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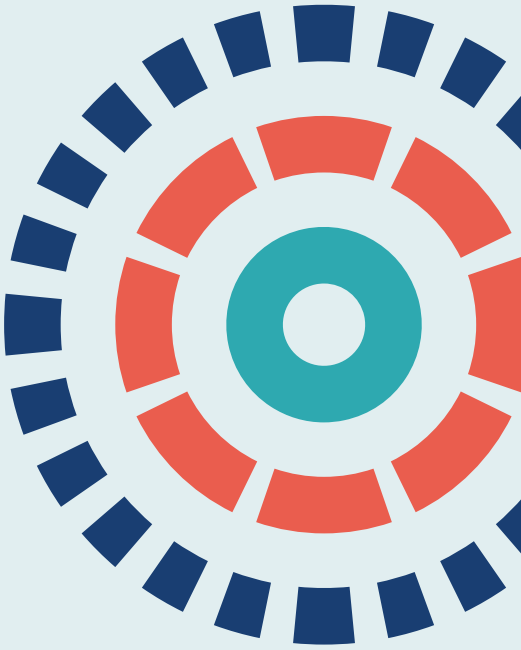

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Chris Stinton,[1] Mary Jordan,[1] Hannah Fraser,[1] Peter Auguste,[1] Rachel Court,[1] Lena Al-Khudairy,[1] Jason Madan,[1] Dimitris Grammatopoulos[2] and Sian Taylor-Phillips[1*]

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This report

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Abstract

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

Chris Stinton,[1] Mary Jordan,[1] Hannah Fraser,[1] Peter Auguste,[1] Rachel Court,[1] Lena Al-Khudairy,[1] Jason Madan,[1] Dimitris Grammatopoulos[2] and Sian Taylor-Phillips[1*]

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Background: Lynch syndrome is an inherited genetic condition that is associated with an increased risk of certain cancers. The National Institute for Health and Care Excellence has recommended that people with colorectal cancer are tested for Lynch syndrome. Routine testing for Lynch syndrome among people with endometrial cancer is not currently conducted.

Objectives: To systematically review the evidence on the test accuracy of immunohistochemistry- and microsatellite instability-based strategies to detect Lynch syndrome among people who have endometrial cancer, and the clinical effectiveness and the cost-effectiveness of testing for Lynch syndrome among people who have been diagnosed with endometrial cancer.

Data sources: Searches were conducted in the following databases, from inception to August 2019 – MEDLINE ALL, EMBASE (both via Ovid), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (both via Wiley Online Library), Database of Abstracts of Reviews of Effects, Health Technology Assessment Database (both via the Centre for Reviews and Dissemination), Science Citation Index, Conference Proceedings Citation Index – Science (both via Web of Science), PROSPERO international prospective register of systematic reviews (via the Centre for Reviews and Dissemination), NHS Economic Evaluation Database, Cost-Effectiveness Analysis Registry, EconPapers (Research Papers in Economics) and School of Health and Related Research Health Utilities Database. The references of included studies and relevant systematic reviews were also checked and experts on the team were consulted.

Review methods: Eligible studies included people with endometrial cancer who were tested for Lynch syndrome using immunohistochemistry- and/or microsatellite instability-based testing [with or without mutL homologue 1 (*MLH1*) promoter hypermethylation testing], with Lynch syndrome diagnosis being established though germline testing of normal (non-tumour) tissue for constitutional mutations in mismatch repair. The risk of bias in studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool, the Consolidated Health Economic Reporting Standards and the Philips' checklist. Two reviewers independently conducted each stage of the review. A meta-analysis of test accuracy was not possible because of the number and heterogeneity of studies. A narrative summary of test accuracy results was provided, reporting test accuracy estimates and presenting forest plots. The economic model constituted a decision tree followed by Markov models for the impact of colorectal and endometrial surveillance, and aspirin prophylaxis with a lifetime time horizon.

Results: The clinical effectiveness search identified 3308 studies; 38 studies of test accuracy were included. (No studies of clinical effectiveness of endometrial cancer surveillance met the inclusion criteria.) Four test accuracy studies compared microsatellite instability with immunohistochemistry. No clear difference in accuracy between immunohistochemistry and microsatellite instability was observed. There was some evidence that specificity of immunohistochemistry could be improved with the addition of methylation testing. There was high concordance between immunohistochemistry and microsatellite instability. The economic model indicated that all testing strategies, compared with no testing, were cost-effective at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year. Immunohistochemistry with *MLH1* promoter hypermethylation testing was the most cost-effective strategy, with an incremental cost-effectiveness ratio of £9420 per quality-adjusted life-year. The second most cost-effective strategy was immunohistochemistry testing alone, but incremental analysis produced an incremental cost-effectiveness ratio exceeding £130,000. Results were robust across all scenario analyses. Incremental cost-effectiveness ratios ranged from £5690 to £20,740; only removing the benefits of colorectal cancer surveillance produced an incremental cost-effectiveness ratio in excess of the £20,000 willingness-to-pay threshold. A sensitivity analysis identified the main cost drivers of the incremental cost-effectiveness ratio as percentage of relatives accepting counselling and prevalence of Lynch syndrome in the population. A probabilistic sensitivity analysis showed, at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year, a 0.93 probability that immunohistochemistry with *MLH1* promoter hypermethylation testing is cost-effective, compared with no testing.

Limitations: The systematic review excluded grey literature, studies written in non-English languages and studies for which the reference standard could not be established. Studies were included when Lynch syndrome was diagnosed by genetic confirmation of constitutional variants in the four mismatch repair genes (i.e. *MLH1*, mutS homologue 2, mutS homologue 6 and postmeiotic segregation increased 2). Variants of uncertain significance were reported as per the studies. There were limitations in the economic model around uncertainty in the model parameters and a lack of modelling of the potential harms of gynaecological surveillance and specific pathway modelling of genetic testing for somatic mismatch repair mutations.

Conclusion: The economic model suggests that testing women with endometrial cancer for Lynch syndrome is cost-effective, but that results should be treated with caution because of uncertain model inputs.

Future work: Randomised controlled trials could provide evidence on the effect of earlier intervention on outcomes and the balance of benefits and harms of gynaecological cancer surveillance. Follow-up of negative cases through disease registers could be used to determine false negative cases.

Study registration: This study is registered as PROSPERO CRD42019147185.

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Glossary

Cascadee A relative of someone who presents with cancer of interest, who can be further identified as a first- or second-degree relative.

Constitutional Present in every cell of the body.

Deoxyribonucleic acid sequencing Gene sequencing to detect point mutations and small insertions or deletions in genes. Next-generation deoxyribonucleic acid sequencing is also used for copy number variation analysis. Next-generation sequencing is also referred to as 'massive parallel sequencing' or 'second-generation sequencing'.

Germline Inherited.

Immunohistochemistry This is an index test performed on tumour tissue involving chemical staining of a selected panel of proteins to identify errors in these specific proteins.

Incremental cost-effectiveness ratio Difference in costs divided by the difference in effects of two different treatment strategies/interventions to produce a summary ratio of cost-effectiveness.

Lynch syndrome assumed Status given to probands with a positive tumour test but who have declined germline testing, or first-degree relatives who have declined germline testing.

Lynch syndrome negative People who have had germline testing and have obtained a negative result. These may be probands or relatives.

Lynch syndrome positive People who have had germline testing and have obtained a positive result. These may be probands or relatives.

Lynch-like People who have had a negative germline test and a negative somatic tumour testing.

Multiplex ligation-dependent probe amplification This is used to detect larger structural changes to genes (deletions, duplications or rearrangements); next-generation sequencing data can also identify structural variants.

MutL homologue 1 One of the four proteins identified leading to diagnosis of Lynch syndrome when a mismatch repair error occurs in one of these at germline level.

MutS homologue 2 One of the four proteins identified leading to diagnosis of Lynch syndrome when a mismatch repair error occurs in one of these at germline level.

MutS homologue 6 One of the four proteins identified leading to diagnosis of Lynch syndrome when a mismatch repair error occurs in one of these at germline level.

Postmeiotic segregation increased 2 One of the four proteins identified leading to diagnosis of Lynch syndrome when a mismatch repair error occurs in one of these at germline level.

Probabilistic sensitivity analysis Modelling technique using sample distributions from across input parameters to reflect uncertainty in a decision problem.

Proband A person who presents with a tumour of a cancer of interest.

Putative Lynch syndrome Alternative term for people with Lynch-like diagnosis.

Reference standard Germline testing of normal (non-tumour) tissue for constitutional mutations in mismatch repair genes (i.e. inherited mutations that are present in every cell). This involves both deoxyribonucleic acid sequencing and multiplex ligation-dependent probe amplification techniques.

Selected sample A group of participants limited to only those with particular characteristics, for example aged < 50 years without a personal/family history of cancer.

Somatic mutation Non-inherited mutations.

Unselected sample A group of participants not limited to those with particular characteristics.

Variant of uncertain significance People who have had a positive germline test, but the mutation found is not known to be pathogenic for Lynch syndrome.

List of abbreviations

CA-125	cancer antigen-125
CAPP2	Colorectal Adenoma/carcinoma Prevention Programme 2
CEAC	cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CRC	colorectal cancer
CRD	Centre for Reviews and Dissemination
DNA	deoxyribonucleic acid
EAG	external assessment group
EPCAM	epithelial cellular adhesion molecule
GP	general practitioner
H-BSO	hysterectomy and bilateral salpingo-oophorectomy
HNPCC	hereditary non-polyposis colorectal cancer
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IHC	immunohistochemistry
MLH1	mutL homologue 1
MLPA	multiplex ligation-dependent probe amplification
MMR	mismatch repair
MSH2	mutS homologue 2
MSH6	mutS homologue 6
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSI-L	microsatellite instability-low
MSS	microsatellite stable
NGS	next-generation sequencing
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
PCR	polymerase chain reaction
PETALS	Proportion of Endometrial Tumours Associated with Lynch Syndrome
PICO	population, intervention, comparator and outcome
PLSD	Prospective Lynch Syndrome Database
PMS2	postmeiotic segregation increased 2
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality-adjusted life-year
QAREL	quality appraisal tool for studies of diagnostic reliability
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	randomised controlled trial
SGO	Society of Gynaecologic Oncology
VUS	variant of uncertain significance
WTP	willingness to pay

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Lynch syndrome is an inherited condition that is caused by a problem in the genes. People who have Lynch syndrome have a higher risk of some types of cancer (such as bowel and womb cancers) than people who do not have it. Identifying Lynch syndrome could stop cancers developing, lead to earlier treatment for cancers and help to find other family members who might have it. Currently, the National Institute for Health and Care Excellence guidance recommends testing for Lynch syndrome in people who have bowel cancer. Our aim was to investigate whether or not we should test for Lynch syndrome in women with womb cancer, and their relatives. We investigated two main tests: immunohistochemistry and microsatellite instability. There was no clear evidence that one of these tests is better than the other. There is some evidence that both tests are reasonably accurate. There was no good-quality evidence about whether or not treating women with Lynch syndrome with extra cancer screening and aspirin improves their outcomes. We used the best evidence available in our economic model, but it was at high risk of bias. The economic model suggested that testing women with endometrial cancer for Lynch syndrome is cost-effective. The best test in the model was immunohistochemistry followed by methylation testing. We are unsure of these results because of the low quality of evidence available.

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.

Funding

This project was funded by the National Institute for Health Research (NIHR) Evidence Synthesis programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 42. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Description of the health problem

Purpose of the decision to be made

Lynch syndrome is an inherited genetic condition. It is caused by mutations in genes that are involved in repairing errors that occur in deoxyribonucleic acid (DNA) when cells replicate. When mutations occur in these genes, DNA errors are not repaired. Over time, this can lead to uncontrolled cell growth. Lynch syndrome is associated with an increased risk of cancers, including colorectal, endometrial, gastric, pancreatic and kidney cancers. There is 50 : 50 chance that a person with Lynch syndrome will pass it to their children.

Recently, the National Institute for Health and Care Excellence (NICE) has recommended that people who are diagnosed with colorectal cancer (CRC) are tested for Lynch syndrome.[1] 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 to earlier treatment of cancers.[2,3]

The external assessment group (EAG) assessed the accuracy of immunohistochemistry (IHC)-based and microsatellite instability (MSI)-based testing strategies to identify people who are at high risk of Lynch syndrome, and assessed the clinical effectiveness and cost-effectiveness of testing for Lynch syndrome among people who have endometrial cancer and their biological relatives. This will inform the NICE Diagnostics Advisory Committee guidance on whether or not testing for Lynch syndrome in people who have endometrial cancer represents a cost-effective use of NHS resources.

Population and target condition

Population: people with endometrial cancer

Endometrial cancer (cancer that develops from the lining of the uterus) is the most common gynaecological cancer in the Western world.[5] Each year in the UK, there are approximately 9300 new cases of endometrial cancer and 2200 endometrial cancer-related deaths.[6,7] The incidence of endometrial cancer generally increases with age, reaching a peak of 97.3 per 100,000 population between the ages of 75 and 79 years.[6,7] The most recent estimates suggest that people with endometrial cancers have a 1-year survival rate of 89.6% and a 5-year survival rate of 75.7%.[8] Risk factors for the development of endometrial cancer include obesity, nulliparity, early age at menarche, use of hormone-replacement therapy and Lynch syndrome.[9–11]

Target condition: Lynch syndrome

Lynch syndrome, formally called hereditary non-polyposis colorectal cancer (HNPCC), is a cancer-predisposition syndrome. It is estimated that there are approximately 175,000 people with Lynch syndrome in the UK.[12]

Lynch syndrome is usually caused by mutations to any one of four DNA mismatch repair (MMR) genes: mutL homologue 1 (*MLH1*), mutS homologue 2 (*MSH2*), mutS homologue 6 (*MSH6*) or postmeiotic segregation increased 2 (*PMS2*).[13] A small proportion of Lynch syndrome cases are caused by deletions to the epithelial cellular adhesion molecule (*EPCAM*) gene, which leads to epigenetic silencing of *MSH2*.[13] MMR genes encode proteins that are involved in recognising and repairing errors that occur in DNA during cell division. Mutations in MMR genes prevent DNA errors from being corrected. This can lead to uncontrolled cell growth and the development of cancer. A range of cancers have been associated with Lynch syndrome, the most common of which are endometrial and colorectal.[14] Lynch syndrome accounts for 2–9% of endometrial cancers.[15,16] By the age of 75 years, approximately 57% of people with Lynch syndrome will have endometrial cancer.[14] The type and prevalence of cancer appears to vary according to which of the genes are affected.[14]

Lynch syndrome has an autosomal dominant inheritance pattern, meaning that a person has a 50% chance of passing the mutated gene(s) onto their children.

Description of technologies under assessment

Three tests are considered in this assessment (see *Testing strategies*). There are two primary diagnostic tests (IHC and MSI), and a third test, *MLH1* promoter hypermethylation testing, may be added to either or both of these two. Eleven predefined testing strategies are considered, involving varying combinations of the three tests.

Immunohistochemistry

Immunohistochemistry, in this case, uses antibodies to look for the expression of four MMR proteins (*MLH1*, *MSH2*, *MSH6* and *PMS2*). An absence of staining for any of the proteins suggests a genetic mutation. IHC testing identifies which MMR gene is potentially affected. If *MLH1* has an abnormal expression, an additional test (*MLH1* promoter hypermethylation testing) can be conducted (see MLH1 *promoter hypermethylation testing*). IHC can detect non-functional, but antibody-binding, *MLH1* proteins (which would be incorrectly classified as normal);[17] therefore, this may lead to a false negative result.

Microsatellite instability testing

Microsatellites are short repeats of DNA sequences. These repeats are prone to acquiring errors. When the MMR genes are not functioning, these errors are not corrected. Mutations in MMR genes lead to variations in the size of these repeats. This is called MSI. MSI testing is used to determine whether or not there are differences in the repeat numbers between tumour and non-tumour regions in a person being tested. Various markers have been described.[18] The Bethesda guidelines[19] identify five markers (*BAT25*, *BAT26*, *DS123*, *D17S250* and *D5S346*) for MSI for Lynch syndrome. Typically, three classifications are derived from this approach:

1. MSI-high – two or more markers show instability/> 30% of markers show instability.
2. MSI-low – one marker shows instability/< 30% of markers show instability.
3. MSI-stable – zero markers show instability [also known as microsatellite stable (MSS)].

Additional testing can be conducted to help rule out sporadic epigenetic silencing of *MLH1*, which might present as Lynch syndrome (see MLH1 *promoter hypermethylation testing*).

MLH1 *promoter hypermethylation testing*

Hypermethylation is an epigenetic process that stops a protein being produced by a gene. *MLH1* promoter hypermethylation testing is initially conducted on tumours. The test is undertaken following IHC or MSI testing, usually on patients with a MSI-high result or IHC loss in the *MLH1* protein.
A positive result on this test suggests that the tumour is sporadic and not a result of Lynch syndrome. However, there is some evidence that constitutional epimutations of *MLH1* in normal tissue may be a cause of Lynch syndrome in a small number of cases.[20]

Comparators

The comparator currently used in the UK is no diagnostic testing for Lynch syndrome in those with endometrial cancer, and therefore no subsequent cascade testing of family members.

Reference standard

Typically, Lynch syndrome is diagnosed on the basis of constitutional mutations (i.e. mutations that are present in every cell) in MMR genes, which involves sequencing [including next-generation sequencing (NGS)] to detect point mutation, small insertions or deletions in these genes and multiplex ligation-dependent probe amplification (MLPA) or NGS to detect larger structural changes (such as deletions, duplications or rearrangements) to genetic sequences that could be missed by sequencing alone. Sequencing and MLPA may be used in combination to diagnose Lynch syndrome. However, these techniques also detect novel sequence variation in MMR genes that are of unknown significance. Sequencing of tumours can be used to identify sporadic tumours (i.e. those not caused by Lynch syndrome). If a person has deficient MMR (from tumour testing), but no germline mutation is identified and no somatic cause is identified, they can be considered to have Lynch-like syndrome (also known as putative or cryptic Lynch syndrome). Additional testing has been suggested in cases for which tumour testing is positive, but no Lynch syndrome-related pathogenic variants are identified.[21,22] This includes testing for other somatic or germline pathogenic variants [e.g. biallelic mutY DNA glycosylase (MUTYH), DNA polymerase epsilon (POLE), double somatic MMR variants].

Testing strategies

The NICE has published guidance on testing for Lynch syndrome among people diagnosed with CRC.[1] Currently, there is no NICE guidance for testing for Lynch syndrome in people who have endometrial cancer. The NHS National Genomic Test Directory provides testing criteria for people who have Lynch syndrome-related cancers.[23] In brief, testing is recommended in people who have a family history of Lynch syndrome-related cancers or who have been diagnosed with endometrial cancer before the age of 50 years. The 11 proposed testing pathways for the current review are outlined in *Figures 1–11*. Testing strategies include all possible combinations of index tests, followed by reference standard testing.

Possible diagnostic pathways and approaches to the management of Lynch syndrome have been suggested by a range of societies and expert groups, including the British Gynaecological Cancer Society,[24] the European HNPCC Expert group,[25] the Royal College of Obstetricians and Gynaecologists,[26] and the Manchester International Consensus Group.[22]

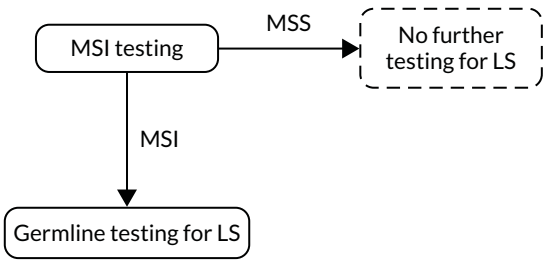

FIGURE 1 Strategy 1: MSI testing alone. LS, Lynch syndrome.

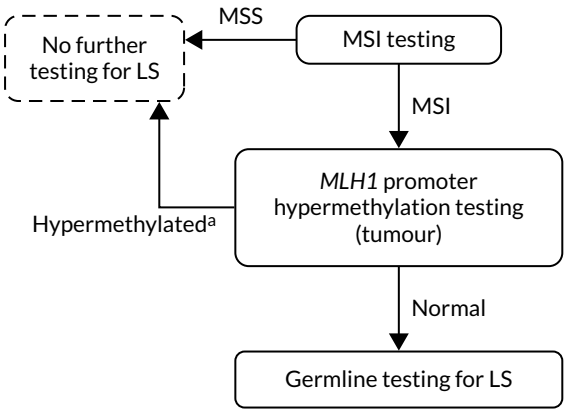

FIGURE 2 Strategy 2: MSI testing with *MLH1* promoter hypermethylation testing. a, If a germline sample is tested and is also hypermethylated, diagnose LS. LS, Lynch syndrome.

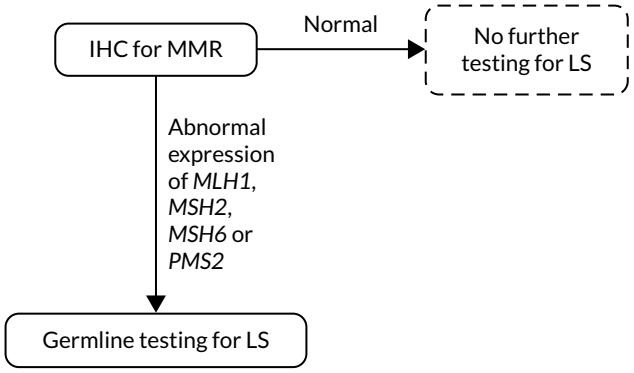

FIGURE 3 Strategy 3: IHC-based testing. LS, Lynch syndrome.

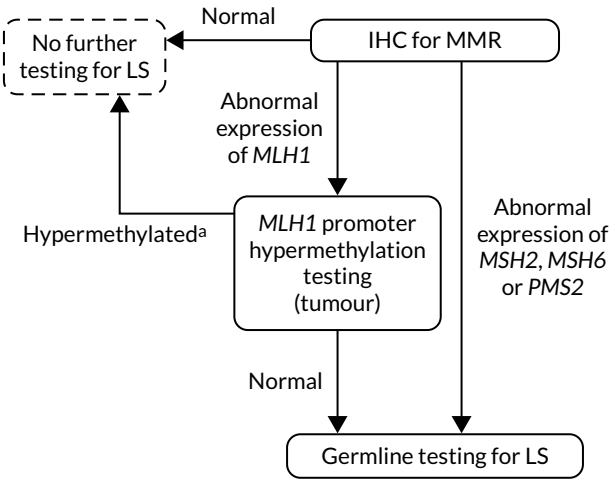

FIGURE 4 Strategy 4: IHC testing with *MLH1* promoter hypermethylation testing. a, If a germline sample is tested and is also hypermethylated, diagnose LS. LS, Lynch syndrome.

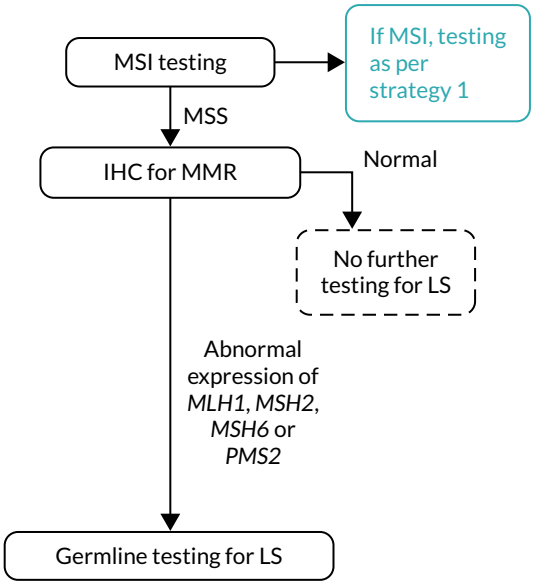

FIGURE 5 Strategy 5: MSI testing followed by IHC testing. LS, Lynch syndrome.

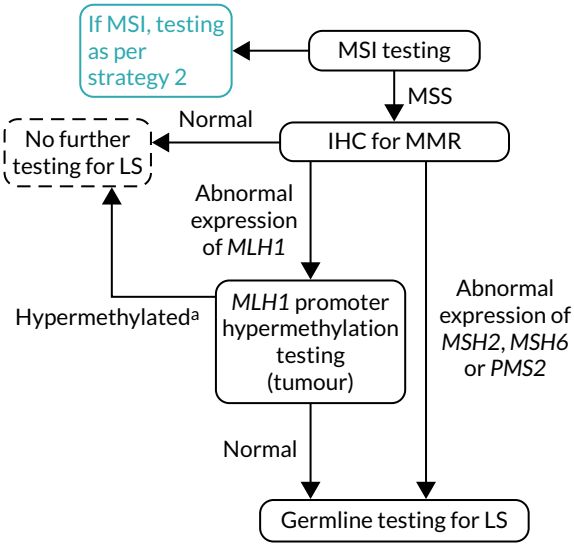

FIGURE 6 Strategy 6: MSI testing followed by IHC testing with *MLH1* promoter hypermethylation testing. a, If a germline sample is tested and is also hypermethylated, diagnose LS. LS, Lynch syndrome.

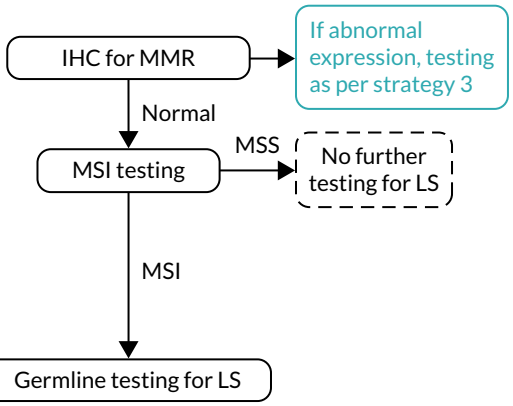

FIGURE 7 Strategy 7: IHC followed by MSI testing. LS, Lynch syndrome.

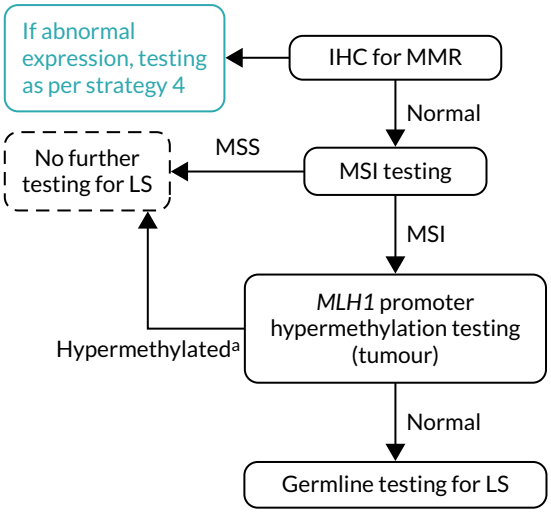

FIGURE 8 Strategy 8: IHC testing followed by MSI testing with *MLH1* promoter hypermethylation testing. a, If a germline sample is tested and is also hypermethylated, diagnose LS. LS, Lynch syndrome.

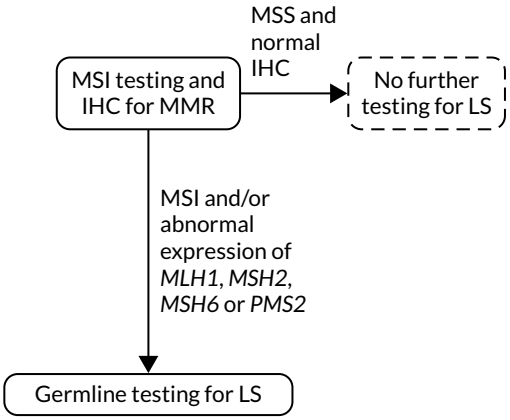

FIGURE 9 Strategy 9: MSI and IHC testing. LS, Lynch syndrome.

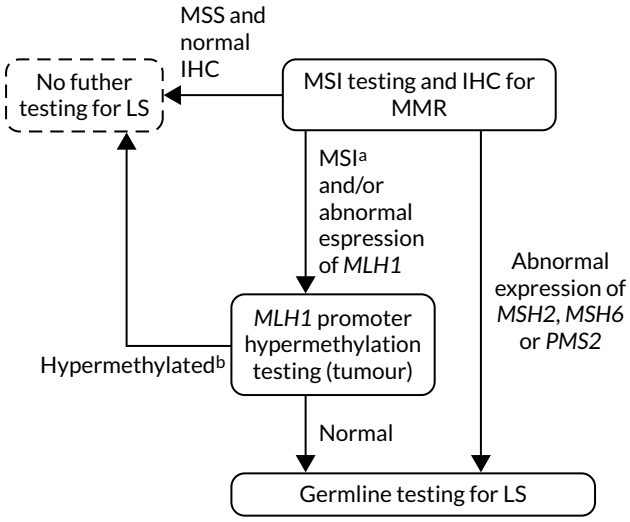

FIGURE 10 Strategy 10: MSI and IHC testing with *MLH1* promoter hypermethylation testing. a, *MLH1* promoter hypermethylation testing not conducted after MSI if *MLH1* expression on IHC is normal and abnormal expression of other MMR proteins is present; b, If a germline sample is tested and is also hypermethylated, diagnose LS. LS, Lynch syndrome.

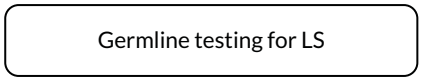

FIGURE 11 Strategy 11: germline testing only.

Care pathways

Currently, there is no NICE guidance on the testing and management of Lynch syndrome in people with endometrial cancer. There is NICE guidance available on molecular testing strategies and a care pathway for people with CRC.[1] NHS England's National Genomic Test Directory (Testing Criteria for Rare and Inherited Disease) specifies testing criteria for inherited MMR deficiency (Lynch syndrome).[23] Affected individuals with Lynch syndrome-related cancer should meet one of the following criteria:

- CRC (any age, as per NICE guidance[1]).
- Lynch syndrome-related cancer (aged < 50 years).
- Two Lynch syndrome-related cancers (any age, one is colorectal or endometrial).
- Lynch syndrome-related cancer and one or more first-degree relative has Lynch syndrome-related cancer (both occurred before the age of 60 years, one is colorectal or endometrial).
- Lynch syndrome-related cancer and two or more relatives (first-/second-/third-degree relatives) have Lynch syndrome-related cancer (all occurring before the age of 75 years, one is colorectal or endometrial).
- Lynch syndrome-related cancer and three or more relatives (first-/second-/third-degree relatives) have Lynch syndrome-related cancer (occurring at any age, one is colorectal or endometrial).

The recommended follow-up care for those with CRC diagnosed with Lynch syndrome is outlined in the guidelines for the management of hereditary CRC from the British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/UK Cancer Genetics Group,[27] NICE diagnostics guidance 27[1] and the NICE draft guideline on the effectiveness of aspirin in the prevention of CRC.[28] The main follow-on care recommended includes biennial colonoscopy surveillance, daily aspirin use for those with CRC and cascade testing for CRC probands. As of August 2018, uptake of the guidance on molecular testing strategies for CRC is around 97.5%.[1]

Testing for Lynch syndrome in people with endometrial cancer in the UK varies, with some NHS services testing all tumours and others doing no routine testing. The Manchester International Consensus Group,[22] American College of Obstetricians and Gynecologists,[29] and European Society for Medical Oncology[30] clinical practice guidelines recommended a range of surveillance and preventative measures for those with gynaecological cancers, including risk-reducing total hysterectomy and bilateral salpingo-oophorectomy (H-BSO), individualised counselling, colorectal surveillance, lifestyle modifications, use of the combined oral contraceptive and daily aspirin for those with MMR pathogenic variant carriers.

Outcomes

The outcomes from the clinical effectiveness assessment were as follows:

- prevalence of Lynch syndrome and variants of uncertain significance (VUSs)
- test accuracy.

The outcome from the cost-effectiveness analysis is cost per quality-adjusted life-year (QALY) for each of the 11 testing strategies, compared with usual care. Other intermediate outcomes reported include the following:

- number of probands with Lynch syndrome receiving Lynch syndrome surveillance (true positive accepting)
- number of probands with Lynch syndrome not receiving Lynch syndrome surveillance (Lynch syndrome positive who decline and those assumed to be false negative, although without testing this cannot be confirmed)
- number of VUSs and Lynch-assumed diagnoses.

Chapter 2 Decision questions and objectives

The overall aims of this project were to examine the test accuracy of IHC- and MSI-based strategies to detect Lynch syndrome in people who have endometrial cancer (key question 1), and to examine the clinical effectiveness (key question 2) and cost-effectiveness (key question 3) of testing for Lynch syndrome among people who have been diagnosed with endometrial cancers. The key questions for this review were as follows:

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

  1a. What is the concordance between IHC- and MSI-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 MSI testing and a low risk according to IHC (or vice versa) have particular gene mutations, a family history of Lynch syndrome, different age profiles?]
  2. What are the types and frequencies of MMR 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 CRC 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 IHC- and MSI-based strategies, compared with the current pathway for the diagnosis of Lynch syndrome?

Chapter 3 Methods

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Methods for assessing test accuracy

What are the test accuracy, test failure rates, and time to diagnosis of IHC- and MSI-based strategies for detecting Lynch syndrome in people who have a diagnosis of endometrial cancer?

Review subquestions:

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

Systematic review methods followed the principles outlined in the Cochrane *Handbook for Diagnostic Test Accuracy Reviews*[31] and the NICE Diagnostics Assessment Programme manual.[32]

Identification and selection of studies

Search strategy

The search strategy comprised the following main elements:

- searching of electronic bibliographic databases
- contacting experts in the field
- scrutiny of references of included studies and relevant systematic reviews.

A comprehensive search for test accuracy and clinical effectiveness studies was developed iteratively, with reference to a previous Lynch syndrome assessment[1,12] and scoping searches (Donna Barnes, NICE, 2019, personal communication). Searches were undertaken in a range of relevant bibliographic databases in August 2019. The search was developed in MEDLINE (via Ovid) and adapted appropriately for other databases. Search terms related to endometrial cancer and Lynch syndrome. No limits on study design, date or language were applied. Full details of the search strategies are provided in *Appendix 1*.

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 (CRD)], Health Technology Assessment (HTA) Database (via the CRD), 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 CRD).

In addition, references of included studies and relevant systematic reviews were checked and experts on the team were consulted.

Records were exported to EndNote X9 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA], where duplicates were systematically identified and removed.

Study eligibility criteria

The population, intervention, comparator and outcome (PICO) framework is used in *Table 1* to present the study inclusion criteria.

