Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes

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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 assessed the cost-effectiveness of a genetic test to identify patients with a mitochondrial mutation (1555A>G) which may predispose them to hearing loss, in patients with cystic fibrosis receiving aminoglycosides for the treatment of respiratory infections. 1555A>G testing was not a cost-effective alternative to the current option of no testing from the perspective of US society, although high uncertainty was found around this result. The study was well conducted and the authors’ conclusions are likely to be valid.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The objective was to assess the cost-effectiveness of a genetic test to identify patients with a mitochondrial mutation (1555A>G) which may predispose them to the development of hearing loss, in patients with cystic fibrosis (CF) receiving aminoglycoside antibiotics for the treatment of respiratory infections.

Interventions
Genetic testing for the identification of 1555A>G was performed and those who tested positive received intravenous ciprofloxacin (500mg every eight hours for 14 days) and ceftazidime (2000mg every eight hours for 14 days), while those who tested negative were treated with tobramycin (375mg daily for 14 days) and ceftazidime (same dosage). This testing strategy was compared with no testing. Patients in the no testing branch received tobramycin and ceftazidime (same dosages).

Location/setting
USA/secondary care.

Methods
Analytical approach:
This economic evaluation was based on a decision model which compared the clinical and economic consequences of patients receiving or not receiving the genetic test. A lifetime horizon was considered and the authors reported that a societal perspective was adopted.

Effectiveness data:
The clinical data were derived from a critical review of the literature and from the US Cystic Fibrosis Foundation National Patient Registry. The search criteria were reported. Test accuracy was mainly obtained from a population-based study. The 1555A>G prevalence was taken from US studies. Details on other studies used to populate the model were provided. However, given the lack of published evidence, some assumptions were required.

Monetary benefit and utility valuations:
The utility valuations were derived from studies based on preferences elicited from samples of patients, doctors, and parents of individuals with CF. The time trade-off approach was used in one of these studies. Some of the utility values came from a meta-analysis of published studies.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure. These were discounted at an annual rate of 3%. The percentage of patients with aminoglycoside-induced severe hearing loss was also reported, but was not combined with the costs.

Cost data:
The economic analysis included the direct and indirect costs of the 1555A>G test, cochlear implant (acquisition and maintenance), drugs, and treatment of mild-to-moderate hearing loss. The types of indirect costs were not described. The costs and quantities were derived from multiple sources, including published cost-effectiveness studies, an economic analysis of the societal costs of hearing loss, test manufacturers, and data from large US hospitals. A 3% annual discount rate was applied to future costs. All costs were in US dollars ($) and the price year was 2006.

Analysis of uncertainty:
A deterministic sensitivity analysis was carried out on all the model inputs. The ranges of values were derived from the literature or were based on authors' opinions (plus or minus 25% of the base-case values). A scenario analysis was performed in order to consider the impact of improved test specificity at an additional cost.

Results
The 1555A>G test strategy reduced the lifetime risk of aminoglycoside-induced severe hearing loss by 0.12%. The total costs were $1,603 with testing and $1,265 with no testing.

The expected QALYs were 17.16467 with testing and 17.16041 with no testing. The incremental cost per QALY gained with testing over no testing was $79,300.

The sensitivity analysis highlighted the high degree of uncertainty surrounding this result. Variations in the model inputs produced results ranging from the test strategy being dominated by the no test strategy (more effective and less expensive) through to an incremental cost per QALY gained of $33,000. The most influential model inputs were the mortality associated with not using aminoglycoside antibiotics and the discount rate. In particular, at mortality higher than 0.8% the test strategy was dominated. Prevalence of 1555A>G and test specificity were also important factors in determining the cost-effectiveness of testing versus no testing. An improvement in test specificity for a positive test, lead to an increase in the cost-effectiveness ratio for the test strategy to $670,000 per QALY, since more patients in the test strategy received aminoglycoside antibiotics.

Authors' conclusions
The authors concluded that 1555A>G testing was not likely to represent a cost-effective alternative to the current option of no testing from the perspective of US society, mainly due to the low prevalence of the 1555A>G mutation and the high rate of false positives. They stated that further studies should be carried out to provide more reliable data.

CRD commentary
Interventions:
The selection of no testing as the background comparator was appropriate as it represents the standard care in the authors' setting.

Effectiveness/benefits:
The authors provided some details of the method used to derive the clinical data. They also provided a description of the key characteristics of the primary sources of data and discussed their selection of the key clinical estimates. The need for assumptions was justified and the authors acknowledged that some of the studies found in the literature were small and restricted to very specific patient populations (high-risk families). To overcome some issues about the uncertainty of model inputs, the sensitivity analysis considered variations in all probability data. The derivation of utility valuations was clearly described. The use of QALYs represents a positive feature of the analysis, given the validity and generalisability of this benefit measure.

Costs:
The authors stated that a societal perspective was adopted. However, the costs were presented as macro-categories and a detailed breakdown of items was not given. The sources used were not extensively described, especially when published
economic evaluations were used. Furthermore, a description of the types of indirect costs was not provided and this limits the transparency of the economic analysis. The price year and the use of discounting were reported. The sensitivity analysis investigated the impact of variations in the cost estimates.

Analysis and results:
The costs and benefits were appropriately synthesised. The issue of uncertainty was addressed, although it focused on individual parameters in one-way sensitivity analyses. The results of both the base-case and the sensitivity analyses were clearly presented and discussed. The authors noted some limitations of their analysis, all of which were related to the uncertain estimates derived from the literature review.

Concluding remarks:
The study was generally well conducted, although some economic aspects of the analysis were not clearly described. Overall, the authors’ conclusions are valid.

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