Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis

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 strategies to identify Lynch syndrome, in patients who were newly diagnosed with colorectal cancer, considering the effects by gender, by age at screening, and for those tested and their relatives. The authors concluded that strategies to identify families with Lynch syndrome could provide substantial clinical benefits at acceptable costs, especially for women. The cost-effectiveness depended on the uptake of screening among relatives. The methods were valid, which supports the authors’ conclusions.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
This study examined the cost-effectiveness of strategies to identify Lynch syndrome, in patients who were newly diagnosed with colorectal cancer, considering the effects by gender, by age at screening, and for those tested and their relatives.

Interventions
The strategies were the use of clinical criteria or predictive clinical algorithms, tumour testing, and up-front germline testing for mutations in the DNA mismatch repair genes, MLH1, MSH2, MSH6, or PMS2.

The clinical criteria and prediction models included Amsterdam II criteria, revised Bethesda guidelines, the Mismatch Repair (MMR)predict model, the MMRpro model, and the Prediction of Mismatch Repair Gene Mutations in MLH1, MSH2, and MSH6 (PREMM₁,₂,₆) model. Tumour-testing strategies included immunohistochemistry, testing for mutation of the BRAF gene, and testing for microsatellite instability. Combinations of options were considered.

If a mutation was identified, relatives with a 50% risk of carrying that mutation (first-degree relatives) were offered single-site germline testing. The reference strategy was no active effort to diagnose Lynch syndrome.

Location/setting
USA/secondary care.

Methods
Analytical approach:
The analysis was based on Markov model that incorporated the risks of colorectal, endometrial, and ovarian cancers. A lifetime horizon was considered. The authors stated that the analysis took the perspective of the third-party payer.

Effectiveness data:
The clinical data were from published studies, identified by a literature search. Systematic reviews and meta-analyses performed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative were sought first. Then PubMed was searched for further studies; meta-analyses and systematic reviews were chosen as the main sources. The Surveillance, Epidemiology, and End Results (SEER) database was used, especially for model calibration and validation. The accuracy (sensitivity and specificity) of the screening strategies was a key input for the model.

Monetary benefit and utility valuations:
Measure of benefit:
Life-years were the summary benefit measure and were discounted at an annual rate of 3%.

Cost data:
The economic analysis included the direct medical costs of cancer care, screening for Lynch syndrome, germline testing, preventive interventions, complications, and genetic counselling. These data were from published sources and Medicare professional and facility fee schedules. The costs of cancer care were from a published health technology assessment conducted in the USA. All costs were in US dollars ($) and the price year was 2010. A 3% annual discount rate was applied.

Analysis of uncertainty:
One-way and threshold analyses were carried out to assess the uncertainty around the model inputs. The ranges of values were mainly from the literature. A probabilistic sensitivity analysis was performed, using Monte Carlo simulation, with conventional probability distributions for the model inputs. Median estimates for the model outputs and cost-effectiveness acceptability curves were produced.

Results
The costs and life-years were reported for all strategies. Dominated strategies, which were less effective and more costly or less cost-effective than another strategy, were excluded.

In the base case, for clinical criteria strategies, the incremental cost per life-year gained over the next best strategy, was $30,600 with MMRpro plus immunohistochemistry, over no testing, $39,600 with Bethesda plus immunohistochemistry, $41,400 with MMRpro plus germline, and $50,200 with Bethesda plus germline.

For tumour-testing strategies, the incremental cost per life-year gained over the next best strategy was $117,000 with microsatellite instability plus immunohistochemistry with BRAF testing, over Bethesda plus germline. Excluding the clinical criteria strategies, it was $36,200 with immunohistochemistry with BRAF testing, over no testing.

For up-front germline testing, the incremental cost-effectiveness ratio (ICER) was $293,000 per life-year gained, over microsatellite instability plus immunohistochemistry with BRAF testing.

Greater benefits and lower ICERs were observed for women, for relatives with a mutation associated with Lynch syndrome, and with higher germline test acceptance rates. A driver of the analysis was the number of relatives tested per proband (tested patient); the ICERs of all strategies improved as more relatives were tested. Variations did not alter the preferred strategies.

At a threshold of $50,000 per life-year gained, immunohistochemistry with BRAF testing was the best strategy in 53% of iterations; MMRpro plus germline was best in 15% of iterations. At a threshold of $100,000 per life-year gained, immunohistochemistry with BRAF testing was the best strategy in 59% of iterations; microsatellite instability plus immunohistochemistry with BRAF testing was best in 26% of iterations.

Authors' conclusions
The authors concluded that strategies to identify families with Lynch syndrome could provide substantial clinical benefits at acceptable costs, especially for women. The cost-effectiveness depended on the uptake of screening and preventive measures among relatives.

CRD commentary
Interventions:
A wide range of screening strategies was considered. The reference strategy (no active diagnosis) applied to most clinical settings, enhancing the external validity of the comparison.

Effectiveness/benefits:
A systematic search of the literature was conducted to identify the key published sources for the clinical inputs, in
addition to those already identified by the EGAPP initiative. The main sources were meta-analyses and systematic reviews, which should ensure high validity, but the designs of the studies included in the meta-analyses were not given. Extensive sensitivity analysis was conducted on all the clinical estimates. The authors stated that quality-of-life estimates were not available for the risk categories used in their model, so quality-adjusted life-years were not used as the summary benefit measure. Life-years were appropriate for capturing the impact of the disease on the patients’ health and they allow comparisons to be made with the benefits of other health care interventions.

Costs:
The sources of costs and the items included were consistent with the perspective of the third-party payer, as stated by the authors. Most of the costs were from valid US sources including Medicare tariffs and a technology assessment. They were reported for each item, or as yearly costs (for cancer treatment). The cost estimates were varied stochastically and the ranges of values were reported. Details, such as the price year and discount rate, were reported.

Analysis and results:
The expected costs and life-years were extensively presented for all strategies, as well as the projected cases and deaths associated with colorectal, endometrial, and ovarian cancer. Incremental cost-effectiveness ratios were calculated to identify the best strategy at commonly used cost-effectiveness thresholds. Appropriate sensitivity analyses were carried out to assess the uncertainty, and the results were clearly presented and discussed. For each model input, the probabilistic distribution and its values were given. The authors acknowledged some limitations to their analysis, such as the exclusion of other potentially relevant types of cancer and second-degree relatives. In general, the results appear to be specific to the USA.

Concluding remarks:
The methods were valid, which supports the authors’ conclusions.

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