Prioritizing pharmacogenetic research: a value of information analysis of CYP2D6 testing to guide breast cancer treatment

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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
The objective was to compare the cost-effectiveness of pharmacogenetic testing and treatment for early-stage breast cancer, and to assess the uncertainty around the estimates. The authors concluded that a large adjuvant aromatase inhibitor trial should be retrospectively analysed to investigate any association between the CYP2D6 genotype and tamoxifen outcome. The methods were good, and the study was reported in detail. Given the limitations of the evidence, the authors’ conclusions appear to be appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to compare the cost-effectiveness of pharmacogenetic testing and treatment strategies for early-stage breast cancer, and to assess the uncertainty around the estimates.

Interventions
Four strategies were investigated: tamoxifen treatment; anastrozole treatment; testing for the CYP2D6 genotype, with tamoxifen for both homozygous and heterozygous wild-type patients (wt/wt and wt/*4) and anastrozole for *4/*4 patients; and testing for the CYP2D6 genotype, with tamoxifen for homozygous wild-type patients and anastrozole for all other patients.

Location/setting
UK/secondary care.

Methods
Analytical approach:
A Markov model was used to evaluate the costs and benefits of the four strategies. The time horizon was 35 years. The authors stated that the UK NHS perspective was adopted.

Effectiveness data:
The clinical evidence was from a randomised controlled trial, that compared anastrozole with tamoxifen (Arimidex, Tamoxifen, Alone or in Combination – ATAC – trial), and an observational study of the efficacy of tamoxifen in patients with the CYP2D6 genotypes wt/wt, wt/*4 and *4/*4. The main measure of effectiveness was the five-year recurrence-free survival. Both the source studies were identified by published systematic reviews.

Monetary benefit and utility valuations:
The utility data were from a study of the health profiles of patients with breast cancer in Sweden, elicited using the EQ-5D questionnaire. This study was identified by a published systematic review of utility data for patients with breast cancer.

Measure of benefit:
Quality-adjusted life-years (QALYs) gained were the measure of benefit. Future benefits were discounted at an annual rate of 3.5%.
Cost data:
The direct costs included those of the genotype tests; consultant appointments and mammograms; tamoxifen and anastrozole; disease-free survival follow-up; and treatment for cancer recurrence, including terminal care. The costs of genetic testing were provided by Roche, the manufacturers of the test. The drug treatment costs were from the British National Formulary. As the patent for anastrozole was expected to expire in February 2011, an 82% lower price for generic anastrozole was also assessed. The costs for consultant appointments and mammograms were from NHS sources. The costs of treatment for recurrence were from a published UK study of the resources used by 199 patients with early breast cancer, who relapsed. The price year was 2007. All costs were reported in UK £, and future costs were discounted at an annual rate of 3.5%.

Analysis of uncertainty:
Probabilistic sensitivity analysis was undertaken, with 1,000 Monte Carlo simulations and conventional distributions for the model inputs. Cost-effectiveness acceptability curves were generated. The expected value of perfect information was calculated to estimate the value of eliminating all uncertainty relating to the decision.

Results
The average QALYs gained were 9.20 with tamoxifen, 9.28 with testing and tamoxifen for heterozygous patients, 9.35 with testing and anastrozole for heterozygous patients, and 9.36 with anastrozole. The average cost per patient was £6,816 with tamoxifen, £7,234 with testing and tamoxifen, £8,088 with testing and anastrozole, and £10,169 with anastrozole.

Compared with tamoxifen, testing and tamoxifen had an incremental cost-utility ratio (ICUR) of £4,774 per QALY gained. Compared with testing and tamoxifen, testing and anastrozole had an ICUR of £13,864 per QALY gained. Compared with testing and anastrozole, anastrozole had an ICUR of £177,096 per QALY gained.

Assuming a generic price for anastrozole, the average cost per patient was £7,063 with testing and tamoxifen, £7,001 with testing and anastrozole, and £6,777 with anastrozole. Tamoxifen, testing and tamoxifen, and testing and anastrozole were dominated by anastrozole, as anastrozole was less costly and more effective.

The probabilistic sensitivity analysis showed that at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained, testing and anastrozole was cost-effective in between 50% and 60% of simulations, assuming the patent price for anastrozole, and anastrozole was cost-effective in approximately 60% of simulations, assuming its generic price. The expected value of perfect information analysis suggested that further research was feasible, as the value of the research was likely to exceed its cost.

Authors' conclusions
The authors concluded that one of the large adjuvant aromatase inhibitor trials should be retrospectively analysed to investigate any association between the CYP2D6 genotype and tamoxifen outcome.

CRD commentary
Interventions:
The interventions were reported clearly and in detail.

Effectiveness/benefits:
Evidence on effectiveness was a synthesis of outcome data from a large randomised controlled trial and an observational study. Both of which were identified by published systematic reviews of the literature. The authors explicitly reported the reasons why these studies were selected over other studies found by the reviews. It is likely that all the relevant information on effectiveness was considered for inclusion in the model.

Costs:
The perspective was explicitly reported to be that of the UK NHS. For this perspective, all the major relevant cost categories and costs appear to have been included. The sources for the cost information were reported in detail. The price year, time horizon, discount rate, and currency were all reported.

Analysis and results:
The outcome and cost information was synthesised using a Markov model. The model structure was provided, with a diagram. Uncertainty in the results was exhaustively assessed in a probabilistic sensitivity analysis and an expected value of information analysis. As the main limitation to their study, the authors reported that the evidence, on the associations between the CYP2D6 genotype and tamoxifen outcomes, was very uncertain.

Concluding remarks:
The study methods were good, and they, the results and the limitations of the study were reported in detail. Given the limitations of the evidence, the authors’ conclusions appear to be appropriate.

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