Papers that fulfilled the following criteria were excluded: non-human studies, letters, editorials and communications; qualitative studies; studies of women who have pre-cancerous conditions of the uterus (i.e. atypical endometrial hyperplasia); studies in which > 10% of the sample does not meet our inclusion criteria; studies without extractable numerical data; studies that provided insufficient information for assessment of methodological quality/risk of bias; articles not available in English;

TABLE 1 The PICO for key question 1

PICO element	Description
Population	All test accuracy questions: • People with endometrial cancer with no known diagnosis of Lynch syndrome
Target condition	All test accuracy questions: • Lynch syndrome
Intervention	All test accuracy questions: • Strategy 1: MSI-based testing without *MLH1* promoter hypermethylation testing • Strategy 2: MSI-based testing with *MLH1* promoter hypermethylation testing • Strategy 3: IHC without *MLH1* promoter hypermethylation testing • Strategy 4: IHC with *MLH1* promoter hypermethylation testing • Strategy 5: MSI-based testing followed by IHC without *MLH1* promoter hypermethylation testing • Strategy 6: MSI-based testing followed by IHC with *MLH1* promoter hypermethylation testing • Strategy 7: IHC followed by MSI-based testing without *MLH1* promoter hypermethylation testing • Strategy 8: IHC followed by MSI-based testing with *MLH1* promoter hypermethylation testing • Strategy 9: IHC and MSI-based tests consecutively without *MLH1* promoter hypermethylation testing • Strategy 10: IHC- and MSI-based tests consecutively with *MLH1* promoter hypermethylation testing
Reference standard	All test accuracy questions: • Genetic verifications of constitutional mutations in the MMR genes through sequencing with or without MLPA. If there are insufficient studies using these reference standards, we included studies using other diagnostic tests outlined in the Association for Clinical Genomic Science best-practice guidelines[33] for genetic testing and diagnosis of Lynch syndrome, (i.e. array-based comparative genomic hybridisation and long-range PCR)
Comparator	Key question: • No reflex testing Subquestions 1a and 1b: • IHC without *MLH1* promoter hypermethylation testing • IHC with *MLH1* promoter hypermethylation testing • MSI-based testing without *MLH1* promoter hypermethylation testing • MSI-based testing with *MLH1* promoter hypermethylation testing Subquestion 2: • No reflex testing

TABLE 1 The PICO for key question 1 (*continued*)

PICO element	Description
Outcome	Key question: • Test accuracy; detection rate; sensitivity and specificity; predictive values; likelihood ratios; diagnostic odds ratios; ROC curves and numbers of true positive, false positive, true negative and false negative results; and number of Lynch syndrome diagnoses • Test failures (rates, and data on inconclusive, indeterminate and excluded samples, failure due to insufficient tissue or any other reason) • Time to diagnosis • Time from test being conducted to test result being given, and/or time from test being conducted to diagnosis being given Subquestion 1a: • Concordance between IHC and MSI (fractions, kappa, % agreement) Subquestion 1b: • Any available characteristics of the population or tumours, including family history, and results of germline testing Subquestion 2: Types and frequencies of Lynch syndrome-related genetic mutations (*MLH1*, *MSH2*, *MSH6*, *PMS2*) in people newly diagnosed with Lynch syndrome after endometrial cancer, including results of *MLH1* promoter hypermethylation testing
Study design	Key question: • All study designs were included, including cross-sectional test accuracy studies, RCTs, cohort studies and case–control studies. Head-to-head (direct comparison) studies were prioritised Subquestions 1a and 1b: • Head-to-head studies only – cross-sectional test accuracy studies, test quality or accuracy studies nested within RCTs or cohort studies, case–control studies, test sets Subquestion 2: • All study designs were included, including RCTs, cross-sectional test accuracy studies, cohort studies and case–control studies
Publication type	All test accuracy questions: • Peer-reviewed papers • Abstracts and manufacturer data were included only if they provided numerical data and sufficient detail on methodology to enable assessment of study quality/risk of bias. Furthermore, only data on outcomes that have not been reported in peer-reviewed full-text papers were extracted and reported
Language	All test accuracy questions: • English

PCR, polymerase chain reaction; RCT, randomised controlled trial; ROC, receiver operating characteristic.

studies using index tests other than those specified in the inclusion criteria; and studies reporting the test accuracy of IHC- and MSI-based testing strategies in the general population (estimates arising from the general population are not generalisable to people who are at higher risk of Lynch syndrome because of the different risk profile). If sufficient head-to-head studies were identified that could provide meaningful analysis then other study designs were excluded.

Review strategy

Two reviewers (CS and LAK/HF) independently screened the titles and abstracts of records identified by the searches. Any disagreements were resolved through discussion or retrieval of the full publication. Potentially relevant publications were obtained, and assessed independently by two reviewers (CS and LAK/HF) with a coding tool (using inclusion/exclusion criteria) that has been piloted on a subsample of papers. Disagreements were resolved through consensus, with the inclusion of a third reviewer (HF/LAK, STP) if required. Records that were excluded at full-text stage are documented in *Appendix 3*, along with the reasons for their exclusion.

Extraction and study quality

Data extraction strategy

Two reviewers (CS and LAK/HF) extracted data independently using a piloted data extraction form (see *Appendix 2*). Disagreements were resolved through consensus, with the inclusion of a third reviewer (HF/LAK, STP) when required.

Assessment of study risk of bias

The risk of bias of test accuracy studies was assessed using a modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[34,35] Two reviewers (CS and LAK/HF) independently assessed study risks of bias. Disagreements were resolved through consensus, with the inclusion of a third reviewer (HF/LAK, STP) when required. As recommended by the QUADAS-2 group, an overall quality score was not determined.[34] The results of each risk-of-bias item are presented in *Tables 4–6*.

Methods of analysis/synthesis

In the gold-standard study design for assessing test accuracy, an entire sample of participants receives both the index test and the reference standard. This allows direct, unbiased comparisons of the agreement between the two tests. For reasons such as cost and practicality, in many test accuracy studies only a subsample of participants receive both tests, that is individuals who are index-test positive (at higher risk for the disease or condition) receive the reference standard, whereas individuals who are index-test negative do not receive the reference standard. Although this approach accurately reflects how tests are used in clinical practice, it leads to partial verification bias (also called detection bias or workup bias); data are missing and the true diagnostic status of participants who are negative on the index is not known. Partial verification can lead to overestimation of sensitivity and underestimation (or overestimation) of specificity.[36] Inaccurate test accuracy metrics can have an impact on clinical practice in relation to referral decisions and costs.

In this report, test accuracy results are divided into 'complete' test accuracy studies (in which all participants receive both the index test and the reference standard) and 'partial' test accuracy studies (in which only participants who are index-test positive receive the reference standard). For 'complete' test accuracy studies, we present results on all available test accuracy metrics, that is true positives, false positives, true negatives, false negatives, sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs). For 'partial' test accuracy studies, we present results for only those test accuracy metrics that relate to participants who have received both the index test and the reference standard, that is true positives, false positives and PPVs. Furthermore, as there is a risk that the likelihood that someone will receive the reference standard is associated with disease status (e.g. individuals who truly have a disease may be more likely to get the reference standard than those who do not have the disease), which biases PPV upwards, we included only studies in which at least 95% of women who were eligible for germline testing (i.e. those who were index-test positive) received it. The sensitivity, specificity, PPVs and NPVs presented in this report were all calculated by the review authors and based on the true positive, false positive, false negative and true negative values that were reported in individual papers. Confidence intervals (CIs) were calculated using Wilson's continuity correction.[37]

Test accuracy results are presented for testing strategies 1–10, comparing the index tests with the eligible reference standards. Test accuracy was not assessed for strategy 11, as this approach does not include an index test. For studies that included an initial test followed by *MLH1* promoter hypermethylation testing, we have analysed data at each stage of the process: (1a) IHC alone, then; (1b) IHC plus *MLH1* promoter hypermethylation testing; and (2a) MSI-based testing alone, then; (2b) MSI-based testing plus *MLH1* promoter hypermethylation testing. For IHC results, we have reported results together and separately for each protein. For MSI results, we have reported the panel used as per the papers, and provided a narrative summary of results on microsatellite instability-low (MSI-L) and microsatellite instability-high (MSI-H) patients. A subgroup analysis was not conducted for the different combinations of microsatellite markers because of the small number of studies and the wide range of panels used. The main analysis assumed that MSI-L was a negative test result. Owing to insufficient data, we did not conduct subgroup analyses of test accuracy by (1) age (≤ vs. > 70 years) or (2) people who have had a prior Lynch syndrome-related cancer (as defined in NHS England's *National Genomic Test Directory: Testing Criteria for Rare and Inherited Disease*[23]). A narrative summary of the evidence is presented because meta-analysis was not possible as a result of heterogeneity.

Variants of uncertain clinical significance on germline testing are not considered to have Lynch syndrome in our test accuracy analysis. The EAG has recorded how many of these there are for a scenario analysis in the economic modelling, considering either all or none as having Lynch syndrome. In practice, patients with a negative germline test result (with no somatic cause of the tumour identified), but a positive index test, may be considered to have Lynch-like syndrome (also known as putative or cryptic Lynch syndrome) and undergo further investigation or surveillance. In particular, further investigation is undertaken if there is family history of Lynch syndrome. Because of this, the EAG descriptively recorded the characteristics of these cases such as family history, IHC results and discordant cases between the two index tests. This provides contextual information about the possibility of Lynch-like syndrome, and variants of uncertain clinical significance. However, for the reporting of test accuracy data, germline testing using sequencing with or without MLPA was considered the primary reference standard. We included studies using other diagnostic tests outlined in the Association for Clinical Genomic Science best-practice guidelines[33] for genetic testing and diagnosis of Lynch syndrome, that is array-based comparative genomic hybridisation, and long-range polymerase chain reaction (PCR). The uncertainty around the effectiveness of germline testing to diagnose all cases of Lynch syndrome (see above regarding Lynch-like syndrome) is a potential weakness of the reference standard and a limitation of this review. As a subanalysis, for studies that report extra steps to the reference standard (e.g. sequencing of tumours or incorporating family history data), we recorded the additional tests that were used. Owing to the small number of studies using alternative tests, we did not compare the results of these multistage reference standards with the results of germline testing for *MLH1*, *MSH2*, *MSH6*, and *PMS2* using sequencing with or without MLPA.

Quality assessment strategy for test accuracy studies

Quality assessment of eligible test accuracy studies was undertaken with a tailored QUADAS-2 tool. Methodological quality was assessed by two independent reviewers. Disagreements were resolved by consensus or a third reviewer.

Modifications to tailor the form of the QUADAS-2 tool to the research question in terms of the risk-of-bias assessment are outlined in *Appendix 2* (the tailored QUADAS-2 form and guidance notes). No additional questions were added to the patient selection domain, the reference standard domain, flow and timing domain or any of the applicability sections. One question was added to the index test domain to assess whether or not quality assurance measures were in place.

Methods for assessing clinical effectiveness

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 CRC 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?

This question is to identify 'end-to-end studies', or 'test–treat trials'. End-to-end studies follow people from initial testing to treatment and final outcomes. These studies can remove the need for separate searches for model parameters for cost-effectiveness modelling.[32] We conducted a literature search to identify end-to-end studies of testing for Lynch syndrome among people who have been diagnosed with endometrial cancer, and/or their relatives. The same review searches and methods that were used for the test accuracy question (see *Methods for assessing test accuracy*) were employed to address this question. The subquestions are designed to identify the benefits and harms of the two main surveillance strategies that would be employed after identification of Lynch syndrome.

Systematic review methods followed the principles outlined in the CRD guidance for undertaking reviews in health care[38] and the NICE Diagnostics Assessment Programme manual.[32]

Identification and selection of studies

Search strategy

The same search strategy as described in the methods for test accuracy was used (see *Identification and selection of studies*).

Study eligibility criteria

Table 2 shows the study eligibility criteria.

Papers that fulfilled the following criteria were excluded: non-human studies, letters, editorials and communications; qualitative studies; studies of women who have pre-cancerous conditions of the uterus (i.e. atypical endometrial hyperplasia); studies in which > 10% of the sample does not meet our inclusion criteria; studies without extractable numerical data; studies that provided insufficient information for assessment of methodological quality/risk of bias; articles not available in English; and studies using index tests other than those specified in the inclusion criteria.

Review strategy

Two reviewers (CS and LAK/HF) independently screened the titles and abstracts of records identified by the searches. Any disagreements were resolved through discussion or retrieval of the full publication. Potentially relevant publications were obtained, and were assessed independently by two reviewers (CS and LAK/HF) with a coding tool (using inclusion/exclusion criteria) that had been piloted on a subsample of papers. Disagreements were resolved through consensus, with the inclusion of a third reviewer (HF/LAK or STP) when required.

Extraction and study quality

Data extraction strategy

No studies met the inclusion criteria; therefore, no data extraction took place.

TABLE 2 The PICO for key question 2

PICO element	Description
Population	Key question: • People with endometrial cancer with no known diagnosis of Lynch syndrome, and/or their relatives Subquestions 1 and 2: • People with endometrial cancer who have also been diagnosed with Lynch syndrome, and/or their relatives
Target condition	Key question: • Lynch syndrome Subquestion 1: • CRC Subquestion 2: • Gynaecological cancers (endometrial, ovarian, cervical, vaginal and vulval)
Intervention	Key question: • MSI-based testing (with/without *MLH1* promoter hypermethylation testing) followed by germline testing (sequencing with or without MLPA.; if there are insufficient studies using these reference standards, we will include studies using array-based comparative genomic hybridisation, and long-range PCR) for Lynch syndrome-related mutations (*MLH1*, *MSH2*, *MSH6*, *PMS2*), followed by any intervention for Lynch syndrome including preventative hysterectomy, aspirin, surveillance/testing for CRC or gynaecological cancers • IHC (with/without *MLH1* promoter hypermethylation testing) followed by germline testing (sequencing with or without MLPA; if there are insufficient studies using these reference standards, we will include studies using array-based comparative genomic hybridisation, and long-range PCR) for Lynch syndrome-related mutations (MLH1, MSH2, MSH6, PMS2), followed by any intervention for Lynch syndrome including preventative hysterectomy, aspirin, surveillance/testing for CRC or gynaecological cancers • Combinations of MSI-based testing and IHC (with/without *MLH1* promoter hypermethylation testing) followed by germline testing (sequencing with or without MLPA; if there are insufficient studies using these reference standards, we will include studies using array-based comparative genomic hybridisation, and long-range PCR) for Lynch syndrome-related mutations (*MLH1*, *MSH2*, *MSH6*, *PMS2*), followed by any intervention for Lynch syndrome including preventative hysterectomy, aspirin, surveillance/testing for CRC or gynaecological cancers Subquestion 1: • Surveillance/testing for CRC Subquestion 2: • Surveillance/testing for gynaecological cancers (endometrial, ovarian, cervical, vaginal and vulval)
Comparator	Key question: • No testing for Lynch syndrome Subquestions 1 and 2: • No surveillance/testing
Outcome	Key question: • Mortality • Morbidity • Type and number of Lynch syndrome-related cancers • HRQoL using validated tools • Anxiety using validated tools • Depression using validated tools • Change in patient management • Number of cascade tests on first-/second-degree relatives

continued

TABLE 2 The PICO for key question 2 (*continued*)

PICO element	Description
	• Morbidity and mortality of first-/second-degree relatives • Number of interventions related to surveillance for Lynch syndrome-related cancers • Number of risk-reducing interventions for Lynch syndrome-related cancer Subquestion 1: • CRC incidence • Number of interventions related to surveillance for Lynch syndrome-related cancers • Number of risk-reducing interventions for Lynch syndrome-related cancer • CRC-related mortality • CRC-related morbidity • HRQoL using validated tools • Anxiety using validated tools • Depression using validated tools • Change in patient management Subquestion 2: • Gynaecological cancer incidence (overall and by type) • Number of interventions related to surveillance for Lynch syndrome-related cancers • Number of risk-reducing interventions for Lynch syndrome-related cancer • Gynaecological cancer-related mortality (overall and by type) • Gynaecological cancer-related morbidity (overall and by type) • HRQoL using validated tools • Anxiety using validated tools • Depression using validated tools • Change in patient management
Study design	All questions: • RCTs • Controlled trials
Publication type	All questions: • Peer-reviewed papers • Abstracts and manufacturer data were included only if they provided numerical data and sufficient detail on methodology to enable assessment of study quality/risk of bias. Furthermore, only data on outcomes that have not been reported in peer-reviewed full-text papers were extracted and reported
Language	All questions: • English

HRQoL, health-related quality of life; RCT, randomised controlled trial.

Assessment of study risk of bias

We planned to assess the risk of bias using the Cochrane Risk of Bias 2 (RoB 2) revised tool to assess risk of bias in randomised trials[39] and the Cochrane Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool.[40] No studies were included, so no risk-of-bias assessments took place.

Methods of analysis/synthesis

No studies were identified that met the inclusion criteria, and so no data synthesis was undertaken.

Methods for assessing cost-effectiveness

Key question 3

What is the cost-effectiveness of testing for Lynch syndrome among people diagnosed with endometrial cancer using IHC- and MSI-based strategies, compared with the current pathway for the diagnosis of Lynch syndrome?

Review of existing cost-effectiveness models

Systematic review of existing cost-effectiveness evidence

Study identification

A comprehensive search of the literature for published economic evaluations, cost studies and health-related quality of life (HRQoL) studies was performed in a range of relevant bibliographic databases in August 2019. The database searches were developed iteratively and combined terms for Lynch syndrome and economic evaluations/cost studies/HRQoL studies, or endometrial cancer and testing and economic evaluations/cost studies/HRQoL studies. The search was informed by the strategy developed for the clinical effectiveness review and established economic and HRQoL search filters. No limits on date or language were applied. Full details of the search strategies are provided in *Appendix 1*.

The following databases were searched, from inception: MEDLINE ALL (via Ovid), EMBASE (via Ovid), NHS Economic Evaluation Database (NHS EED) and HTA Database (via CRD), Science Citation Index (via Web of Science), Conference Proceedings Citation Index – Science (via Web of Science), Cost-Effectiveness Analysis (CEA) Registry, EconPapers (Research Papers in Economics), and School of Health and Related Research Health Utilities Database (ScHARRHUD).

The reference lists of included studies and results of the clinical effectiveness search were also checked.

Records were exported to EndNote X9, where duplicates were systematically identified and removed.

Inclusion and exclusion of relevant studies

Inclusion criteria

To be included in the review, the following criteria were applied.

- Population: women with endometrial cancer with no known diagnosis of Lynch syndrome, and/or their relatives.
- Intervention: interventions used to identify women with Lynch syndrome –
    - MSI-based testing (with/without *MLH1* promoter hypermethylation testing) followed by germline testing
    - IHC (with/without *MLH1* promoter hypermethylation testing) followed by germline testing
    - combination of MSI-based testing and IHC (with/without *MLH1* promoter hypermethylation testing) followed by germline testing
    - germline testing alone.
- Comparator: no testing for Lynch syndrome.
- Outcome measures: cost and cost-effectiveness outcomes [costs for each screening strategy, direct medical care costs, incremental cost-effectiveness ratios (ICERs), e.g. cost per QALY gained].
- Study design: studies comprising an economic evaluation (cost analysis, cost–consequences analysis, cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), and any model-based economic evaluation involving direct comparison between strategies used to diagnose Lynch syndrome.
- Other inclusion criteria:
    - full-text reports published in English
    - abstracts (only if they are companion publications to full-text included studies)
    - only humans.

Methods

The search was run by our information specialist (RC). Sifting was undertaken by two reviewers. Mary Jordan led the review sifting abstracts and titles of all identified studies, and Chris Stinton, James Keasley, Hannah Fraser and Lena Al-Khudairy acted as second reviewers. Results between the first and second reviewer were then compared, and anomalies resolved through discussion or, if this was not possible, by recourse to the full team of reviewers. Full texts of the results of the first sift were obtained and screened using the same process.

Data extraction

Information was extracted by one reviewer using a pre-piloted data extraction form (see *Appendix 2*) for the full economic evaluation studies. The data extraction form was developed to summarise the main characteristics of the studies and to capture useful information from the economic analysis. We extracted information about study details (title, author and year of study), baseline characteristics (PICO), methods (study perspective, time horizon, discount rate, measure of effectiveness current, assumptions and analytical methods), results (study parameters, base-case and sensitivity analyses results), discussion (study findings, limitations of the models and generalisability), other (source of funding and conflicts of interests), overall reviewer comments and conclusions (of authors and reviewers). Each completed data extraction form was cross-checked by another reviewer, with any discrepancies resolved by discussion, or recourse to a third reviewer if an agreement could not be reached.

Quality assessment

The reporting quality of the studies included in the systematic review was assessed against the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[41] checklist and the Philips' checklist.[42]

The economic evaluations were appraised against a framework for best practice for reporting economic evaluation studies developed by the CHEERS task force.[41] The CHEERS assessment tool comprises six dimensions: title and abstract, introduction, methods, results, discussion and other. Under these dimensions, a series of questions check whether or not the criteria have been clearly reported. In addition, the models were critically appraised against a framework for best practice for reporting decision-analytical models developed by Philips *et al.*[42] The Philips' quality assessment tool comprises two main dimensions: model structure and data used to parameterise the model. Under these dimensions, several questions assess whether or not the criteria have been clearly reported (see *Appendix 2*).

Study quality was assessed by one reviewer and cross-checked by a second reviewer. Any disagreements were resolved by discussion or by recourse to a third reviewer.

Data synthesis

Information extracted from the included studies was summarised narratively. Owing to the nature of economic analyses (different aims/objectives, study designs, populations and methods) these findings from individual studies were compared narratively, and recommendations for future economic models are discussed.

Model structure for independent economic assessment

A de novo economic model was developed. The model structure reflected the decision problem: to determine the costs and benefits associated with implementing a policy to offer genetic testing to identify Lynch syndrome in women newly diagnosed with endometrial cancer; to offer testing to relatives of those thereby identified as having Lynch syndrome; and to offer interventions to those identified as having Lynch syndrome (probands and cascadees) aimed at reducing the risk of them developing (further) Lynch syndrome cancers, and improving outcomes if they do.

This decision problem can be analysed in two stages. The first stage is to determine what the costs and consequences are of the initial and cascade testing strategy being considered. This stage results in estimates of the total number of individuals with Lynch syndrome identified (probands and cascadees), together with the costs incurred in identifying them. The second stage involves estimating the incremental impact of being identified with Lynch syndrome compared with not knowing this. The impact occurs as a result of various risk reduction and surveillance interventions that can be offered once it is known that a person has Lynch syndrome. The costs and consequences of these interventions need to be modelled from the point when they are offered over the lifetime of a recipient.

We adopted a modular approach involving two submodels, one for each of these stages. The first stage was modelled with a decision tree structure, as testing strategies naturally lend themselves to this approach. The second stage was modelled with a Markov cohort model structure, to analyse the lifetime incidence of CRC and endometrial cancer from the point when an individual is identified with Lynch syndrome until their death (from CRC, endometrial cancer or another cause). The outputs from this Markov model were the (mean and variance) lifetime discounted costs and QALYs resulting from risk reduction measures, surveillance and cancer. These were calculated for a range of ages at which Lynch syndrome might be identified, as a table. This table became an input for the decision tree model, hence integrating the two submodels in a unified model.

Construction of the model involved consulting the previous HTA report undertaken by Snowsill *et al.*[12] comparing diagnostic strategies to identify Lynch syndrome in people with CRC. This also comprised two separate stages: a diagnostic stage and a management stage. The first stage used a decision tree structure to estimate the number of probands and their relatives who would be diagnosed with Lynch syndrome, and the resource use and costs involved. The second stage used an individual patient-level model to simulate the long-term costs and benefits (life-years and QALYs accrued) associated with management and surveillance, and prophylactic treatment for probands and relatives with Lynch syndrome. In addition, data and the modelling approach used by Snowsill *et al.*[43] in their cost-effectiveness analysis of reflex testing for Lynch syndrome in women with endometrial cancer were drawn on, as this was the model identified as being the closest to address the current decision problem under review.

The resultant model constitutes an initial diagnostic section, a decision tree model built in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), and a subsequent Markov cohort state transition model, in R software package (The R Foundation for Statistical Computing, Vienna, Austria), to estimate the long-term benefits accrued through risk reduction and surveillance measures for both CRC and endometrial cancer as a result of Lynch syndrome identification and cascade testing of relatives.

The diagnostic pathway in the decision tree component of the model is assumed to take place within 1 year, with no discounting applied to costs. The Markov model covers a lifetime time horizon (until death or age 100 years) with annual cycles in which costs and QALYs are discounted at a rate of 3.5% per year. Both models are conducted from an NHS and Personal Social Services (PSS) perspective.

The model will now be described in greater detail.

Diagnostic decision tree

This section of the model estimates the number of endometrial cancer probands and their relatives diagnosed with Lynch syndrome using the 11 strategies for inclusion in this review against the comparative strategy of no reflex testing. *Figure 12* shows an overview of the testing pathway modelled for endometrial cancer probands undergoing one of the available strategies and *Figure 13* shows an overview of the testing and management pathway for relatives of probands identified with Lynch syndrome or who are assumed to have Lynch syndrome.

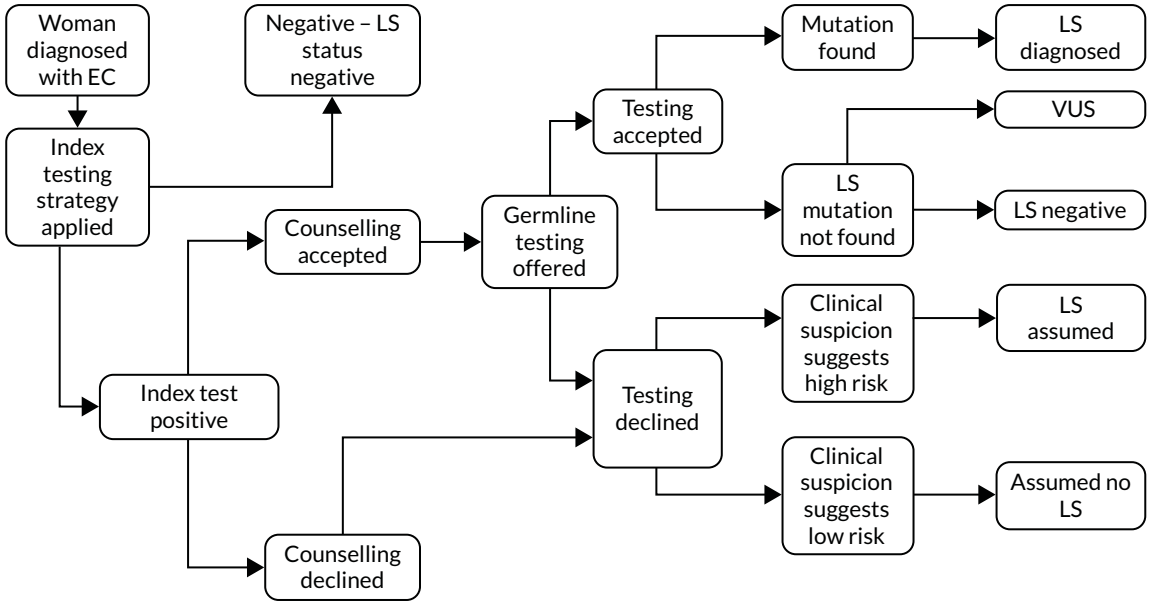

FIGURE 12 Overview of diagnostic model for probands. EC, endometrial cancer; LS, Lynch syndrome.

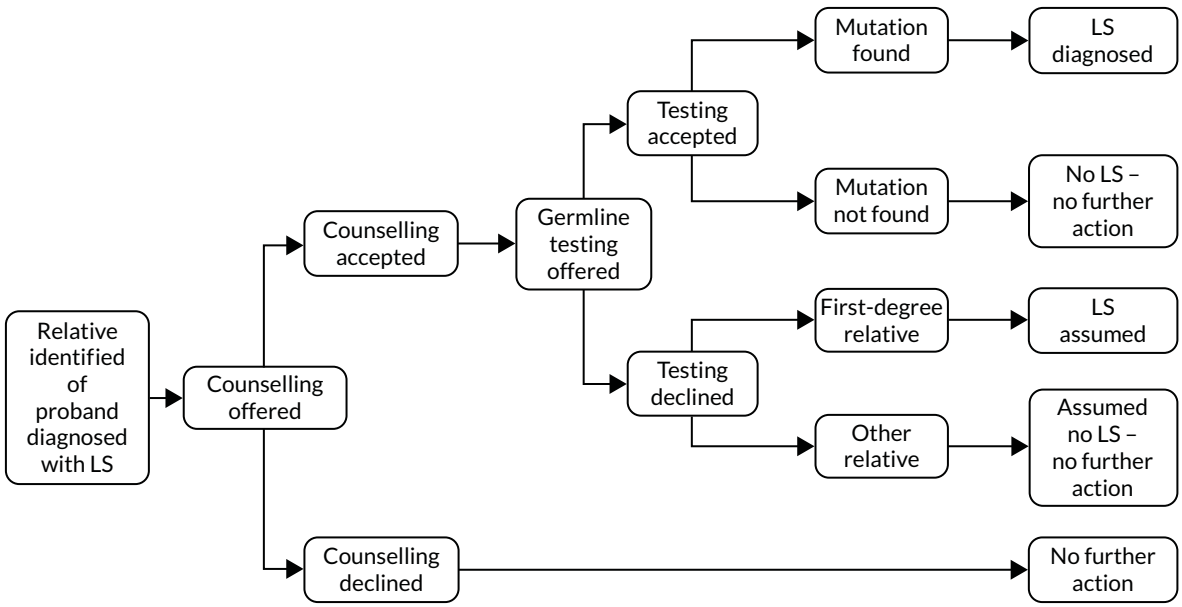

FIGURE 13 Overview of testing and management pathway for relatives of probands. LS, Lynch syndrome.

Probands with endometrial cancer enter the model and are assigned to one of the 11 diagnostic strategies under assessment. Their path through the model is dependent on the result of the index test (combination of tests in the strategy) that they receive. Those with a positive index result are offered confirmatory germline testing. This is via a process of accepting genetic counselling and then accepting the genetic test. The proband can choose to accept or decline counselling, and those who accept counselling may then either accept or decline genetic testing. For probands who do consent to germline testing, Lynch syndrome status is confirmed.

Probands with a positive index test result and positive germline result are diagnosed with Lynch syndrome. Those with a positive index result and negative germline result are considered Lynch syndrome negative, but management of this group of individuals is subject to further investigation, as described in detail below. Probands with a positive index result who decline germline testing are

assumed Lynch syndrome mutation negative, except for a specified proportion who are assumed Lynch syndrome, based on clinical suspicion.

Probands with a negative index result are not offered any further testing and are diagnosed with sporadic endometrial cancer.

In the final strategy, no index testing is performed, but probands proceed straight to genetic testing. In this case, genetic counselling and testing are offered directly to all endometrial cancer probands.

Diagnostic strategies for probands

The strategies modelled in the diagnostic component are as follows:

1. MSI testing followed by germline testing for Lynch syndrome-related mutations.
2. MSI testing followed by *MLH1* promoter hypermethylation testing, followed by germline testing for Lynch syndrome-related mutations.
3. IHC MMR testing followed by germline testing for Lynch syndrome-related mutations.
4. IHC MMR testing followed by *MLH1* promoter hypermethylation testing, followed by germline testing for Lynch syndrome-related mutations.
5. MSI followed by IHC then germline testing for Lynch syndrome-related mutations.
6. MSI followed by IHC plus *MLH1* promoter hypermethylation testing then germline testing for Lynch syndrome-related mutations.
7. IHC followed by MSI then germline testing for Lynch syndrome-related mutations.
8. IHC followed by MSI plus *MLH1* promoter hypermethylation testing then germline testing for Lynch syndrome-related mutations.
9. MSI and IHC done simultaneously, then germline testing for Lynch syndrome-related mutations.
10. MSI and IHC done simultaneously plus *MLH1* promoter hypermethylation testing, then germline testing for Lynch syndrome-related mutations.
11. germline testing for Lynch syndrome-related mutations.

These strategies were compared with no testing for Lynch syndrome-related mutations and a fully incremental analysis was performed to report outcomes as ICERs based on cost per QALY.

Outcomes of diagnostic model for probands

Probands who test positive for a pathogenic mutation at germline testing are diagnosed with Lynch syndrome and offered Lynch syndrome surveillance for CRC and risk-reducing interventions, as appropriate. This is subject to the individual accepting these management options. Cascade testing is also triggered by Lynch syndrome-positive identification of the proband, whereby systematic testing of biologically at-risk relatives is undertaken. Output from the model is the number of probands with Lynch syndrome receiving Lynch syndrome surveillance and the number of probands with Lynch syndrome not receiving Lynch syndrome surveillance. As endometrial cancer probands are considered not to be at risk of further endometrial cancer, only female relatives of endometrial cancer probands who are diagnosed with Lynch syndrome are offered risk-reducing interventions for endometrial cancer.

Probands who test negative for a pathogenic mutation on index testing are diagnosed with sporadic endometrial cancer and continue with standard endometrial cancer management. They are not offered surveillance, nor is cascade testing pursued with their relatives.

Probands who decline germline testing after positive index test results are assumed a Lynch syndrome status based on clinical suspicion. Those who are assumed to not have Lynch syndrome are not offered surveillance or onward testing for their relatives. For those assumed to have Lynch syndrome (Lynch syndrome assumed), surveillance and risk reduction are offered, as well as surveillance and risk reduction for their first-degree relatives.

Probands with positive index test results on tumour tissue and negative germline results are considered Lynch syndrome negative, but, for a proportion of these, the clinical suspicion of Lynch syndrome remains. Similarly, despite negative results for currently identified pathogenic mutations for Lynch syndrome, germline testing may detect other mutation variances on these genes. These VUSs may or may not be later identified as pathogenic for Lynch syndrome, in which case status and management can be upgraded or downgraded accordingly. In these cases, it is assumed that further testing occurs on tumour tissue (somatic analysis) to either confirm sporadic cause of tumour or establish that the VUS is non-pathogenic for Lynch syndrome and management is then downgraded to that of non-Lynch syndrome individuals. Identification of new pathogenic variants is an alternative outcome of further testing, in which case individuals are modelled as being offered surveillance, as per Lynch syndrome assumed.

Probands who decline germline testing following a positive index test result are further categorised into 'assumed non-Lynch syndrome' or 'Lynch syndrome assumed', and managed accordingly.

Diagnostic strategies for relatives

Relatives follow strategy 11, straight to germline testing. This is also subject, in the model, to their acceptance of genetic counselling and acceptance of genetic testing following this counselling.

Outcomes of diagnostic model for relatives

Relatives who test positive for a pathogenic mutation at germline testing are diagnosed with Lynch syndrome and offered Lynch syndrome surveillance for CRC and risk-reducing interventions, as appropriate. This is subject to the individual accepting these management options.

Relatives who test negative for a pathogenic mutation at germline testing are not diagnosed with Lynch syndrome and no further surveillance measures are offered.

First-degree relatives who decline germline testing are diagnosed Lynch syndrome assumed and offered surveillance for CRC. Second-degree relatives and more distant relatives are subject to no further action.

Outcomes of diagnostic model summary

- Number of probands with Lynch syndrome receiving Lynch syndrome surveillance (true positive accepting).
- Number of probands without Lynch syndrome receiving Lynch syndrome surveillance (false positive accepting).
- Number of probands without Lynch syndrome who do not receive Lynch syndrome surveillance (delineated as those identified as Lynch syndrome positive who decline surveillance and those diagnosed as Lynch syndrome negative) (false positive declining and true negative not offered).
- Number of VUSs and Lynch syndrome assumed diagnoses.

Long-term outcomes model

We estimated the benefits of cascade testing by developing cohort state-transition models that simulate the incidence and mortality associated with Lynch syndrome-related cancers. We use these models to predict the benefit of being identified with Lynch syndrome through cascade testing by simulating incidence and mortality with, and without, surveillance and risk reduction measures, which we assume are adopted once Lynch syndrome has been identified. The cohort that is modelled consists of a group of individuals identical in terms of age at which they were identified as having Lynch syndrome, sex and previous Lynch syndrome cancer history (the model is repeated for a wide range of cohorts to provide the information needed for the decision tree model; this is described further in *Figure 14*).

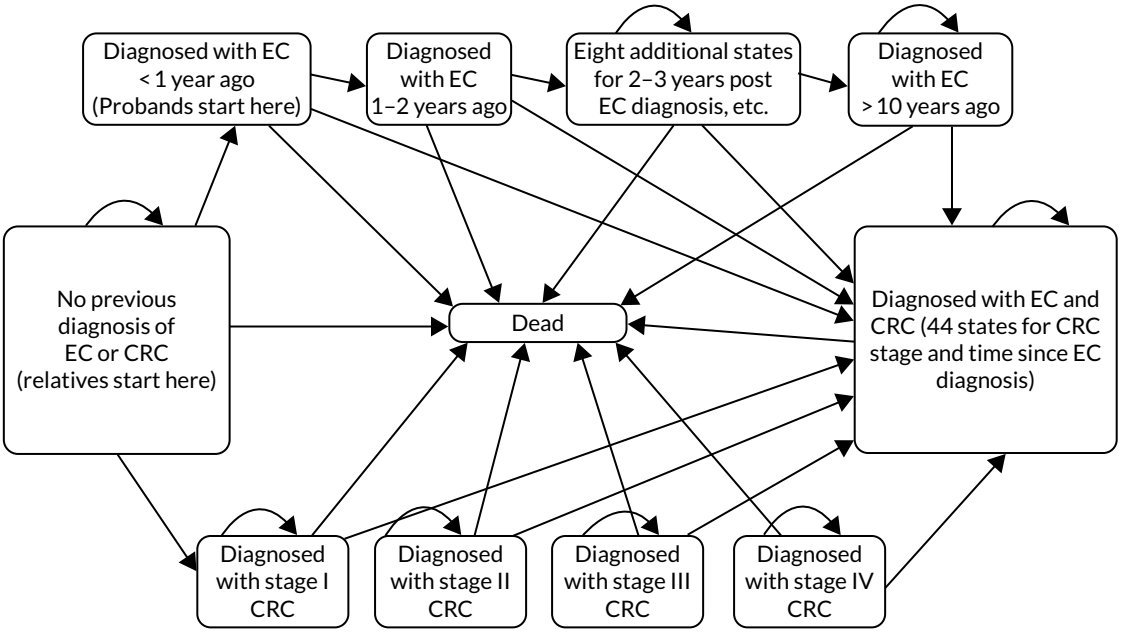

FIGURE 14 Overview of long-term model diagram. EC, endometrial cancer.

