A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing

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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 to adjust the warfarin dose, using a model based on the international normalised ratio, for patients with atrial fibrillation who had just started long-term warfarin therapy. The authors concluded that warfarin pharmacogenomic testing provided some clinical benefit, but with significant uncertainty in the economic value. The study had a conventional and well-conducted cost-effectiveness framework and it showed a high uncertainty in the cost-effectiveness results. The authors’ conclusions appear to be robust.

Type of economic evaluation
Cost-utility analysis

Study objective
This study examined the cost-effectiveness of genetic testing to adjust the warfarin dose, using a model based on the international normalised ratio (INR) for anticoagulation, in patients with atrial fibrillation who had just started long-term warfarin therapy.

Interventions
Genetic testing was compared with standard care by a pharmacist specialising in anticoagulation. The testing identified variants of the cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex, subunit 1 (VKORC1) genes.

Location/setting
USA/out-patient.

Methods
Analytical approach:
The study was based on a decision tree, followed by a Markov model, in which patients were stratified by genotype. A lifetime horizon was considered and the authors stated that the perspective of the third-party payer was adopted.

Effectiveness data:
The clinical data were from a selection of relevant studies, including large cohort studies, clinical trials, and national reports. The relationship between the INR and the incidence of bleeds and thromboembolisms was the key clinical input and the data were from a large longitudinal study. The effect of genetic testing on the INR was derived from the COUMAGEN trial, which included 200 patients who were about to be initiated on warfarin. A one-month follow-up was considered.

Monetary benefit and utility valuations:
The utility values were from US population-based European Quality of life (EQ-5D) questionnaire scores.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and a 3% annual discount rate was applied.

Cost data:
The economic analysis included the costs of warfarin, genetic test, and events such as transient ischaemic attack, ischaemic stroke, myocardial infarction, extracranial bleed, intracranial haemorrhage, and sequelae. The unit costs were from various sources including the Intermountain Healthcare database, publicly available tests, and the NHS Economic Evaluation Database (NHS EED).
Healthcare Cost and Utilization Project database. All costs were in US dollars ($) and were discounted at an annual rate of 3%. The price year was 2007.

Analysis of uncertainty:
A series of one-way sensitivity analyses was carried out for all the model inputs, using plausible ranges of values, based on published sources or authors’ opinions. A probabilistic analysis, based on a Monte Carlo simulation, was also performed to provide confidence intervals around the model outcomes. Alternative scenarios were considered, with various assumptions on the risk of bleeding and the effect of genetic testing.

Results
Genetic testing increased the QALYs by 0.0027 or one day (95% CI -0.0048 to 0.0101) and increased the costs by $162 (95% CI 22 to 386) compared with standard care, resulting in an incremental cost per QALY gained of $60,725. In the subgroup of CYP2C9 non-wild-type variants, standard care was dominant as it was more effective and less expensive, while the incremental cost per QALY with testing fell to $13,500 in CYP2C9 wild-types with VKORC1 BB and rose to $72,000 in CYP2C9 wild-types with VKORC1 AA or AB.

The most influential inputs were the cost and effectiveness of the test, the proportion of bleeds with above-range INRs, and the relative risk of bleeds in CYP2C9 variant patients. If the test cost was below $13, testing was dominant. At a threshold of $50,000 per QALY, the probability of testing being cost-effective was 46% and at $100,000 it was 67%. In general, the model was highly sensitive to many input parameters and changes in the model assumptions altered the conclusions.

Authors’ conclusions
The authors concluded that warfarin pharmacogenomic testing provided a small clinical benefit, but with significant uncertainty in the economic value.

CRD commentary
Interventions:
The rationale for the selection of the comparators was clear as the novel genetic testing was compared against the standard care for patients starting on warfarin therapy. A full description of the usual care was not given, but the authors stated that it followed the US clinical practice guidelines.

Effectiveness/benefits:
No systematic review was reported to identify the relevant data sources and their methods were not fully reported. The authors stated that the relationship between the INR and clinical events was from a large longitudinal study that reflected the standard clinical care. The effect of testing was from a clinical trial, which should have good internal validity. This trial was selected because it represented US clinical practice better than other published trials, but the authors acknowledged that it had a small sample and a short follow-up. A clear description of the method used to model the clinical events, using the INR, was provided. The EQ-5D questionnaire was used to estimate the health-related quality of life, but limited information was given on the derivation of these estimates. QALYs appear to have been an appropriate benefit measure, given the impact of atrial fibrillation on both survival and quality of life.

Costs:
The categories of costs and their sources were consistent with the economic viewpoint. Limited information on the unit costs and quantities of resources used was provided, as most of the costs were presented as category totals. The authors stated that the inclusion of caregiver costs would have had a negligible effect on the total costs, and so they were not assessed. The price year and the use of discounting were clearly reported. The impact of variations in the economic inputs was extensively considered in the sensitivity analyses.

Analysis and results:
An appropriate incremental approach was used to synthesise the costs and benefits, and the results were clearly reported. Appropriate ways were used to assess uncertainty, including both deterministic and probabilistic analyses. Alternative scenarios were presented and they demonstrated the high variability in the results. The model was validated using published data. The authors compared their results with those of two other published economic
evaluations that had reported contrasting results.

**Concluding remarks:**
The study was based on a conventional and well-conducted cost-effectiveness framework and showed a high uncertainty in the cost-effectiveness results. The authors' conclusions appear to be robust.

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