The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer
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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 compared the cost-effectiveness of two epidermal growth factor receptor (EGFR) tests in second-line therapy for patients with advanced non-small cell lung cancer. The authors concluded that EGFR gene copy number testing could improve quality-adjusted survival, but the uncertainty around the results warranted further research. Despite some limited reporting on the clinical side, the study was well conducted. Given the high uncertainty in the results, the need for further research was justifiably acknowledged by the authors.

Type of economic evaluation
Cost-utility analysis

Study objective
The aim was to compare the cost-effectiveness of strategies, based on the genome determining the response to a drug (pharmacogenomic), for epidermal growth factor receptor (EGFR) testing, before the initiation of second-line therapy, in 60-year-old patients with advanced (stage IIIB or IV) refractory non-small cell lung cancer that had not responded to one platinum-based chemotherapy.

Interventions
Two EGFR testing strategies were compared. The EGFR protein expression test (EGFR PharmDx kit produced by DakoCytomation, Glostrup, Denmark) was followed by erlotinib therapy for patients with high expression and docetaxel for patients with low expression. The EGFR gene copy number test, using fluorescence in situ hybridisation, was followed by erlotinib for patients with a high copy number and docetaxel for patients with a low number. Erlotinib monotherapy, without testing, was used as the comparator.

Location/setting
USA/secondary care.

Methods
Analytical approach:
A decision tree with a two-year time horizon was used. The authors reported that a US societal perspective was adopted.

Effectiveness data:
The data on overall and progression-free survival and time in progressive disease were obtained from published randomised controlled trials (RCTs). Survival, in the testing arms, was estimated by the authors and their methods were reported. The primary clinical outcomes were overall and progression-free survival. Adverse event rates were included in the analysis.

Monetary benefit and utility valuations:
The patients’ utilities were from two community-based studies, conducted in the UK, that used the standard gamble interview and the visual analogue scale.

Measure of benefit:
The summary measure of benefit was the number of quality-adjusted life-years (QALYs) and an annual discount rate of 3% was applied.
Cost data:
The economic analysis included the costs of medications and medical services, such as hospitalisation, out-patient and in-patient consultations, EGFR, and laboratory tests. The resource use for medications was obtained from the RCTs that were used for the effectiveness data. The other resource use data were obtained from published sources. The unit costs were derived from official national sources and wholesale acquisition costs were used for the drugs. All costs were appropriately adjusted for inflation and reported for the price year 2006 in US dollars ($). An annual discount rate of 3% was applied.

Analysis of uncertainty:
One-way sensitivity analysis was performed on all the model parameters. The ranges of values were obtained from published sources or were based on expert opinion. Probabilistic sensitivity analysis, using Monte Carlo simulations, was also performed. A cost-effectiveness acceptability frontier was generated and the expected value of perfect information (EVPI) for the US population over a five-year horizon was calculated.

Results
The expected QALYs were 0.44 with erlotinib monotherapy, 0.48 with protein expression and 0.50 with gene copy testing. The expected costs were $57,238 with erlotinib, $63,512 with protein expression, and $66,447 with gene copy testing.

Compared with erlotinib, gene copy testing resulted in an incremental cost of $162,018 per QALY gained, while protein expression testing resulted in an incremental cost of $179,612 per QALY gained. Gene copy dominated protein expression testing by extension, which means that its average cost per QALY was lower and it was more effective.

The deterministic sensitivity analysis showed that the effectiveness was most sensitive to variation in the overall and progression-free survival and the utility scores for intravenous therapy. The costs were most sensitive to variation in the overall and progression-free survival estimates and the monthly cost of progressive disease.

The probabilistic sensitivity analysis indicated that, at a willingness-to-pay for an additional QALY of less than $150,000, erlotinib was the preferred strategy, while, above this threshold, gene copy testing became the best strategy. The EVPI for the USA over a five-year period was $31.4 million at a willingness-to-pay for an additional QALY of $100,000.

Authors’ conclusions
The authors concluded that gene copy testing could improve quality-adjusted survival compared with erlotinib monotherapy, but there was high uncertainty in the results, as shown in the EVPI estimates. They stated that further research should be conducted in this area to produce more robust results.

CRD commentary
Interventions:
The rationale for the selection of the comparators was explicitly described. Erlotinib monotherapy, without testing, was used as the comparator and this was the standard practice in the authors’ setting.

Effectiveness/benefits:
No systematic review of the literature was reported. The sources searched, the inclusion and exclusion criteria, and the details of the source studies were not reported. More detail would have been useful in judging the validity of the clinical estimates. The utilities were derived from published sources and the valuation methods were reported. QALYs are a validated and appropriate benefit measure given the impact of the disease on both quality of life and survival.

Costs:
The authors reported that a societal perspective was adopted, but not all productivity losses were included. Time lost due to travel was included, but the relevant resource use or unit costs were not reported. For medications, the unit costs were presented separately from the resource quantities, but all the other costs were reported as total categories due to the use of current procedural terminology data. The sources of costs, price year, use of discounting, and probability distributions were well reported.
Analysis and results:
The costs and benefits were clearly reported. The authors calculated the incremental cost-effectiveness ratio (ICER) of each intervention compared with erlotinib alone instead of comparing each one with the next most effective one. There also appears to have been a miscalculation of the ICER for gene copy testing versus erlotinib, but neither of these issues affect the conclusions. The uncertainty was thoroughly assessed, using deterministic as well as probabilistic sensitivity analyses. The authors highlighted the uncertainty around their results. They provided a balanced discussion on the limitations of their study, which mainly related to the availability and poor quality of the clinical data.

Concluding remarks:
The study was well conducted and, despite some limited reporting on the clinical side, the issue of uncertainty was extensively and appropriately investigated. Given the high uncertainty around the findings, the need for further research was justifiably acknowledged by the authors.

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