The model has five states: cancer free, CRC, endometrial cancer, both CRC and endometrial cancer, and dead. The endometrial cancer state comprises 10 'tunnel states' reflecting time since incidence of endometrial cancer. These are known as tunnel states because a person in this state must move to the next state in the sequence at the end of the cycle (unless they move to death). The cohort can be of any age from 0 to 100 years and be male or female, and can start in any state. The state for women who have both endometrial cancer and CRC, therefore, has four substates, each with 10 tunnel states. For this decision problem, we simulate cohorts who 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. We do not model outcomes for those without Lynch syndrome, on the assumption that they experience no long-term costs or benefits from Lynch syndrome testing.

For the comparator, we assume that, as the person is unaware of their Lynch syndrome status, no surveillance or risk reduction measures are offered. We model age-related annual incidence of CRC and endometrial cancer. For CRC, we further assume that incidence is gene dependent. In line with Snowsill *et al.*,[43] we assume that this incidence has a log-normal distribution. Previous work in this field has drawn on data on individuals with Lynch syndrome who benefit from colonoscopic surveillance. We follow that work in assuming that, based on Järvinen *et al.*,[44] surveillance reduces incidence with a hazard ratio of 0.387. We apply this to the log-normal distribution to derive the incidence rates illustrated in *Figures 15* and *16*.

For endometrial cancer, we sourced incidence data from the Prospective Lynch Syndrome Database (PLSD).[45] This database reported gene-based risk of cancer based on 6350 individuals with Lynch syndrome. Risks are reported at ages 25, 40, 50, 60, 70 and 75 years. We fitted a piecewise linear model to these data. The cumulative lifetime incidence of endometrial cancer in the absence of preventative measures implied by this assumption is illustrated in *Figure 17*.

For CRC, we assumed that the proportion presenting with stages I to IV were 18.8%, 48.8%, 21.3% and 11.3%, respectively. We assumed a one-off cost of treatment, dependent on age and stage at diagnosis (*Table 3*).

We assumed that CRC mortality is stage dependent, with transition probabilities of 0.009, 0.035, 0.098 and 0.543 for stages I to IV, respectively.[43]

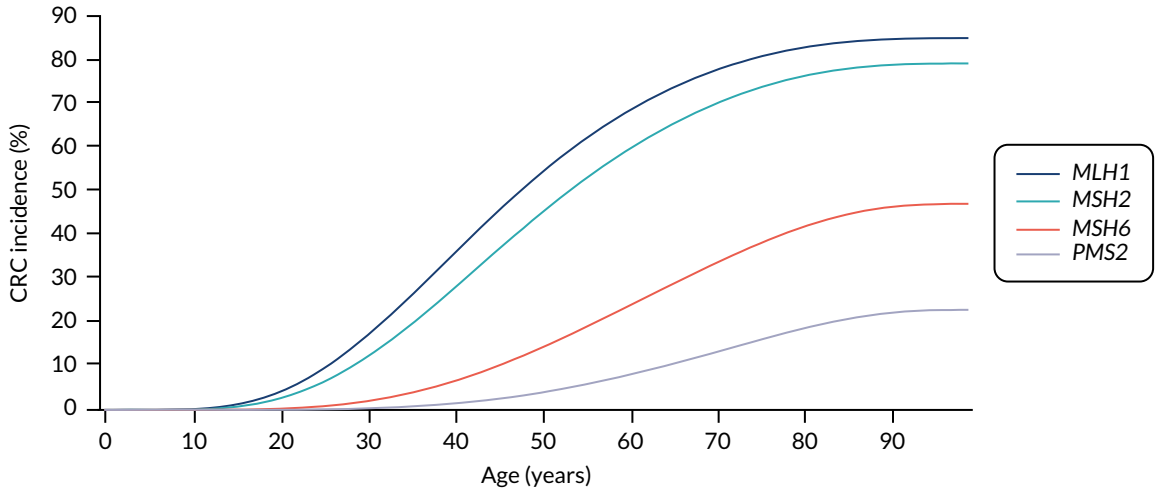

FIGURE 15 Modelled cumulative incidence of CRC in females with Lynch syndrome, assuming no surveillance.

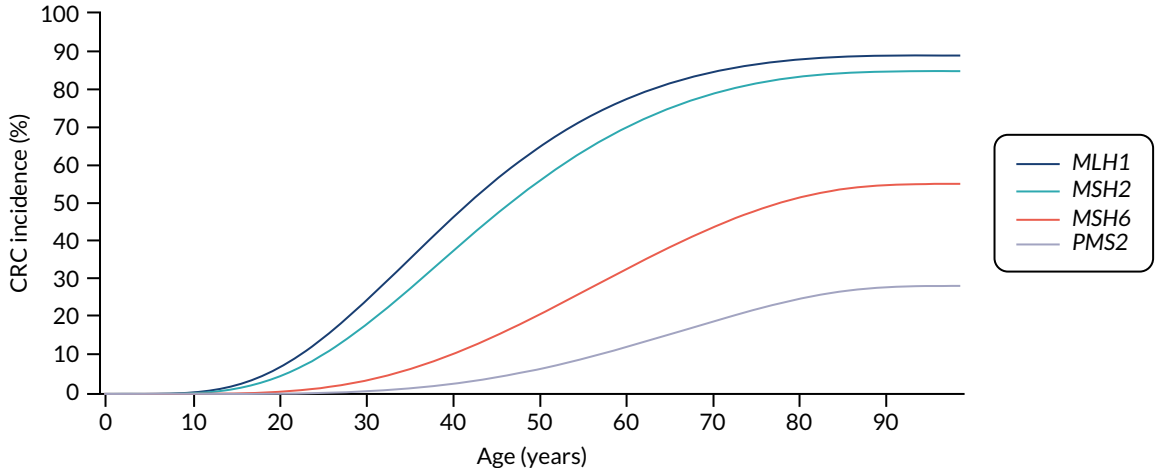

FIGURE 16 Modelled cumulative incidence of CRC in males with Lynch syndrome, assuming no surveillance.

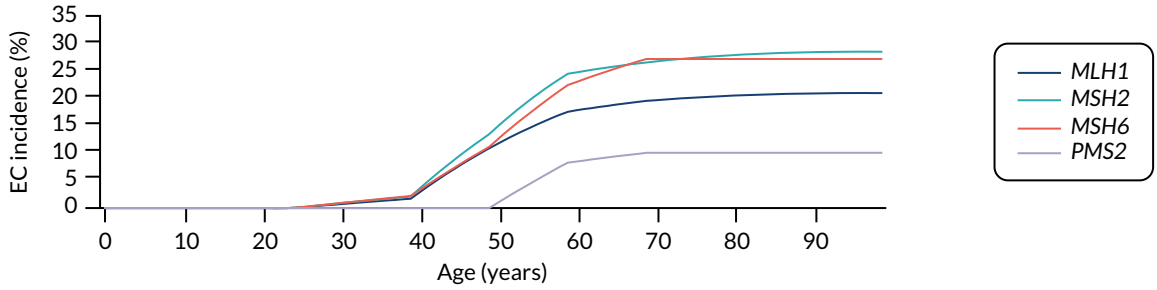

FIGURE 17 Modelled cumulative incidence of EC in females with Lynch syndrome. EC, endometrial cancer.

TABLE 3 One-off whole-diease treatment costs of CRC by age and stage

	Cost (£)			
Age (years)	Stage I	Stage II	Stage III	Stage IV
0–49	8754.12	8740.53	14,489.51	11,704.91
50–59	5712.39	7015.84	9691.73	8443.68
60–69	4623.22	5351.77	7259.39	6508.89
70–79	3177.62	3454.61	4485.25	4365.04
≥ 80	1379.75	1545.95	1560.59	806.95

For endometrial cancer, we assumed a one-off treatment cost of £6510, in line with previous work.[12] We drew on Cancer Research UK-reported statistics on endometrial cancer mortality,[46] and assumed that these were the same for those with Lynch syndrome as for those without. We assumed that those who have one Lynch syndrome risk cancer are at the same risk of developing the second one as if they were cancer free, conditional on not having died from the first cancer. We also applied an age-dependent transition probability for mortality from other causes. All those still alive in the model were assigned an age-dependent quality-of-life utility weighting using accepted methodology by Ara and Brazier,[47] except that those with CRC stage IV were assigned a utility of 0.178, as modelled by Snowsill *et al.*[12]

With these assumptions, we ran the cohort model separately for a number of cohorts defined as having the same age at identification, sex and cancer history. For each cohort, we estimated the mean lifetime costs and QALYs incurred.

We then assumed that the following risk reduction and surveillance methods were offered when an individual is identified as having Lynch syndrome.

Chemoprophylaxis

We assume that, once identified with Lynch syndrome, individuals take aspirin as indicated in the Colorectal Adenoma/carcinoma Prevention Programme 2 (CAPP2) trial[48] and, based on the results of that trial, their probability of developing cancer each year is reduced by a factor of 0.56 (applied equally to endometrial cancer and CRC risk).

Colorectal cancer surveillance

We assume that individuals known to have Lynch syndrome have biennial colonoscopies from age 25 years (or age at identification of Lynch syndrome if later) until age 74 years. We assume the cost of colonoscopy is £325.[49] We assume that 100,000 colonoscopies result in 8.3 deaths, 40 perforations, and 55 bleeding events necessitating hospital treatment (of which 40 are mild, 10 are moderate and five are severe). This increases the average cost of colonoscopy by £2.89. We assume that this surveillance affects both incidence and stage at presentation. For stage at presentation, the assumed proportions for those participating in surveillance are 68.6%, 10.5%, 12.8% and 8.1% for stages I to IV, respectively.

Surgical prophylaxis to prevent endometrial cancer

We assume that women with Lynch syndrome can opt for hysterectomy and oophorectomy (H-BSO), and that this eliminates their risk of endometrial cancer. We make the assumption that the uptake of this increases with age, based on consideration of the average age at diagnosis of probands and subsequent ages of their identified relatives, and when women might feel ready based on completion of family, menopause, etc. The cost of this is assumed to be £3428. This assumption is illustrated in *Figure 18*.

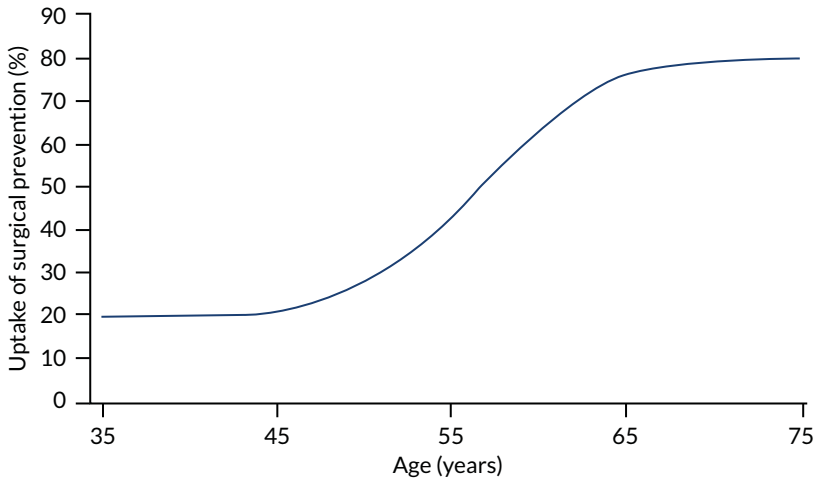

FIGURE 18 Uptake of surgical prophylaxis.

Gynaecological surveillance

We assume that women who have not had surgical prophylaxis undergo annual surveillance to detect endometrial cancer. The cost is £39, plus an additional cost of £473.41 for those requiring referral for invasive surveillance. We assume that this referral occurs in 10% of cases. This does not affect the incidence of endometrial cancer, but reduces mortality by 10.2%.

Parameters

Parameter input values for both diagnostic and long-term components of the model were sourced from literature obtained during the clinical effectiveness and cost-effectiveness systematic literature review process, with the best available evidence used to inform the base case. When suitable input parameters were not obtained, targeted searches were undertaken and individual publications critiqued. Additional information was also provided by clinical experts in the field. Discussion and critique of the sources of each parameter are detailed in *Chapter 6*, *Discussion of model input parameters*.

The model runs in 1-year cycles. The starting population is of the same age and sex, in the same state, (i.e. cancer free or recent diagnosis of endometrial cancer).

Each year:

- Transition occurs from all states to the death state based on annual mortality rates for all causes other than CRC or endometrial cancer. Death from the respective cancer state is accounted for in further transition from CRC, based on stage, and from endometrial cancer based on length of time they have spent in the endometrial cancer state. Transitions from all states to death are based on all-cause mortality.
- Further transitions from CRC or CRC plus endometrial cancer to death based on stage (CRC) or dwell time in state (endometrial cancer).
- Survivors in the endometrial cancer or endometrial cancer plus CRC states at the end of each cycle move on to the next tunnel state or remain in the final tunnel state prior to death. All those in the endometrial cancer or endometrial cancer plus CRC state who survive move to the next tunnel state (or stay in tunnel state 10). A quality-of-life score is assigned to the average number of individuals inhabiting each state at the start and end of each cycle.

Treatment costs of the respective cancers are assigned to an individual on entry to the cancer state and applied to the first year only (as a single, whole-disease cost). The average of the number of individuals in each state at the start and end of the cycle is assigned a quality-of-life score based on their age.

Those who move to a cancer state during the cycle are assigned treatment costs (all treatment costs are assumed to occur in the first year in the state). The model is run twice for each cohort: once assuming no Lynch syndrome-ameliorating measures (e.g. screening, prophylactic drugs), and once assuming measures are applied (as the model starts at the age at which an individual would be identified with Lynch syndrome were they to undergo genetic testing). These measures affect transition probabilities such as incidence and mortality, thereby capturing the benefit of the measures. Costs are also captured for those eligible for such measures. Colonoscopy is costed every other cycle. The number of women undergoing surgical prophylaxis is estimated from the number of women in the cancer-free or CRC states, by applying a proportion based on age, as described previously. It is assumed that the costs of aspirin, as a cheap over-the-counter medication, are not borne by the NHS.

The outputs from the model were the incremental costs and QALYs resulting from the addition of Lynch syndrome cancer-ameliorating measures. These were calculated separately by sex, for those cancer-free and those recently diagnosed with endometrial cancer, and for ages 25–74 years in 1-year intervals. These results provide an estimate of the benefit of Lynch syndrome cancer-ameliorating measures, and how these benefits vary by age and sex. To further illustrate how benefits arise in the model, results were extracted on the numbers in, and moving between, each state. These allowed the calculation of life-years gained, cancers avoided and cancer deaths prevented.

To allow these results to inform the decision tree model, we assumed that cascadees were equally likely to be any age between 25 and 74 years, and that the mean age of probands was 49 years. From this, we were able to define an output from the model as the average of the incremental results across all ages for cascadees, and the incremental results for women aged 49 years recently diagnosed with endometrial cancer for the probands. These results were used as the pay-offs for the terminal node in the decision tree model, so that the costs and QALYs per strategy could be calculated.

Quality assurance

Modelling of the independent economic assessment was conducted by two health economists, with primary development of each of the two components of the model done independently, and then checked by the second. Internal review by a senior health economist was also undertaken, with code review and cross-checking of input parameters to ensure that they originated from the described source. Furthermore, the reviewer constructed an alternative version of the diagnostic model in TreeAge (TreeAge Software, Inc., Williamstown, MA, USA) (rather than Excel) so cross-checking of results could also be carried out.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was used to determine the impact of joint parameter uncertainty. Model parameters were assigned a distribution reflecting the amount and pattern of variation, and cost-effectiveness results were calculated by simultaneously selecting random values from each distribution. This process was repeated 10,000 times, with simulations plotted on an incremental cost-effectiveness plane, with each point representing uncertainty in the incremental mean costs and QALYs between the strategies being compared. The results from these simulations were used to obtain cost-effectiveness acceptability curves (CEACs), which illustrate the effect of sampling uncertainty, and present the probability that the testing strategy is optimal at a range of willingness-to-pay (WTP) threshold values.

To propagate uncertainty across the decision tree and lifetime cohort models, we first carried out Monte Carlo simulation for the lifetime model with distributions assigned to all stochastic parameters. This produced an output set that could be used as an input table for the pay-off nodes for probands and relatives with Lynch syndrome in the decision tree model when it was run stochastically, producing PSA outputs that reflected joint uncertainty across the two models.

Sensitivity analysis

Univariate one-way sensitivity analysis was used to explore the impact of varying one parameter at a time, while keeping all other inputs constant, to assess the robustness of the model. We varied parameter values using upper and lower limits and presented results in the form of a tornado plot.

Scenario analyses

Alternative analyses were conducted for the following scenarios:

1. Strategy-level test accuracy obtained from the Proportion of Endometrial Tumours Associated with Lynch Syndrome (PETALS) study (Dr Neil AJ Ryan, University of Manchester, 11 November 2019, personal communication).
2. Costs of testing obtained from the PETALS study (Dr Neil AJ Ryan, personal communication).
3. Strategy-level test accuracy obtained from the PETALS study (Dr Neil AJ Ryan, personal communication) and costs of testing obtained from Ryan *et al.*[50]
4. Disutility increment as a result of having cancer increased from the value modelled in the base case.
5. Gynaecological surveillance excluded.
6. Three-year colonoscopy surveillance.
7. Excluding benefit from aspirin.
8. Excluding hazard ratio reducing incidence of CRC as a result of surveillance.

Assumptions in base case

- Microsatellite instability-high results are treated as a positive indicator of Lynch syndrome, whereas MSI-L results are treated as a negative indicator of Lynch syndrome.
- The sensitivity of MSI and IHC testing did not depend on which MMR gene is mutated.
- The average number of relatives per proband was six (2.5 of whom were first-degree relatives).
- Colorectal surveillance colonoscopies occurred every 2 years, starting age 25 years and stopping at age 75 years.
- Surveillance colonoscopies are effective immediately on commencement of surveillance and ineffective immediately after discontinuation (i.e. no lag time).
- Disutility is applied only to people with stage IV CRC.
- Endometrial cancer is not modelled for women without Lynch syndrome-causing mutations.
- Treatment for endometrial cancer is assumed to be total abdominal H-BSO with/without chemotherapy with/without radiotherapy.
- Survival of probands with endometrial cancer is not affected by Lynch syndrome status.
- Surveillance for endometrial cancer comprises an annual review with their general practitioner (GP), with 10% of women attending referred for invasive gynaecological surveillance, consisting of gynaecological examination, transvaginal ultrasonography, endometrial biopsy and cancer antigen-125 (CA-125) testing.
- Gynaecological surveillance reduced the risk of mortality from endometrial cancer by 10.2%.
- No disutility arising from prophylactic hysterectomy was assumed.
- Prophylactic hysterectomy (total abdominal H-BSO) eliminates risk of endometrial cancer.
- Prophylactic hysterectomy (total abdominal H-BSO) is offered to all female relatives, with no age restrictions.

Chapter 4 Clinical effectiveness results

Clinical effectiveness results

Search results

The study selection process for the clinical effectiveness review is illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in *Figure 19*. The search identified 6259 records through database and other searches. Following duplicate removal we screened 3308 records. One additional unpublished study, the PETALS study, was provided by NICE and included for key question 1 (Dr Neil AJ Ryan, personal communication). A total of 2981 studies were excluded by their titles and abstracts, leaving 327 full texts to be assessed for eligibility for inclusion in the review. Of these, 282 papers were subsequently excluded, leaving 45 papers (including the unpublished PETALS study).[15,16,51–92] All 45 papers were relevant for key question 1: the test accuracy of MSI- and IHC-based strategies for determining Lynch syndrome in people with endometrial cancer. The most common reasons for exclusion of test accuracy studies at this stage were that there was no eligible reference standard in the studies and that too little information was included to enable quality appraisal. The full list of excluded studies with reasons for exclusion can be found in *Appendix 3*.

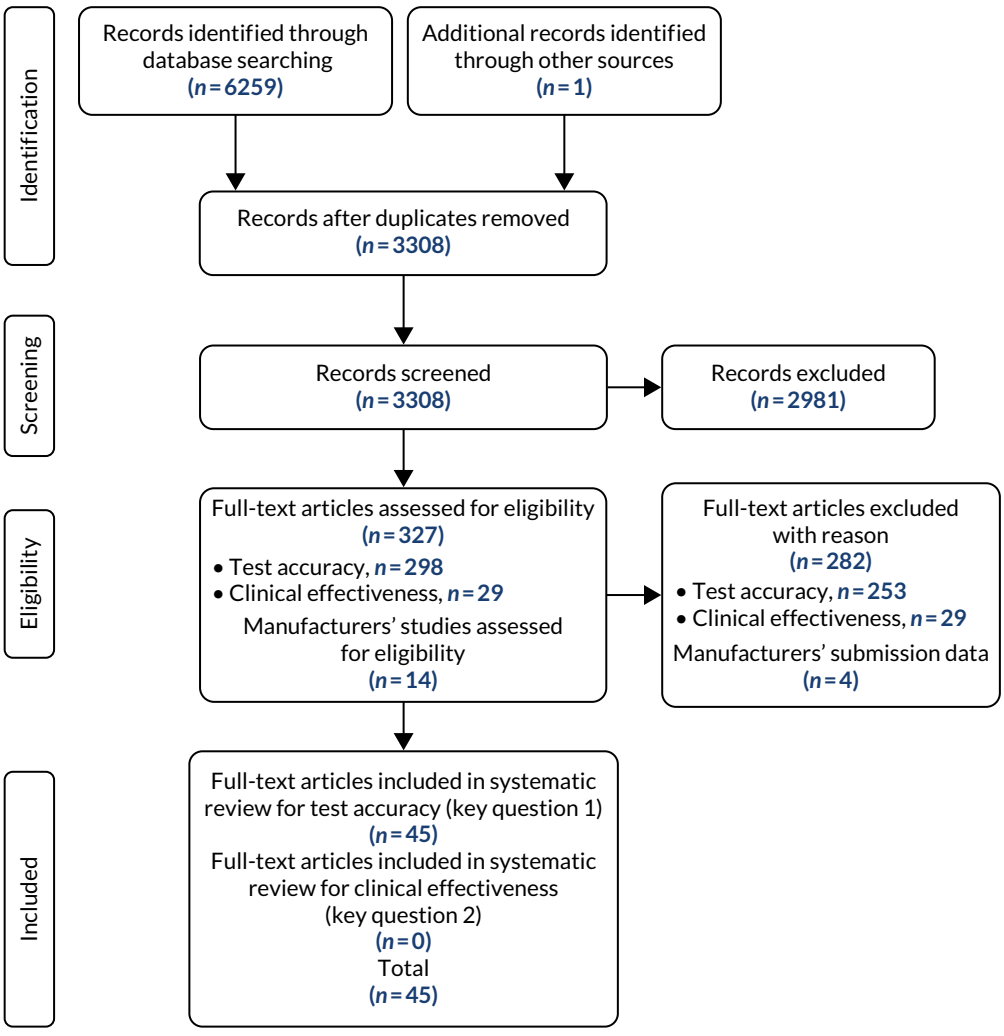

FIGURE 19 The PRISMA flow diagram showing the study selection process for the clinical effectiveness review.

For key question 2, on the clinical effectiveness benefits and harms of testing for Lynch syndrome among people who have endometrial cancer, and/or their relatives, the search identified 29 studies that were potentially eligible for this review. We carried out the full-text assessment of the 29 records against the predefined inclusion criteria as stated in *Table 2*. No studies were identified that were relevant for key question 2 on the clinical effectiveness benefits and harms of testing for Lynch syndrome among people who have endometrial cancer, and/or their relatives. The most common reason for exclusion of clinical effectiveness studies at this stage was study design [not randomised controlled trials (RCTs)]. The full list of excluded studies with reasons for exclusion can be found in *Appendix 3*.

Study characteristics

The characteristics of the 45 studies included in the clinical effectiveness review are described in *Appendix 4*. 'Unselected' is defined in the table as including all patients in the setting over the study time period, without restrictions by age, cancer histology or family history.

Population

The 45 included papers included approximately 10,600 participants, with sample sizes ranging from 12[85] to 1459 participants.[56] The results of five studies were reported in more than one paper.[53,56,57,60,65,68,70,76,87,89] These papers have been reported together (i.e. two papers are combined into one study) throughout this report. Only two studies took place in the UK [one published[51] and the PETALS study (Dr Neil AJ Ryan, personal communication)], with the majority taking place in the USA (15/45; 33%) and Europe (11/45; 24%). However, ethnicity was largely unreported [32/45 (71%) did not report ethnicity]. Several studies included age as an inclusion criterion, often limiting patients to $\leq$ 50 years for inclusion in a study.[16,51,54,79] In the remaining studies, ages ranged from 17 to 100 years.[15,63] Only 24% of studies (10/41) were in unselected populations, meaning that all patients in particular settings were included over the study time period, without any restrictions by age, cancer histology or family history. Two studies have been classified as unselected populations but limited to all adults (all those aged > 18 years).[55,81]

A total of 44% (18/41) of studies reported on patients who had previous or concurrent cancers. The number of patients included across the studies who had a history of cancer ranged from 0 to 100.[58,74,80,85] This range can be explained by studies using a history of cancer as an inclusion or exclusion criterion. For studies not using cancer history as an inclusion or exclusion criterion, the proportion ranged from 0.8% to 22.4%.[54,77,90] The types of cancer reported were ovarian, pancreatic, colon, endometrial, urinary tract, brain, breast, skin, bladder, cervical and gastric cancers.

Index tests

Nine studies (11 papers) included IHC only,[52,56,59,65,69,70,76,77,84,88,90] three studies included MSI-based testing only,[15,64,74] 28 studies (31 papers, including the unpublished PETALS study) included both tests[16,51,53–55,57,58,60–63,66–68,71–73,75,78–83,85–87,89,91,92] and 24 studies (29 papers, including the unpublished PETALS study) included *MLH1* promoter hypermethylation testing in combination with IHC or MSI testing (MSI and *MLH1* promoter hypermethylation testing, $n = 2$; IHC and *MLH1* promoter hypermethylation testing, $n = 6$; MSI, IHC and *MLH1* promoter hypermethylation testing, $n = 16$).[15,16,55–61,63–65,67–72,76–78,81,83,84,86,87,89,92]

Comparator and reference standard

The reference standards considered appropriate in this review were sequencing in combination with MLPA, long-range PCR or targeted array comparative genomic hybridisation. Of the 33 studies (36 papers) that included a reference standard, 21 studies (24 papers, including the unpublished PETALS study) included sequencing in combination with an additional method deemed appropriate by this review to detect larger structural changes.[15,16,51,52,55,57–59,61–63,65–68,77,78,81–83,85,88–90] Two studies (three papers) reported only sequencing, and did not report any details on the method of sequencing.[60,70,92] One study did not mention sequencing, but used array comparative genomic hybridisation, PCR and MLPA in combination.[84]

Two studies (three papers) did not report clearly the methods of germline testing.[56,69,76] Six of the included studies used an additional reference standard test prior to sequencing that was not an eligible reference standard in this review. Two studies used single-strand conformational variance.[64,74] The studies by Berends *et al.*,[54] Rubio *et al.*[82] and Mercado *et al.*[73] used denaturing gel electrophoresis, and the study reported across two papers by Baldinu *et al.*[53] and Strazzullo *et al.*[87] used denaturing high-performance liquid chromatography.

Outcomes

Data on the number of Lynch syndrome diagnoses among women with endometrial cancer were reported in 32 studies (including the unpublished PETALS study).[15,16,51–59,61–64,66,67,69,70,77,78,81–85,88–90,92] Four studies provided head-to-head test accuracy data for IHC- and MSI-based testing.[16,54,58,82] Complete test accuracy data were provided by five studies for IHC,[16,54,58,82,90] four studies for MSI-based testing[16,54,58,82] and four studies for IHC, MSI-based testing and *MLH1* promoter hypermethylation testing.[16,58,81,83] An additional nine studies provided partial test accuracy data (true positives, false positives and PPVs) in which only women who tested positive on index tests were considered for germline testing.[16,54,58,63,66,78,82,90,92]

Concordance between IHC and MSI-based testing was assessed in 23 studies.[15,16,51,54,55,58,61–63,67,68,71,72,75,78–82,85–87,91]

Setting

The majority of the participants in the included studies were recruited from hospitals [26/41 (63%)].[15,51,52,57–68,70,77–79,81–84,88,89,92] Other studies took place in cancer registries [5/41 (12%)], cancer and radiation centres/clinics [6/41 (15%)], medical centres [2/41 (5%)] and tissue biobank repositories [1/41 (2%)]. In one study, the setting was not reported.[71]

Study design

All the studies in this review had a cohort design. A total of 39% of studies (16/41) were prospective cohort studies, 46% (19/41) were retrospective and 12% (6/41) had both prospective and retrospective elements. One study had a mixed design, comprising both a prospective cohort study looking at MMR assessments and a cross-sectional study comparing clinical and pathological features between Lynch syndrome and Lynch-like syndrome groups.[60,70]

Quality considerations of included studies

Quality Assessment of Diagnostic Accuracy Studies-2

In the proposed testing strategies 1–10 (below), only women who tested positive on the index tests would be offered germline testing. Some studies report results from implementing the strategies of interest; however, these are partial test accuracy studies because data on true negatives and false negatives are not available. It is not, and it would not be, possible to calculate sensitivity, specificity or NPVs from these studies because of a lack of follow-up of women who were negative on the index tests. Studies in which all patients receive the reference standard provide sensitivity, specificity, PPVs and NPVs, and have been defined here as full test accuracy data studies. A total of 41 studies (45 papers) were identified, of which seven provided full test accuracy data (as all participants received both the index test and reference standard),[16,54,55,58,82,83,90] 26 studies (29 papers, including the PETALS study) provided partial test accuracy data (as only a subsample of participants received both the index test and reference standard)[15,51–53,55–57,59–64,66–70,73,74,76–78,84,85,88,89,92] and 23 studies (including the PETALS study) provided data on concordance.[16,51,54,55,58,61,63,67,68,71,72,75,78–80,82,86,87,91]

The studies providing test accuracy information were appraised using the QUADAS-2 tool and the seven complete test accuracy studies are presented prior to, and separately from, the partial test accuracy studies. Studies reporting on concordance were appraised using the quality appraisal tool for studies of diagnostic reliability (QAREL). Sixteen studies (16 papers, including the PETALS study) reported both test accuracy and concordance and were appraised using both tools.[15,16,51,54,55,58,61–64,67,68,78,82,85]

Quality considerations of included studies: complete test accuracy studies

The assessment of risk of bias and applicability for the seven complete test accuracy studies using the QUADAS-2 tool are summarised in *Table 4*.[16,54,55,58,82,83,90] Six of the seven studies included both MSI and IHC index tests, and four included additional *MLH1* promoter hypermethylation testing.[16,55,58,83] All index tests have been reported separately.

Risk of bias for complete test accuracy studies

In general, the methodological and reporting quality of the included studies was poor, with risk of bias considered high in two or more domains for five studies (71%).[54,55,58,82,90] One study was judged to be at high risk of bias in one domain,[90] and the remaining study was rated as having an unclear risk of bias in the majority of domains [5/7 domains (71%)].[16] No study was rated as having a low risk of bias in all domains. In 71% of studies (5/7), the risk of bias for patient selection was deemed high (domain 1: patient selection).[54,55,58,82,90] In these studies, patients were selected for inclusion by excluding patients on the grounds of age, having synchronous cancers or deemed judgement of low risk (by age and family history). In 14.5% of studies (1/7), there was not enough information to determine the risk of bias in how patients had been selected.[16] Only one study was deemed to have a low risk of bias in the patient selection: consecutive enrolment of patients in a cohort study, with no exclusions.[83]

Six out of seven studies were head-to-head studies, testing patients using both MSI and IHC index tests, with one test using IHC alone.[90] In all studies, for both tests [6/6 MSI, 7/7 IHC (100%)], the risk of bias was unclear because of a lack of information around blinding between index test and reference standard results, whether thresholds were prespecified or determined pragmatically, and whether or not the laboratories performing the index tests participated in an accredited quality assessment/control scheme (domain 2: index tests). Four out of seven studies also undertook *MLH1* promoter hypermethylation testing, all of which lacked information on blinding and quality assessment and so were also rated as having an unclear risk of bias.[16,55,58,90]

Unclear reporting was common in the reference standard domain (domain 3: reference standard). In all studies, there was not enough information to determine whether or not the results of germline testing (reference standard) were determined without knowledge of the MSI and IHC test results (index tests). In addition, for many of the studies, it was unclear whether or not the reference standard used would correctly identify Lynch syndrome [5/7 (71%)], because there was a lack of information about the testing methods used and/or whether or not quality assurance was in place.[54,55,58,82,83] If the reference standard used in the studies does not correctly identify Lynch syndrome, this may make the index tests appear more or less accurate than they actually are. Lynch syndrome can be determined by using sequencing to detect point mutations in combination with MLPA, next-generation copy number, long-range PCR or targeted array comparative genomic hybridisation to detect larger rearrangements or for dosage analysis. One study used sequencing alongside denaturing gradient gel electrophoresis, which is not a recognised reference standard for the purpose of this study.[54] Five studies did not report information on the reference standard being carried out in accordance with best-practice guidelines (e.g. Association for Clinical Genetic Services Best Practice Guidelines for Genetic Testing and Diagnosis of Lynch Syndrome,[33] American College of Medical Genetics technical standards and guidelines for genetic testing for inherited CRC[18]) in appropriately accredited laboratories (e.g. according to the UK Accreditation Service, the Clinical Laboratory Improvement Amendments).[54,55,58,82,83]

The flow of participants through a study was rated as having a high risk of bias in 57% of studies (4/7, domain 4: flow and timing).[54,58,82,90] Three of the studies did not include all participants in their analysis,[58,82,90] and one study did not give all participants the same reference standard: sequencing was given only to those with aberrant band patterns using denaturing gradient gel electrophoresis.[54] The remaining three studies were deemed to have a low risk of bias, with all participants receiving the reference standard, all participants receiving the same reference standard and all participants being included in the analysis.[16,55,83]

TABLE 4 Judgement of risk of bias and applicability of included complete test accuracy studies

	Risk of bias							Applicability concern level				
Study and year	Patient selection	Index test: MSI	Index test: IHC	Index test: *MLH1* promoter hypermethylation	Reference test	Flow and timing	Role of sponsor	Patient selection	Index Test: MSI	Index test: IHC	Index test: *MLH1* promoter hypermethylation	Reference standard
Berends *et al.*[54] 2003	High	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Unclear	NA	High
Chao *et al.*[58] 2019	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Low	Low	Low	Low
Lu *et al.*[16] 2007	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Unclear	Unclear	Unclear	Low
Bruegl *et al.*[55] 2016	High	Unclear	Unclear	Unclear	Unclear	Low	high	High	Low	Low	Low	Low
Rubio *et al.*[82] 2016	High	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Unclear	NA	Low
Salvador *et al.*[83] 2019	Low	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	Unclear	Unclear	Unclear	Low
Tian *et al.*[90] 2019	High	NA	Unclear	NA	Unclear	High	Unclear	High	NA	Unclear	NA	Unclear

NA, not applicable.

The risk of bias associated with the role of the sponsor in four of the seven studies was deemed to be low (domain 6: role of the sponsor).[16,54,58,82] In two studies, multiple authors were employed by genetics companies who funded the studies.[55,83] In one study the funding was not specified.[90]

Applicability of study findings for complete test accuracy studies

The applicability of study findings was assessed in regard to three domains: patient selection, index test (MSI, IHC and *MLH1* promoter hypermethylation testing) and reference standard (germline testing). There were significant concerns regarding the applicability of the studies to UK practice for patient selection in six of the seven studies (86%; domain 1: patient selection).[16,54,55,58,82,90] In one study,[83] there was not enough information to determine whether or not the population was comparable to that of the review question. Based on this review's scope, were tests to be implemented, the test would be given to any patient with endometrial cancer, regardless of age or ethnicity. In all six studies, the populations were not ethnically comparable to the UK and/or were limited by age. None of the seven studies was undertaken in the UK.

Concerns regarding index testing (MSI and IHC) were low in 29% of studies (2/7; domain 2: index tests), with tests carried out according to best-practice guidelines and via laboratories that are participating in quality assurance programmes.[55,58] In the remaining studies, there was not enough information to ascertain the applicability of index testing [5/7 (71%) IHC and 4/6 MSI (67%)].[16,54,82] Only four of the studies reported on *MLH1* promoter hypermethylation testing; of those, 50% (2/4) had a high level of concern regarding applicability,[55,58] and 50% did not report enough information to make a judgement.[16,83]

Only one study was rated as having a high level of concern for the applicability with respect to the reference standard, as a non-applicable reference standard (denaturing gel electrophoresis) was used as the primary reference standard, with some patients also receiving sequencing.[54] The remainder were all rated as having a low level of concern regarding applicability, bar one study that did not report enough information for the raters to make a determination of applicability.[90]

All judgements of risk of bias and applicability concerns for studies reporting complete test accuracy data can be found in *Table 4*.

