Cost-effectiveness of genetic testing in family members of patients with long-QT syndrome
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study examined the cost-effectiveness of genetic testing of 10-year-old first-degree relatives of patients with established long-QT syndrome (LQTS), compared with either watchful waiting or empirical treatment. Genetic testing was potentially cost-effective, particularly for relatives with a high pre-test probability of LQTS or from high-risk families. The analytic framework appears to have been robust, but there was a need for some assumptions. The authors’ conclusions appear to be valid.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
This study examined the cost-effectiveness of genetic testing for young first-degree relatives of patients with established long-QT syndrome (LQTS), compared with either watchful waiting or empirical treatment.

Interventions
Three strategies for 10-year-old first-degree relatives of patients (index cases) who had definitive clinical evidence of LQTS were examined: genetic testing; beta-blocker treatment; and watchful waiting, with treatment if symptoms developed.

With genetic testing, the index case was tested using exon sequencing of five genes; if no mutation was identified, the relative was assigned to watchful waiting, if any mutation was found the relative underwent genetic testing and those found to have the mutation were treated with β-blockers.

With watchful waiting, relatives were monitored for the development of symptoms; those with minor symptoms were started on β-blockers, while those with major symptoms were treated with an implantable cardioverter defibrillator (ICD).

With empirical treatment, relatives were treated with β-blockers regardless of evidence of LQTS, and those patients on β-blockers who developed recurrent syncope or resuscitated cardiac arrest were given an ICD.

Location/setting
USA/secondary care.

Methods
Analytical approach:
The analysis was based on a Markov model, with a 60-year time horizon. The authors stated that it was carried out from a societal perspective.

Effectiveness data:
The clinical data were from a selection of relevant studies, and some authors’ assumptions were needed. The key inputs were the rates of developing minor and major symptoms, and the LQTS-related mortality. These data were from published cohort studies. The efficacy of β-blockers was from a prospective matched-period before-and-after analysis. Other data were from published studies.
Monetary benefit and utility valuations:
Quality-of-life adjustments for treatment with β-blockers and with ICD implants were from published studies.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure for the cost-utility analysis, and life-years were the measure for the cost-effectiveness analysis. Both measures were discounted at an annual rate of 3%.

Cost data:
The economic analysis included the costs of drugs, which were their retail prices at the time, the cost of genetic testing, which was based on manufacturer data, and the costs of hospitalisations, ICD implantation, and clinic visits, which were from Medicare reimbursements. All costs were in US dollars ($) and a 3% discount rate per annum was applied. The price year was 2008.

Analysis of uncertainty:
One-way sensitivity analyses were carried out on the model inputs, using a range of plausible values for the event rates, costs, and utilities.

Results
The projected costs were $16,048 with watchful waiting, $24,563 with treatment, and $25,467 with genetic testing. The life-years were 25.65 with watchful waiting, 26.07 with treatment, and 25.94 with testing. The QALYs were 25.16 with watchful waiting, 24.89 with treatment, and 25.30 with testing.

In the cost-effectiveness analysis, genetic testing was dominated by treatment, which was more effective and less expensive. The incremental cost per life-year gained with treatment over watchful waiting was $19,900. In the cost-utility analysis, treatment was dominated by watchful waiting. The incremental cost per QALY gained with genetic testing over watchful waiting was $67,400. These different results were due to the decrements in quality of life while on β-blocker treatment.

The most influential inputs were the annual risk of death, the pre-test probability of LQTS in first-degree relatives of the index case, and the probability of developing symptoms. The reductions in quality of life due to β-blockers and the efficacy of treatment were also influential parameters.

The cost-utility of genetic testing was below the threshold of $50,000 per QALY when the annual risk of death was 0.48% or more, if genetic testing provided pharmacogenomic information, or with an increasing number of family members to be tested (two or more; the cost of testing the index case was only incurred once). Watchful waiting was the preferred strategy in relatives with a low pre-test probability of LQTS, genetic testing was the preferred strategy in relatives with an intermediate probability (between 0.65 and 0.81 the incremental cost-utility ratio was under $50,000), and empirical treatment was the preferred strategy at higher probabilities.

Authors' conclusions
The authors concluded that genetic testing was potentially cost-effective, particularly for relatives with a high pre-test probability of LQTS or from high-risk families.

CRD commentary
Interventions:
An appropriate selection of comparators was considered as the three strategies were the possible options for managing first-degree relatives of patients with established LQTS. An extensive description of the three strategies was given.

Effectiveness/benefits:
The method used to identify and select the data sources was not reported and the methods and characteristics of these sources were not reported. This limits the ability to judge the validity of the clinical inputs. Authors’ assumptions were made, which introduced further uncertainty into these estimates, some of which were extensively varied in the sensitivity analyses. The two benefit measures were appropriately selected as the disease affects both expected survival and health-related quality of life. The analysis highlighted the importance of quality adjustments, which altered the cost-
effectiveness of the interventions. No information on the derivation of the utility values was reported.

Costs:
The authors stated that the analysis was carried out from a societal perspective, but it appears to have included only the direct medical costs. The data sources (retail prices and Medicare reimbursement rates) appear to have reflected the viewpoint of the health care system or the third-party payer. The unit costs were not reported as most of the costs were presented as category totals. Similarly, limited information on the resource quantities was presented. These issues reduce the transparency of the analysis, but changes in the cost estimates had little impact on the cost-effectiveness results. Other details, such as the price year and discounting, were reported.

Analysis and results:
The results were extensively presented. An incremental analysis was appropriately used to combine the costs and benefits of the strategies. A deterministic approach was used to investigate alternative scenarios and variations in the model assumptions. A multivariate approach would have been more appropriate to test the overall uncertainty in the model results. The authors provided an extensive discussion on the importance of some model parameters in determining the relative cost-effectiveness of the strategies. The results depended strongly on the level of risk in the population considered. The analysis appears to be transferable to settings with similar epidemiology and cost structures.

Concluding remarks:
The analytic framework appears to have been robust, but there was a need for some assumptions. The authors’ conclusions appear to be valid.

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