Cost-effectiveness of microsatellite instability screening as a method for detecting hereditary nonpolyposis colorectal 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.

Health technology
The use of microsatellite instability (MSI) screening as a method for detecting hereditary nonpolyposis colorectal cancer (HNPCC) in patients with newly diagnosed colorectal cancer (CRC). The intervention consisted of an initial office-based screening to determine eligibility, as stated by the Bethesda guidelines, followed by tumour testing for MSI. Those with MSI were offered genetic testing for HNPCC. The siblings and children of patients with CRC and HNPCC mutation were offered genetic testing, and those who were found to carry the mutation received lifelong CRC screening every 3 years, beginning at 25 years or their current age, whichever was greater.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with newly diagnosed CRC, and their siblings and children.

Setting
The setting was secondary care. The economic study was performed in Seattle, USA.

Dates to which data relate
Most of the effectiveness data were collected from studies published between 1983 and 2000. The cost data were mainly collected from studies published between 1993 and 2001. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, a personal communication, a study submitted for publication, authors’ assumptions and expert opinion.

Modelling
A decision model was used to model the cost-effectiveness of identifying HNPCC carriers among patients with newly diagnosed CRC. Two scenarios were considered in the base-case analysis. One scenario considered the costs and outcomes for newly diagnosed CRC patients only. A second scenario included the costs and outcomes not only for patients found to be mutation carriers, but also for their siblings and children.
Outcomes assessed in the review
Only the model parameters of test efficacy and treatment efficacy are mentioned here. However, various epidemiological, compliance and other variables were derived in the review. The effectiveness parameters included, amongst others, the sensitivity and specificity of the guidelines, the MSI test and the mismatch repair mutation (MMR) test, the proportion of non-positive and non-negative MMR test results that are inconclusive, and the probability of death caused by colectomy.

Some of the effectiveness parameters for siblings and children were the relative mortality risk for increased surveillance in HNPCC-positive patients, and the probability that siblings and children are HNPCC positive given that the proband is either HNPCC positive or negative.

Study designs and other criteria for inclusion in the review
A systematic review was not undertaken. It appears that the estimates were derived from, amongst others, a case-control study, a randomised study, at least one clinical trial, and some census and statistical data studies. However, neither the design of the other primary studies nor the criteria used for their inclusion were reported by the authors.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
At least 20 published studies were included in the review as sources of effectiveness data.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
Only effectiveness parameters of tests and colectomy are reported here (other results are provided in the paper).

The sensitivity of the guidelines was 70% and the specificity was 85%.

The sensitivity of the MSI test was 91% and the specificity was 93%.

The proportions of inconclusive non-positive and non-negative MMR test results were 20% (non-positive) and 6% (non-negative), respectively.

The sensitivity of the MMR test was 92.5% and the specificity was 99.7%.

The probability of death caused by colectomy was 0.
For siblings and children, the relative mortality risk for increased surveillance in HNPCC-positive patients was 34.8%; and

the probability that siblings and children were HNPCC positive was 0.5 if the patient was HNPCC positive, and 0.02 if the patient was HNPCC negative.

**Methods used to derive estimates of effectiveness**

Estimates of effectiveness were derived from experts' opinions and authors' assumptions.

**Estimates of effectiveness and key assumptions**

From the experts' opinions, the probability of locating a sibling was 0.65, the probability of locating a child was 0.75, and the probability that CRC patients agreed to the guideline assessment was 1.

The authors assumed that the life expectancy was one third higher for patients with HNPCC mutations and early-stage cancer than for those with sporadic cancer, and the life expectancy for HNPCC carriers decreased with more advanced stages at diagnosis.

**Measure of benefits used in the economic analysis**

The summary measure of benefit used in the economic analysis was the number of life-years gained (LYG). A Weibull model was used to convert survival rates to expected years of life. However, the number of HNPCC carriers identified in a hypothetical cohort of 129,400 newly diagnosed CRC patients was also synthesised with costs and several other intermediate outcomes determined by the model. A discount rate of 3% was also applied to the LYG.

**Direct costs**

The direct costs considered in the analysis appear to have been those of the health service. These included the cost of MSI, genetic counselling, genetic testing, CRC treatment and surveillance under usual care, and prophylactic colectomy for HNPCC-mutation carriers. When the siblings and children of the newly diagnosed CRC patients were considered, the costs associated with the location, diagnosis and follow-up of the relatives were also included.

The direct costs were obtained from a national survey of reimbursements to laboratories (which was undertaken for this study, as reported by the authors), a survey on reimbursements for services by the National Society of Genetic Counsellors, and the SEER-Medicare database. Therefore, the costs were estimated on the basis of actual data. The resource quantities and the costs were not reported separately. The costs reported were the average costs per procedure or per person. The price year stated was 1999. Discounting was performed using a 3% discount rate. This was appropriate since this is the discount rate commonly used in the USA and, moreover, the costs were estimated over a lifetime horizon.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

No indirect costs were reported.

**Currency**

US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were performed on all variables in the model to investigate variability in the data. The ranges over which the variables were varied were derived from the 95% confidence intervals (CIs), if available from the literature, or on expert opinion. A multi-way probabilistic sensitivity analysis was also performed to obtain a 90% CI for the cost-effectiveness estimators. This was based on 1,000 replications of the analysis with values drawn from distributions applied for the 15 most sensitive variables in the one-way analysis.