Quality considerations of included studies: partial test accuracy studies

The assessment of risk of bias and applicability for the 26 partial test accuracy studies (29 papers, including the PETALS study) using the QUADAS-2 tool are summarised in *Table 5*.[15,51–53,55–57,59–64,66–70,73,74,76–78,84,85,88,89,92] Sixteen studies included both MSI and IHC index tests (62%; 16/26), one study reported only MSI[64] and nine studies reported only IHC.[52,59,69,74,76,77,84,88,89] Seventeen studies (20 papers, including the PETALS study) included the additional *MLH1* promoter hypermethylation testing.[15,51,55–57,59–61,63,64,67–70,76,77,84,89,92] All index tests have been reported separately.

Risk of bias for partial test accuracy studies

Two domains were rated as having a high risk of bias. The first was patient selection (domain 1: patient selection), with 62% (16/26) of studies rated as having a high risk of bias in this domain.[15,51,53,56,57,62–64,67–69,73,74,76–78,88,92] As per the full test accuracy papers, this was because studies had strict inclusion criteria (such as age, previous/synchronous cancers or family history) that excluded many of the suitable population. The second domain in which a large proportion of studies were rated as having a high risk of bias was flow and timing, with 100% (26/26) rated as having a high risk of bias. In these studies, not all patients were given the reference standard; rather, it was usually only those believed to have the disease based on the index test result who were given the reference standard. The role of the sponsor was low in all studies bar four, in which not enough information was provided to make a determination.[53,63,66,73] In all other domains, the majority of the studies were rated as having an unclear risk of bias because of a lack of evidence provided [16/17 (94%), domain 2: index test MSI; 23/25 (92%), domain 2: index test IHC; 11/17 (65%), domain 2: index test *MLH1* promoter hypermethylation testing; and 22/26 (85%), domain 3: reference standard]. The only domain with a low risk of bias was domain 5:

TABLE 5 Judgement of risk of bias and applicability of included partial test accuracy studies

	Risk of bias							Applicability concern level				
Study and year	Patient selection	Index test: MSI	Index test: IHC	Index test: *MLH1* promoter hypermethylation	Reference test	Flow and timing	Role of sponsor	Patients	Index test: MSI	Index test: IHC	Index test: *MLH1* promoter hypermethylation	Reference
Anagnostopoulos *et al.*[51] 2017	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Unclear	Unclear	Low
Backes *et al.*[52] 2009	Low	NA	Unclear	NA	Unclear	High	Low	Unclear	NA	Unclear	NA	Unclear
Baldinu *et al.*[53] 2002	High	Unclear	Unclear	NA	Unclear	High	Unclear	Unclear	Unclear	Unclear	NA	Low
Bruegl *et al.*[55] 2017	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Low	Unclear	Low
Buchanan *et al.*[56] 2014/Nagle *et al.*[76] 2018	High	NA	Unclear	Unclear	Unclear	High	Low	Unclear	NA	Unclear	Unclear	Low
Dillon *et al.*[59] 2017	Low	NA	Unclear	Unclear	Unclear	High	Low	Unclear	NA	Unclear	Unclear	Low
Egoavil *et al.*[61] 2013	Low	Unclear	Unclear	Low	Unclear	High	Low	Unclear	Unclear	Unclear	Low	Low
Ferguson *et al.*[62] 2014	High	Unclear	Unclear	NA	Unclear	High	Low	Unclear	Unclear	Unclear	NA	Low
Goodfellow *et al.*[64] 2003	High	Unclear	NA	Unclear	High	High	Low	Unclear	Unclear	NA	Unclear	High
Goodfellow *et al.*[63] 2015	High	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Hampel *et al.*[15] 2006	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Unclear	Unclear	Low
Latham *et al.*[66] 2019	Unclear	Unclear	Unclear	NA	Unclear	High	Unclear	Unclear	Unclear	Unclear	NA	Low
Leenen *et al.*[67] 2012	High	Unclear	Unclear	Low	Unclear	High	Low	High	Unclear	Unclear	Low	Low

continued

TABLE 5 Judgement of risk of bias and applicability of included partial test accuracy studies (*continued*)

	Risk of bias							Applicability concern level				
Study and year	Patient selection	Index test: MSI	Index test: IHC	Index test: *MLH1* promoter hypermethylation	Reference test	Flow and timing	Role of sponsor	Patients	Index test: MSI	Index test: IHC	Index test: *MLH1* promoter hypermethylation	Reference
Libera *et al.*[68] 2017/Carnevali *et al.*[57] 2017	High	Unclear	Unclear	Low	Unclear	High	Low	High	Unclear	Unclear	Low	Low
Lin and Hecht[69] 2016	High	NA	Unclear	Unclear	Unclear	High	Low	High	NA	Unclear	Unclear	Unclear
Mas-Moya *et al.*[70] 2015/Dudley *et al.*[60] 2015	Low	Unclear	Unclear	Low	Unclear	High	Low	Unclear	Unclear	Unclear	Low	Low
Mercado *et al.*[73] 2012	High	Unclear	Unclear	NA	High	High	Unclear	High	Unclear	Unclear	NA	Unclear
Millar *et al.*[74] 1999	High	NA	Unclear	NA	High	High	Low	High	NA	Unclear	NA	High
Najdawi *et al.*[77] 2017	High	NA	Unclear	Low	Unclear	High	Low	Unclear	NA	Unclear	Low	Low
Ollikainen *et al.*[78] 2005	High	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Low	NA	Low
PETALS study (Dr Neil AJ Ryan, personal communication)	Low	Low	Unclear	Low	Unclear	High	Low	Low	Low	Low	Low	Low
Sarode and Robinson[84] 2018	Unclear	NA	Low	Unclear	High	High	Low	High	NA	Low	Low	High
Shin *et al.*[85] 2015	Unclear	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Unclear	NA	Low
Svampane *et al.*[88] 2014	High	NA	Unclear	NA	Unclear	High	Low	Unclear	NA	Unclear	NA	Low
Takahashi *et al.*[89] 2017	Unclear	NA	High	Unclear	Unclear	High	Low	High	NA	Unclear	Unclear	Low
Yoon *et al.*[92] 2008	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Unclear	Unclear	Low

NA, not applicable.

the role of the sponsor, with 85% (22/26) of studies rated as having a low risk of bias for this domain. The remaining four studies did not report enough information to judge the risk of bias surrounding sponsor involvement.[53,63,66,73]

Applicability of study findings for partial test accuracy studies

There were applicability concerns in one domain. A total of 50% (13/26) of studies had high levels of applicability concerns in the patient selection domain (domain 1: patient selection), with these studies narrowing their inclusion criteria by age and personal/familial cancer history.[15,51,55,57,67–69,73,74,78,84,85,89,92] The only other domain with a high level of applicability concern was the reference standard (domain 3: reference standard). A total of 12% of studies (3/26) were rated as having a high level of applicability concern for the reference standard, with differing methods of germline testing than were recognised in this review. Two of the studies primarily used single-strand conformational variant analysis, and the remaining study used array-based comparative genomic hybridisation/long-range PCR.[64,74,84] All other studies were considered to have a low level of applicability concern, as they provided sequencing followed by PCR or MLPA. The majority of index test ratings were unclear, with little information describing whether or not the conduct and interpretation of the tests was undertaken in accordance to best-practice guidelines and via laboratories that are participating in quality assurance programmes [16/17 (94%), domain 2: index test MSI; 21/25 (84%), domain 2: index test IHC; and 10/17 (59%), domain 2: index test *MLH1* promoter hypermethylation testing]. All judgements of risk of bias and applicability concerns for studies reporting partial test accuracy data can be found in *Table 5*.

Quality appraisal tool for studies of diagnostic reliability

Twenty-three studies (including the unpublished PETALS study) provided data on concordance.[15,16,51,54,55,58,61–63,67,68,71,72,75,78–80,82,85–87,91] These studies were appraised using the QAREL. Two of the questions in the QAREL were deemed not applicable to the studies. Question 7, 'were raters blinded to additional cues that were not part of the test?', was not applicable, as this is covered by question 6 on clinical information. Question 9, 'was the time interval between repeated measurements compatible with the stability (or theoretical stability) of the variable being measured?', was also judged as not applicable following guidance from clinical advisors.

Quality considerations in the included concordance studies are shown in *Table 6*. In general, the quality of the included studies was poor, with only one study (the unpublished PETALS study) having > 50% of the answers meeting the desired criteria in the questions. In particular, the representativeness of the sample was problematic in 78% of studies (18/23).[15,16,51,54,55,61,62,67,68,71,72,78–80,82,85–87] The studies were not comparable to clinical practice in the UK, with populations selected based on age, type of endometrial cancer and presence of synchronous/metachronous cancers (question 1). Only 13% of studies (3/23, including the PETALS study) were deemed representative.[55,61] Similarly, there were concerns regarding the representativeness of the raters performing the tests (question 2). In 87% of studies (20/23), there was not enough information reported to determine whether or not tests were conducted/interpreted by individuals who have undertaken the appropriate training and in laboratories that are participating in quality assurance programmes (e.g. UK National External Quality Assessment Scheme, Nordic immunohistochemical Quality Control, Clinical Laboratory Improvement Amendments).[15,16,51,54,55,58,62,67,68,71,72,75,78–80,82,85–87]

There was a consistent lack of reporting regarding blinding across the studies. In 83% of studies (19/23), it was unclear whether or not raters were blinded to the findings of other raters (question 3); in 90% of studies (21/23), it was unclear whether or not raters were blinded to their own findings (question 4); in 65% of studies (11/17; six studies were concordance only studies with no reference standard, so this question was not applicable), it was unclear whether or not raters were blinded to the results from the reference standard (question 5); and, in 96% of studies (22/23, including the PETALS study), it was unclear whether or not raters were blinded to a patient's clinical information (question 6).[16,51,54,55,58,61,63,67,68,71,72,75,78–80,82,87,91]

TABLE 6 Judgement of quality using the QAREL for concordance studies

Study and year	QAREL question										
	Was the sample of subjects representative?	Was the sample of raters representative?	Were raters blinded to the findings of other raters?	Were raters blinded to their own prior findings?	Were raters blinded to the accepted reference standard?	Were raters blinded to clinical information not part of test?	Were raters blinded to additional non-clinical cues?	Was the order of examination varied?	Was the time interval between repeated measures appropriate?	Was the test applied correctly and interpreted appropriately?	Were appropriate statistical measures of agreement used?
Anagnostopoulos *et al.*[51] 2017	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Berends *et al.*[54] 2003	No	Unclear	Yes	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Bruegl *et al.*[55] 2017	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Chao *et al.*[58] 2019	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Egoavil *et al.*[61] 2013	Yes	Yes	Yes	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Ferguson *et al.*[62] 2014	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Goodfellow *et al.*[63] 2015	No	Yes	Unclear	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Hampel *et al.*[15] 2006	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Leenen 2012[67]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Libera *et al.*[68] 2017	No	Unclear	Unclear	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Lu *et al.*[16] 2007	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Masuda *et al.*[71] 2012	No	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	NA	Unclear	No
McConechy *et al.*[72] 2015	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	NA	Unclear	Yes

TABLE 6 Judgement of quality using the QAREL for concordance studies (*continued*)

Study and year	QAREL question										
	Was the sample of subjects representative?	Was the sample of raters representative?	Were raters blinded to the findings of other raters?	Were raters blinded to their own prior findings?	Were raters blinded to the accepted reference standard?	Were raters blinded to clinical information not part of test?	Were raters blinded to additional non-clinical cues?	Was the order of examination varied?	Was the time interval between repeated measures appropriate?	Was the test applied correctly and interpreted appropriately?	Were appropriate statistical measures of agreement used?
Modica *et al.*[75] 2007	No	Unclear	Unclear	Yes	NA	Unclear	NA	No	NA	Unclear	No
Ollikainen *et al.*[78] 2005	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Pecorino *et al.*[79] 2017	No	Unclear	Unclear	Unclear	NA	Unclear	NA	No	NA	Unclear	No
Planck *et al.*[80] 2017	No	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	NA	Unclear	No
Rubio *et al.*[82] 2016	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
PETALS study (Dr Neil AJ Ryan, personal communication)	Yes	Yes	Yes	Unclear	Yes	Unclear	NA	Unclear	NA	Yes	No
Shin *et al.*[85] 2015	No	Unclear	Unclear	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Stelloo *et al.*[86] 2017	No	Unclear	Unclear	Unclear	Unclear	Yes	NA	No	NA	Unclear	Yes
Strazzullo *et al.*[87] 2003	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Wang *et al.*[91] 2017	Unclear	Yes	Yes	NA	NA	Unclear	NA	No	NA	Yes	No

NA, not applicable.

In addition, there was a lack of reporting on how the tests were undertaken, meaning that it could not be determined whether or not the order of the testing varied [question 8; 19/23, including the PETALS study (83%)],[15,16,51,54,55,58,61–63,67,68,71,72,78,80,82,85,87] or if tests had been conducted according to best-practice guidelines/via laboratories that are participating in quality assurance programmes [question 10; 21/23 (91%)].[15,16,51,54,55,58,61–63,67,68,71,72,75,78–80,82,85–87] The majority of studies [21/23, including the PETALS study (91%)] reported raw data, but did not use any appropriate statistical measures (such as Bland–Altman plots or intraclass correlations, or between categorical/ordinal data with kappas).[15,16,51,54,55,58,61–63,67,68,71,75,78–80,82,85,87,91]

Assessment of test accuracy

Number of Lynch syndrome diagnoses

Thirty-three studies provided data on Lynch syndrome diagnoses,[15,16,51–59,61–64,66,67,69,70,73,77,78,81–85,88–90,92] including the unpublished PETALS study (Dr Neil AJ Ryan, personal communication). Full details of the number of women identified with Lynch syndrome and VUSs/Lynch-like syndrome, and the types and frequencies of mutations, are reported in *Appendix 4*. Across all 33 studies, 349 cases of Lynch syndrome were identified from 7367 women tested. The reported prevalence of Lynch syndrome ranged from 0% (0 out of 140 women tested, in a clinical experience study from the USA that included all women undergoing hysterectomies at two hospitals) to 62%.[73] The prevalence of Lynch syndrome was typically lower in studies that recruited unselected samples of women (median 3.2%, range 0–5.3%) than in studies of selected samples of women (median 7.5%, range 0.9–62%). The prevalence of Lynch syndrome in two UK studies was (confidential information has been removed) [(confidential information has been removed) women tested, including (confidential information has been removed) women with known Lynch syndrome] in an unselected sample of women (PETALS study) and 8.5% (3 out of 35 women tested) in a selected sample of women aged < 50 years.[51] The types and frequencies of MMR gene mutations varied between studies. Combining data from all studies, variants in *MSH2* gene mutations were the most common (38.6% of Lynch syndrome cases), followed by *MSH6* (30.4% of Lynch syndrome cases), *MLH1* (23.6% of Lynch syndrome cases) and *PMS2* (7.3% of Lynch syndrome cases). One study did not report which of the MMR genes were mutated,[83] and 10 studies did not assess all four MMR genes.[16,53,54,64,74,78,82,85,88,92] *MHL1* and *MSH2* were not assessed in one study,[64] *MSH6* was not assessed in three studies[53,74,85] and *PMS2* was not assessed in 10 studies.[16,53,54,64,74,78,82,85,88,92] Combining data from studies of unselected samples of women, variants in *MSH6* were the most common (39.1% of Lynch syndrome cases), followed by *MSH2* (32.2% of Lynch syndrome cases), *MLH1* (19.5% of Lynch syndrome cases) and *PMS2* (9.2% of Lynch syndrome cases). Combining data from studies of selected samples of women, variants in *MSH2* were the most common (42.1% of Lynch syndrome cases), followed by *MSH6* (25.7% of Lynch syndrome cases), *MLH1* (25.4% of Lynch syndrome cases) and *PMS2* (6.8% of Lynch syndrome cases).

Eighty-nine VUSs were reported in 10 studies (including the PETALS study), ranging from 2–15 cases per study.[15,16,54–58,61,63,82,90] In one study (confidential information has been removed) of the VUSs were identified in women who were (confidential information has been removed). Nine women were reported to have Lynch-like syndrome from two studies, ranging from 3 to 6 cases per study.[59,70]

Accuracy of screening tests

The methods, the thresholds to determine positivity of index tests and the diagnostic tests varied between studies. Results were considered positive when they exceeded the threshold as set in the individual study. Results are reported by complete test accuracy, concordance, partial test accuracy, test failures and indeterminate results. No studies reported the time from index test to result or diagnosis.

Complete test accuracy studies

Head-to-head studies

Four studies provided head-to-head test accuracy data for IHC- and MSI-based testing, although the numbers of included tumours were not identical for each of the tests because of insufficient tumour tissue being available and test failures.[16,54,58,82] Three studies had a larger number of results for IHC than for MSI: 102 versus 83,[58] 99 versus 95[16] and 94 versus 83.[82] One study had a larger number of results for MSI than for IHC: 57 versus 51.[54] All four studies comprised selected samples of women. Two studies excluded women aged > 50 years,[16,54] one study excluded women with recurrent or synchronous cancers[58] and one study excluded women (1) without a personal/family history of Lynch syndrome or (2) who were aged > 50 years.[82] Two studies included an ineligible reference standard (conformational-sensitive gel electrophoresis/denaturing gradient gel electrophoresis) as part of their diagnostic process.[54,82] Three of the studies were judged to be at high risk of bias.[54,58,82] The remaining study was judged to have an unclear risk of bias, as insufficient information was presented on which to make an assessment.[16] All four studies were rated as having high applicability concerns (see *Risk of bias for complete test accuracy studies* and *Applicability of study findings for complete test accuracy studies* for further details).

For IHC, there were 28 true positives, 78 false positives, 235 true negatives and 5 false negatives; point estimates ranged from 66.7% to 100% for sensitivity, 60.9% to 83.3% for specificity, 14.3% to 37.5% for PPVs and 95.2% to 100% for NPVs. For MSI testing, there were 21 true positives, 57 false positives, 232 true negatives and 8 false negatives; point estimates ranged from 41.7% to 100% for sensitivity, 69.2% to 89.9% for specificity, 20% to 33.3% for PPVs and 88.7% to 100% for NPVs. There were no statistically significant differences (on the basis of CIs) between MSI and IHC on any of the four tests' accuracy metrics.

Immunohistochemistry- and microsatellite instability-based testing, with MLH1 *promoter hypermethylation testing*

Four studies provided test accuracy data for IHC- and MSI-based testing, where a lack of expression on IHC without *MLH1* methylation or MSI-H (two or more unstable markers) test was considered index-test positive.[16,58,81,83] Full details are reported in *Table 7*. The circumstances under which *MLH1* promoter hypermethylation testing was conducted varied in the studies. In two studies, methylation testing was conducted in women who had tumours that were categorised as MSI-H or had IHC loss (*MLH1* or *MLH1*/*PMS2*);[16,83] in one study, methylation testing was conducted in women who had IHC *MLH1* loss only.[58] In the remaining paper, the circumstances under which *MLH1* promoter hypermethylation testing was conducted were not reported.[81] Three studies comprised selected samples of women,[16,58,83] and one study comprised an unselected sample of women.[81] One study excluded women aged > 50 years;[16] one study excluded women with recurrent or synchronous cancers;[58] and one study included an unselected sample of women, but did not report data on women with uninformative MMR results or without prior tumour testing.[83] Each study used a different panel of MSI markers. There were 85 true positives, 290 false positives, 475 true negatives and 4 false negatives. Two studies reported the gene variants in Lynch syndrome cases.[16,58] The most commonly affected gene was *MSH2* [9/15 cases of Lynch syndrome (60%)], followed by *MSH6* [4/15 cases of Lynch syndrome (26.7%)], *MLH1* [2/15 cases of Lynch syndrome (13.3%)] and *PMS2* [0/15 cases of Lynch syndrome (0%)]. *PMS2* was assessed in only one study.[58] In two studies, 25 VUSs were identified (median 12.5; 11–14 cases per study).[16,58] One study did not report VUSs.[83] In the remaining study, 25 VUSs were identified, but the study did not report whether or not the participants had undergone index testing.[81] Point estimates ranged from 90.5% to 100% for sensitivity, 6.6% to 92.3% for specificity, 18.3% to 56.3% for PPVs and 75.0% to 100% for NPVs. In the study with an unselected sample of women,[81] there were 19 true positives, 32 false positives, 312 true negatives and 2 false negatives. Comparing CIs, there was no statistically significant difference in sensitivity, specificity, PPVs or NPVs between the studies with selected samples and those with unselected samples.

TABLE 7 Studies reporting complete test accuracy for MSI, IHC and *MLH1* promoter hypermethylation testing

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Chao *et al.*[58] 2019	93	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): negative staining of any of MMR protein MSI: MSI-H (two or more unstable markers)	NGS, Sanger sequencing	6	24	63	0	100.0 (51.7 to 100.0)	72.4 (61.6 to 81.2)	20.0 (8.4 to 39.1)	100.0 (92.8 to 100.0)
Lu *et al.*[16] 2007	100	IHC (*MLH1*, *MSH2*, *MSH6*): loss of protein expression MSI: MSI-H (two or more unstable markers)	Sequencing, unspecified test for large deletions	9	7	84	0	100.0 (62.9 to 100.0)	92.3 (84.3 to 96.6)	56.3 (30.6 to 79.2)	100.0 (94.6 to 100.0)
Ring *et al.*[81] 2016	365	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): complete absence of MMR protein expression MSI: MSI-H, but cut-off point not reported	MLPA, NGS	19	32	312	2	90.5 (68.2 to 98.3)	90.7 (87.0 to 93.5)	37.3 (24.5 to 51.9)	99.4 (97.5 to 99.9)
Salvador *et al.*[83] 2019	296	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): cut-off point not reported MSI: MSI-H (two or more unstable markers)	MLPA, NGS	51	227	16	2	96.2 (85.9 to 99.3)	6.6 (3.9 to 10.7)	18.3 (14.1 to 23.5)	75.0 (35.6 to 88.9)

Two studies reported the results of *MLH1* promoter hypermethylation testing.[16,58] Twelve out of 13 tumours (92.3%)[16] and 12 out of 15 tumours (80%) were hypermethylated.[58]

A secondary analysis of test accuracy in which VUSs were considered germline positive was possible for two studies.[16,58] Estimates of test accuracy were as follows: sensitivity, 100.0% (95% CI 80.0% to 100.0%); specificity, 86.3% (95% CI 75.8% to 92.9%); PPV, 66.7% (95% CI 47.1% to 82.1%); and NPV, 100.0% (95% CI 92.8 to 100.0%);[58] and sensitivity, 100.0% (95% CI 80.0% to 100.0%); specificity, 78.8% (95% CI 67.9% to 86.8%); PPV, 54.1% (95% CI 37.1 to 70.2%); and NPV, 100.0% (95% CI 92.8 to 100.0%).[16] These were similar to estimates in which VUSs were consider to be germline negative, with the exception of PPV for Chao *et al.*,[58] which was higher when VUSs were considered to be germline positive [66.7% (95% CI 47.1% to 82.1%) vs. 20.0% (95% CI 8.4% to 39.1%) for germline positive vs. germline negative, respectively].

Immunohistochemistry alone

Five studies provided test accuracy data for IHC.[16,54,58,82,90] Full details are provided in *Table 8*. All five studies comprised selected samples of women. Two studies excluded women aged > 50 years;[16,54] one study excluded women with recurrent or synchronous cancers;[58] one study excluded women (1) without a personal/family history of Lynch syndrome-related cancer or (2) who were aged > 50 years;[82] and one study excluded women who were (1) aged > 50 years, (2) without a personal/family history of Lynch syndrome-related cancer or (3) did not have loss of expression of any MMR protein on IHC testing.[90] Four studies assessed all four MMR proteins[54,58,82,90] and one study assessed *MHL1*, *MSH2* and *MSH6*.[16] There were 69 true positives, 193 false positives, 243 true negatives and 6 false negatives in the five included studies. The most commonly affected gene was *MSH2* [34/69 cases of Lynch syndrome (49.3%)], followed by *MSH6* [18/69 cases of Lynch syndrome (26.1%)], *MLH1* [14/69 cases of Lynch syndrome (20.3%)] and *PMS2* [3/69 cases of Lynch syndrome (4.3%)]. *PMS2* was assessed in only two studies.[58,90] In total, 33 VUSs were identified in the five studies (median 4; 3–11 cases per study). The point estimates ranged from 66.7% to 100% for sensitivity, from 6.5% to 83.3% for specificity, from 14.3% to 37.5% for PPV and from 88.9% to 100% for NPV (see *Figure 23*). With the exception of PPV in the study by Tian *et al.*,[90] CIs between studies overlapped for each of the test accuracy metrics. Test accuracy estimates for the single study that employed only *MLH1*, *MSH2* and *MSH6* were within the ranges reported by the studies using all four MMR proteins.

Of the five studies, one presented data in sufficient detail to estimate test accuracy by individual proteins.[16] This study reported on *MLH1*, *MSH2* and *MSH6* in 99 patients. True positives were determined by the individual protein test's ability to detect any germline mutation, not necessarily the corresponding mutation. There was wide variation in the test accuracy between the different proteins. Sensitivity was 11.1% (95% CI 0.6% to 49.3%) for *MLH1*, 66.7% (95% CI 30.9% to 91.0%) for *MSH6* and 77.8% (95% CI 40.2% to 96.1%) for *MSH2*. Specificity was 87.8% (95% CI 79.2% to 93.2%) for *MLH1*, 95.6% (95% CI 88.4% to 98.6%) for *MSH6* and 95.7% (95% CI 88.6% to 98.6%) for *MSH2*. PPV was 7.7% (95% CI 0.4% to 37.9%) for *MLH1*, 60.0% (95% CI 27.4% to 86.3%) for *MSH6* and 63.6% (95% CI 31.6% to 87.6%) for *MSH2*. NPV was 90.7% (82.0% to 95.6%) for *MLH1*, 96.6% (95% CI 89.8% to 99.1%) for *MSH6* and 97.6% (95% CI 91.0% to 99.6%) for *MSH2*. The wide variations between the test accuracy for *MLH1* and the other proteins may be accounted for by the difference in the number of false positives. There were 12 false positives when testing using *MLH1*, compared with only four for *MSH2* and *MSH6*.

In three of the studies, information on the IHC result by individual protein was presented only for those with a germline mutation,[54,82,90] and, in the remaining study, eight IHC cases were not reported and there were discrepancies between values reported in the text and table.[58]

A secondary analysis of test accuracy in which VUSs were considered germline positive was possible for four studies.[16,54,58,82] Estimates of test accuracy were as follows: sensitivity, 100.0% (95% CI 59.8% to 100.0%); specificity, 62.8% (95% CI 46.7% to 76.6%); PPV, 33.3% (95% CI 16.4% to 55.3%);

TABLE 8 Studies reporting complete test accuracy for IHC alone

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Berends *et al.*[54] 2003	51	IHC (*MLH1*, *MSH2*, and *MSH6*): absence of detectable nuclear staining of cancer cells	DGGE, sequencing, MLPA	5	18	28	0	100 (46.3 to 100)	60.9 (45.4 to 74.5)	21.7 (8.3 to 44.2)	100 (85 to 100)
Chao *et al.*[58] 2019	102	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): negative staining of any of MMR protein	NGS, Sanger sequencing	4	24	72	2	66.7 (24.1 to 94.0)	75.0 (64.9 to 83.0)	14.3 (4.7 to 33.6)	97.3 (89.7 to 99.5)
Lu *et al.*[16] 2007	99	IHC (*MHL1*, *MSH2*, *MSH6*): loss of protein expression	Sequencing, unspecified test for large deletions	9	15	75	0	100.0 (62.9 to 100.0)	83.3 (73.7 to 90.1)	37.5 (19.5 to 59.2)	100.0 (93.9 to 100.0)
Rubio *et al.*[82] 2016	94	IHC: cut-off point not reported	CSGE, sequencing, MLPA	10	21	60	3	76.9 (46 to 93.8)	74.1 (62.9 to 82.9)	32.3 (17.3 to 51.5)	95.2 (85.8 to 98.8)
Tian *et al.*[90] 2019	165	IHC: cut-off point not reported	Sequencing/ NGS, MLPA	41	115	8	1	97.6 (85.9 to 99.9)	6.5 (3.1 to 12.8)	26.3 (19.7 to 34.0)	88.9 (50.7 to 99.4)

CSGE, conformation-sensitive gel electrophoresis; DGGE, denaturing gradient gel electrophoresis.

and NPV, 100.0% (95% CI 84.5% to 100.0%);[54] sensitivity, 90.0% (95% CI 66.9% to 98.2%); specificity, 75.6% (95% CI 64.7% to 84.1%); PPV, 47.4% (95% CI 31.3% to 64.0%); and NPV, 96.9% (95% CI 88.2% to 99.5%);[58] sensitivity, 100.0% (95% CI 80.0% to 100.0%); specificity, 83.5% (95% CI 73.1% to 90.6%); PPV, 60.6% (95% CI 42.2% to 76.6%); and NPV, 100.0% (95% CI 93.1% to 100.0%);[16] and sensitivity, 82.4% (55.8% to 95.3%); specificity, 75.3% (64.0% to 84.1%); PPV, 42.4% (26.0% to 60.6%); and NPV, 95.1% (85.4% to 98.7%).[82] These were similar to estimates in which VUSs were considered to be germline negative.

Microsatellite instability-based testing alone

Four studies provided test accuracy data for MSI-based testing.[16,54,58,82] Full details are provided in *Table 9*. All four studies comprised selected samples of women. Two studies excluded women aged > 50 years;[16,54] one study excluded women with recurrent or synchronous cancers,[58] and one study excluded women (1) without a personal/family history of Lynch syndrome or (2) who were aged > 50 years.[82] Three different panels of markers were used in the four studies; only two studies used the same panel of markers.[16,82] Using MSI-H (two or more unstable markers) as a cut-off point, there were 21 true positives, 57 false positive, 232 true negatives and 8 false negatives in the four included studies. The most commonly affected gene was *MSH2* [13/21 cases of Lynch syndrome (61.9%)], followed by *MSH6* [4/21 cases of Lynch syndrome (19%)] and *MLH1* [4/21 cases of Lynch syndrome (19%)]. *PMS2* was assessed in only one study;[58] there were no cases of Lynch syndrome with a *PMS2* mutation. In total, 29 VUSs were identified in the four studies (median 7; 3–12 cases per study). Point estimates ranged from 41.7% to 100% for sensitivity, from 69.2% to 89.9% for specificity, from 20% to 89.9% for PPV and from 88.7% to 100% for NPV. One of the included studies reported data that allowed us to calculate test accuracy using MSI-H or MSI-L (one or more unstable marker) as a cut-off point.[82] There were 5 true positives, 17 false positives, 54 true negatives and 7 false negatives.[82] The most commonly affected gene was *MSH2* [3/5 cases of Lynch syndrome (60.0%)], followed by *MSH6* [1/5 cases of Lynch syndrome (20%)] and *MLH1* [1/5 cases of Lynch syndrome (20%)]. *PMS2* was not assessed. Three VUSs were identified. Test accuracy metrics were similar to those reported using MSI-H as a cut-off point: sensitivity was 41.7%, specificity was 76.1%, PPV was 22.7% and NPV was 88.5%. Using a cut-off point of one or more stable markers changed the status of one index test result from true negative to false positive.

A secondary analysis of test accuracy in which VUSs were considered germline positive was possible for four studies.[16,54,58,82] Estimates of test accuracy were as follows: sensitivity, 87.5% (95% CI 46.7% to 99.3%); specificity, 69.4% (95% CI 54.4% to 81.3%); PPV, 31.8% (95% CI 14.7% to 54.9%); and NPV, 97.1% (95% CI 83.4% to 99.9%);[54] sensitivity, 100.0% (95% CI 75.9% to 100.0%); specificity, 91.0% (95% CI 80.9% to 96.3%); PPV, 72.7% (95% CI 49.6% to 88.4%); and NPV, 100.0% (95% CI 92.6% to 100.0%);[58] sensitivity, 100.0% (95% CI 79.1% to 100.0%); specificity, 80.3% (95% CI 69.2% to 88.2%); PPV, 55.9% (95% CI 38.1% to 72.4%); and NPV, 100.0% (95% CI 92.6% to 100.0%);[16] and sensitivity, 53.3% (95% CI 27.4% to 77.7%); specificity, 76.5% (95% CI 64.4% to 85.6%); PPV, 33.3% (95% CI 16.4% to 55.3%); and NPV, 88.1% (95% CI 76.5% to 94.7%).[82] These were similar to estimates in which VUSs were considered to be germline negative.

Concordance between immunohistochemistry- and microsatellite instability-based testing

Twenty-three studies, including the unpublished PETALS study (Dr Neil AJ Ryan, personal communication), provided data on concordance between IHC- and MSI-based testing.[15,16,51,54,55,58,61–63,67,68,71,72,75,78–80,82,85–87,91] Twenty studies provided complete concordance data (agreement/disagreement between IHC positive/negative and IHC negative), and three studies provided partial concordance data (IHC conducted only for MSI-H tumours,[87] MSI conducted only for women with IHC loss[79] and IHC conducted only for women with MSS results[15]). Full details of concordance are reported in *Appendix 5*. In the studies providing complete concordance data, there was a high level of agreement between the results of the tests (median agreement 91.8%, with the lowest level of agreement being 68.2% and the highest level of agreement being 100%) and a low level of disagreement (median disagreement 9.8%, with the lowest level of disagreement being 0% and the highest level of disagreement being 31.8%), median kappa 0.84 (range 0.32–0.97). Kappa values were calculated by the reviewers.

TABLE 9 Studies reporting complete test accuracy for MSI testing alone

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
MSI only (MSI-H vs. MSI-L/MSS)											
Berends *et al.*[54] 2003	57	MSI: MSI-H (two or more unstable markers)	DGGE, sequencing, MLPA	4	16	36	1	80 (29.9 to 98.9)	69.2 (54.7 to 80.9)	20 (6.6 to 44.3)	97.3 (84.2 to 99.9)
Chao *et al.*[58] 2019	83	MSI: MSI-H (two or more unstable markers)	NGS, Sanger sequencing	4	8	71	0	100.0 (39.6 to 100.0)	89.9 (80.5 to 95.2)	33.3 (11.3 to 64.6)	100.0 (93.6 to 100.0)
Lu *et al.*[16] 2007	95	MSI: MSI-H (two or more unstable markers)	Sequencing, unspecified test for large deletions	8	17	70	0	100.0 (59.8 to 100.0)	80.5 (70.3 to 87.9)	32.0 (15.7 to 53.6)	100.0 (93.5 to 100.0)
Rubio *et al.*[82] 2016	83	MSI: MSI-H, number of markers not specified	CSGE, sequencing, MLPA	5	16	55	7	41.7 (16.5 to 71.4)	77.5 (65.7 to 86.2)	23.8 (9.1 to 47.6)	88.7 (77.5 to 95)
MSI only (MSI-H/MSI-L vs. MSS)											
Rubio *et al.*[82] 2016	83	MSI: MSI-H/ MSI-L, number of markers not specified	CSGE, sequencing, MLPA	5	17	54	7	41.7 (16.5 to 71.4)	76.1 (64.2 to 85.1)	22.7 (8.7 to 45.8)	88.5 (77.2 to 94.9)

CSGE, conformation-sensitive gel electrophoresis; DGGE, denaturing gradient gel electrophoresis.

Few studies examined characteristics of discordant cases. Four studies reported that *MLH1* promoter hypermethylation was common in discordant cases: 50% (1/2 cases),[71] 75% (3/4 cases),[72] 80% (4/5 cases)[55] and 83% (10/12 cases).[86] Seven of the 23 concordance studies reported on the characteristics of discordant cases of MSI and IHC testing.[15,16,51,55,63,72,85] In two of these seven studies, it was possible to determine germline results for the discordant cases.[15,55] Bruegl *et al.*[55] found 5.1% disagreement, with seven out of 197 discordant cases. Of these seven, only one was found to have a germline mutation and this was in the *MSH6* variant. Likewise, Hampel *et al.*[15] found that the only discordant case with a germline mutation was in the *MSH6* variant. By contrast, Lu *et al.*[16] found that, of the five discordant cases, all were germline mutation negative.

