Testing strategies for Lynch syndrome in people with endometrial cancer: systematic reviews and economic evaluation

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Scientific summary

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Scientific summary

Background

Lynch syndrome is an inherited genetic condition. Lynch syndrome is associated with an increased risk of cancer, including colorectal, endometrial, gastric, pancreatic and kidney cancers. Recently, the National Institute for Health and Care Excellence has recommended that people who are diagnosed with colorectal cancer are tested for Lynch syndrome [National Institute for Health and Care Excellence. *Molecular Testing Strategies for Lynch Syndrome in People with Colorectal Cancer*. Diagnostics guidance [DG27]. 2017. URL: www.nice.org.uk/guidance/dg27 (accessed 2 August 2019)].

Routine testing for Lynch syndrome among people with endometrial cancer is not currently conducted. Detection of Lynch syndrome might lead to reductions in the risk of developing cancer for both the individual and their family members (through surveillance and risk-reducing strategies such as chemoprevention) and the earlier treatment of cancers.

Objectives

The overall objective was to inform the National Institute for Health and Care Excellence diagnostics advisory committee on whether or not testing for Lynch syndrome in people who have endometrial cancer represents a cost-effective use of NHS resources.

Research questions

- Key question 1: what are the test accuracy, test failure rates and time to diagnosis of immunohistochemistry- and microsatellite instability-based strategies for detecting Lynch syndrome in people who have a diagnosis of endometrial cancer?
  Subquestions –

  1a. What is the concordance between immunohistochemistry- and microsatellite instability-based strategies for detecting Lynch syndrome in people who have a diagnosis of endometrial cancer?
  1b. What are the characteristics of discordant cases? [e.g. Do people with a high risk according to microsatellite instability testing and a low risk according to immunohistochemistry (or vice versa) have particular gene mutations, a family history of Lynch syndrome, different age profiles?]
  2. What are the types and frequencies of mismatch repair genetic mutations detected in people with endometrial cancer who are diagnosed with Lynch syndrome?

- Key question 2: what are the benefits and harms of testing for Lynch syndrome among people who have endometrial cancer, and/or their relatives?
  Subquestions –

  1. What are the benefits and harms of colorectal cancer surveillance for people with Lynch syndrome identified following a diagnosis of endometrial cancer, and/or their relatives?
  2. What are the benefits and harms of gynaecological cancer surveillance for people with Lynch syndrome identified following a diagnosis of endometrial cancer, and/or their relatives?

- Key question 3: what is the cost-effectiveness of testing for Lynch syndrome among people diagnosed with endometrial cancer using immunohistochemistry- and microsatellite instability-based strategies, compared with the current pathway for the diagnosis of Lynch syndrome?

The testing strategies investigated were as follows:

- strategy 1 – microsatellite instability testing alone
- strategy 2 – microsatellite instability testing with mutL homologue 1 (MLH1) promoter hypermethylation testing
- strategy 3 – immunohistochemistry-based testing
- strategy 4 – immunohistochemistry testing with *MLH1* promoter hypermethylation testing
- strategy 5 – microsatellite instability testing followed by immunohistochemistry testing
- strategy 6 – microsatellite instability followed by immunohistochemistry testing with *MLH1* promoter hypermethylation testing
- strategy 7 – immunohistochemistry followed by microsatellite instability testing
- strategy 8 – immunohistochemistry testing followed by microsatellite instability testing with *MLH1* promoter hypermethylation testing
- strategy 9 – microsatellite instability and immunohistochemistry testing
- strategy 10 – microsatellite instability and immunohistochemistry testing with *MLH1* promoter hypermethylation testing
- strategy 11 – germline testing only.

Methods

Search terms for endometrial cancer and Lynch syndrome or the associated proteins were used to identify studies to answer key questions 1 and 2. Searches were conducted in the following databases, from inception: MEDLINE ALL (via Ovid), EMBASE (via Ovid), Cochrane Database of Systematic Reviews (via Wiley Online Library), Cochrane Central Register of Controlled Trials (via Wiley Online Library), Database of Abstracts of Reviews of Effects (via the Centre for Reviews and Dissemination), Health Technology Assessment Database (via the Centre for Reviews and Dissemination), Science Citation Index (via Web of Science), Conference Proceedings Citation Index – Science (via Web of Science) and the PROSPERO international prospective register of systematic reviews (via the Centre for Reviews and Dissemination). In addition, references of included studies and relevant systematic reviews were checked and experts on the team were consulted.

Studies were included for key question 1 if they provided test accuracy data using the defined reference standard or information on concordance between index tests, test failures or time to diagnosis. The reference standards considered appropriate in this review were sequencing in combination with multiplex ligation-dependent probe amplification, long-range polymerase chain reaction and targeted array comparative genomic hybridisation. Head-to-head test accuracy studies were prioritised. Non-human studies, letters, editorials, qualitative studies and studies of women with pre-cancerous conditions of the uterus were excluded. For question 2, end-to end studies of testing for Lynch syndrome among people who had been diagnosed with endometrial cancer followed by colorectal or gynaecological cancer surveillance were included. Studies that assessed only the surveillance were also included for the subquestions. Studies that did not have endometrial cancer probands or a randomised controlled trial design were excluded. Assessment for inclusion was undertaken by two reviewers.

