals with conclusive scores are estimated to receive an ICD, which is relatively expensive, as part of the treatment strategy. However, with testing, many individuals with conclusive scores but with Type 1 LQTS or with negative genetic tests can usually be treated with beta-blockers instead of potentially obtaining ICDs.

Among the 60% of individuals that are likely to have *inconclusive* LQTS clinical scores, the primary benefit is targeting treatment to those who are more likely to have LQTS while avoiding treatment for those who do not. Without genetic testing, 90% of the individuals having an "inconclusive" clinical score are nonetheless receiving therapy and are often restricted from competitive sports. However, with genetic testing, only one-third of these individuals will have a positive test and will receive treatment, while two-thirds of these individuals will have a negative test, which could prompt a reconsideration of the clinical veracity of the diagnosis.

Sensitivity Analyses

We conducted extensive sensitivity analyses using cost per life years saved as the outcome. The results were generally robust, although they were sensitive to some key variables. As the cumulative mortality rate for untreated individuals with LQTS increases, the cost-effectiveness of testing increases, e.g., if the mortality rate doubles to 30%, the cost-effectiveness of testing falls to $1200 per year of life saved. However, testing becomes both more costly and

less effective if the mortality rate is <1.5%. As the cost of an ICD increases, testing becomes more cost-effective; if ICD costs are greater than $120,000, then testing becomes cost saving. As the population for whom testing is requested has a smaller proportion of individuals with a definitive LQTS score, testing becomes more cost-effective; if 30% of patients have a definitive score, the cost-effectiveness of testing increases to $1500 per year of life saved. This is because, without genetic testing, more patients may actually be concluded to have "borderline" LQTS and receive therapy because physicians were unable to rule out LQTS. This is estimated to occur despite the fact that the genetic testing cannot "rule out" LQTS on its own as the current genetic test is estimated to capture approximately 75% of LQTS.[16] Nonetheless, it is speculated that a combination of an inconclusive clinical score coupled with a negative genetic test will cause a reconsideration of the clinical diagnosis and an anticipated move away from the diagnosis and its accompanied treatment algorithm. If the percentage of inconclusive individuals who do not have a mutation but actually have LQTS increases then the cost-effectiveness of testing decreases; if this percentage increases to 20%, the cost-effectiveness of testing increases to $3300. Lastly, if the proportions of untested individuals who have inconclusive LQTS scores are increasingly assumed in the future to actually not have LQTS rather than the current default diagnosis of "borderline" LQTS, then the cost-effectiveness of genetic testing decreases.

Results were not very sensitive to our assumptions about the number of life years saved per death averted. If only five years of life are saved per death averted (instead of 20), the cost per year of life saved increases to $8000. Thus, genetic testing would still be highly cost-effective.

DISCUSSION

We found that a genetic test for familial LQTS is cost-effective relative to no testing, given our assumptions and the available data about this initial target population of suspected index cases to be tested. The cost per year of life saved ($2500) compares very favorably to other similar health care interventions, e.g., newborn ECG screening for QT prolongation as a predictor of sudden infant death syndrome ($3403-$118,900 per year of life saved for screening in high risk neonates or universal screening, respectively),[19] BRCA1/2 screening and oophorectomy ($3900-$1,600,000 per year of life saved for high or average risk women, respectively),[20] and mammography screening ($21,400-$117,680 per year of life saved for women ages 50-69 and ages 70-79 respectively).[21, 22]

Our study is limited by the inherent complexities of analyzing LQTS, a condition underscored by profound genotypic, phenotypic, and clinical heterogeneity. The impact of LQTS testing on costs and outcomes is a complex issue and re-analysis will be needed as our initial estimates become refined over time. Our analyses reflect our best estimates of one typical scenario. However, we conducted sensitivity analyses to identify areas of particular uncertainty and many of our estimates were conservative. In addition, cost-effectiveness analysis is designed to be used when data are incomplete, as with new interventions such as genetic testing.[7-9, 23, 24] Cost-effectiveness analysis helps identify what characteristics an intervention must have in order to be cost-effective; for example, what type of population should be targeted.

We found that the primary benefit of testing is to more accurately diagnose and treat individuals based on a combination of the “Schwartz and Moss” clinical score and the genetic test results. Another benefit is that individuals with specific genotypes can receive more

appropriate treatment, a benefit that may increase as more mutations are discovered. However, the actual benefits of testing will depend upon prevailing practice patterns and the ability of providers to interpret and apply test results. The primary benefit of testing is likely to be for individuals with inconclusive clinical scores, rather than those with definite scores. Thus, it will be important to assess the extent to which individuals with inconclusive clinical scores and negative genetic test results can appropriately receive "watchful waiting" rather than be treated as having borderline LQTS. It will also be important to examine the costs and benefits of testing over a longer timeframe. From the vantage point of LQTS referral practices, it is our belief that the current state of clinical practice often entails aggressive treatment including primary ICD implantation and hefty restrictions upon the patient with an inconclusive clinical score as if he/she had LQTS. Thus, one of the major benefits of genetic testing is to provide more objective information so that the clinician can make a more informed judgment about treatment, particularly when individuals have clearly inconclusive negative scores and negative test results. We recognize, however, that any test is imperfect and that the possibility of false negatives has to be weighed against the risk of false positives.

Our results support earlier work on the benefits of LQTS testing. Vincent (2001) points out that LQTS testing is likely to be beneficial because of the tremendous variability of expression and reduced penetrance (1/3-1/2 of gene carriers never have symptoms and 4-5% of gene carriers experience sudden death).[25] Thus, he estimated that genotyping would be very important for the 35% of gene carriers with borderline QTc intervals – which is consistent with our primary finding. Vincent, however, also points out that it is less clear whether LQTS testing will be beneficial in altering treatment strategies for those with particular genotypes, which is also similar to our conclusions.

Our analysis suggests that identifying the relevant population to be tested is critical, and our results are only relevant to a specific population, in this case symptomatic index cases with clinically suspected LQTS. The full costs and benefits of testing cannot be estimated without considering testing of family members that would be prompted following the elucidation of a LQTS-causing mutation in an index case. It is likely that the cost-effectiveness of testing will be even more favorable for family members and other relatives because the cost of this relative-specific confirmatory test is much less and there is a higher pre-test probability that some family members will have pre-clinical or concealed LQTS. However, it would greatly have increased the complexity of this study to include family members, pediatric patients, or a broader population of potential LQTS patients, and thus such analyses should be considered in the future. It will also be important to consider the broader environment within which testing will be conducted, including the relevant regulations and payer reimbursement policies.[26, 27] As with most health care interventions, testing will increase costs at least in the short-term. Cost-effectiveness analyses thus also provide a means by which these cost increases can be evaluated in light of the health benefit.

CONCLUSION

We conclude that a genetic test for familial LQTS is cost-effective relative to no genetic testing, given our assumptions about the population to be tested and the relevant probabilities and costs. We found that the primary benefit of testing is to more accurately diagnose and treat individuals based on a combination of clinical scores and genetic test results. Future economic analyses of testing for familial LQTS should consider the potential benefits of testing of family members and other relatives.

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