Across three studies,[16,55,72] 20–57% (4/7, 1/5 and 2/6) of discordant results were due to *MLH1* promoter hypermethylation, suggestive of epigenetic changes rather than Lynch syndrome.

For one study,[51] discordance was associated with the classification of MSI-L cases. When MSI-L cases were grouped with MSS cases there were two discordant cases, whereas when MSI-H or MSI-L cases were grouped together and compared with MSS cases, there were no cases of discordance between MSI and IHC testing results.[51]

It was possible to calculate the average age for discordant cases in three studies.[15,51,85] In Anagnostopoulos *et al.*,[51] discordant cases ($n = 2$) had a median age of 39.5 years, which was lower than the overall median of 48 years in the sample. Although Shin *et al.*[85] and Hampel *et al.*[15] found no real difference in age between discordant cases and the whole sample, Shin *et al.*[85] found two discordant cases with a mean age of 55 years at diagnosis of endometrial cancer and a mean age of 52.5 years at diagnosis of CRC, compared with the overall sample mean age of 52.5 years at endometrial cancer and 54.5 years at CRC.[85] Hampel *et al.*[15] found a mean age of 60.5 years in discordant cases, compared with the overall mean of 60.9 years in the whole sample.

One study[85] reported on the comorbidities of other cancers in discordant cases. All cases in the study had a history of both endometrial cancer and CRC. They found that one of the two discordant cases also had a history of bladder cancer. Likewise, this was the only study to discuss family history in relation to discordant cases, and noted that both cases met the Amsterdam II criteria.[93]

Testing pathways under review: partial test accuracy studies

In the proposed testing strategies 1–10, only women who test positive on the index tests would be offered germline testing. Some studies report results from implementing the strategies of interest; these are partial test accuracy studies because data on true negatives and false negatives are not available. It is not possible to calculate sensitivity, specificity or NPVs from these studies because of a lack of follow-up of women who were negative on the index tests. Studies in which full test accuracy could be extracted/calculated have already been reported (see *Assessment of test accuracy*), so here we report results from any studies (full or partial test accuracy) that report the numbers of true positive and false positive results for each strategy. Full details of all the strategies are provided in *Table 10*.

There is a risk that the likelihood that someone receives the reference standard is associated with disease status, for example individuals who truly have a disease may be more likely to get the reference standard than those who do not have the disease. This biases the PPV upwards. Therefore, we included only studies in which at least 95% of women who were eligible for germline testing (i.e. those who were index-test positive) received it.

Strategy 1: microsatellite instability testing alone

Eight studies, including the unpublished PETALS study (Dr Neil AJ Ryan, personal communication), provided test accuracy data for this strategy.[16,54,58,66,73,78,82]

TABLE 10 Partial test accuracy

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Strategy 1: MSI testing alone											
Berends *et al.*[54] 2003	57	MSI: MSI-H – ≥ 2 unstable markers	DGGE, sequencing, MLPA	4	16	NA	NA	NA	NA	20.0 (6.6 to 44.3)	NA
Chao *et al.*[58] 2019	83	MSI: MSI-H – ≥ 2 unstable markers	NGS, Sanger sequencing	4	8	NA	NA	NA	NA	33.3 (11.3 to 64.6)	NA
Latham *et al.*[66] 2019	525	MSI: MSI sensor scores of ≥ 10	NGS	7	112	NA	NA	NA	NA	5.9 (2.6 to 12.2)	NA
Lu *et al.*[16] 2007	95	MSI: MSI-H – ≥ 2 unstable markers	Sequencing, unspecified test for large deletions	8	17	NA	NA	NA	NA	32.0 (15.7 to 53.6)	NA
Mercado *et al.*[73] 2012	24	MSI: MSI-H – ≥ 2 unstable markers	DHPLC, sequencing	15	5	NA	NA	NA	NA	75 (50.6 to 90.4)	NA
Ollikainen *et al.*[78] 2005	23	MSI: MSI-H – ≥ 2 unstable markers	Sequencing & MLPA	2	1	NA	NA	NA	NA	66.7 (12.5 to 98.2)	NA
PETALS study (Dr Neil AJ Ryan, personal communication)	Confidential information has been removed	MSI: MSI-H – ≥ 2 unstable markers	NGS, MLPA, long-range PCR, constitutional *MLH1* promoter hypermethylation testing	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Rubio *et al.*[82] 2016	83	MSI: MSI-H, number of markers not specified	CSGE, sequencing, MLPA	5	16	NA	NA	NA	NA	23.8 (9.1 to 47.6)	NA
Strategy 2: MSI testing with* MLH1 *promoter hypermethylation testing											
No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Strategy 3: IHC alone											
Berends *et al.*[54] 2003	51	IHC: absence of detectable nuclear staining of cancer cells	DGGE, sequencing, MLPA	5	18	NA	NA	NA	NA	21.7 (8.3 to 44.2)	NA
Chao *et al.*[58] 2019	102	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): negative staining of any of MMR protein	NGS, Sanger sequencing	4	24	NA	NA	NA	NA	14.3 (4.7 to 33.6)	NA
Lu *et al.*[16] 2007	99	IHC (*MHL1*, *MSH2*, *MSH6*): loss of protein expression	Sequencing, unspecified test for large deletions	9	15	NA	NA	NA	NA	37.5 (19.5 to 59.2)	NA
Mercado *et al.*[73] 2012	• *MLH1* = 70 • *MSH2* = 74 • *MSH6* = 69 • *PMS2* = 52	IHC (*MHL1*, *MSH2*, *MSH6*, *PMS2*): loss of protein expression	DHPLC, sequencing	• *MLH1* = 22 • *MSH2* = 21 • *MSH6* = 24 • *PMS2* = 18	• *MLH1* = 4 • *MSH2* = 7 • *MSH6* = 7 • *PMS2* = 4	NA	NA	NA	NA	• *MLH1* = 84.6 (64.3 to 95.0) • *MSH2* = 75.0 (54.8 to 88.6) • *MSH6* = 77.4 (58.5 to 89.7) • *PMS2* = 81.8 (59.0 to 94.0)	NA
PETALS study (Dr Neil AJ Ryan, personal communication)	Confidential information has been removed	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): protein loss	NGS, MLPA, long-range PCR, constitutional *MLH1* promoter hypermethylation testing	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Rubio *et al.*[82] 2016	94	IHC: cut-off point not reported	CSGE, sequencing, MLPA	10	21	NA	NA	NA	NA	32.3 (17.3 to 51.5)	NA
Tian *et al.*[90] 2019	165	IHC: cut-off point not reported	Sequencing/NGS, MLPA	41	115	NA	NA	NA	NA	26.3 (19.7 to 34.0)	NA

continued

TABLE 10 Partial test accuracy (*continued*)

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Strategy 4: IHC with* MLH1 *promoter hypermethylation testing											
Lu *et al.*[16] 2007	99	IHC (*MHL1*, *MSH2*, *MSH6*): loss of protein expression	Sequencing, unspecified test for large deletions	9	15	NA	NA	NA	NA	37.5 (19.5 to 59.2)	NA
Ollikainen *et al.*[78] 2005	23	IHC (*MLH1*, *MSH2*, *MSH6*): cut-off point not reported	Sequencing and MLPA	2	8	NA	NA	NA	NA	20.0 (3.5 to 55.8)	NA
PETALS study (Dr Neil AJ Ryan, personal communication)	Confidential information has been removed	IHC (*MHL1*, *MSH2*, *MSH6*, *PMS2*): protein low	NGS, MLPA, long-range PCR, constitutional *MLH1* promoter hypermethylation testing	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Strategy 5: MSI testing followed by IHC testing											
No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Strategy 6: MSI followed by IHC testing with* MLH1 *promoter hypermethylation testing											
No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Strategy 7: IHC followed by MSI-based testing											
No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Strategy 8: IHC testing followed by MSI testing with* MLH1 *promoter hypermethylation testing											
No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Strategy 9: MSI and IHC testing											
No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Strategy 10: MSI and IHC testing with* MLH1 *promoter hypermethylation testing											
Chao *et al.*[58] 2019	77	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): negative staining of any of MMR protein MSI: MSI-H – ≥ 2 unstable markers	NGS, Sanger sequencing	6	14	NA	NA	NA	NA	30.0 (12.8 to 54.3)	NA
Goodfellow *et al.*[63] 2015	1002	IHC (*MLH1*, *MSH2*, *MSH6*, plus *PMS2* in subset: cut-off point not reported MSI: MSI-H – ≥ 2 unstable markers	NGS	22	29	NA	NA	NA	NA	43.1 (29.6 to 57.7)	
Lu *et al.*[16] 2007	100	IHC (*MHL1*, *MSH2*, *MSH6*): loss of protein expression MSI: MSI-H – ≥ 2 unstable markers	Sequencing, unspecified test for large deletions	9	24	NA	NA	NA	NA	27.3 (13.9 to 45.8)	NA
Ollikainen *et al.*[78] 2005	23	IHC (*MLH1*, *MSH2*, *MSH6*): cut-off point not reported MSI: MSI-H – ≥ 2 unstable markers	Sequencing and MLPA	2	8	NA	NA	NA	NA	20.0 (3.5 to 55.8)	NA
Salvador *et al.*[83] 2019	296	IHC (*MLH1*, *MSH2*, *MSH6*, *PMS2*): cut-off point not reported MSI: MSI-H – ≥ 2 unstable markers	MLPA, NGS	51	227	NA	NA	NA	NA	18.3 (14.1 to 23.5)	NA

continued

TABLE 10 Partial test accuracy (*continued*)

Study and year	Number tested	Index test and cut-off point	Reference standard	2 × 2 table (*n*)				% (95% CI)			
				True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV
Yoon *et al.*[92] 2008	113	MSI: MSI-H – ≥ 2 unstable markers IHC (*MHL1*, *MSH2*, *MSH6*): no evidence of expression	Sequencing	4	9	NA	NA	NA	NA	30.8 (10.4 to 61.1)	NA
Strategy 11: germline only											
Study	*Number tested*	*Reference standard*		*Number of Lynch syndrome diagnoses (%)*				*Notes*			
Berends *et al.*[54] 2003	57	DGGE, sequencing, MLPA		5 (8.8)				Initial reference standard was DGGE (followed, in case of aberrant band patterns, by direct sequencing of independently amplified PCR products)			
Chao *et al.*[58] 2019	111	NGS and Sanger sequencing		6 (5.4)				–			
Ferguson *et al.*[62] 2014	89	Sequencing, MLPA		7/89 (7.9)				–			
Millar *et al.*[74] 1999	40	SSCV, sequencing		7 (17.5)				All of the women included had endometrial cancer and CC			
Lu *et al.*[16] 2007	100	Sequencing, unspecified test for large deletions		9 (9)				–			
Ring *et al.*[81] 2016	381	MLPA, NGS		22 (5.8)				Two women diagnosed with Lynch syndrome had mutations in *EPCAM* that extended into *MSH2*			
Rubio *et al.*[82] 2016	103	CSGE, sequencing, MLPA		14 (13.6)				–			
Salvador *et al.*[83] 2019	296	NGS, MLPA, ACGH		51 (17.3)				–			
Tian *et al.*[90] 2019	198	Sequencing, NGS, MLPA		45 (22.7)				–			

ACGH, array comparative genomic hybridisation; CSGE, conformation-sensitive gel electrophoresis; DGGE, denaturing gradient gel electrophoresis; DHPLC, denaturing high-performance liquid chromatography; NA, not applicable; SSCV, single-strand conformational variance.

Six studies comprised selected samples of women,[16,54,58,73,78,82] one study provided insufficient information on which to make an assessment of sample selection type[66] and the PETALS study comprised an unselected sample of women (Dr Neil AJ Ryan, personal communication). Two studies excluded women aged > 50 years,[16,54] one study excluded women with recurrent or synchronous cancers,[58] one study included only women with a family history of endometrial cancer[78] and one study excluded women (1) without a personal/family history of Lynch syndrome-related cancer or (2) who were aged > 50 years.[73,82]

There were (confidential information has been removed) true positives and (confidential information has been removed) false positives out of (confidential information has been removed) women tested. The most commonly affected gene was *MSH2* [(confidential information has been removed) cases of Lynch syndrome (confidential information has been removed)], followed by *MSH6* [(confidential information has been removed) cases of Lynch syndrome (confidential information has been removed)], *MLH1* [(confidential information has been removed) cases of Lynch syndrome (confidential information has been removed)] and *PMS2* [(confidential information has been removed) cases of Lynch syndrome (confidential information has been removed)]. *PMS2* was assessed in only four out of the eight studies (including the PETALS study).[58,66,73] In total, (confidential information has been removed) VUSs were identified in the seven studies [median (confidential information has been removed); (confidential information has been removed) cases per study]. Point estimates for PPVs ranged from (confidential information has been removed) to (confidential information has been removed).

Strategy 2: microsatellite instability testing with MLH1 *promoter hypermethylation testing*

No studies were identified that examined this strategy.

Strategy 3: immunohistochemistry-based testing alone

Six studies provided test accuracy data for this strategy.[16,54,58,73,82,90] All six studies comprised selected samples of women. Two studies excluded women aged > 50 years;[16,54] one study excluded women with recurrent or synchronous cancers;[58] one study excluded women (1) without a personal/family history of Lynch syndrome-related cancer or (2) who were aged > 50 years;[82] and one study excluded women who (1) were aged > 50 years, (2) were without a personal/family history of Lynch syndrome-related cancer or (3) did not have loss of expression of any MMR protein on IHC testing.[73,90] In the five studies in which MMR genes were considered together, there were 69 true positives and 193 false positives, out of 552 women tested. The most commonly affected gene was *MSH2* [34/69 cases of Lynch syndrome (49.3%)], followed by *MSH6* [18/69 cases of Lynch syndrome (26.1%)], *MLH1* [14/69 cases of Lynch syndrome (20.3%)] and *PMS2* [3/69 cases of Lynch syndrome (3%)]. *PMS2* was assessed in only three out of the six studies.[58,73,90] In total, 22 VUSs were identified in the seven studies (median 3; 2–11 cases per study). In the single study in which MMR genes were considered separately, the most commonly affected gene was *MSH2* [40/80 cases of Lynch syndrome (50%)], followed by *MLH1* [31/80 cases of Lynch syndrome (38.8%)] and *MSH6* [9/81 cases of Lynch syndrome (11.2%)].[73] Point estimates for PPVs ranged from 12.2% to 37.5% in the studies that reported on all four MMR genes,[16,54,58,82,90] and from 77.4% to 84.6% in the study that reported each gene separately.[73]

Strategy 4: immunohistochemistry testing with MLH1 *promoter hypermethylation testing*

Three studies provided test accuracy data for this strategy, including the PETALS study (Dr Neil AJ Ryan, personal communication).[16,78] Two studies comprised selected samples of women.[16,78] One study excluded women aged > 50 years,[16] and one study included only women with a family history of endometrial cancer.[78] The PETALS study was conducted in an unselected sample of women with endometrial cancer (Dr Neil AJ Ryan, personal communication). There were (confidential information has been removed) true positives and (confidential information has been removed) false positives out of (confidential information has been removed) women tested. The most commonly affected gene was *MSH2* [(confidential information has been removed) cases of Lynch syndrome, (confidential information has been removed)] followed by *MSH6* [(confidential information has been removed) cases of Lynch syndrome (confidential information has been removed)], *MLH1* [(confidential information has been removed) cases of Lynch syndrome (confidential information has been removed)] and *PMS2* [(confidential information has been removed) cases

of Lynch syndrome (confidential information has been removed)]. Only the PETALS study assessed *PMS2* (Dr Neil AJ Ryan, personal communication). In total, (confidential information has been removed) VUSs were identified in the three studies [median (confidential information has been removed); (confidential information has been removed) cases per study]. Point estimates for PPVs ranged from (confidential information has been removed) to (confidential information has been removed). All three studies reported the results of *MLH1* promoter hypermethylation testing. (Confidential information has been removed) out of (confidential information has been removed) tumours (confidential information has been removed),[78] (confidential information has been removed) out of (confidential information has been removed) tumours (confidential information has been removed)[16] and (confidential information has been removed) (PETALS study, Dr Neil AJ Ryan, personal communication) were hypermethylated.

Strategy 5: microsatellite instability testing followed by immunohistochemistry testing

No studies were identified that examined this strategy.

Strategy 6: microsatellite instability followed by immunohistochemistry testing with MLH1 *promoter hypermethylation testing*

No studies were identified that examined this strategy.

Strategy 7: immunohistochemistry followed by microsatellite instability testing

No studies were identified that examined this strategy.

Strategy 8: immunohistochemistry testing followed by microsatellite instability testing with MLH1 *promoter hypermethylation testing*

No studies were identified that examined this strategy.

Strategy 9: microsatellite instability and immunohistochemistry testing

No studies were identified that examined this strategy.

Strategy 10: microsatellite instability and immunohistochemistry testing with MLH1 *promoter hypermethylation testing*

Six studies provided test accuracy data for this strategy.[16,58,63,78,83,92] All six studies comprised selected samples of women. One study excluded women with recurrent or synchronous cancers;[58] one study excluded women who were not considered suitable candidates for surgery, who had had prior retroperitoneal surgery or prior pelvic or abdominal radiation therapy, or who were pregnant;[63] one study excluded women aged > 50 years;[16] one study included only women with a family history of endometrial cancer;[78] one study included an unselected sample of women, but did not report data on women with uninformative MMR results or without prior tumour testing;[83] and one study included only women who answered questions about family/personal history of cancer and who had tumour and normal tissue available for analysis.[92] Four panels of markers were used in the six studies; the studies by Berends *et al.*[54] and Ollikainen *et al.*[78] used the same five-marker panel, and the studies by Lu *et al.*[16] and Rubio *et al.*[82] used the same six-marker panel. There were 94 true positives and 311 false positives out of 1627 women tested. Five studies reported the affected genes.[16,58,63,78,92] The most commonly affected gene was *MSH2* [19/43 cases of Lynch syndrome (44.2%)], followed by *MSH6* [16/43 cases of Lynch syndrome (37.2%)], *MLH1* [5/43 cases of Lynch syndrome (11.6%)] and *PMS2* [3 out of 43 cases of Lynch syndrome (7.0%)]. Only two studies assessed *PMS2*.[58,63] Five studies reported details of VUSs.[16,58,63,78,92] In total, 18 VUSs were identified (median 2; 0–14 cases per study). Point estimates for PPVs ranged from 18.3% to 43.1%. Five studies reported the results of *MLH1* promoter hypermethylation testing.[16,58,63,78,92] From 14.3% to 92.3% of tumours were hypermethylated (368/516 tumours).

Strategy 11: germline testing only

Nine studies provided data on germline-only testing, whereby women were offered the reference standard(s), irrespective of the result of index tests.[16,54,58,62,74,81–83,90] Lynch syndrome was identified in 166 out of 1375 (12.1%) women tested (median 9; 5–51 cases of Lynch syndrome per study). In total, 47 VUSs were identified (median 3; 0–15 cases per study).

Full details on strategies 1–11 are provided in *Table 10*.

Test failures and indeterminate results

Data on test failures and/or indeterminate results can be found in *Appendix 5*.

Complete test accuracy studies

Head-to-head studies

Test failures were reported for 0–1% of tumours for IHC (1/356 tumours). No test failures were reported for MSI-based testing. No indeterminate results were reported for either of the tests. Testing was not conducted for 0–12.1% of participants (25/372 tumours) for IHC, and for 1.7–25.2% of participants (54/372 tumours) for MSI-based testing because of insufficient tumour tissue (or unspecified reasons).

Studies of immunohistochemistry alone

Test failures were reported for 0–1% of tumours for IHC (1/522 tumours). No indeterminate results were reported. Testing was not conducted for 0–16.2% of participants (57/372 tumours) for IHC because of insufficient tumour tissue (or unspecified reasons).

Studies of microsatellite instability alone

No test failures or indeterminate results were reported for MSI-based testing in any of the included studies. Testing was not conducted for 1.7–25.2% of participants (54/372 tumours) because of insufficient tumour tissue (or unspecified reasons).

Studies of immunohistochemistry/microsatellite instability and *MLH1* promoter hypermethylation testing combined

Data on test failures, indeterminate results or lack of testing were reported in full for two studies.[16,58] One study did not report any data on test failures, indeterminate results or lack of testing,[81] and one study did not provide these data for *MLH1* promoter hypermethylation testing.[83] Test failures were reported for 0–1% of tumours for IHC (1/567 tumours). No test failures were reported for MSI-based testing or *MLH1* promoter hypermethylation testing. No indeterminate results were reported for any of the three tests. Testing was not conducted for 0–8.1% of participants (9/576 tumours) for IHC, and for 0.5–25.2% of participants (39/372 tumours) for MSI-based testing because of insufficient tumour tissue (or unspecified reasons). There were no reported instances in which *MLH1* promoter hypermethylation testing could not be carried out.

Partial test accuracy

Strategy 1: microsatellite instability alone

Test failures were reported in the PETALS study for (confidential information has been removed) of tumours for MSI testing [(confidential information has been removed) tumours tested]. None of the other studies reported test failures. No study reported indeterminate results. No testing was conducted for (confidential information has been removed) of participants [(confidential information has been removed) tumours] because of insufficient tumour tissue.

Strategy 3: immunohistochemistry alone

No test failures or indeterminate results were reported. No testing was conducted for 0–16.2% of participants (57/644 tumours) because of insufficient tumour tissue.

Strategy 4: immunohistochemistry with *MLH1* promoter hypermethylation testing

Test failures were reported in one study, in which (confidential information has been removed) out of (confidential information has been removed) IHC tests failed (but were all successful on retesting), and (confidential information has been removed) out of (confidential information has been removed) *MLH1* promoter hypermethylation tests failed multiple times (the PETALS study, Dr Neil AJ Ryan, personal communication). No other test failures or indeterminate results were reported, and all tumours had sufficient tissue for testing.

Strategy 10: microsatellite instability and immunohistochemistry with *MLH1* promoter hypermethylation testing

Test failures were reported for 0–8.1% of tumours for IHC (13/1686 tumours), no tumours for MSI-based testing and 0–3.7% of tumours for *MLH1* promoter hypermethylation testing (39/1163 of tumours). No indeterminate results were reported for any of the three tests. No testing was conducted for 0–8.1% of participants (9/1686 tumours) for IHC, for 0–25.2% of participants (28/1163 tumours) for MSI-based testing and for 0% (out of 173 tumours – number of tumours tested not reported for two studies[83,92]) of participants for *MLH1* promoter hypermethylation testing because of insufficient tumour tissue.

Decline rates

A total of 33 studies reported on index test and germline testing. There were approximately (confidential information has been removed) patients included across these 32 studies. Six studies [seven papers, including the PETALS study (Dr Neil AJ Ryan, personal communication)] reported on the number of declines at baseline, prior to testing.[15,55,56,62,74,76,88] Across five of the six studies, (confidential information has been removed) people declined or failed to respond to the study invite out of approximately (confidential information has been removed) invited (incomplete reporting of denominator). From the remaining study,[55] (confidential information has been removed) people failed to provide insurance to enable testing or declined, or there was insufficient tumour sample, but it was not specified precisely how many declined. Seven studies reported no declines at baseline.[61,64,65,67,77,89,90,92]

Seven studies, including the PETALS study, reported on the numbers declining genetic counselling.[51,61,62,67,74,77] (Confidential information has been removed) patients declined genetic counselling out of the (confidential information has been removed) offered it.

Fifteen studies (16 papers, including the PETALS study) reported on the number declining germline testing.[16,51,52,55,60–63,67,69,70,77,81–83] Across these 15 studies, (confidential information has been removed) patients declined germline testing out of the (confidential information has been removed) patients offered the test. In addition, in two studies (including the PETALS study),[61] (confidential information has been removed) patients died prior to germline testing, (confidential information has been removed) were lost to follow-up and (confidential information has been removed) were already known carriers for Lynch syndrome.

Assessment of studies of clinical effectiveness (key question 2)

No eligible studies were identified that reported on the clinical effectiveness (benefits and harms) of testing for Lynch syndrome among people who have endometrial cancer, and/or their relatives. Most studies were excluded for multiple reasons. The most common reasons for exclusion were that studies were not RCTs (and so subject to greater risk of bias) and/or they did not have any relevant outcomes. A further limitation was that most studies were in the broader Lynch syndrome population rather than among those who had endometrial cancer, which limits applicability to our question. Reasons for exclusion are given in *Appendix 3*.

Some of the excluded studies are discussed here. These were all considered for inclusion in the economic model, alongside other sources. de Jong *et al.*[94] describe reducing time trends in CRC mortality, which they associate with increasing surveillance for Lynch syndrome over time. These time trends are subject to confounding. Järvinen *et al.*,[95] in an observational cohort, compared Lynch mutation-positive relatives (who were offered colorectal and endometrial surveillance) with Lynch mutation-negative relatives (who received no such surveillance). They found no difference between the groups over 11 years of follow-up, although this analysis was probably underpowered, with very wide CIs, and biased because of the differences in risk profile between groups at baseline. Järvinen *et al.*[44] found that screening Lynch syndrome patients for CRC was associated with a reduction in CRC incidence. However, patients were not randomly allocated; they self-selected into screened and unscreened groups, so this study is subject to selection bias. HNPCC registry studies describe women's outcomes after endometrial cancer surveillance, for example in Denmark[96] and Finland.[97] These studies did not have a comparator group of unscreened women. There are RCTs of different aspirin doses in people with Lynch syndrome, in Australia[98] and Israel.[99] These ongoing RCTs do not yet have any results available.

Summary of the clinical effectiveness findings and implications for the health economic model

The estimates used for prevalence, Lynch syndrome gene type and frequency, test failure and test accuracy for each strategy were taken from the clinical effectiveness analysis, as described in this section. The rest of the economic model inputs can be found in *Assessment of studies of clinical effectiveness (key question 2)*.

Prevalence

For the health economic model, we incorporated data from the nine studies (reported in 11 papers) that assessed prevalence of Lynch syndrome in unselected samples of women with endometrial cancer; these studies were the most applicable to our population of interest, that is they did not limit on the basis of age or prior cancers. The median prevalence of Lynch syndrome in these papers [including the PETALS study (Dr Neil AJ Ryan, personal communication)] was 3.2% (range 0–5.3%).[15,52,55,56,59–61,70,76,88] This was used in our base case as overall prevalence of Lynch syndrome in endometrial cancer.

Ryan *et al.*[100] also systematically reviewed the evidence on the prevalence of Lynch syndrome among endometrial cancer patients. Few studies undertook germline testing in all women with endometrial cancer, so Ryan *et al.*[100] took a stepwise approach to estimation. They conducted a series of meta-analyses of test positivity of IHC (*MLH1* specific and across all proteins), MSI and methylation. They combined data from these separate meta-analyses on overlapping, but differing, populations to estimate what proportion of women would be referred for germline analysis using a combination of these tests. They then meta-analysed the proportion of women who were positive for Lynch syndrome in germline testing in a population that was an approximation to the testing strategy positive population. They combined these analyses to estimate that 3% of women with endometrial cancer have Lynch syndrome. This approach enabled the combination of data from a large number of studies, but made assumptions about the equivalence of different populations, and was inclusive of studies that did not exactly represent the population or test of interest.

Both reviews suggest a figure for overall prevalence of around the 3% level (confidential information has been removed) [(confidential information has been removed) out of (confidential information has been removed) women tested, including (confidential information has been removed) women with known Lynch syndrome] present in their sample.

A higher base-case prevalence of 3.91% obtained through random-effects meta-analysis of results from 15 studies was used by Snowsill *et al.*[43] However, when studies at risk of bias as a result of high dropout rates ($\geq$ 10%) were excluded ($n = 7$), the estimated prevalence obtained was reduced to 3.0%, nearer to the figure used in our base case.

When we varied our approach from using studies with unselected endometrial cancer probands to using studies with selection criteria, prevalence estimates increased to a median of 6.5% (range 0.9–36.1%). In the systematic review by Ryan *et al.*,[100] a subgroup analysis of studies that did not use a tumour triage stage, but proceeded directly to germline testing, also found a higher proportion of Lynch syndrome carriers, of 6%. We have therefore conducted a sensitivity analysis using an increased overall prevalence figure of 6.5%.

Prevalence by individual gene

Four studies retrieved in the systematic review [including the PETALS study (Dr Neil AJ Ryan, personal communication)] assessed all four MMR genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) using sequencing plus MLPA as a reference standard in an unselected sample of women with endometrial cancer.[15,55,61] Data from the four studies were combined to produce prevalence estimates of MMR genes among women diagnosed with Lynch syndrome: *MLH1*, 17.1%; *MSH2*, 24.4%; *MSH6*, 46.4%; and *PMS2*, 12.2%.

When studies from our review with unselected samples were also included, which had all four genes, and any reference standard ($n = 8$), the results were as follows: *MLH1*, 16.1%; *MSH2*, 31.7%; *MSH6*, 40.5%; and *PMS2*, 10.1%. The model by Snowsill *et al.*[43] produced the following figures: *MLH1*, 16.9%; *MSH2*, 24.6%; *MSH6*, 47.7%; and *PMS2*, 10.8%. Figures do not vary substantially despite differing methodology to elicit data, although our combined estimates inflate the proportion of *MHS2*, while reducing *MSH6* prevalence. Our preferred base-case parameters were therefore taken from the unselected studies in our review.

Test failure

Test failure rates of MSI, IHC and *MLH1* promoter hypermethylation testing were all extremely low in all studies identified in the systematic literature review, with median values of 0% for all. This is likely to be explained by testing protocols in laboratories when tumours with insufficient samples were not tested. However, some test failures did occur, with the range greater for MSI (0–43.3%) than for IHC (0–11.8%); the range for *MLH1* promoter hypermethylation was the lowest (0–0.03%). As all tests had a median 0% failure rate, this was used in our base case, with parameters set around this for the PSA.

Diagnostic accuracy

Initially, we attempted to identify the best test accuracy estimate per strategy from the systematic review. However, we did not use this approach in the economic model, because of issues of inconsistency described below. Instead, we used data from Lu *et al.*[16] to ensure consistency across strategies and to aid comparison between strategies. We undertook sensitivity analyses using estimates from the PETALS study and Snowsill *et al.*[43]

Most applicable and least biased test accuracy per strategy approach

Although we found 45 papers describing at least partial test accuracy, only seven gave full test accuracy data from which we could extract 2 × 2 tables. Seven studies provided complete test accuracy data (i.e. sensitivity, specificity, PPVs and NPVs).[16,54,58,81–83,90] None was conducted in the UK, and most of these covered only a small subset of the strategies, so meta-analysis within each strategy was not possible because of the small number of heterogeneous studies. We identified the most applicable, least biased, study from this group. The rationale for each is outlined in the following paragraphs. Overall, data from Chao *et al.*[58] were considered the most applicable and least biased for strategies 1 and 3, but did not provide data for many of the other strategies. Lu *et al.*[16] provided data for more strategies, but for some strategies no data were available.

Strategy 1: microsatellite instability testing alone

Four studies provided data for this strategy.[16,54,58,82] Chao *et al.*[58] were considered to provide the most applicable and least biased data, as they included an unselected sample of women with endometrial cancer, although the study was not conducted in a country with demographics comparable to those of the UK, and had very few cases of Lynch syndrome, with an incomplete head-to-head design.

Strategy 3: immunohistochemistry alone

Five studies provided data for this strategy.[16,54,58,82,90] Chao *et al.*[58] were considered to provide the most applicable and least biased data, as they included an unselected sample of women with endometrial cancer, although the study was not conducted in a country with demographics comparable to those of the UK.

Strategies 4, 5, 7 and 9

No study directly assessed these strategies. One study (comprising a selected sample of women aged ≤ 50 years) presented sufficient data for us to estimate test accuracy data for this testing strategy.[16] In this study IHC, MSI-based testing and analysis of *MLH1* promoter hypermethylation were employed, with the results of each test present for each of the 100 participants.

These data can be used to estimate what could have happened for strategies 4, 5, 7 and 9.

Strategy 10: microsatellite instability and immunohistochemistry testing with MLH1 *promoter hypermethylation testing*

Four studies provided data for this strategy.[16,58,81,83] Two studies were excluded from consideration as either they included a selected sample of women (aged < 50 years at diagnosis),[16] or data were not extractable for the whole sample.[83] The most applicable and least biased accuracy data were considered to come from combining the remaining two studies, as they were similar in terms of participant selection, testing methods, choice of reference standards and sample sizes, with neither one being conducted in a country with demographics comparable to those of the UK: one was conducted in China[58] and one in the USA.[81]

No data were available from these papers to populate the model for the following testing strategies:

- strategy 2: MSI testing with *MLH1* promoter hypermethylation testing
- strategy 6: MSI followed by IHC testing with *MLH1* promoter hypermethylation testing
- strategy 8: IHC testing followed by MSI testing with *MLH1* promoter hypermethylation testing.

The small sample sizes, different biases, exact tests and populations between the studies means that these estimates would have made some tests spuriously appear more cost-effective than others as a result of differences between studies, rather than tests. For example, although the Chao *et al.*[58] study was considered to contain the best evidence for IHC and MSI accuracy, there were only four cases of Lynch syndrome for IHC and six for MSI, so, in this study, the small numbers and incomplete testing for women introduced biases suggesting a strong advantage in accuracy of MSI over IHC, which was not reflected in the rest of the literature. Furthermore, Chao *et al.*[58] did not give information for the pathways including *MLH1* promoter hypermethylation testing, so accuracy of strategies with and strategies without *MLH1* promoter hypermethylation testing would be logically inconsistent.

Consistent test accuracy estimates from Lu *et al.*[16]

The base-case estimates for test accuracy used in the model are all from Lu *et al.*[16] Details can be found in *Table 11*. This is the only paper that provides individual-level data, which can be used to estimate test accuracy for most strategies, and therefore allows some comparison of cost-effectiveness between strategies, with caveats and limitations. There are 100 cases of endometrial cancer, of which nine have Lynch syndrome, so it is a small sample with higher than expected prevalence of Lynch syndrome. It is also in a US setting, all of the participants were diagnosed with endometrial cancer before the age of 50 years and not all patients received *MLH1* promoter hypermethylation testing, particularly those who were MSI-H. Furthermore, it did not include the *PMS2* protein in the IHC testing panel.

Test accuracy data were extracted for strategies 1, 3–5, 7, 9 and 11 by using the individual patient data reported to calculate whether each patient was a true positive, false positive, true negative or false negative for Lynch syndrome. There were very low numbers of missing data for these strategies.

TABLE 11 Test accuracy data from Lu *et al.*[16] extracted for strategies 1–10

Strategy	Germline (*n*)		Totals (*n*)	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
	Positive	Negative			
1: MSI testing alone					
Index test positive	8	17	25	NA	NA
Index test negative	0	70	70	NA	NA
Totals	8	87	95	100.0 (63.06 to 100)	80.46 (70.57 to 88.19)
2: MSI testing with* MLH1 *promoter hypermethylation testing					
Index test positive	5	3	8	NA	NA
Index test negative	3	84	87	NA	NA
Totals	8	87	95	62.50 (24.49 to 91.48)	96.55 (90.25 to 99.28)
3: IHC-based testing alone					
Index test positive	9	15	24	NA	NA
Index test negative	0	75	75	NA	NA
Totals	9	90	99	100.0 (66.37 to 100)	83.33 (74.00 to 90.36)
4: IHC testing with* MLH1 *promoter hypermethylation testing					
Index test positive	8	3	11	NA	NA
Index test negative	0	87	87	NA	NA
Totals	8	90	98	100.0 (63.06 to 100)	96.67 (90.57 to 99.31)
5: MSI testing followed by IHC testing					
Index test positive	8	19	27	NA	NA
Index test negative	0	68	68	NA	NA
Totals	8	87	95	100.0 (63.06 to 100)	78.16 (68.02 to 86.31)
6: MSI followed by IHC testing with* MLH1 *promoter hypermethylation testing					
Index test positive	5	4	9	NA	NA
Index test negative	3	83	86	NA	NA
Totals	8	87	95	62.50 (24.49 to 91.48)	95.40 (88.64 to 98.73)
7: IHC followed by MSI testing					
Index test positive	9	18	27	NA	NA
Index test negative	0	68	68	NA	NA
Totals	9	86	95	100.0 (66.37 to 100)	79.07 (68.95 to 87.10)
8: IHC followed by MSI testing					
Index test positive	8	5	13	NA	NA
Index test negative	0	81	81	NA	NA
Totals	8	86	94	100.0 (63.06 to 100)	94.19 (86.95 to 98.09)
9: MSI and IHC testing					
Index test positive	8	18	26	NA	NA
Index test negative	0	68	68	NA	NA
Totals	8	86	94	100.0 (63.06 to 100)	79.07 (68.95 to 87.10)
10: MSI and IHC testing with* MLH1 *promoter hypermethylation testing					
Index test positive	8	5	13	NA	NA
Index test negative	0	81	81	NA	NA
Totals	8	86	94	100.0 (63.06 to 100.00)	94.19 (86.95 to 98.09)

NA, not applicable.