Estimated benefits used in the economic analysis
Assuming that 129,400 CRC cases would be detected during the first year of the programme, the number of HNPCC carriers identified would be 860. The undiscounted LYG with screening would be 1,082 for newly diagnosed CRC patients and 9,102 for the siblings and children of these patients. The discounted LYG for the probands and their relations from screening was 2009. The authors reported that the number of LYG was discounted at a 3% discount rate.

Cost results
The additional discounted cost incurred when the siblings and children were included for screening, compared with no testing, was $15,181,504. No absolute or incremental value was reported for just testing probands in comparison with no testing. Only selective costs are reported here (other costs are provided in the paper).

The guidelines assessment cost $33, the MSI test cost $120, and the MMR test for siblings and children cost $78.

The mean attributable cost for second diagnosis was $27,794 at stage 1, $28,872 at stage 2, $33,658 at stage 3, and $49,352 at stage 4.

The mean attributable cost for first diagnosis was $25,516 at stage 1, $28,166 at stage 2, $31,907 at stage 3, and $45,393 at stage 4.

Synthesis of costs and benefits
The costs and the benefits were combined by calculating a cost-effectiveness ratio (CER) and an incremental CER (ICER). The CER was calculated as the cost per carrier detected with the screening procedure. The ICER was calculated as the added cost per LYG with screening, compared to no screening, using a 3% discount rate for both the benefits and costs. The CER and ICER were calculated for newly diagnosed CRC patients, both alone and including their siblings and children.

When the costs and benefits were considered only for the newly diagnosed CRC patients, the CER was $12,815 per carrier detected with MSI screening. The ICER was $42,210 per LYG with MSI screening in comparison with no screening.

When the costs and benefits also considered the siblings and children, the resultant CER was $1,047 per carrier detected with MSI screening. The ICER was $7,556 per additional LYG with MSI screening in comparison with no screening.

The model was most sensitive to the estimated survival gain from screening siblings and children, the prevalence of HNPCC mutations among patients with newly diagnosed CRC, and the discount rate.

The 90% CI obtained for the ICER from the multi-way probabilistic analysis was $4,874, $21,576 per LYG.

Authors’ conclusions
Microsatellite instability (MSI) screening is cost-effective for the screening of patients with newly diagnosed colorectal cancer (CRC) and an appropriate personal and family cancer history. The cost-effectiveness of the intervention improves greatly if the siblings and children of mutation carriers can also be identified and screened.

CRD COMMENTARY - Selection of comparators
The choice of a 'do-nothing' alternative as the comparator was justified on the grounds that it was the current practice in the authors' setting. You must decide if this is an extended practice in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been undertaken, so the degree of internal validity was hard to assess. Consequently, the effectiveness estimates appear to have been taken from selected studies. The authors did not report the sources searched to identify primary studies, the criteria used to ensure the validity of the data, or the methods used to ensure the relevance and validity of the extracted data. Some estimates of effectiveness were derived from experts' opinions. The authors did not report the method used, the number and specialisation of the experts who participated, or the method by which they were selected. Given the inherent uncertainty with this type of study, sensitivity analyses on the model variables showed no impact on the overall cost-effectiveness of MSI screening. Some authors' assumptions were also used to derive estimates of effectiveness, but the authors did not justify these with reference to the medical literature. These facts introduce uncertainty into the reliability of the conclusions.

**Validity of estimate of measure of benefit**
The estimate of benefits was modelled using a Weibull model that converted survival rates in to estimated years of life. This instrument may have been appropriate since it has been used similarly in other studies. The authors reported the incremental benefits obtained with screening when compared to no screening, but the benefits for each of the strategies, separately, were not reported. As the authors stated, the quality of life of patients undergoing the MSI screening programme may deteriorate. For the intervention to be effective, the gains in quality of life obtained by preventing CRC must outweigh the costs in terms of deterioration in the quality of life of this cohort of patients, but this was not considered in the study.

**Validity of estimate of costs**
The authors reported that a societal perspective was adopted but they did not include the indirect costs, which, as they acknowledged, appear to have been relevant for the target population under analysis. Most of the cost categories relevant to the health service perspective finally adopted may have been included in the economic analysis. However, the authors reported that some costs were not included, such as those associated with starting the screening programme. These may be relevant since MSI screening does not seem to be a widely used technology, and therefore, these costs would be important when implementing the intervention. The price year was stated. The resource quantities and the costs were not reported separately, which hinders reflation exercises to other settings. Moreover, it was unclear which of the costs were considered for the comparator. Uncertainty in the cost results was investigated through appropriate sensitivity analyses.

**Other issues**
Appropriate comparisons of the findings with those from other studies were not reported. The issue of the generalisability of the results to other settings was addressed, in the sense that the authors recommended that further research be performed to obtain the prevalence of HNPCC in non-European groups if the use of an MSI screening programme is to be widespread. The authors' conclusions reflected the scope of the analysis. The full absolute cost and benefit results could have been reported. In addition, the testing of relations along with probands could have been compared with testing only probands in an incremental analysis.

**Implications of the study**
The authors recommended further research to investigate the prevalence of HNPCC in a wider range of population groups, apart from the European populations, before undertaking widespread MSI screening in a heterogeneous population. They warned about the legal, health insurance and health system barriers that contacting and screening relatives imply. These issues must be considered before implementing an MSI screening policy to detect HNPCC.

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**Other publications of related interest**


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