Quality assessment of eligible test accuracy studies was undertaken with a tailored Quality Assessment of Diagnostic Accuracy Studies-2 tool, and the quality appraisal tool for studies of diagnostic reliability for concordance studies. Methodological quality was assessed by two independent reviewers.

A de novo economic model was constructed to estimate the cost-effectiveness of alternative strategies for testing for Lynch syndrome. The model comprises two parts: a decision tree component, used to calculate the yield from each strategy, and a flexible cohort lifetime model, used to calculate the impact of being identified with Lynch syndrome at different ages, for males and females, for those without diagnosed colorectal or endometrial cancer and those recently diagnosed with endometrial cancer.

The decision tree part-models all 11 testing strategies outlined previously. The outcome model simulates lifetime incidence and survival of colorectal and endometrial cancer for a cohort of individuals who have Lynch syndrome, from the point of discovery onwards. Costs and quality-adjusted life-years are discounted at a rate of 3.5% per year. Both models are conducted from an NHS and Personal Social Services perspective. The model has five states: cancer free, colorectal cancer, endometrial cancer, both colorectal and endometrial cancer, and dead. The endometrial cancer state comprises 10 'tunnel states' reflecting time since incidence. The cohort can be of any age from 0 to 100 years, male or female, and start in any state. For this decision problem, cohorts are simulated that are cancer free or recently diagnosed with endometrial cancer, male or female, and aged in annual increments between 25 and 74 years. This gives 200 cohorts in total. Outcomes were not modelled for those without Lynch syndrome, on the assumption that they experience no long-term costs and benefits from Lynch syndrome testing.

Data sources to inform the model were drawn from the systematic review and from previous work conducted for the National Institute for Health and Care Excellence to assess the clinical effectiveness and cost-effectiveness of Lynch syndrome testing for those recently diagnosed with colorectal cancer. We made a number of assumptions, mainly in line with the previous work, including that, for every woman recently diagnosed with endometrial cancer found to have Lynch syndrome, six relatives would be offered cascade testing, of whom 2.5 would be first-degree relatives. Those who are found to have Lynch syndrome are offered biennial colonoscopies and (for women who are endometrial cancer free) prophylactic hysterectomy and bilateral salpingo-oophorectomy. Assumptions also included that biennial colonoscopies would be offered between the ages 25 and 74 years, with uptake rates of 100%; prophylactic hysterectomy and bilateral salpingo-oophorectomy would be offered between the ages of 25 and 70 years; and uptake by age 50 years would be 28%, rising to 75% by age 65 years, and peaking at 80%. Gynaecological surveillance was assumed to reduce annual mortality from endometrial cancer by 10.2%, but not to reduce incidence. Aspirin chemoprophylaxis would be offered to all, assuming 100% uptake, with the probability of developing cancer reduced by a factor of 0.56 each year (applied equally to endometrial and colorectal cancer risks). Scenario analyses were used to investigate changing model inputs for test accuracy and test costs; the disutility associated with cancer, excluding the estimated benefits of gynaecological surveillance and aspirin prophylaxis; and extending the colorectal screening interval to 3 years. This was to reflect the uncertainty surrounding data available from the literature to inform these model inputs.

Results (research findings)

Clinical effectiveness

The search identified 6259 records, of which 44 were eligible for key question 1. One additional unpublished study was provided by the National Institute for Health and Care Excellence, and was included for key question 1 [The Proportion of Endometrial Tumours Associated with Lynch Syndrome (PETALS) study; Dr Neil AJ Ryan, University of Manchester, 11 November 2019, personal communication]. For question 1, the 45 included studies reported on approximately 10,600 participants, ranging from 12 patients to 1459 patients.

The median prevalence of Lynch syndrome across studies in unselected populations was 3.2%. Thirty-two studies provided prevalence data based on 349 cases of Lynch syndrome and 89 variants of uncertain significance.

For key question 1, the 45 papers described 40 studies, of which seven provided full test accuracy data, 25 studies (28 papers) provided partial test accuracy data (incomplete 2 × 2 table) and 23 provided data on concordance. The most common reason for providing only partial test accuracy data was failure to give the reference standard test to index test-negative patients. In general, the methodological and reporting quality of the complete test accuracy studies were poor, with no study rated as having a low risk of bias in all domains.

A meta-analysis of test accuracy was not possible because of the small number of heterogeneous studies. Four studies provided head-to-head test accuracy data for immunohistochemistry- and microsatellite instability-based testing, although the numbers of included tumours were not identical for each of the tests owing to insufficient tumour tissue being available and to test failures. For immunohistochemistry, there were 28 true positives, 78 false positives, 235 true negatives and five false negatives; point estimates ranged from 66.7% to 100% for sensitivity, and from 60.9% to 83.3% for specificity. For microsatellite instability testing, there were 21 true positives, 57 false positives, 232 true negatives and eight false negatives; point estimates ranged from 41.7% to 100% for sensitivity, and from 69.2% to 89.9% for specificity.