When data were missing on the pathway in question, we excluded the case; when we could follow the whole strategy for that patient, we included them, even if there were missing data elsewhere. There were also incomplete data for *MLH1* promoter hypermethylation testing after IHC, but, of the 13 *MLH1*-deficient tumours identified through IHC testing (so potentially eligible for *MLH1* promoter hypermethylation testing), 12 had *MLH1* promoter hypermethylation testing results. We excluded the one case without results, which was a germline-positive mutation on *MLH1*. There was a particular problem with lack of data on *MLH1* promoter hypermethylation testing for MSI-H, affecting strategies 2, 6, 8 and 10. Overall, of the 25 cases who tested MSI-H, only 13 tested MSI status, and all 13 were in patients without a germline mutation (two were in VUSs). Excluding these would have excluded all patients with the disease. There is some evidence from an Australian study[56] on the accuracy of methylation testing in cases demonstrating *MLH1*/*PMS2* IHC loss: out of 127 cases, 111 were hypermethylated, all of whom were germline MLH1 negative. However, accuracy of methylation testing in MSI-H cases, beyond those who also have IHC *MLH1* loss, is not known, so a conservative estimate was considered appropriate.[56] We pragmatically decided, for the purposes of the model, to estimate that methylation is correct 66% of the time to the nearest whole number, estimated separately for germline-positive and germline-negative cases. These estimates affected strategies 2 and 6 most acutely, with 13 cases in each (out of totals of 94 and 95, respectively) when *MLH1* promoter hypermethylation testing results were assumed. This is because these strategies start with MSI-based testing, then hypermethylation of cases if instability is detected. For strategy 8, this method of estimation was applied to 3 out of 98 cases, and to 4 out of 94 cases for strategy 10. Test accuracy estimates should be viewed with extreme caution (in particular strategies 2, 6, 8 and 10).

Sensitivity analyses

Owing to uncertainties in the base case, a sensitivity analysis was performed, using data from a large, as yet unpublished, UK-based study (Dr Neil AJ Ryan, personal communication). (Confidential information has been removed.)

Chapter 5 Systematic literature review of other economic models

The literature search identified 4682 records through electronic database searches and other sources. After removing duplicates, 2882 records were screened for inclusion. On the basis of title and abstract, 2854 records were excluded. The remaining 28 records were included for full-text screening. A further 23 articles were excluded at the full-text stage, mainly because of being an abstract only or having an irrelevant study population. The literature search identified five studies[43,101–104] that undertook an economic analysis to assess the cost-effectiveness of screening strategies used to identify Lynch syndrome in women diagnosed with endometrial cancer. The flow diagram is shown in *Figure 20*.

Summary of the economic analyses undertaken

In this section, we summarise the economic analyses used to compare different screening strategies available to diagnose Lynch syndrome in women diagnosed with endometrial cancer.

Resnick et al.[101]

Resnick *et al.*[101] used a decision tree illustrative model structure to assess the cost-effectiveness of screening strategies for diagnosing Lynch syndrome among newly diagnosed endometrial cancer patients. The model depicted the clinical pathway that endometrial cancer patients would take while

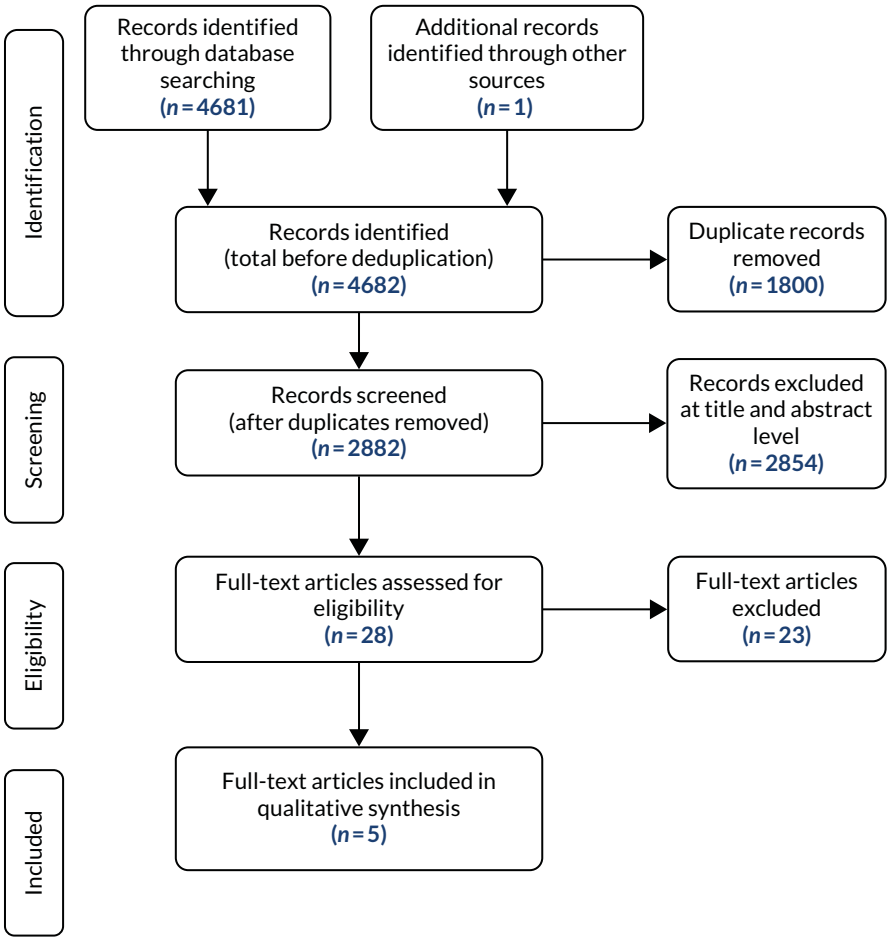

FIGURE 20 Flow diagram of the economic model review.

being screened for Lynch syndrome. The model started with a hypothetical cohort of 40,000 women expected to have endometrial cancer who underwent a screening strategy: Amsterdam criteria[93] (full gene sequencing for women with endometrial cancer who met the revised Amsterdam criteria), sequence all (full gene sequencing for all women with endometrial cancer), sequence for all women aged < 60 years with endometrial cancer and IHC/single-gene strategy (IHC for all women with endometrial cancer after gene sequencing). After testing, women were categorised as Lynch positive or Lynch negative. With the IHC and sequencing testing strategy, women were categorised as *MLH1* ≥ 60 years of age, *MLH1* < 60 years of age, *MSH6* or *MSH2*. Women with *MSH6* deletion were considered to be Lynch positive, and women with *MSH6* normal were categorised as *MSH2* deletion (Lynch positive) or *MSH2* normal (Lynch negative).

Clinical as well as cost information was required to populate the model, and this was obtained from published sources. Clinical information included the probability of fulfilling the Amsterdam criteria,[93] people who do fulfil the Amsterdam criteria and have Lynch syndrome, all women with Lynch syndrome, women with Lynch syndrome stratified by age (< 60 years and ≥ 60 years) and people with normal IHC results. Resource use and costs were required for genetic consultation, full genetic sequencing, IHC and *MLH1*, *MSH2* and *MSH6* sequencing. All costs included in the model were reported in 2008 US dollars. The analysis was conducted from a third-party payer perspective, with the results presented in terms of an ICER, expressed as cost per additional Lynch syndrome case detected. Authors undertook a scenario analysis around the cost of full gene sequencing.

The base-case deterministic results showed that IHC/single-gene strategy, when compared with the Amsterdam testing strategy, had an ICER of approximately US$13,800 per Lynch syndrome case detected. The results of the scenario analysis showed that the ICER was sensitive to the cost of the full gene sequencing. Authors acknowledged and discussed the limitations of the economic analysis, then concluded that the testing strategy IHC and sequencing was the most cost-effective for identifying Lynch syndrome in women diagnosed with endometrial cancer.

The economic analysis provides a useful starting point to assess the cost-effectiveness of different testing strategies to detect Lynch syndrome in women diagnosed with endometrial cancer. Although the decision tree structure was appropriate to address the research question, the analysis was limited, as the 'downstream' costs and benefits associated with identifying women Lynch syndrome were not captured in the economic model. Thus, the impact of identifying these additional cases remains unanswered. In addition, the authors acknowledged that the testing strategy genotyping for the screening of MMR deficiency was not included in the economic analysis. In general, the economic evaluation was transparent and adhered to the reporting guidelines for undertaking economic analyses. Future model-based analyses could build on this simplistic model to capture the impact of including testing and treating of women with Lynch syndrome in a single cost-effectiveness analysis.

Kwon et al.[102]

Kwon *et al.*[102] used a Markov Monte Carlo simulation model to assess the cost-effectiveness of different testing strategies to identify Lynch syndrome in women diagnosed with endometrial cancer. The model started with a hypothetical cohort of women who had received treatment for endometrial cancer and were now receiving one of the following testing strategies endometrial cancer: aged < 50 years with at least one first-degree relative with a Lynch syndrome-associated cancer, endometrial cancer at < 50 years (IHC triage), endometrial cancer at < 60 years (IHC triage), endometrial cancer at any age with at least one first-degree relative with a Lynch syndrome-associated cancer (IHC triage), all endometrial cancers and any age (IHC triage), compared with Amsterdam II criteria.[93] Authors have outlined and justified why they have excluded testing strategies that include MSI.

The model was populated with clinical parameters, as well as information about resource use and costs. Clinical parameters included the prevalence, sensitivity and specificity of each testing strategy; the lifetime risk of CRC; and the 5-year mortality from CRC, all of which were obtained from the published

literature. Resource use and costs included the costs for genetic counselling, gene sequencing, IHC for MMR proteins, colonoscopy and CRC treatment costs. Details of resource use and costs were provided, and references reported. All costs were reported in US dollars and reported in 2010 prices. Several simplifying assumptions were made to have a workable model structure.

The base-case analysis was undertaken from the societal perspective, with costs incurred and benefits accrued discounted based on 3% per annum. The economic analysis concluded at a lifetime time horizon, with the results reported as an ICER expressed as cost per life-year gained. It should be noted that the costs included in the analysis did not accurately reflect the viewpoint of the analysis. To our knowledge, only costs incurred by the health-care provider were included in the economic analysis, thereby reflecting a narrower perspective (third-party provider).

Deterministic results showed that IHC triage of women of any age with at least one first-degree relative with Lynch syndrome-associated cancer, when compared with women aged < 50 years and with at least one first-degree relative with Lynch syndrome-associated cancer, had an ICER of approximately US$9100 per life-year gained. Furthermore, results were reported on the number of women who would undergo IHC and, subsequently, the women diagnosed with Lynch syndrome and those who went on to develop CRC. Sensitivity and scenario analyses results showed that the ICER was robust to changes made to the model input parameters. Under the current model structure, model inputs and assumptions led the authors to conclude that IHC triage of women of any age, with at least one first-degree relative with Lynch syndrome-associated cancer, was the most cost-effective testing strategy when compared with using the Amsterdam II criteria.[93]

This economic analysis adds to the existing literature about which screening strategies provide good value for money in diagnosing Lynch syndrome in women with endometrial cancer. However, there were several concerns related to this analysis. First, it is unclear about the patient pathway following testing, as no illustrative structures have been presented in the main document or online supplementary material. Second, it is unclear what assumptions are being made about the CRC mortality rate derived from the 5-year mortality obtained from the published literature. Third, care should be taken when interpreting the deterministic results, as the analysis was undertaken from the societal perspective, but the costs included in the analysis did not reflect this viewpoint.

Bruegl et al.[103]

Bruegl *et al.*[103] undertook an economic analysis alongside a clinical study to assess the cost-effectiveness of universal tissue testing (IHC for all and *MLH1* methylation analysis when indicated) versus the Society of Gynaecologic Oncology (SGO) 5–10% clinical criteria[105] ($n = 97$) for identifying Lynch syndrome in a cohort ($n = 412$ cases) of unselected women with endometrial cancer. Two approaches were used to assess the cost-effectiveness. First, the direct costs associated with identifying patients with probable Lynch syndrome and, second, the direct costs associated with identifying cases with probable Lynch syndrome among women with endometrial cancer, as well as their potentially affected first-degree relatives.

The analysis was conducted from a third-party payer perspective, with all costs reported in US dollars, in 2012 prices. The economic analyses included hospital and health-care professional costs associated with identifying women with probable Lynch syndrome. Costs included initial genetic counselling and follow-up visits; IHC for *MLH1*, *MSH2*, *MSH6* and *PMS2*; *MLH1* promoter hypermethylation assay for tumours with loss of *MLH1*; and single germline-mutation testing.

Under the SGO 5–10% clinical criteria,[105] 97 women would undergo further evaluation, of which 15 would be diagnosed with probable Lynch syndrome, resulting in a cost of approximately US$6100 per probable Lynch syndrome case diagnosed. Including screening for probable Lynch syndrome and their first-degree relatives under the SGO 5–10% clinical criteria[105] strategy would cost approximately US$6300 per probable Lynch syndrome case diagnosed. This is based on the average number of first-degree relatives (5.3 relatives) and the estimated germline mutation rates among probable

Lynch syndrome endometrial cancer patients' first-degree relatives eligible for single-site gene mutation analysis. Under the universal tumour testing strategy, 43 women with probable Lynch syndrome would be identified, resulting in a cost of approximately US$5900 per probable Lynch syndrome case diagnosed. Including universal tumour screening for probable Lynch syndrome and screening their first-degree relatives would cost approximately US$6500 per probable Lynch syndrome case diagnosed. This is based on the average number of first-degree relatives (5.5 relatives) and the estimated germline mutation rates among probable Lynch syndrome endometrial cancer patients' first-degree relatives eligible for single-site gene mutation analysis.

The authors concluded that, under the existing SGO 5–10% clinical criteria[105] to identify Lynch syndrome in women diagnosed with endometrial cancer, this strategy is likely to miss some cases, when compared with using a universal tumour-testing strategy (IHC for DNA MMR proteins and PCR-based *MLH1* methylation analysis for tumours with loss of *MLH1*).

The economic analysis presented here is conducted alongside a clinical trial to assess the clinical effectiveness and cost-effectiveness of different strategies that can be used to identify and diagnose women (and their first-degree relatives) with Lynch syndrome. Although the analysis adds to the existing literature, there are some concerns regarding the transferability and robustness of these results. First, as acknowledged by the authors, all potentially relevant strategies have not been included in the analysis; this is common in clinical trials. Second, the authors assumed that there is a 100% genetic counselling referral rate for endometrial cancer patients meeting the SGO 5–10% criteria,[105] but referral rates are likely to be between 17% and 48%. Third, it is assumed that all patients meeting the SGO 5–10% criteria, or with tumour testing suggestive of Lynch syndrome, will accept germline counselling and/or germline testing, but this is not likely to be 100%. Fourth, the resource quantity used to derive costs is unclear, which limits the transparency about how costs were derived. Finally, the authors did not conduct sensitivity analyses to address uncertainty in the economic analysis.

Goverde et al.[104]

Authors undertook an economic analysis of a population-based cohort of endometrial cancer patients aged ≤ 70 years undergoing routine screening for Lynch syndrome. The economic analysis compared routine screening for Lynch syndrome by analysis of MSI and IHC for *MLH1*, *MSH2*, *MSH6* and *PMS2* protein expression in endometrial cancer patients up to the age of 70 years with screening for Lynch syndrome in endometrial cancer patients using an age cut-off point.

The analysis required clinical and cost information. Clinical parameters included acceptance of prophylactic gynaecological surgery, complication rate following colonoscopy, lifetime risk of developing CRC for Lynch syndrome carriers and reduction in CRC risks by Lynch syndrome surveillance. Resource use and costs included MSI analysis, genetic counselling and germline mutation analysis, IHC and *MLH1* promoter hypermethylation testing, which were derived using microcosting methodology. All costs were reported in euros, in 2013 prices.

The analysis was undertaken from the third-party payer perspective, with costs incurred and benefits accrued discounted based on 3% per annum. The economic analysis concluded at a lifetime time horizon, with the results reported as an ICER, expressed as cost per life-year gained. Base-case deterministic results showed that routine screening of endometrial cancer patients up to the age of 70 years for Lynch syndrome by analysis of MSI, IHC and *MLH1* promoter hypermethylation testing was cost-effective when compared with screening up to the age of 50 years, with an ICER of approximately €5300 per life-year gained. Sensitivity analysis results showed that economic analysis was sensitive to the life-years gained per female relative. The authors concluded that routine screening by analysis of MSI, IHC and *MLH1* promoter hypermethylation testing for Lynch syndrome in people diagnosed with endometrial cancer up to the age of 70 years was the most cost-effective strategy, compared with an age cut-off point of 50 years.

The economic analysis builds on the current cost-effectiveness evidence of different strategies to detect Lynch syndrome in women diagnosed with endometrial cancer. In comparison to previous analyses, this analysis included the costs and benefits for first-degree relatives of probands.

Snowsill et al.[43]

Authors conducted an economic analysis by using a decision tree structure with Markov nodes to assess the cost-effectiveness of different testing strategies (MSI with methylation, direct mutation testing, IHC with methylation, MSI alone, IHC and a no-testing strategy) to identify Lynch syndrome in women treated for endometrial cancer. Authors clearly provided an illustrative model structure that depicted the patient pathway for endometrial cancer survivors undergoing screening for Lynch syndrome. The model started with a hypothetical cohort of women undergoing one of the screening strategies. In general, women were diagnosed as actually Lynch syndrome, actually sporadic Lynch syndrome or probable Lynch syndrome. Following diagnosis, women received CRC surveillance.

The model required clinical information (natural history, epidemiology, HRQoL, diagnostic accuracy, preventative effectiveness and utility values) and resource use and cost information (testing strategies, events and outcomes) for women undergoing screening for Lynch syndrome.

The analysis was conducted from the NHS and PSS perspective, with all costs reported in Great British pounds, in 2016/17 prices. All costs incurred and benefits accrued were discounted based on a 3.5% per annum rate. The analysis was conducted over a lifetime time horizon, with the results presented in terms of an ICER, expressed as cost per QALY. An ICER at or below the £20,000 per QALY WTP threshold was cost-effective. Several one-way sensitivity analyses, including PSAs, were undertaken based on the cost per QALY.

The base-case deterministic results showed that the IHC with methylation strategy was the most cost-effective strategy, with an ICER of approximately £14,200 per QALY. The IHC-alone strategy yielded the most QALYs and was most costly, but the results did not reach cost-effectiveness when compared with IHC with methylation, with an ICER of approximately £129,000 per QALY. The PSA results showed that there was a 0.36 probability that IHC with methylation was the most-cost-effective strategy at a WTP threshold of £20,000 per QALY. One-way sensitivity analysis results showed that the ICER was sensitive to the age of the proband and the effectiveness of colonoscopy in reducing CRC incidence. Scenario analysis results showed that, by using the effectiveness of colonoscopic surveillance to reduce the CRC incidence derived from information obtained from Arrigoni *et al.*,[106] none of the testing strategies was cost-effective.

The economic analysis builds on the existing cost-effectiveness evidence in this disease area, by including the diagnosis of Lynch syndrome and the benefit to probands of CRC screening. This analysis could have been improved by reporting the results in terms of the natural units, in addition to reporting the results in terms of cost per QALY alone. In addition, the model was sensitive to some model input parameters. Specific attention in the form of systematic reviews around these key parameters with a detailed critique between sources would improve the transparency in the selection of model inputs.

Characteristics of included studies

Appendix 4 summarises the characteristics of the studies included in this systematic review. Three economic analyses were undertaken in the USA,[101–103] one in the Netherlands[104] and one in the UK.[43] Three studies[43,101,102] undertook a model-based economic analysis, and the remaining two studies[103,104] conducted an economic analysis alongside observational information or a trial. Of the studies that used an economic model to depict/illustrate the patient experience, one analysis[101] used a decision tree structure, one a Markov model structure[102] and the other[43] a combination of a decision tree structure and Markov model. All economic analyses clearly stated the research question, with all comparing strategies to identify Lynch syndrome in women diagnosed with endometrial cancer. It is notable that

there was some overlap in terms of the strategies being compared between studies. It should be noted that no analysis included all strategies; however, exclusion of these testing strategies has been discussed.

The economic analyses were mainly undertaken from a third-party payer perspective, with one study[102] from the societal perspective; however, the costs included did not reflect a societal viewpoint. All analyses except Snowsill *et al.*[43] reported their results in terms of natural units. Snowsill *et al.*[43] reported an ICER, expressed as cost per QALY. All studies attempted a one-way sensitivity analysis and/or a scenario analysis. One study undertook a PSA.[43]

Three studies included the benefit to probands of reduction of the incidence of CRC.[43,102,104] Other 'downstream' cancers were not included. Surveillance was the only risk reduction measure included in these analyses. Benefit was also extended to first-degree relatives in these three studies.[43,102,104]

Quality assessment of the modelling methods and economic analyses

Full details of the quality appraisal of included economic studies can be found in *Appendix 6*.

Structure

The structures of the models included were of judged to be of satisfactory quality. Studies clearly stated their decision problem or research questions, the viewpoint of their analysis, and the objectives of the models and economic analyses, which were coherent with the decision problem. Only one study[43] provided extensive detail about pre-model analyses conducted to estimate the prevalence of Lynch syndrome in endometrial cancer patients, test performance on the sensitivity and specificity of the different testing strategies, and incidence of developing other 'downstream' cancers. When appropriate, all studies were conducted over a lifetime time horizon and included discounting costs incurred and the benefits accrued using appropriate rates.

Most studies that conducted a model-based analysis clearly showed the illustrative model structures, which depicted the clinical pathway for endometrial cancer patients undergoing screening for Lynch syndrome. Earlier models were simplistic, but were adequate to address the decision problem, and only included screening and diagnosis of Lynch syndrome. Subsequent models were more complex, and, in general, their model structures followed the screening → diagnosis → surveillance → treatment pathway. In general, authors assessed testing strategies that included IHC (with/without *MLH1* methylation) followed by germline testing, MSI (with/without methylation) followed by germline testing, direct mutation testing (using the SGO 5–10% clinical criteria,[105] Amsterdam II criteria,[93] Bethesda guidelines[19]) or a no-testing strategy; confirmatory diagnosis by use of germline testing was included in all analyses. Studies that included risk-reducing interventions considered surveillance as a means to reduce the incidence of CRC. Other risk reduction interventions (e.g. surgery, chemoprevention and aspirin) were not included. Authors have alluded to this as a limitation and have provided reasonable justification for not including these interventions. Goverde *et al.*[104] included costs associated with gynaecologic surveillance for relatives.

Data

All studies required clinical as well as cost information to undertake the economic analyses. The methods used to identify relevant information were clearly stated. References were provided for all inputs, but authors were not clear about the choices made between sources of information, especially when more than one source was available. In addition, it was not clear if quality appraisal of these studies was undertaken. Information to populate the economic models was obtained mainly from published sources and supplemented with information from unpublished sources, which included clinical expert opinion. To our knowledge, no study undertook systematic reviews to identify studies reporting key inputs.

Studies clearly reported clinical (natural history, mortality, diagnostic accuracy for each testing strategy, preventative effectiveness and utility values) information and resource use and costs (testing strategy, colonoscopic surveillance for probands and relatives, treatment of CRC, genetic counselling and

germline mutation analysis for relatives, and prophylactic surgical treatment for relatives) information required. Natural history information was required for the prevalence of Lynch syndrome, mutation status, lifetime risk of CRC, endometrial cancer mortality and CRC mortality. The prevalence of Lynch syndrome was required in all studies. Prevalence was reported by age of the proband[101,102] and overall prevalence.[43,103,104] All studies reported the references for individual studies, but only Snowsill *et al.*[43] elaborated on the methods used to estimate the prevalence. The distribution of gene mutation status was reported in all studies. In general, studies reported gene mutation status for the overall population,[102–104] older/younger than 60 years of age[101] and by a given age.[43] The lifetime risk of CRC was required in three studies.[43,102,104] Both Kwon *et al.*[102] and Goverde *et al.*[104] provided estimates for lifetime risk of CRC, for which information was obtained from the literature. However, Kwon *et al.*[102] provided lifetime risk of CRC by mutation status and in the absence or presence of screening. Goverde *et al.*[104] provided estimates for Lynch syndrome carriers only. These two studies did not elaborate on the methods used to combine/pool the results from individual studies that reported lifetime risk of developing CRC. Conversely, Snowsill *et al.*[43] provided details about the methods used to estimate the lifetime risk of CRC. All economic analyses undertaken over a lifetime time horizon included mortality. People were subjected to endometrial cancer mortality, CRC mortality and age- and sex-specific mortality according to their respective locations. Snowsill *et al.*[43] derived transition probabilities for the risk of CRC mortality for people with/people without Lynch syndrome and by stage of the cancer. However, it was unclear if stage-specific risks of CRC mortality were derived in other analyses.

Information was required about the performance (sensitivity and specificity) of the different testing strategies included in the economic analyses. Derivation of sensitivity and specificity varied across studies, with most studies obtaining information from the literature, but authors have provided little information about how the evidence was appraised or synthesised. One study[43] clearly stated the methodology used to derive pooled estimates, where appropriate. In addition, it was unclear what assumptions were made when combining the test accuracy of individual tests to form a testing strategy.

In all studies, the effectiveness of Lynch syndrome screening was based on cases of Lynch syndrome diagnosed. In addition, studies included the health benefit to women with Lynch syndrome and their first-degree relatives.[43,102,104] Economic analyses that included colonoscopic surveillance estimated the effectiveness/impact of surveillance on the incidence of CRC and mortality.[43,102,104]

One study[43] reported their results in terms of QALYs. Snowsill *et al.*[43] elaborated on the assumptions made, with justification about how utility values were estimated. First, baseline utility values were estimated from age- and sex-specific population values. Second, it was assumed that there was no disutility associated with people with stages I–III CRC. People with stage IV CRC had their utility scaled by 0.79, as opposed to 1.00 for stages I–III CRC. Finally, it was assumed that genetic counselling or testing had no impact on QALYs.

All studies reported the perspective of the analysis, but, in one study,[102] these costs did not reflect the viewpoint stated. Resource use and costs were required for the costs of screening tests/strategies, genetic consultation and testing, CRC screening and treatment of CRC. All studies reported the sources of costs but, in some studies, it was difficult to decipher the resource use that was used to estimate unit costs.

Uncertainty

Most analyses[43,101,102,104] included a one-way sensitivity analysis or scenario analysis by varying key input parameters to reflect lower and upper limits, or by making changes to input parameters if multiple sources of information were available to assess the impact on the base-case ICER, and/or to determine the key drivers of the economic model. It was unclear in some analyses if the sensitivity analysis was exhaustive, as no tornado plots were reported. Results were reported for all sensitivity and scenario analyses. Authors reported which input parameters were the most influential. To our knowledge, 'best-case' and 'worst-case' analyses were not undertaken. Snowsill *et al.*[43] explored

heterogeneity and undertook a PSA. In addition, no economic analysis undertook a value-of-information assessment.

Assumptions

Authors clearly stated the assumptions made to have an executable model. In general, the assumptions made appeared to be feasible, with others being strong in some instances. There was little overlap between studies about the assumptions made. This may be because of the heterogeneous nature between the economic analyses. As expected, as model complexity increased, so did the number of assumptions. Details of the assumptions made for each study are reported in *Appendix 4*.

Discussion

The published economic evidence of strategies used to identify Lynch syndrome in women with endometrial cancer is limited to five studies. We identified three studies[43,101,102] that undertook a model-based economic analysis and two studies[103,104] that conducted an economic analysis alongside trial/observational data. Given the heterogeneous nature of economic analyses, these studies were discussed narratively and appraised using frameworks on best practice for reporting an economic evaluation and economic modelling. We found that studies were mainly transparent in the information used to undertake the analyses, but less so in the selection of inputs and the methods of evidence synthesis.

This systematic review was undertaken to identify the suitability of existing cost-effectiveness analyses, which primarily involves the comparative analysis of alternative interventions in terms of the costs and consequences.[107] To increase the transparency of the economic analyses and the confidence/robustness of the results, guidelines[41,42] stipulate the importance of reporting the structure, the inputs, the assumptions and the handling of uncertainty. All studies clearly reported a statement of the decision problem, which included information about the disease/condition (Lynch syndrome), description of the patient population (women treated for endometrial cancer), strategies available to identify and diagnose Lynch syndrome (e.g. IHC and MSI) and objective(s) of the economic model. Three studies[43,101,103] clearly provided definitions for people with Lynch syndrome, probable Lynch syndrome or sporadic Lynch syndrome, which increases the transparency and relevance to other settings. All analyses provided a statement of the perspective/viewpoint of the analysis, with one study[102] stating that the analysis was undertaken from a societal perspective, which we later considered to be undertaken from a narrower perspective, as the costs included in the analysis did not reflect a societal viewpoint.

Understandably, the two economic analyses that were conducted alongside trial/observational data did not include all possible strategies. Likewise, no model-based economic evaluation included a comparison of all feasible strategies. However, analysts have provided justification about why models were constrained to the strategies included.

The choice of illustrative model structures appeared to be appropriate to address the decision problem. However, in one study,[102] we were unclear of the illustrative structure used, which limits the transparency of the clinical course of Lynch syndrome in women with endometrial cancer and, hence, the reproducibility of the economic analysis. Philips *et al.*[42] reiterate that analysts should provide justification for the choice of model type and present an illustrative model structure.

Information required to parameterise the economic analyses included clinical and cost information. Despite all studies providing the sources of inputs, little information was provided about the methods used to identify inputs, details of any pre-model analysis and justification of incorporating inputs into the analyses. Inputs were mainly obtained from the literature (with no studies undertaking a systematic review) and supplemented with information from clinical experts. Studies that used clinical expert opinion have not elaborated/documented the methods used to identify and elicit information from clinicians. Philips *et al.*[42] provide guidance about eliciting information from clinical experts.

All analyses required information about the prevalence of Lynch syndrome and the sensitivity and specificity of the different strategies. In most cases, several individual studies provided prevalence information and several reported test performance information. However, only Snowsill *et al.*[43] elaborated on the methods used to synthesise the evidence for prevalence, sensitivity and specificity. Deriving point estimates (as well as their confidence/credible intervals) should follow acceptable methods for synthesising the evidence.[42] These pre-model analyses should be clearly reported on or signposted. The process of data incorporation was unsatisfactory in most analyses, as authors have not provided justification when choosing between inputs, especially when more than one source of information is available, or, more so, when an input is a key driver for the economic analysis.

Snowsill *et al.*[43] were the exception, as the detailed outline of the model structure for the diagnostic component could easily be followed, with explanations and supplementary material available to support the use of, and methodology used to obtain, all relevant parameters. The thorough approach in reporting, as well as attention to long-term outcomes of probands and relatives, elevated this modelling study above the others reviewed.

Uncertainty is unavoidable and exists in all economic analyses.[42,107] Regardless of the type of economic evaluation, analysts should test the robustness of the results to estimate the probability that the correct decision has been made. It is common practice to undertake one-way and multivariate sensitivity analyses (e.g. deriving an ICER based on a 'best-case' and a 'worst-case' scenario) and a PSA.[108]

This systematic review highlighted that none of the economic analyses undertook a value-of-information analysis. A value-of-information analysis can be used to provide a framework for analysing uncertainty in the economic model by estimating the expected costs associated with imperfect information when deciding between alternative strategies, which can be considered as uncertainty. Reducing uncertainty may lead to alternative strategies being adopted, and the value of this additional information depends on how much this additional information is likely to reduce the uncertainty. A key value-of-information measure is the expected value of perfect information, which represents the monetary value of obtaining perfect information to eliminate uncertainty for key parameters and, thus, the overall decision-making process.[109] If the costs of obtaining further information exceeds the expected value of perfect information, there is little justification for undertaking further research.[109]

The economic analyses, more specifically those using an economic model to assess different strategies to identify Lynch syndrome in women with endometrial cancer, are limited to three studies. Although research in this area can be seen to be in its infancy based on the number of studies, this is not the case, as recent studies were more comprehensive by including the screening of probands and the benefit of surveillance to probands and their first-degree relatives. Development in this area may be due to the research that has been undertaken for identifying Lynch syndrome in people with CRC, and a better understanding of the natural history of endometrial cancer. To build on/develop the current modelling methodology, future advances in economic models should consider all relevant testing strategies available to identify Lynch syndrome in the jurisdiction of interest; discuss the methods used to identify inputs (preferably undertaking a systematic review for key input parameters); elaborate on meta-analysis methods, when appropriate; provide justification of choosing key inputs; include additional risk reduction methods (e.g. use of aspirin) to prevent other 'downstream' cancers; report cost-effectiveness results in terms of their natural units (e.g. diagnostic error avoided, cases of CRCs averted in probands, cases of endometrial cancers avoided in first-degree relatives, life-years gained) and costs per QALY; and undertake extensive sensitivity and scenario analyses, including a value-of-information analysis.

To our knowledge, this is the first systematic review of the cost-effectiveness evidence about the different strategies available to diagnose Lynch syndrome in women with endometrial cancer. This systematic review provides detail about the conduct of each economic analysis, as well as a reporting quality assessment for each study. Moreover, it provides considerations when undertaking future

economic models to build on the existing evidence. There are some limitations to this systematic review. First, study selection was undertaken by Mary Jordan and James Keasley independently. However, data extraction and reporting quality appraisal were undertaken by Peter Auguste and cross-checked by Mary Jordan. Second, we have not provided details of the sources of inputs included in these economic analyses. Third, we have not discussed the transferability of these cost-effectiveness results to a specific setting or jurisdiction.

Conclusion

This systematic review highlights and summarises the studies that compared different screening strategies to identify Lynch syndrome in women treated for endometrial cancer. The results show that the evidence base is limited to five studies, with three studies using an economic model. We noticed that the modelling methodology has developed over time, with earlier models interested in identifying and diagnosing Lynch syndrome only, and more recent models including the benefit of screening to probands in reducing the incidence of other 'downstream' cancers, as well as benefit to first-degree relatives. These analyses all add to the existing evidence and conformed to the best-practice guidelines for the reporting of economic analyses or economic models. However, there were some concerns, which limit the transparency, robustness and, hence, transferability of these results to a specific setting/jurisdiction. Although the transferability of economic results may present challenges because of the nature of economic analyses, future economic analyses, more so those using an economic model, should be transparent in the methods used to identify data inputs, and should be clear about the methods used to synthesise clinical evidence (e.g. prevalence of Lynch syndrome, test/strategy performance and benefit of surveillance to reduce the incidence of other 'downstream' cancers) and the choices made between data sources. Snowsill *et al.*[43] achieved these key quality indicators, and as the most recent and geographically relevant (UK setting), established a comprehensive reference model on which to build our modelling approach.

Chapter 6 Economic model

Discussion of model input parameters

Although none of the cost-effectiveness studies retrieved in the systematic review answered the decision problem in full, the model by Snowsill *et al.*[43] proved particularly useful in terms of structure and of sourcing relevant model inputs. This work, in combination with previous reviews of Lynch syndrome testing in CRC,[12,110] was drawn on to inform the modelling approach. Parameters are discussed for each section of the model in order: diagnostic decision tree, long-term CRC and long-term endometrial cancer components.

Diagnostic model

Diagnostic performance

Test accuracy was extracted from the results obtained from the clinical effectiveness systematic literature review we conducted, with test accuracy figures used in the model derived at a strategy level. Similarly, prevalence, test failure rate and prevalence by mutation were taken from our clinical effectiveness review. Extensive detail on how these figures were calculated is provided in *Chapter 4, Assessment of studies of clinical effectiveness (key question 2)*. In addition, a parameter for the proportion of relatives tested who have positive Lynch syndrome mutations, 44% (95% CI 40.7% to 47.4), was taken from a random-effects meta-analysis of studies conducted by Snowsill *et al.*[110]

Diagnostic mutation testing

A total of 92.5% of probands are expected to attend genetic counselling following positive index test results, irrespective of testing strategy. This figure is elicited from the clinical expert (Dr Ian M Frayling) range 90–95% in Snowsill *et al.*,[110] and independently corroborated more recently by a clinical expert (Demetra Georgiou, Principal Genetic Counsellor, St Mark's Hospital, London North West University Healthcare NHS Trust, 13 December 2019, personal communication). Of those attending genetic counselling, 95% are assumed to undergo genetic testing, based on expert opinion (Demetra Georgiou, personal communication), supported by a rate of 90% assumed by Snowsill *et al.*[12] in their review. Unpublished data by Crosbie *et al.* (acceptability manuscript, Professor Emma Crosbie, University of Manchester, 19 July 2019, personal communication) supports a high acceptability of genetic testing in endometrial cancer probands, although methodology to elicit consent differed to more standard UK practice as pathway to genetic testing was gynaecologist led and did not expressly include prior genetic counselling. Consent rates were found to be (confidential information has been removed).

