KRAS and BRAF mutation analysis in metastatic colorectal cancer: a cost-effectiveness analysis from a Swiss perspective  

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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 testing for the Kirsten rat sarcoma viral oncogene homologue (KRAS) and BRAF mutations, before cetuximab treatment for metastatic colorectal cancer that did not respond to chemotherapy. The authors concluded that testing was clinically and economically favourable, despite its high cost. The cost-effectiveness framework was conventional and various areas of uncertainty were considered. The authors’ conclusions appear to be robust.

Type of economic evaluation
Cost-utility analysis

Study objective
This study assessed the cost-effectiveness of testing for the Kirsten rat sarcoma viral oncogene homologue (KRAS) and BRAF mutations, before cetuximab treatment for metastatic colorectal cancer that did not respond to chemotherapy.

Interventions
Three strategies were examined: KRAS testing; KRAS testing followed by BRAF testing for those with KRAS wild-types; and cetuximab treatment without testing. In each testing strategy, cetuximab treatment was started if no mutations were detected and patients with identified KRAS or BRAF mutations received best supportive care.

Cetuximab was started at a loading dose of 400mg per m$^2$ of body surface area, which was followed by a weekly maintenance dose of 250mg per m$^2$. The background comparator was best supportive care for all patients.

Location/setting
Switzerland/hospital.

Methods
Analytical approach:
The analysis was based on a Markov model with a lifetime horizon. The authors stated that it was carried out from the perspective of the health care system.

Effectiveness data:
The clinical data were from relevant published studies. The treatment effect for cetuximab versus best supportive care was mainly from a phase III randomised trial; the event rates for patients with BRAF mutations were from a retrospective analysis. The sensitivity and specificity of the testing strategies were key inputs and they were from two published studies. The patients’ characteristics (the proportions with wild-type KRAS and BRAF mutations) were based on several published studies. Mortality was from Swiss life tables.

Monetary benefit and utility valuations:
The utility values were from published studies, including the clinical trial that supplied the treatment effect and other European studies. In the clinical trial, the utility weights were collected prospectively, using the Health Utilities Index (HUI-3).

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and they were discounted at an annual rate of 3%.

Cost data:
The economic analysis included the costs of drugs, predictive testing, diagnostic procedures, and hospitalisation. The resource quantities were from published literature, Swiss official statistics (mainly for hospitalisations), or authors’ opinions. The unit costs were from the official Swiss tariff list (laboratory tests, diagnostics and drug administration) and from Swiss pharmacy prices (drugs). All costs were assessed in Swiss francs, and converted into Euros (EUR). A 3% annual discount rate was applied.

Analysis of uncertainty:
One-way sensitivity analyses were carried out to examine the impact of variations in the model inputs on the cost-effectiveness results. The ranges of values were from published sources or authors’ opinions. A probabilistic sensitivity analysis was performed, using second-order Monte Carlo simulation. Beta distributions were used for most of the clinical inputs, with gamma distributions for the median survival times and median time to progression. The unit costs were assumed to be fixed and were not varied in the probabilistic analysis. Several scenario analyses were considered.

Results
The projected lifetime costs were EUR 3,983 with no intervention, EUR 34,771 with KRAS then BRAF, EUR 35,361 with KRAS, and EUR 38,662 with no testing (cetuximab for all). The QALYs were 0.4430 with no intervention, 0.934 with KRAS then BRAF, 0.936 with KRAS, and 0.947 with no testing.

The incremental cost per QALY gained was EUR 62,653 with KRAS then BRAF, compared with no intervention, EUR 313,537 with KRAS, compared with KRAS then BRAF, and EUR 314,588 with no testing, compared with KRAS.

The most influential inputs were the overall survival of patients with the wild-type KRAS mutation, who were on best supportive care, and the utility value for progressive disease. The ranking of the strategies was unaffected by changes in the model inputs.

KRAS then BRAF testing was the preferred strategy over a willingness-to-pay range of EUR 10,000 to EUR 40,000. Above EUR 40,000 per QALY, KRAS was the preferred strategy.

Authors’ conclusions
The authors concluded that testing for KRAS and BRAF mutations, before cetuximab treatment, was clinically and economically favourable, despite the high cost of testing.

CRD commentary
Interventions:
The interventions were appropriately selected; KRAS and BRAF mutations are good indicators of the effectiveness of cetuximab for metastatic colorectal cancer patients.

Effectiveness/benefits:
The clinical inputs were from published sources, but no systematic search was reported to identify them. The treatment effect was mainly from a clinical trial that directly compared the three strategies and was a valid source. The other data sources were not described which makes it difficult to objectively assess them. Extensive sensitivity analysis was conducted on all the model parameters. QALYs were an appropriate measure of benefit, given the impact of cancer on mortality and morbidity. They also allow comparisons with other disease areas. The utility weights were obtained using an appropriate instrument.

Costs:
The perspective was explicitly stated and all the relevant cost categories appear to have been included. The unit costs and resource quantities were presented separately in an appendix aiding the replication of the analysis. Their sources were representative of the Swiss context and were appropriately selected and justified. Variations in the cost estimates were considered in alternative scenarios, but they were not varied in the probabilistic analysis. Reflation exercises for other time periods will be difficult as the price year was not clearly stated.
Analysis and results:
The results were clearly reported. Incremental cost-utility ratios were calculated to synthesise the costs and benefits of the alternative strategies. Both deterministic and probabilistic sensitivity analyses were carried out to investigate the uncertainty, and the methods and results were clearly discussed. The authors acknowledged some limitations of their analysis, and these mainly related to the poor quality of some sources for the clinical inputs. The results were specific to Switzerland, but might be transferable to other settings with similar relative prices and epidemiology.

Concluding remarks:
The cost-effectiveness framework was conventional and various areas of uncertainty were considered. The authors’ conclusions appear to be robust.

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