Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population

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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 twenty primary screening strategies, to identify Lynch syndrome mutations in the general population, to detect colorectal and endometrial cancers. The authors concluded that screening of individuals for mismatch repair gene mutations, starting with a risk assessment between the ages of 25 and 35 years, followed by genetic testing of those whose risk exceeded 5%, was cost-effective. The study was well presented and the methods were valid and accurate. The authors’ conclusions are robust.

Type of economic evaluation
Cost-utility analysis

Study objective
This study examined the cost-effectiveness of several primary screening strategies, using genetic testing, to identify Lynch syndrome mutations in the general population, to detect colorectal and endometrial cancers. The strategies considered various ages for starting risk assessment and various risk thresholds for the implementation of genetic testing.

Interventions
Twenty primary screening strategies were considered, with risk assessment starting at the ages of 20, 25, 30, 35, or 40 years. The risk assessment was followed by four-gene mutation testing for those individuals whose risk of carrying a mutation exceeded the thresholds of zero, 2.5%, 5%, or 10%. These strategies were compared with the usual practice of testing of individuals with appropriate clinical risk factors, after a malignancy was detected, and offering testing to close relatives of those diagnosed with Lynch syndrome.

Location/setting
USA/secondary care.

Methods
Analytical approach:
The analysis was based on the published Archimedes Model, a large-scale model that simulated the natural history of various diseases, including cancer. A lifetime horizon was considered. The authors stated that a societal perspective was adopted.

Effectiveness data:
The clinical data were from the literature and publicly available sources. Literature reviews were conducted with the aim of finding key studies for several model parameters. The details of these studies were given in an appendix and they included clinical trials, prospective and retrospective studies, national databases, and meta-analyses. The accuracy (sensitivity and specificity of genetic testing) was the key input of the model and was from meta-analyses. The authors selected the most appropriate estimate from the published evidence. Where no sources were found, some estimates were assumed by the authors.

Monetary benefit and utility valuations:
The utility values were derived from the literature. Some studies used the Short Form (SF)-36 Health Survey or the European Quality of life (EQ-5D) questionnaire to elicit the preferences for health conditions.
Measure of benefit:
Quality-adjusted life-years (QALYs) 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 the tests and interventions. These included the genetic tests (multiple and single), colonoscopy, ultrasound, biopsy, gynaecologic visits, and treatment of colorectal and endometrial cancers. The genetic test costs came from a survey of US commercial test providers. The costs of procedures and treatments were based on Medicare reimbursement rates and data from a published economic evaluation of the prevention of cancer in Lynch syndrome. The costs were in US dollars ($) and a 3% annual discount rate was applied. The price year was 2009.

Analysis of uncertainty:
One-way sensitivity analyses were conducted on a few key model parameters. The ranges were based on published studies and authors’ assumptions.

Results
In a hypothetical cohort of 100,000 members of the general population, the projected QALYs gained, compared with usual practice, with zero risk, ranged from 933 starting at 20 years to 546 at 40 years. With a risk of 2.5%, they ranged from 313 at 20 years to 220 at 40 years. With a risk of 5%, they ranged from 151 at 20 years to 102 at 40 years. With a risk of 10%, they ranged from 69 at 20 years to 45 at 40 years.

The increase in costs in million, compared with usual care, with zero risk, ranged from $374.2 starting at 20 years to $193.9 at 40 years. With 2.5% risk, it ranged from $18.6 at 20 years to $11.8 at 40 years. With 5% risk, it ranged from $4.7 at 20 years to $2.7 at 40 years. With 10% risk, it ranged from $0.9 at 20 years to $0.3 at 40 years.

Compared with usual care, the average cost-effectiveness ratios ranged from $7,745 per QALY with a 10% risk starting at 40 years to $401,019 with zero risk starting at 20 years. All strategies with a risk threshold of 5% or 10% had an average cost per QALY lower than $50,000 regardless of starting age. When the strategies were compared with each other, the strategy with the highest benefits and with a cost-effectiveness ratio below $50,000 per QALY was to test those with a risk of 5% starting at 25 years.

The most influential model parameters were the discount rate and the prevalence colorectal cancer associated with Lynch syndrome.

Authors’ conclusions
The authors concluded that screening of individuals for mismatch repair gene mutations, starting with a risk assessment between the ages of 25 and 35 years, followed by genetic testing of those whose risk exceeded 5%, was cost-effective.

CRD commentary
Interventions:
The rationale for the selection of the comparators was clear. An appropriate range of screening strategies was selected to reflect the possible age and risk threshold combinations. The background comparator was the usual pattern of care in the authors’ setting and this was widely generalisable to other health care systems.

Effectiveness/benefits:
The clinical data were generally derived from literature reviews. The authors selected the most appropriate studies, which had various designs. In general, the epidemiological data were from large databases or statistics, while the test accuracy, which was a key parameter, was from a meta-analysis, which ensures high internal validity. The authors described the selected studies in the appendix. Little information on the derivation of the utility values was given. Some of the studies used the SF-36 or EQ-5D instruments to elicit preferences for the health conditions and these were appropriate tools. QALYs were an appropriate benefit measure given the impact of the disease on both survival and quality of life.

Costs:
The authors stated that a societal perspective was adopted, but the cost categories reflected a third-party payer viewpoint. The sources were typical of those used in US studies and the costs were generally presented as category totals, as often occurs when Medicare data are used. The resource use and unit costs were not presented separately. Some of the costs were varied in the sensitivity analysis. Other details, such as the price year and discount rate, were given.

**Analysis and results:**
The costs and benefits were extensively presented for all strategies and both average and incremental ratios were calculated. The uncertainty was addressed in one-way sensitivity analyses, which focused on the key model parameters, due to the large number of strategies compared. The authors stated that conservative assumptions were generally made and some potential benefits from genetic tests were omitted. Conventional discounting was applied to both the costs and benefits. The results appear to be typical of the US setting and it is not clear whether they are transferable to other settings.

**Concluding remarks:**
The study was well presented and the methods were valid and accurate. The authors’ conclusions are robust.

**Funding**
Supported by a grant from Myriad Genetic Laboratories, Inc.

**Bibliographic details**

**PubMedID**
21088223

**DOI**
10.1158/1940-6207.CAPR-10-0262

**Original Paper URL**
http://cancerpreventionresearch.aacrjournals.org/content/4/1/9.abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Colorectal Neoplasms, Hereditary Nonpolyposis /economics /genetics; Cost-Benefit Analysis; Endometrial Neoplasms; Female; Genetic Testing /economics; Humans; Incidence; Michigan /epidemiology; Mutation /genetics; Neoplasm Proteins /genetics; Quality-Adjusted Life Years; Risk Assessment; Standard of Care

**AccessionNumber**
22011000281

**Date bibliographic record published**
04/05/2011

**Date abstract record published**
18/05/2011