For strategy 11, whereby probands do not undergo an initial tumour test, the acceptance of genetic testing is assumed to be less than the acceptance in strategies whereby a positive initial test has been performed. This assumption was made in the Snowsill *et al.*[43] model, with acceptance of direct germline testing set at 0.500. No alternative source of data was identified to inform this parameter further; therefore, 0.500 was used in our base case.

The impact of these parameters was investigated further in one-way sensitivity analyses in which the proportion of probands accepting genetic counselling and the proportion accepting genetic testing were varied from 50% to 100%.

Predictive mutation testing

Uptake in genetic testing among relatives is a complex issue, with much variation seen in the methods used to contact 'at-risk' relatives, which subsequently affects the proportions of relatives accepting counselling and testing. Similarly, when patient-directed contact is ultimately reliant on the individual characteristics of the proband, it is difficult to assess the influence a female-only cohort of probands exerts over relatives with a syndrome that affects both males and females.

A combination of data from relevant literature, supplemented by clinical expert opinion, was used to determine parameters. The average number of relatives per proband who are identified through cascade testing and are assumed to be contactable was set at six per proband, in line with a 2017 CRC review,[12] based on data from Snowsill *et al.*,[110] which was updated using Manchester regional Lynch syndrome registry results[111] and unpublished data provided by Ian Frayling in previous work.[12,110]

It was assumed that all six relatives made contact with their GP, with cost of GP contact attributed; of these, 77.5% were assumed to pursue referral to a genetic counsellor, based on findings of a systematic literature review of uptake of pre-symptomatic genetic testing in hereditary breast–ovarian cancer and Lynch syndrome by Menko *et al.*[112] Of those attending genetic counselling, 76.7% were assumed to undergo predictive testing, as reported by Barrow.[111] This figure is the recorded proportion at 12 years after relatives are informed of their 'at-risk' status, which, although considerably higher than the 55.7% who were tested within 3 years of being informed, may still be considered a conservative estimate. A study by Bruwer *et al.*[113] found that up to 97% of relatives underwent predictive testing [median 8.6 years (range 1–12 years)], and clinical expert opinion suggests that almost 90% of relatives who attend genetic counselling pursue testing at some point (Demetra Georgiou, personal communication).

To explore the impact of relative uptake further, sensitivity analyses were undertaken to vary the proportion of relatives accepting genetic counselling and the proportion accepting genetic testing from 50% to 100%. In addition, the number of relatives identified per proband was decreased from six in the base case to three, and then increased to 12 to assess sensitivity to measure.

Colorectal cancer incidence

Age-related annual incidence of CRC is sourced from the modelling work of Snowsill *et al.*[43] Gene-specific data from the PLSD[2,14,114] were used, against which to fit parametric, non-parametric and flexible spline models with best fit resulting from the log-normal model, which we replicated in our long-term model. By applying a hazard ratio of 0.387, as used by Snowsill *et al.*,[12] it was assumed that any benefits associated with CRC surveillance would be countered. This served as the baseline incidence data for CRC incidence among Lynch syndrome-positive individuals who had not been identified and proceeded along the natural history pathway without risk reduction measures.

A more recent (2020) publication from the PLSD has been published since this work,[45] which builds on earlier work by adding a newly recruited cohort of Lynch syndrome individuals to increase the size of the database from 2823 pathogenic mutation carriers to 6350 in total. The new cohort of 3727 was used to validate findings reported previously,[2,14,114] before the merger of the two data sets occurred, which found that cumulative risk of CRC for each of the four affected genes did not differ significantly from the original ($p > 0.05$). The figures used by Snowsill *et al.*[12] were therefore considered to be valid and had been considered appropriate for use by NICE in the recent diagnostics guidance for Lynch syndrome in CRC.[1]

Colorectal cancer surveillance

Surveillance for CRC is by colonoscopy performed every 2 years, which has been assumed to provide benefit by reducing the incidence of CRC through identifying and removing polyps prior to development of cancer and to detect any tumours promptly so that CRC can be diagnosed at an earlier stage, thereby improving outcomes. Similarly to Snowsill *et al.*,[12] we applied a hazard ratio of 0.387, from Järvinen *et al.*,[44] to estimate the beneficial impact that colonoscopic surveillance has on CRC incidence. It is acknowledged that this was an observational study subject to significant bias, in a cohort published in 2000. However, in the absence of more relevant recent evidence in the literature, and given that effectiveness of colonoscopic surveillance is likely to have improved over time through the introduction of clinical standards,[1] the hazard ratio of 0.387 was used in our base case. To reflect the considerable uncertainty around this parameter, we conducted a scenario analysis whereby it was assumed that CRC surveillance had no impact on CRC incidence (see *Table 18*).

Guidelines for the management of Lynch syndrome advise that colonoscopic surveillance should be performed every 2 years.[27] This is the frequency of colonoscopy modelled in our base case, commencing for all individuals at age 25 years. However, recent reports based on reviews of findings from the PLSD[115,116] suggest that intervals between colonoscopic surveillance are not correlated with decreased incidence of CRC or stage at diagnosis. Although the evidence is limited, the suggestion that biennial colonoscopy can be replaced by surveillance every 3 years with limited reduction in effectiveness was explored in scenario analysis 6. The assumption was made that benefit is unaffected.

The reduction in frequency of colonoscopy, investigated in scenario 6, also speaks towards the impact of stratified management by gene-specific mutation, as recommended in the most recent British Society of Gastroenterology guidance on CRC surveillance.[27] In our model, colonoscopy starts at age 25 years for all individuals. However, new guidelines[27] state that individuals with *MLH1* or *MSH2* mutations should commence biennial colonoscopy at age 25 years, whereas those with *MSH6* or *PMS2* mutations can start surveillance later, at age 35 years (see *Appendix 7*).

This would result in fewer overall colonoscopies being performed, as is the case in scenario analysis 6, although the assumption that there would be no change in effectiveness is less secure, as targeted management because of known risk may be expected to improve the effectiveness of surveillance.

Endometrial cancer incidence

For endometrial cancer, we sourced incidence data from the PLSD, published in 2020.[45] This database reported gene-based risk of cancer based on 6350 individuals with Lynch syndrome. Risks are reported at ages 25, 40, 50, 60, 70 and 75 years. We fitted a piecewise linear model to these data to derive annual incidence from cumulative incidence.

Gynaecological surveillance

The benefits of gynaecological surveillance are uncertain, and clinical practice throughout the UK varies with respect to what surveillance involves and to whom it is offered. The most recent guidelines on surveillance practices have been published by the Manchester International Consensus.[22] Invasive gynaecological surveillance in females with Lynch syndrome is no longer recommended because of a lack of evidence that outcomes are improved over symptom awareness and urgent investigation of red-flag symptoms. Instead, an annual review from the age of 25 years, with an appropriate clinician to discuss red-flag symptoms and, when necessary, contraceptive and fertility needs, should be encouraged, and gynaecological referral should be made as a result of a specific need.

We follow these recommendations in our modelling by assuming that all females from the age of 25 years who have not undergone hysterectomy (for treatment of endometrial cancer or as prophylactic surgery) access non-invasive surveillance, which involves an annual review with a GP. We assume that 10% of those attending are referred onward for gynaecological review and invasive surveillance, consisting of gynaecological examination, pelvic ultrasonography, CA-125 analysis and aspiration biopsy. This is assumed to reduce mortality by 10.2%, an assumption in line with previous evaluations of Lynch syndrome screening.[12] However, the evidence for this is not completely robust. Therefore, we estimate the impact of assuming that no such surveillance is offered.

However, with uncertainty as to the benefits that may be accrued, we performed a scenario analysis removing gynaecological surveillance entirely from the model (see *Appendix 7*, *Scenario analysis 5*).

Aspirin

All probands and relatives who enter the long-term model are assumed to receive aspirin as a form of chemoprophylaxis. Based on results seen in the CAPP2 RCT,[48] which show reduced incidence of CRC, we reduce the probability of individuals developing cancer each year by a factor of 0.56, applied equally to the risk of developing endometrial cancer and the risk of developing CRC.

A draft report[48] on the effectiveness of aspirin in the prevention of CRC in people with Lynch syndrome finds that the balance of risks and benefits of regular aspirin use in people with Lynch syndrome supports the use of aspirin for at least 2 years in this population, and the Manchester Consensus Group[22] strongly recommends that MMR pathogenic variant carriers take aspirin chemoprevention. Optimal dosage is currently unknown; the CaPP3 RCT[48] is ongoing to determine this. Therefore, we assume that individuals take daily aspirin over the life course and that benefits continue over time. In scenario analysis 7, we exclude aspirin to assess the bearing this measure has on cost-effectiveness.

Variant of uncertain significance

Probands with positive index results on tumour tissue and negative germline results are considered Lynch syndrome negative, but, for a proportion of these, clinical suspicion of Lynch syndrome remains. Similarly, negative results for currently identified pathogenic mutations on germline testing may be found. These VUSs may be latterly identified as pathogenic for Lynch syndrome, or not, in which case management can either be scaled up or down accordingly. For these cases, it is assumed that further testing occurs on tumour tissue (somatic analysis) to either confirm sporadic cause of tumour or establish that VUS is non-pathogenic for Lynch syndrome and management. Clinical experts suggest that, although somatic analysis may not fully resolve the pathogenic status of VUS patients, around 50–60% of them would derive some benefit from it (Andrew Wallace, Manchester Centre for Genomic Medicine, 27 December 2019, personal communication), allowing upgrading or downgrading of VUS and influencing their associated long-term management.

Work is ongoing to reduce the number of VUSs. The International Society for Gastrointestinal Hereditary Tumors (InSiGHT) MMR Variant Interpretation Committee, which is recognised by ClinGen as the Expert Panel and is in the process of being recognised by the Food and Drug Administration as the MMR Variant Classification Expert Panel, has achieved a reduction in the number of Class-3 VUSs of 35%.[117]

We used a VUS estimate of 1.2% in our model from the clinical effectiveness review, but clinical expert opinion suggests that this figure may be higher, at 2–5% (Demetra Georgiou, personal communication).

Somatic analysis may cost up to £800 (Demetra Georgiou, 16 January 2020, personal communication), which would introduce a significant extra cost to each of the test strategies. However, it is likely that, under current testing guidelines, these individuals would already qualify for somatic testing (as they have a positive index and negative germline result), so this would not be an additional cost due to VUS status alone. This cost is not included in our modelling. We use our estimated proportions of VUSs, which are then varied during sensitivity analysis, to assess the sensitivity of the ICER to this parameter. Given that any additional costs involved may be recouped by the ability to downgrade potential VUSs to lower long-term management costs, further research would be beneficial, but conclusions about the magnitude of this at the individual or national level cannot be reached in our work.

Costs

The majority of costs were obtained directly from previous work presented to NICE[12] because the sources were recent, relevant and local, and, through personal communications, clinical experts confirmed the figures quoted. Hospital-related costs were obtained from the most current (2017/18) NHS reference tables.[49]

Costs are reported in 2017/18 Great British pounds, with estimates for some parameters requiring adjustment using recognised methods in hospital and community health services to inflate to this cost year.

The costs of IHC, MSI and methylation testing were estimated as £210, £217 and £156, respectively, using reported costs from the UK Genetic Testing Network 2018,[118] corroborated through personal communications from clinical experts. The cost of offering counselling to a proband was estimated as £28.25 (based on 15 minutes of band-6 hospital nurse time), with cost of referral for a relative estimated to be £39 (cost of a GP appointment).[6] Pre-test genetic counselling/multidisciplinary team

review was estimated to cost £642.19 for probands and £514.43 for relatives; post-test genetic counselling was estimated to cost £141.44 for both.[114] Diagnostic mutation testing for Lynch syndrome was estimated to cost £755 (with testing conducted on all four genes) and predictive mutation testing for relatives was estimated to cost £165 (testing on single MMR gene under suspicion).[118]

A one-off cost of CRC is incurred at the time of CRC incidence (dependent on patient age and stage at diagnosis), with no further cost being accrued as a result of time in CRC states or at time of death from CRC. These costs were sourced from Snowsill *et al.*,[43] who used reported data by the Economic Evaluation of Health and Social Care Interventions Policy Research Unit, based on a whole-disease model of CRC.

We assume that the cost of colonoscopy is £325.00,[49] averaging across outpatient diagnostic and therapeutic colonoscopies, with an increased cost of £2.89 per colonoscopy secondary to average costs incurred from complications associated with the procedure.[12]

For endometrial cancer, a one-off treatment cost of £6510 is assumed, calculated in line with previous work.[12] A cost of £3428 is assigned to prophylactic H-BSO. Women who have not had surgical prophylaxis undergo annual surveillance to detect endometrial cancer. The cost is £39.00, plus an additional cost of £473.41 for those requiring referral for invasive surveillance. We assume that this referral occurs in 10% of cases.[12] There was no cost assigned to aspirin, as it was assumed to be purchased by the individual as a low-cost over-the-counter medicine, rather than cost on prescription to the NHS. The costs involved in diagnostic testing are taken as averages of costs reported by genetic laboratories throughout the UK,[118] and, as such, reflect the average national cost. The cost of DNA sequencing is decreasing. It is thought that costs of testing may be reduced in the future. A microcosting study of testing strategies for Lynch syndrome by Ryan *et al.*[50] showed that costs of testing at a major tertiary institution were extremely low when staff time, consumables and equipment were calculated. To illustrate the impact of reduced test costs, scenario analysis 2 was performed using these results, mindful that they were not inclusive of capital costs (electricity, rent), which are often significant. As authors also noted, the true cost associated with testing is likely to lie between sourced estimates from experts and costs calculated in their single-site specialist centre.[50] To reflect this, we also use sensitivity analysis to vary costs by 40% above and below our base-case cost, to more realistically determine price change effect.

Health-related quality of life

In our base case, we assume that those with cancer have the same utility as those without cancer, except for those with stage IV CRC and those in their first year of endometrial cancer. This assumption is line with previous work presented to NICE.[12,110] Although that previous work did cite supporting sources of evidence, it could be argued that this underestimates the impact of cancer on quality of life. For example, it seems plausible that those with stage III cancer would experience some disutility, compared with those who were disease free. Furthermore, one might expect that those who die from endometrial cancer experience a period of impaired quality of life prior to death.

To reflect this, we carried out a scenario analysis (scenario analysis 4) in which we assumed that those with stage III CRC experienced utility half-way between those for stage IV cancer and good health. We further assumed that those who died of endometrial cancer experienced 1 year in a health state equivalent to stage IV CRC prior to death.

A paucity of information is available in the literature regarding HRQoL in either Lynch syndrome, endometrial cancer or CRC patients, and efforts to find suitable information to reflect these parameters were unsuccessful. For this reason, the impacts on probands of testing are also not well understood, other than directly from patients, as there is insufficient evidence to support the implementation of a QALY detriment from the literature. Unpublished survey data, provided by University of Manchester via NICE (Thomas Walker, NICE, 19 July 2019, personal communication), recording patient responses to

gynaecological surveillance in Lynch syndrome showed a range of responses to questions regarding anxiety and depression levels associated with their diagnosis. This disaggregated data appeared extremely mixed, and no patterns of psychological outcomes could be identified. This illustrates the difficulty in obtaining such data and, particularly, their transfer for use in health economic models.

Final model input parameters

This section discusses the source of inputs for all model parameters, with *Tables 12* and *13* providing a summary of these.

TABLE 12 Summary of test-related model inputs

Parameter name	Base-case value	Source and year
Diagnostic parameters *Test accuracy*		
Strategy 1: sensitivity	1	Lu *et al.*[16] 2007
Strategy 1: specificity	0.805	Lu *et al.*[16] 2007
Strategy 2: sensitivity	0.625	Lu *et al.*[16] 2007
Strategy 2: specificity	0.966	Lu *et al.*[16] 2007
Strategy 3: sensitivity	1	Lu *et al.*[16] 2007
Strategy 3: specificity	0.833	Lu *et al.*[16] 2007
Strategy 4: sensitivity	1	Lu *et al.*[16] 2007
Strategy 4: specificity	0.967	Lu *et al.*[16] 2007
Strategy 5: sensitivity	1	Lu *et al.*[16] 2007
Strategy 5: specificity	0.782	Lu *et al.*[16] 2007
Strategy 6: sensitivity	0.625	Lu *et al.*[16] 2007
Strategy 6: specificity	0.954	Lu *et al.*[16] 2007
Strategy 7: sensitivity	1	Lu *et al.*[16] 2007
Strategy 7: specificity	0.791	Lu *et al.*[16] 2007
Strategy 8: sensitivity	1	Lu *et al.*[16] 2007
Strategy 8: specificity	0.942	Lu *et al.*[16] 2007
Strategy 9: sensitivity	1	Lu *et al.*[16] 2007
Strategy 9: specificity	0.791	Lu *et al.*[16] 2007
Strategy 10: sensitivity	1	Lu *et al.*[16] 2007
Strategy 10: specificity	0.942	Lu *et al.*[16] 2007
Strategy 11: sensitivity	1	Lu *et al.*[16] 2007
Strategy 11: specificity	1	Lu *et al.*[16] 2007
Test failure rate (all tests)	0	Median from systematic review
Acceptance of diagnostic tests		
MSI	1.000	Assumption
IHC	1.000	Assumption
MLH1 promoter hypermethylation	1.000	
Genetic counselling: proband	0.925	Menko *et al.*[112] 2019, Bruwer *et al.*[113] 2013, unpublished acceptability manuscript (Professor Emma Crosbie, personal communication)

TABLE 12 Summary of test-related model inputs (*continued*)

Parameter name	Base-case value	Source and year
Genetic testing direct	0.500	Assumption
Genetic testing: proband (diagnostic)	0.950	Assumption
Genetic counselling: relative	0.775	Barrow[111] 2014 and Menko *et al.*[112] 2019
Genetic testing: relative (predictive)	0.767	Barrow[111] 2014 and Menko *et al.*[112] 2019
Declined diagnostic testing or no mutation found		
Clinical suspicion of Lynch syndrome	Confidential information has been removed	Based on the PETALS study (number tested)
VUS result obtained	0.12	Assumption, clinical opinion
Costs		
IHC	£210.00	Snowsill *et al.*[12] 2017
MSI	£217.00	UK Genetic Testing Network[118] 2018 (average of three MSI test prices)
MLH1 promoter hypermethylation	£156.00	UK Genetic Testing Network[118] 2018
Offer of counselling	£28.25	Band-6 nurse time
Pre-test clinic-related costs and genetic counselling appointment: proband	£642.19	Slade *et al.*[119] 2016 and expert clinical opinion (Demetra Georgiou, personal communication)
Genetic testing on germline: proband	£755.00	UK Genetic Testing Network[118] 2018
Post-test clinic-related costs and follow-up: proband	£141.44	Expert clinical opinion (Demetra Georgiou, personal communication) and Slade *et al.*[119] 2016
Pre-test clinic-related costs and genetic counselling appointment: relative	£514.43	Expert clinical opinion (Demetra Georgiou, personal communication) and Slade *et al.*[119] 2016
Genetic testing on germline: relative	£165.00	UK Genetic Testing Network[118] 2018
Post-test clinic-related costs and follow-up: relative	£141.44	Expert clinical opinion (Demetra Georgiou, personal communication) and Slade *et al.*[119] 2016
GP appointment	£39.00	NHS Reference Costs 2017/18[49]

TABLE 13 Summary of other model input parameters

Parameter	Base-case value	Source and year
Population		
Number of relatives per proband	6	Snowsill *et al.*[12] 2017
Proportion of relatives who are first-degree relatives of proband	0.424	
Proportion of relatives receiving predictive testing found to have Lynch syndrome	0.440	
Proportion of relatives who are women	0.500	Assumption

continued

TABLE 13 Summary of other model input parameters (*continued*)

Parameter	Base-case value	Source and year
Natural history		
Prevalence of Lynch syndrome among all endometrial cancer	0.032	Nine studies (reported in 11 papers[15,52,55,56,59–61,70,76,88] and the unpublished PETALS study) that assessed prevalence of Lynch syndrome in unselected samples of women with endometrial cancer
Gene distribution among all endometrial cancer (*MLH1/MSH2/MSH6/PMS2*)	0.171 0.244 0.464 0.122	Four unselected studies[15,55,61] from our cost-effectiveness review, including the unpublished PETALS study
CRC incidence with Lynch syndrome (log-normal distribution)		Møller *et al.*[2,14] 2017, 2018 and Snowsill *et al.*[43] 2019
Mu (baseline)	4.306	
Sigma	0.567	
Beta_MSH2	0.100	
Beta_MSH6	0.531	
Beta_PMS2	0.863	
Beta_male	−0.118	
Beta_prevcancer	−0.230	
CRC incidence for women without Lynch syndrome [by age (years), per 100,000 person-years]		Office for National Statistics[8]
< 25	3.1	
25–30	2.7	
30–35	6.5	
35–40	10.7	
40–45	11.8	
45–50	21.5	
50–55	37.6	
55–60	61.8	
60–65	91.4	
65–70	118.2	
70–75	172.1	
75–80	235.6	
80–85	309.3	
85–90	359.5	
> 90	304.2	
CRC incidence for men without Lynch syndrome [by age (years), per 100,000 person years]		Office for National Statistics[8]
< 25	2.3	
25–30	2.3	
30–35	5.6	
35–40	9.1	

TABLE 13 Summary of other model input parameters (*continued*)

Parameter	Base-case value	Source and year
40–45	12.0	
45–50	23.2	
50–55	42.6	
55–60	84.2	
60–65	150.3	
65–70	196.1	
70–75	276.8	
75–80	373.8	
80–85	457.5	
85–90	511.9	
> 90	460.3	
CRC mortality rate (without Lynch syndrome)		Snowsill *et al.*[43] 2019
Stage I	0.014	
Stage II	0.052	
Stage III	0.148	
Stage IV	0.544	
CRC mortality hazard ratio with Lynch syndrome (stages I–III)	0.660	Snowsill *et al.*[43] 2019
Endometrial cancer mortality rate with Lynch syndrome	0.004	Møller *et al.*[2] 2017
Endometrial cancer mortality rate without Lynch syndrome [by age (years)]		Office for National Statistics[8]
15–45	0.026	
45–55	0.028	
55–65	0.031	
65–75	0.048	
> 75	0.092	
Effectiveness of risk reduction		
Age range (years) for gynaecological surveillance	25–75	
Interval of surveillance	1.000	
Mortality rate decrease from gynaecological surveillance	0.102	
Aspirin risk reduction	0.56	Snowsill *et al.*[12] 2017
Effectiveness of risk reduction		
Age range (years) for surveillance colonoscopy	25–75	
Interval between colonoscopies	2.000	
Uptake of colonoscopy if diagnosed with Lynch syndrome	1.000	

continued

TABLE 13 Summary of other model input parameters (*continued*)

Parameter	Base-case value	Source and year
Uptake of colonoscopy if diagnosed putative Lynch syndrome	1.000	Barrow *et al.*[120] 2015
Hazard ratio for CRC incidence if undergoing colonoscopy	0.387	
CRC stage distribution in surveillance		Snowsill *et al.*[12] 2017
Stage I	0.686	
Stage II	0.105	
Stage III	0.128	
Stage IV	0.081	
CRC stage distribution not in surveillance (sporadic)		Snowsill *et al.*[43] 2019
Stage I	0.176	
Stage II	0.270	
Stage III	0.295	
Stage IV	0.259	
CRC stage distribution not in surveillance (Lynch syndrome)		Barnetson *et al.*[121] 2006
Stage I	0.188	
Stage II	0.488	
Stage III	0.213	
Stage IV	0.113	
Diagnostic MMR mutation testing		
Acceptance of counselling (tumour-testing strategies)	0.925	Menko *et al.*[112] 2019 and Heald *et al.*[122] 2013
Acceptance of counselling (direct testing)	0.5	Assumed
Acceptance of diagnostic testing (given accepted counselling)	0.950	Expert opinion (Demetra Georgiou, personal communication)
Sensitivity	1	Assumed
Specificity	1	Assumed
Predictive MMR mutation testing		Barrow *et al.*[120] 2015
Acceptance of counselling	0.775	
Acceptance of predictive testing (given accepted counselling)	0.765	
Costs (£)		
Colonoscopy	583	
Stage I CRC [by age (years)]		
40–49	8754	
50–59	5712	
60–69	4623	
70–79	3178	
80–100	1380	

TABLE 13 Summary of other model input parameters (*continued*)

Parameter	Base-case value	Source and year
Stage II CRC [by age (years)]		
40–49	8741	
50–59	7016	
60–69	5352	
70–79	3455	
80–100	1546	
Stage III CRC [by age (years)]		
40–49	14,490	
50–59	9692	
60–69	7259	
70–79	4485	
80–100	1561	
Stage IV CRC (by age)		
40–49	11,705	
50–59	8444	
60–69	6509	
70–79	4365	
80–100	807	
Utilities		
Baseline utility model		Ara and Brazier[47] 2010
Intercept	0.9509	
Male	0.0212	
Age	−0.0003	
Age^2	-3.32×10^{-6}	
(Resulting baseline utility for proband at start)	0.816	
(Resulting baseline utility for relative at start)	0.850	
Impact of testing on HRQoL (multipliers)		
Declining counselling	1	Assumed
Declining genetic testing	1	Assumed
Diagnosed with Lynch syndrome	1	Assumed
Diagnosed with putative Lynch syndrome	1	Assumed
CRC (multipliers)		
Stage I	1	Assumed
Stage II	1	Assumed
Stage III	1	Assumed
Stage IV	0.789	Snowsill *et al.*[12] 2017
Endometrial cancer (multiplier)	1	Assumed
Utility decrement on diagnosis of endometrial cancer for 1 year	0.036	Snowsill *et al.*[12] 2017

Cost-effectiveness results

The simulated population of the model consists of individual probands at a specified age diagnosed with endometrial cancer, among whom 11 different diagnostic strategies are undertaken to identify Lynch syndrome, and the relatives who would be identified in the event of diagnosis of Lynch syndrome in the proband. In the base case, the age of the proband at diagnosis of endometrial cancer is 49 years. The costs and QALYs accrued throughout each strategy are discounted at a rate of 3.5% per year, with costs reported in Great British pounds. The incremental cost per QALY when each strategy is compared with a no-testing approach in the proband is presented, followed by the pairwise comparative ICERs for all strategies.

Base-case results

Cost-effectiveness results

Table 14 summarises the base-case cost-effectiveness results (prior to rounding). IHC with *MLH1* methylation is the most cost-effective strategy, with germline testing direct incurring the highest costs per QALY, compared with no testing. All 11 strategies are considered cost-effective at a WTP threshold of £20,000 per QALY.

Full incremental analysis

Immunohistochemistry with *MLH1* methylation was the most cost-effective testing strategy, with an ICER of approximately £9420 per QALY. All other strategies were dominated or did not reach acceptable cost-effectiveness threshold levels.

TABLE 14 Base-case results

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER vs. no testing (cost per QALY) (£)	ICER
No testing	0	–	0	0	–	–
MSI with *MLH1* methylation	520	520	0.0419	0.0419	12,298.41	Extendedly dominated
IHC with *MLH1* methylation	630	630	0.0669	0.0669	9459.32	£9420
MSI followed by IHC with *MLH1* methylation	720	90	0.0420	−0.0249	17,045.57	Dominated
IHC	790	160	0.0681	0.0012	11,628.23	£133,330
MSI	840	50	0.0683	0.0002	12,265.95	£250,000
IHC followed by MSI with *MLH1* methylation	870	30	0.0671	−0.0012	12,925.61	Dominated
MSI and IHC simultaneously with *MLH1* methylation	890	20	0.0671	0.0000	13,280.76	Dominated
IHC followed by MSI	1025	185	0.0685	0.0002	14,981.99	£925,000
MSI followed by IHC	1030	5	0.0685	0.0000	15,018.13	Dominated
MSI and IHC simultaneously	1070	45	0.0685	0.0000	15,595.83	Dominated
Germline testing	1160	135	0.0666	−0.0019	17,478.16	Dominated

Base-case results (shown in *Table 14*) show that MSI with *MLH1* methylation was the cheapest strategy, with expected mean costs of approximately £520, and was expected to yield 0.0419 QALYs. The comparison between no testing and IHC with *MLH1* methylation extendedly dominated the comparison between no testing and MSI with *MLH1* methylation (i.e. was less costly and more effective than a combination of other comparators). This demonstrated that IHC with *MLH1* methylation was the most cost-effective testing strategy, with an ICER of £9420 per QALY. Although IHC, MSI and IHC followed by MSI strategies were also on the cost-effectiveness frontier, ICERs were well above the threshold levels accepted in the UK and all strategies were dominated (i.e. more costly and less effective than one or more of the comparators).

Number of people identified as having Lynch syndrome

The number of probands and relatives with Lynch syndrome identified for the 11 strategies are illustrated in *Figure 21*. This shows that very similar numbers of true positive Lynch syndrome individuals are identified across all testing strategies except for strategies 2 and 6 (MSI with *MLH1* promoter hypermethylation testing and MSI followed by IHC with *MLH1* promoter hypermethylation testing). This is expected, as sensitivity of these testing strategies are the lowest of all the strategies, at 62.5%. This is a result of our assumptions on test accuracy, which are uncertain.

Diagnostic performance is diminished across all strategies, as some of the relatives identified decline the offer of predictive testing. In addition, if probands receive a positive diagnosis but no causative mutation is found (i.e. Lynch syndrome-assumed diagnosis), their first-degree relatives are treated as having Lynch syndrome, but second-degree relatives and beyond are treated as not having Lynch syndrome.

Long-term clinical outcomes

Results from long term-modelling of cancer outcomes

Cumulative incidence of identifying Lynch syndrome

The graphs in *Figures 22–24* show model predictions of CRC and endometrial cancer incidence, by gene, from birth, illustrating our assumptions for incidence of the respective cancers in Lynch syndrome individuals without diagnosis/intervention. This is used to simulate outcomes for these individuals with and without interventions as a result of being identified as having Lynch syndrome.

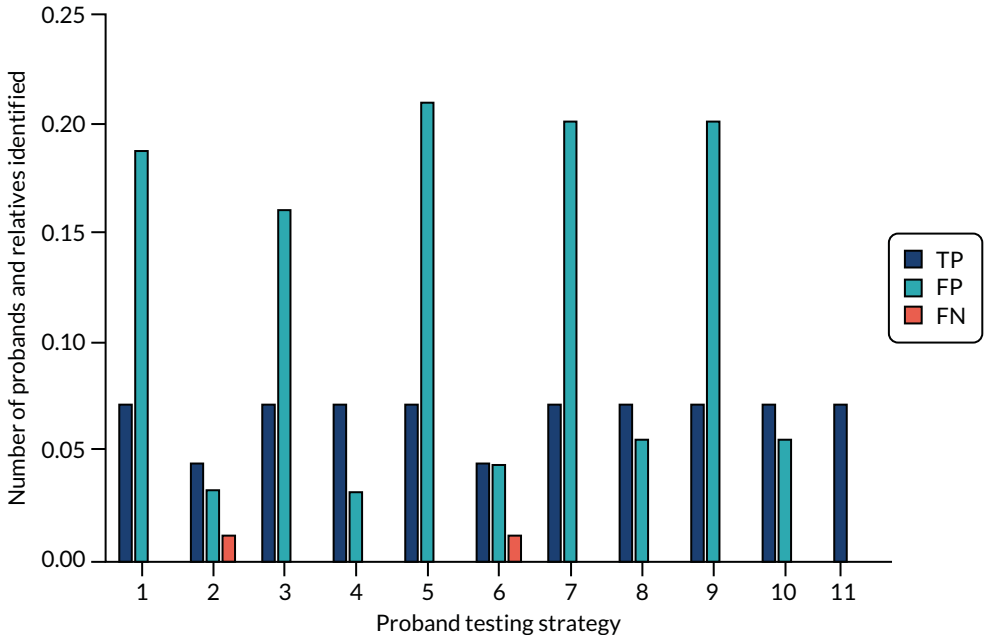

FIGURE 21 Number of probands and relatives with Lynch syndrome identified by each strategy. FN, false negative; FP, false positive; TP true positive.

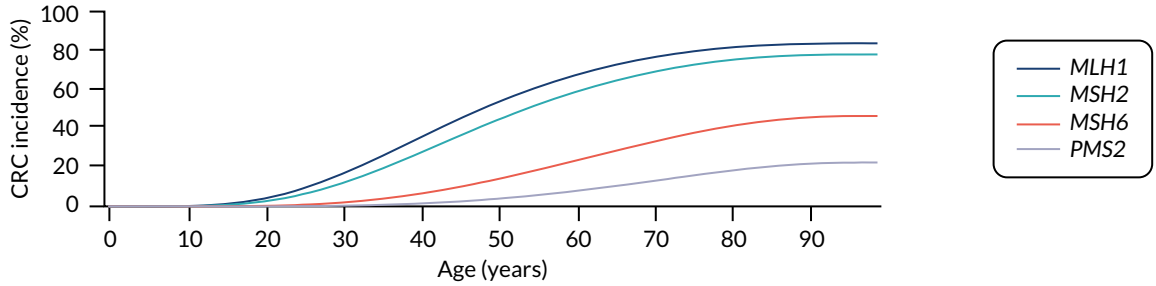

FIGURE 22 Cumulative incidence of CRC among females with Lynch syndrome.

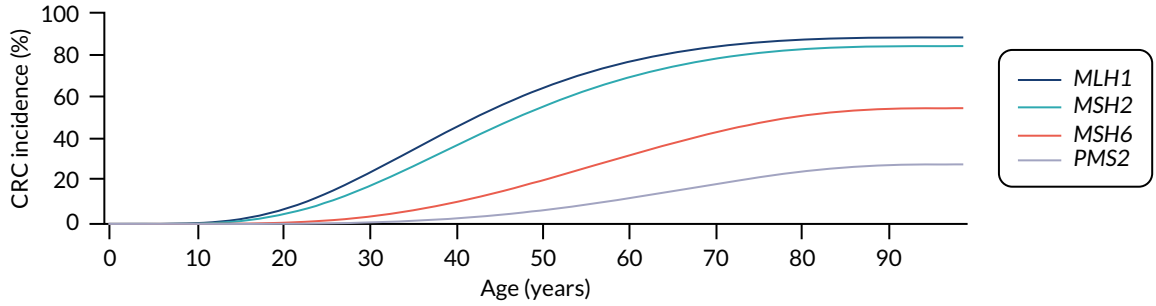

FIGURE 23 Cumulative incidence of CRC among males with Lynch syndrome.

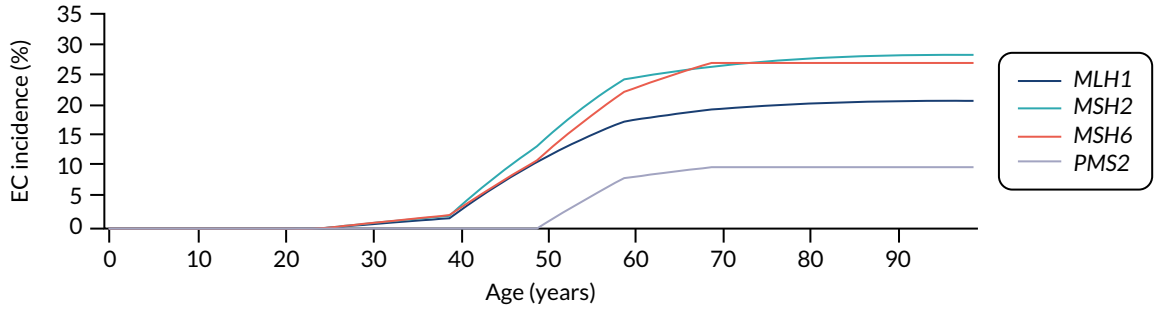

FIGURE 24 Cumulative incidence of EC among females with Lynch syndrome. EC, endometrial cancer.