Accuracy data by strategy were sparse. Considering only index test-positive cases, reference standard results were available for strategies 1, 3, 4 and 10 only. For strategy 1 (microsatellite instability testing alone), eight studies provided data. There were 39 true positives and 212 false positives out of 1402 women tested. For strategy 3 (immunohistochemistry-based testing alone), five studies provided data. There were 69 true positives and 193 false positives out of 552 women tested. For strategy 4 (immunohistochemistry testing with *MLH1* promoter hypermethylation testing), three studies provided test accuracy data. There were 27 true positives and 49 false positives out of 522 women tested. For strategy 10 (microsatellite instability and immunohistochemistry testing with *MLH1* promoter hypermethylation testing), six studies provided data. There were 94 true positives and 311 false positives out of 1627 women tested. For strategy 11 (germline testing only), nine studies provided data, whereby women were offered the reference standard(s) irrespective of the result of index tests. Lynch syndrome was identified in 166 out of 1375 (12.1%) women tested.

Overall, out of 7147 women with endometrial cancer who were eligible for inclusion in the studies, 138 (1.9%) had insufficient tumour tissue available for testing.

Twenty-three studies provided data on concordance between immunohistochemistry- and microsatellite instability-based testing. There was a high level of agreement between the results of the tests (median agreement = 94.3%, lowest level of agreement = 68.2%, highest level of agreement = 100%), which suggests that there may be limited value in using both tests together.

No studies were eligible for key question 2.

Cost-effectiveness

We identified five previous economic analyses on the use of different testing strategies to identify Lynch syndrome in women with endometrial cancer. These informed the design of the economic model.

The economic model indicated that the immunohistochemistry with *MLH1* promoter hypermethylation test strategy for Lynch syndrome was the most cost-effective testing strategy for reflex testing in endometrial cancer probands and their relatives. The base case produced an incremental cost-effectiveness ratio of £9420 per quality-adjusted life-year when compared with a no-testing strategy, so it is cost-effective at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year. The second most cost-effective testing strategy is immunohistochemistry testing alone. However, pairwise analysis, which calculates the additional cost required to generate additional benefits when compared with an adjacent strategy (when ranked by lower cost/benefit), produces an incremental cost-effectiveness ratio in excess of £130,000, which is well above the accepted willingness-to-pay threshold of £20,000 per quality-adjusted life-year.

Results are robust across all scenario analyses undertaken, showing that immunohistochemistry with *MLH1* promoter hypermethylation testing is the most cost-effective testing strategy, with incremental cost-effectiveness ratios ranging from £5690 to £20,740. Scenario 8, in which the benefit of surveillance to reduce colorectal cancer incidence is removed, is the only incremental cost-effectiveness ratio that minimally exceeds the UK willingness-to-pay threshold (at £20,740).

A sensitivity analysis identified the main cost drivers of the incremental cost-effectiveness ratio as the percentage of relatives accepting counselling and the prevalence of Lynch syndrome in the population. Varying these parameters proved highly influential: the incremental cost-effectiveness ratio for immunohistochemistry with *MLH1* promoter hypermethylation testing remained < £20,000 per quality-adjusted life-year throughout. A probabilistic sensitivity analysis of cost-effectiveness acceptability based on 10,000 simulations showed a 93% probability that immunohistochemistry with *MLH1* promoter hypermethylation testing is cost-effective at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year.

Conclusions

The economic model suggests that testing women with endometrial cancer for Lynch syndrome is cost-effective. The most cost-effective testing strategy was immunohistochemistry followed by methylation. However, there were limited data to inform the economic model, for example for test accuracy, and the benefits of colorectal and endometrial surveillance once Lynch syndrome is detected. These estimates have a high risk of bias, and so model results should be interpreted with caution.

Further research is needed to understand:

- The effect of earlier intervention on long-term outcomes, as only observational cohorts at high risk of bias were available. In particular, little is known about the balance of benefits and harms of gynaecological cancer surveillance. Randomised controlled trials would provide evidence with lower risk of bias.
- The sensitivity of the testing strategies. The volume of test accuracy studies was significant, but most did not give the reference standard to index test-negative women. The full test accuracy studies, in which all participants received the reference standard, contained few cases of Lynch syndrome. Therefore, little is known about test sensitivity and false negatives. Although full test accuracy studies with large sample sizes may be prohibitively expensive because of the low prevalence of Lynch syndrome, follow-up of negative cases through disease registers could be used to determine false negative cases. Furthermore, there are very limited data on the test accuracy of microsatellite instability testing followed by *MLH1* promoter hypermethylation testing in women with microsatellite instability-high (i.e. two or more markers show instability/> 30% of markers show instability).

Study registration

This study is registered as PROSPERO CRD42019147185.

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This report

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