Figure 25 shows the predicted improvement in life expectancy when a person of a given age who has not previously had a Lynch syndrome-related cancer is identified with Lynch syndrome (through cascade testing) and measures are initiated to reduce their risks. For women, being identified at age 30 years through cascade testing results in an extra 6.7 years of life, falling to 0.9 years if the woman is identified at age 70 years. For men, the equivalent predicted gains are 7.4 years, falling to 0.7 years.

Despite the magnitude of benefits in terms of life-years gained declining as age of identification rises, this graph demonstrates that some degree of benefit is maintained through identification at any point across the life course until at least age 70 years, as modelled.

Figure 26 shows the benefits of identifying Lynch syndrome in a cohort of women of the same age in terms of cases of CRC and endometrial cancer avoided, and deaths from CRC or endometrial cancer averted, when Lynch syndrome is identified. Results are presented per 100 women identified. *Figure 27* shows the CRC cases prevented and deaths averted per 100 men identified.

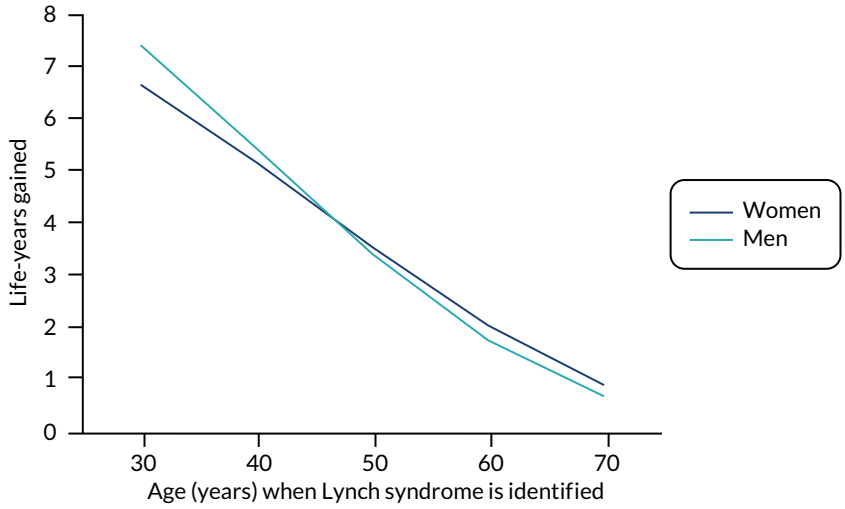

FIGURE 25 Predicted improvement in life expectancy with age at identification.

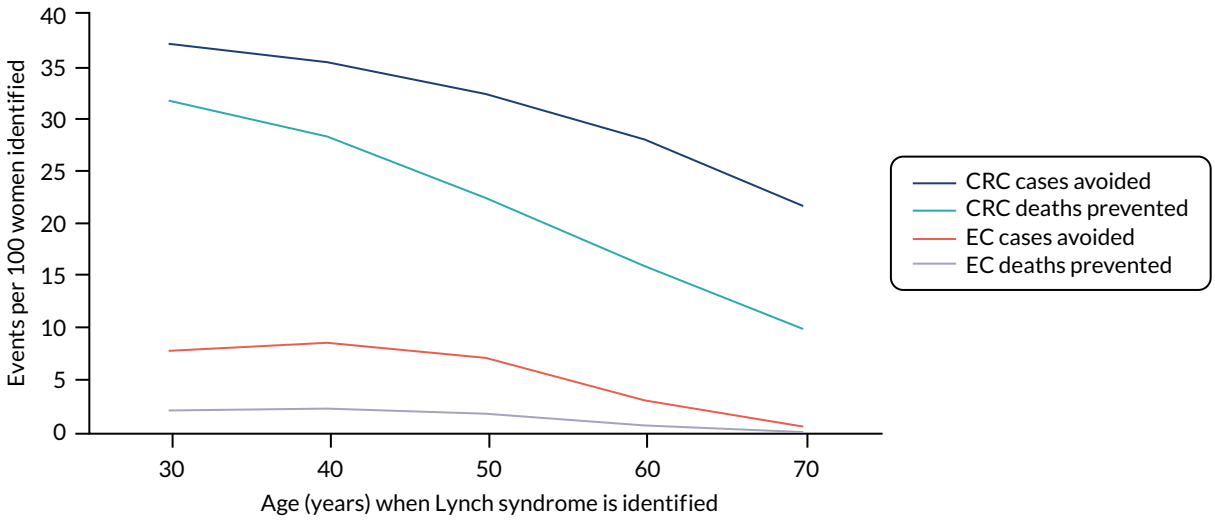

FIGURE 26 Benefits of identifying 100 women with Lynch syndrome in a cohort of the same age. EC, endometrial cancer.

The number of CRC cases and CRC deaths prevented when 100 women of a given age who have Lynch syndrome, and have recently presented with endometrial cancer, benefit from CRC surveillance and risk reduction are presented in *Figure 28*. This declines with age as the relative risk of dying from other causes increases.

Additional outcomes

Predicted lifetime QALY gains by age of Lynch identification *Figure 29* shows the QALY gains predicted by the lifetime cancer model, as a function of the age at which a person is identified with Lynch syndrome. As expected, these decrease with age, as the number of life-years that can be gained falls as the age at which cancer would present increases. QALY gains are similar for the three groups, except for younger men, who gain greater benefit from CRC protection as a result of their increased risk.

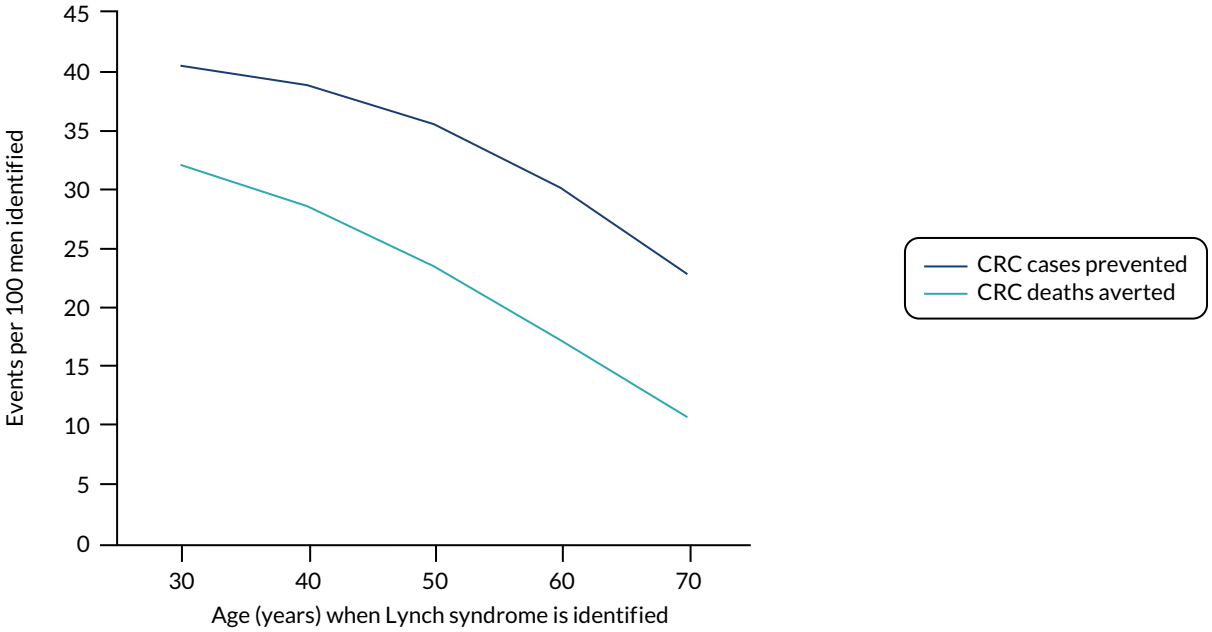

FIGURE 27 Benefits of identifying 100 men with Lynch syndrome in a cohort of the same age.

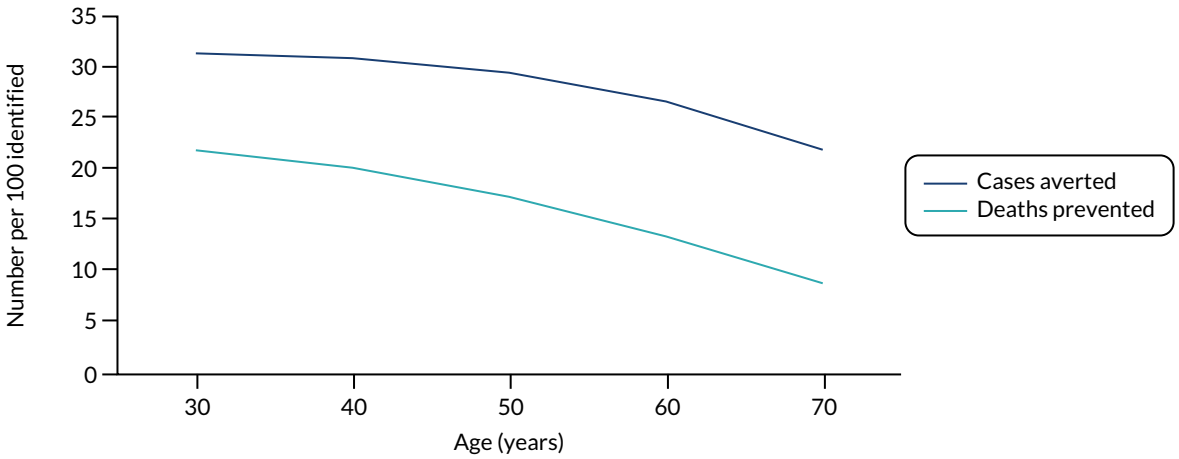

FIGURE 28 Number of CRC cases and CRC deaths prevented by identification of 100 endometrial cancer probands.

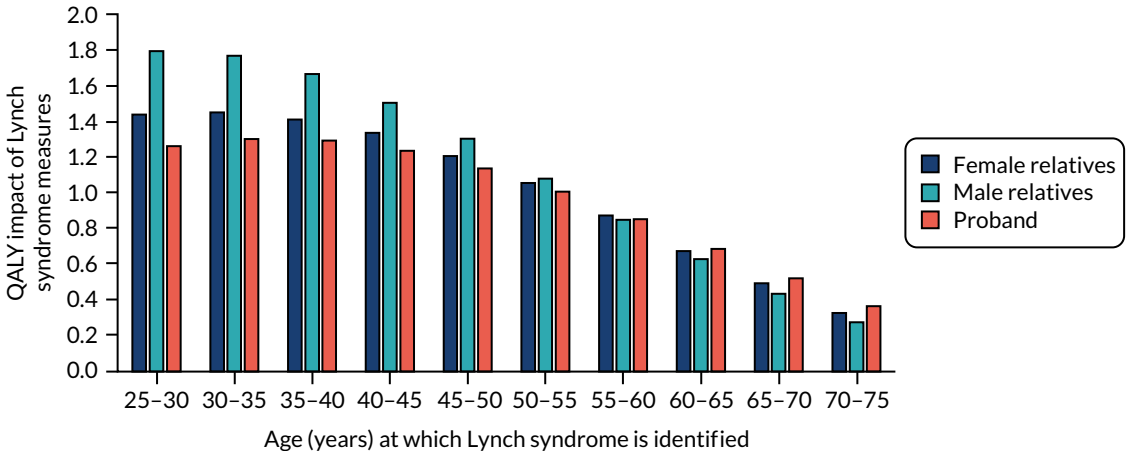

FIGURE 29 The QALY gains predicted by the lifetime cancer model as a function of the age at which a person is identified as having Lynch syndrome.

Disaggregated costs

If a person is identified with Lynch syndrome, they will incur additional costs owing to protective measures such as surveillance and prophylactic surgery. At the same time, they may incur reduced Lynch syndrome-related cancer treatment costs if the protective measures are effective. *Figure 30* shows how the take-up of such measures, from the age at which a person is identified with Lynch syndrome, affects total costs. The costs for female relatives is significantly higher, largely because of the costs of prophylactic surgery to prevent endometrial cancer, which is not incurred by men or by women who have been diagnosed with endometrial cancer.

Subgroup analyses

Potential subgroup analyses of reflex testing in endometrial cancer probands aged < 70 years and probands who had previously had CRC but who did not already have a Lynch syndrome status assigned were not feasible; therefore, no results are presented.

Scenario analyses

Scenario analysis results

We undertook several scenario analyses to estimate the impact to the base case of changing key model input parameters; the full rationale for doing so is detailed in *Discussion of model input parameters* and *Final model input parameters*. The following scenario analyses were undertaken:

- scenario analysis 1 – strategy-level test accuracy obtained from the PETALS study (Dr Neil AJ Ryan, personal communication)
- scenario analysis 2 – costs of testing obtained from Ryan *et al.*[50]
- scenario analysis 3 – strategy-level test accuracy obtained from the PETALS study (Dr Neil AJ Ryan, personal communication) and costs of testing obtained from Ryan *et al.*[50]
- scenario analysis 4 – disutility inflated because of cancer
- scenario analysis 5 – gynaecological surveillance excluded
- scenario analysis 6 – 3-year colonoscopy surveillance
- scenario analysis 7 – excluding benefit from aspirin
- scenario analysis 8 – excluding hazard ratio that reduces incidence of CRC as a result of surveillance.

Scenario analysis 1 results

The results in *Table 15* show that the most cost-effective strategy remains IHC with *MLH1* methylation testing, with an ICER of approximately £9280 per QALY, in comparison with no testing. All other strategies were dominated or did not reach accepted cost-effectiveness threshold levels.

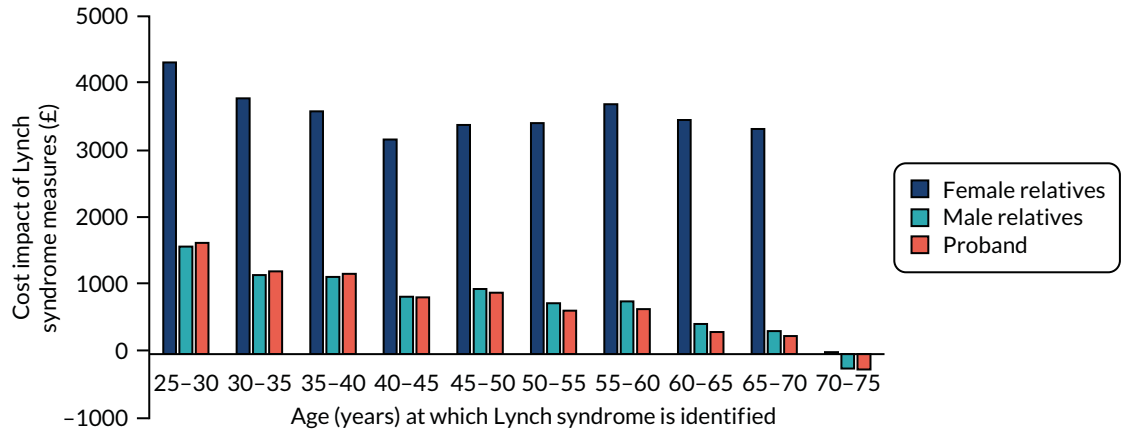

FIGURE 30 Cost impact of Lynch syndrome management across probands and male and female relatives.

TABLE 15 Scenario analysis 1 results

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER
No testing	0	–	0.0000	–	–
MSI with *MLH1* methylation	480	480	0.0378	0.0378	Extendedly dominated
IHC with *MLH1* methylation	620	620	0.0668	0.0668	£9280
MSI	640	20	0.0389	−0.0279	Dominated
MSI followed by IHC with *MLH1* methylation	720	100	0.0420	−0.0248	Dominated
IHC	820	200	0.0683	0.0015	£133,330
MSI and IHC with *MLH1* methylation	860	40	0.0669	−0.0014	Dominated
IHC followed by MSI with *MLH1* methylation	876	56	0.0671	−0.0012	Dominated
IHC followed by MSI	1020	200	0.0685	0.0002	£1,000,000
MSI followed by IHC	1030	10	0.0685	0.0000	Dominated
MSI and IHC	1060	40	0.0684	−0.0001	Dominated
Germline testing	1160	40	0.0666	−0.0019	Dominated

Using the test accuracy estimates from Ryan *et al.*,[100] a small decrease in the ICER of £140 per QALY from the base case was observed. This was driven by a nominal reduction in the average cost of testing of £10 while QALY gains remained static. IHC testing also followed as the next most cost-effective strategy, but equally exceeded the accepted WTP threshold.

Scenario analysis 2 results: costs of testing obtained from Ryan et al.*[50]*

Using the testing costs obtained from Ryan *et al.*,[50] the results (*Table 16*) show that the IHC with *MLH1* methylation testing strategy continues to be the most cost-effective, with an ICER of approximately £5830, when compared with the MSI with *MLH1* methylation testing strategy. All other strategies continue to be dominated or do not reach acceptable cost-effectiveness threshold levels.

The results of the microcosting study produced test cost estimates that were significantly reduced from those used in the base case; therefore, an ICER of almost half that of the base case was expected. As discussed in *Discussion of model input parameters*, these costs are considered grossly under-representative of the true costs involved in testing in the NHS at this point in time.

Scenario analysis 3 results: strategy-level test accuracy obtained from the PETALS study and costs of testing obtained from Ryan et al.*[50]*

The results in *Table 17* show that IHC with *MLH1* methylation testing continues to be the most cost-effective strategy, with an ICER of £5690 per QALY.

The results tables for scenario analyses 4–7 (see *Appendix 7*) illustrate that IHC with *MLH1* methylation testing is the most cost-effective strategy under each scenario.

Scenario analysis 8 results: excluding hazard ratio that reduces incidence of colorectal cancer as a result of surveillance

In contrast with the base case, here we assume that colonoscopic surveillance reduces CRC incidence, with a hazard rate of 0.387, mirroring the assumptions made by Snowsill *et al.*[110] on CRC incidence in the presence/absence of surveillance (*Table 18*). The ICER increases to £20,740, exceeding the cost-effectiveness threshold of £20,000 per QALY. This is the greatest change in the ICER found across all scenario analyses.

TABLE 16 Scenario analysis 2 results

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER
No testing	0	–	0.0000	–	–
MSI with *MLH1* methylation	270	–	0.0419	–	–
MSI followed by IHC with *MLH1* methylation	300	30	0.0420	0.0001	Extendedly dominated
IHC with *MLH1* methylation	390	390	0.0669	0.0669	£5830
IHC followed by MSI with *MLH1* methylation	436	46	0.0671	0.0002	Extendedly dominated
MSI and IHC with *MLH1* methylation	438	2	0.0671	0.0000	Dominated
IHC	500	110	0.0681	0.0012	£91,670
MSI	540	40	0.0683	0.0002	Extendedly dominated
IHC followed by MSI	560	60	0.0685	0.0004	£150,000
MSI and IHC	570	10	0.0685	0.0004	Dominated
MSI followed by IHC	573	3	0.0685	0.0000	Dominated
Germline testing	880	320	0.0666	−0.0019	Dominated

TABLE 17 Scenario analysis 3 results

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER
No testing	0	–	0.0000	–	–
MSI with *MLH1* methylation	250	250	0.0378	0.0378	Extendedly dominated
MSI followed by IHC with *MLH1* methylation	300	300	0.0420	0.0042	Extendedly dominated
MSI	360	60	0.0389	−0.0031	Dominated
IHC with *MLH1* methylation	380	380	0.0668	0.0668	£5690
MSI and IHC with *MLH1* methylation	420	40	0.0669	0.0001	Extendedly dominated
IHC followed by MSI with *MLH1* methylation	440	20	0.0671	0.0002	Extendedly dominated
IHC	530	150	0.0683	0.0015	£100,000
IHC followed by MSI	560	30	0.0685	0.0002	£150,000
MSI and IHC	566	6	0.0684	−0.0001	Dominated
MSI followed by IHC	573	13	0.0685	0.0000	Dominated
Germline testing	880	320	0.0666	−0.0019	Dominated

Scenario analysis 8

TABLE 18 Scenario analysis 8 results

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER (£)
No testing	0	–	0.0000	–	–
MSI with *MLH1* methylation	540	540	0.0203	0.0203	Extendedly dominated
IHC with *MLH1* methylation	670	670	0.0323	0.0323	20,740
MSI followed by IHC with *MLH1* methylation	740	70	0.0204	−0.0119	Dominated
IHC	830	160	0.0333	0.0010	160,000
MSI	870	40	0.0335	0.0002	200,000
IHC followed by MSI with *MLH1* methylation	900	30	0.0325	−0.0010	Dominated
MSI and IHC simultaneously with *MLH1* methylation	930	60	0.0325	−0.0010	Dominated
IHC followed by MSI	1060	190	0.0336	0.0001	Extendedly dominated
MSI followed by IHC	1070	200	0.0337	0.0002	1,000,000
MSI and IHC simultaneously	1100	30	0.0336	−0.0001	Dominated
Germline testing	1200	130	0.0321	−0.0016	Dominated

Summary

We undertook several scenario analyses to assess the impact of these changes on our base-case ICER. Under these scenarios, the results remained robust, with IHC with *MLH1* methylation testing being the most cost-effective strategy.

Deterministic/probabilistic sensitivity analyses

One-way sensitivity analysis results

Deterministic sensitivity analysis results were conducted by varying key model input parameters used in the base-case analysis to assess the impact on the cost per QALY, and presented in the form of tornado plots. *Figure 31* shows the tornado plot for the comparison between IHC with *MLH1* methylation and a no-testing strategy. We chose this comparison because, in the base-case analysis, the incremental results showed that IHC with *MLH1* methylation was the most cost-effective strategy. In addition, IHC with *MLH1* methylation had the most cost-effective ICER (approximately £9460 per QALY) when each testing strategy was compared with a no-testing strategy. The sensitivity analysis results show which parameter is the key driver of the cost-effectiveness. These results show that varying the percentage of relatives accepting counselling was the most influential parameter. Decreasing the number of relatives who accept counselling by 50% led to an increase in the ICER. Likewise, increasing the percentage of relatives who accept counselling led to a decrease in the ICER. In the model, these relatives receive the germline tests if appropriate, but do not incur the costs of genetic counselling. Moreover, as expected, if there was a decrease in the prevalence of Lynch syndrome among women with endometrial cancer, the ICER increased to approximately £13,640 per QALY. Similarly, if the prevalence was increased to 6.4%, this resulted in an ICER of approximately £7350 per QALY. Based on the parameters varied, the ICER changed slightly, but remained below current WTP thresholds.

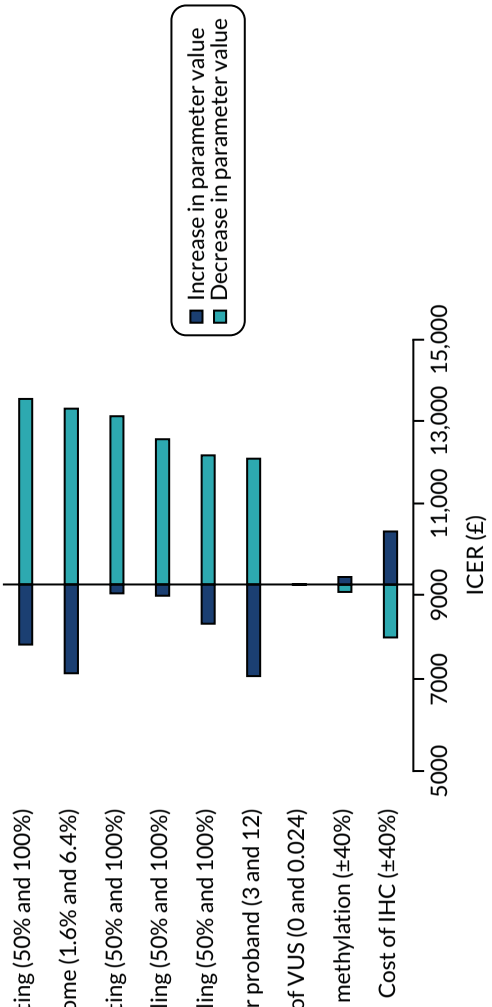

FIGURE 31 Tornado plot for the impact of a ± 50% change in individual parameters on the ICER per QALY gained.

Probabilistic sensitivity analysis results

We report the PSA results that were generated by assigning distributions to key input parameters and randomly sampling from these distributions over 10,000 simulations to derive any uncertainty in the costs and outcomes. The PSA results for IHC with methylation, compared with no testing, produced an incremental cost of £600 and an incremental QALY of 0.0517, giving an ICER of £11,600 per QALY gained. Exact results have been obtained from TreeAge but were rounded by the authors. We chose this comparison because this strategy was shown to be the most cost-effective in the base-case analysis, and, across all scenario analyses, the results remained robust. Including the combined uncertainty across the parameters included in the PSA showed that the expected mean costs and QALYs yielded in the base case were underestimated, which resulted in an ICER greater than that in the deterministic results.

The probabilistic results are presented in the form of an incremental scatterplot and its corresponding CEACs. *Figure 32* presents the results of the 10,000 runs of the Monte Carlo simulations; the scatterplot shows that there is some variation in the incremental costs and QALYs. *Figure 33* shows the probabilistic results presented in the form of a CEAC, which shows the probability that an intervention is cost-effective at different WTP thresholds per QALY. At a WTP threshold of £20,000 per QALY, IHC has a 0.93 probability of being cost-effective when compared with no testing.

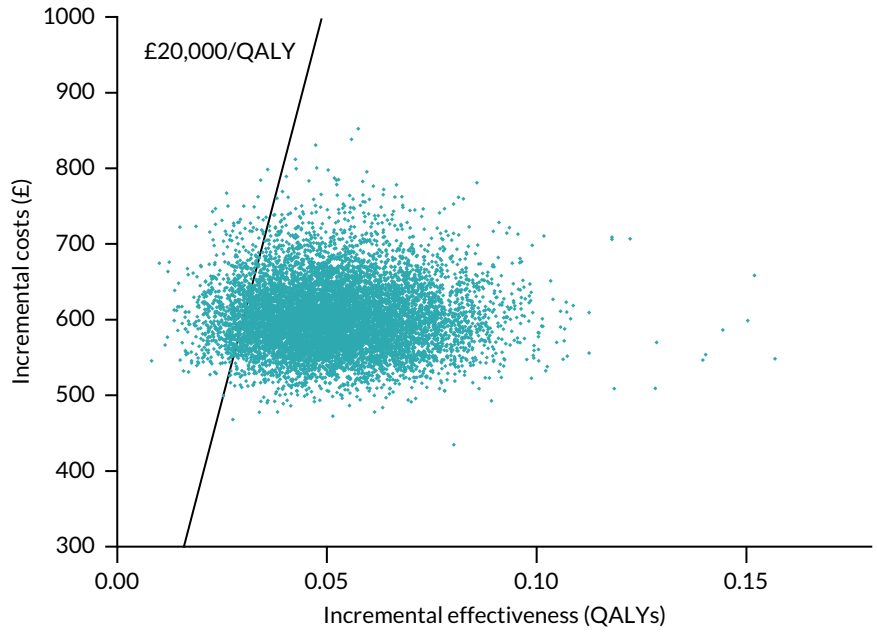

FIGURE 32 Incremental cost-effectiveness scatterplot for the comparison between IHC with *MLH1* versus no screening.

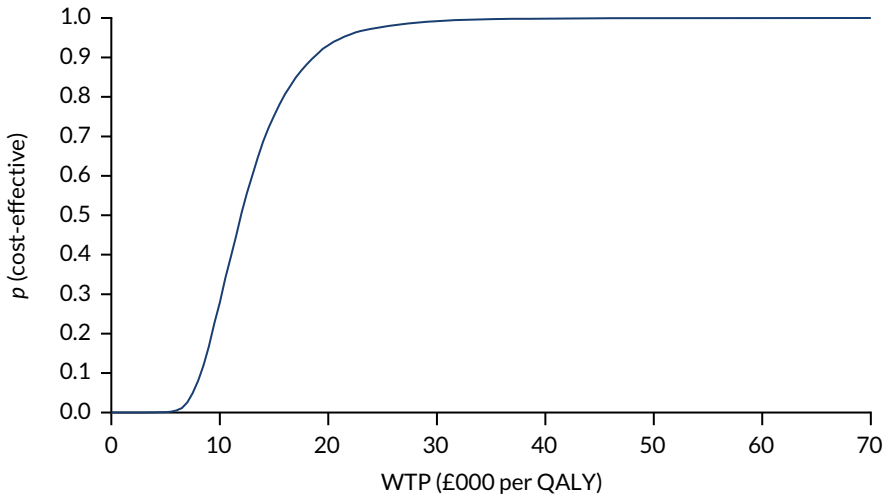

FIGURE 33 The CEAC for the IHC with methylation strategy at different WTP thresholds.

Chapter 7 Discussion

Statement of principal findings

The clinical effectiveness search identified 3308 studies; of these, 38 studies of test accuracy were included, of which seven provided full 2 × 2 data. There were four head-to-head test accuracy studies comparing MSI with IHC. None of these studies demonstrated a clear difference in accuracy between IHC and MSI. Other studies indicated that the specificity of IHC may be improved through methylation testing of patients with IHC deficiency in *MLH1*. There was very little evidence on accuracy of methylation testing in MSI-H patients. The test failure rate was consistently low for both tests. There was high concordance between IHC and MSI tests in most studies. No studies of clinical effectiveness of endometrial cancer surveillance met the inclusion criteria. Therefore, there were limited data on test accuracy and effectiveness of colorectal and gynaecological screening to populate the economic model, and available evidence was deemed to be at a high risk of bias. The economic model indicated that the IHC with *MLH1* methylation strategy was the most cost-effective testing strategy, with an ICER of approximately £9420 per QALY. Sensitivity analyses examining different model assumptions were generally cost-effective at a WTP threshold of £20,000 per QALY.

Strengths and limitations of the assessment

The major strength of this assessment is that we followed the gold-standard methodology for conducting systematic reviews (which included independent assessment at every stage and input from expert clinicians) to identify evidence on test accuracy, disease prevalence, and the benefits and harms of gynaecologic and colorectal surveillance of women identified with Lynch syndrome. The economic model was directly informed by this systematic review.

The clinical effectiveness review had a number of limitations. First, we excluded studies for which we could not establish which reference standard(s) were used. For each study that did not explicitly state how a diagnosis of Lynch syndrome was established, we contacted the corresponding author to seek clarification. Of the authors who responded, none was able to confirm the tests used, informing us that samples were sent to commercial laboratories (sometimes multiple laboratories). We followed this up with the companies specified, but they were unable to confirm which tests had been used without us providing details of individual study participants. This was not possible; therefore, we cannot be certain if these excluded studies used the reference standards of interest for our review and if they could have provided additional information on the test accuracy of IHC and MSI for Lynch syndrome. Second, in our PICO framework, we specified that Lynch syndrome must have been diagnosed by genetic verifications of constitutional variants in the MMR genes (*MHL1*, *MSH2*, *MSH6* or *PMS2*) using diagnostic tests outlined in the Association for Clinical Genomic Science best-practice guidelines for genetic testing and diagnosis of Lynch syndrome, prioritising sequencing with/without MLPA.[33] Variants in these four genes are thought to account for 97–99% of Lynch syndrome cases.[123] There is some evidence that variants in a fifth gene (*EPCAM*) may be responsible for 1–3% of Lynch syndrome cases.[13] The exclusion of *EPCAM* may have led to us slightly underestimating the prevalence of Lynch syndrome. Furthermore, studies that employed diagnostic tests other than the ones we specified would not have been captured in our review. Third, the number of VUS cases were reported as stated in individual studies. Over time, VUSs may be reclassified. For example, Mersch *et al.*[124] reported that, from a sample of 26,670 unique VUSs, 2048 (7.7%) were reclassified. In the majority of cases, these were downgraded to benign/likely benign [91.2% (1867/2048)], with only a minority being upgraded to pathogenic/likely pathogenic [8.7% (178/2048)].[124] Data in our review came from studies published from 1999 to 2019, with the earliest cases of VUSs being reported in a study from 2003.[54] We considered VUSs to be

germline negative. However, it is possible that the pathogenic status of these variants has now changed and that these individuals would now be considered to have Lynch syndrome. Fourth, we did not search for grey literature or studies published in languages other than English. It is possible that other relevant studies could have been missed by employing this approach.

In this assessment, a full systematic review was undertaken to identify evidence on test accuracy, disease prevalence, and benefits and harms of gynaecologic and colorectal surveillance in women identified with Lynch syndrome. A strength is that the economic model was directly informed by this systematic review, although articles were limited to the English language.

Conclusions from the economic model are similar to those of Snowsill *et al.*,[43] which is the closest equivalent review to ours in that it is constructed to review testing of endometrial cancer probands and their relatives in the UK setting, presents results in costs and QALYs, and uses a no-testing comparator. IHC with *MLH1* promoter hypermethylation testing was found to be the most cost-effective strategy, with an ICER of £14,200. Although this is more expensive than our ICER of £9420 per QALY, some key differences between the base-case assumptions provide a viable explanation. First, we modelled surveillance and risk reduction interventions for both CRC and endometrial cancer, including aspirin prophylaxis, whereas the Snowsill *et al.*[43] model included only CRC surveillance measures. Although this is likely to reduce long-term costs in the form of surveillance, it is also likely to exclude potentially valuable benefits accrued through these practices. Second, in their base-case analysis, Snowsill *et al.*[43] modelled endometrial cancer probands entering the model at a specific age of 60 years, whereas proband entry to our model occurred at 49 years of age, thereby limiting comparison, as cost-effectiveness is sensitive to age of probands. However, a PSA was conducted by Snowsill *et al.*[43] on an alternative scenario in which probands entered their model aged 50 years, allowing more direct evaluation, and showed the probability of IHC with *MLH1* methylation testing being cost-effective in 90% of the 1000 iterations.

A similar model by Snowsill *et al.*[12] examined optimal testing strategies for Lynch syndrome in CRC probands and their relatives. This model identified IHC plus *BRAF* plus *MLH1* promoter hypermethylation testing as the most cost-effective strategy, with an ICER of £11,008 per QALY in their base-case analysis with CRC probands of mean age 58 years. Although the testing strategies are not relevant to the endometrial cancer population, the cost-effectiveness results are similar to our estimates for endometrial cancer probands. Cost-effectiveness was sensitive to the accuracy of tumour tests, the acceptance of genetic counselling and testing, and the number of relatives identified through cascade testing per proband. The effectiveness of surveillance colonoscopy and the lifetime risk of CRC for people with Lynch syndrome were also key determinants of cost-effectiveness. This mirrors our findings and highlights the need for further research to provide evidence for these parameters, both for robust inputs for use in economic modelling and to address the practical implications of implementation of testing and monitoring.

The main limitation of our economic model was the uncertainty in model input parameters (see *Uncertainties*). High-quality estimates of the effectiveness of surveillance colonoscopies are required, as the benefits of long-term effectiveness of screening for Lynch syndrome come primarily from this source. The value of offering colonoscopy in this setting needs to be ascertained so modelling in this area can be more reliable. There is even greater uncertainty about the benefits and harms of gynaecological surveillance. We have modelled only benefits, but we do not know if the benefits outweigh the harms, or even how gynaecological surveillance would be undertaken. However, our scenario analysis indicated that removing the benefits of endometrial cancer surveillance did not affect conclusions.

We also have not included any specific pathway modelling of genetic testing for somatic MMR mutations, which is sometimes used (typically in research settings) to confirm that a MMR-deficient tumour, with no constitutional pathogenic variant identified, has arisen as a result of somatic MMR mutations, rather than from Lynch syndrome. This may also be used to identify VUSs and potentially guide their long-term management. This additional layer of testing would be expected to increase total

diagnostic costs, but may provide longer-term cost savings through more directed management/surveillance practices. Furthermore, it was difficult to adequately reflect the full genetic counselling process in our model, and we modelled the whole diagnostic process as occurring within 1 year, which may not represent the potentially more elongated process in practice.

Uncertainties

There was no RCT evidence on the effect of earlier detection of Lynch syndrome and intervention on long-term outcomes, only observational cohorts at high risk of bias. In particular, little is known about the balance of benefits and harms of gynaecological cancer surveillance, and there is no consensus on which tests such surveillance entails. There was only observational evidence, rated as having a high risk of bias, for the benefit of CRC screening in individuals with Lynch syndrome, with no evidence indicating whether the test should be faecal immunochemical or colonoscopy, and what the ages of eligibility or screening intervals should be in this cohort. The EAG notes recent publication of a trial of aspirin chemoprevention.[125] The results of this 10-year follow-up support the case for prevention of CRC with aspirin among people with Lynch syndrome, demonstrating a significantly reduced hazard ratio of 0.65 (95% CI 0.43 to 0.97; $p = 0.035$) for aspirin versus placebo in the intention-to-treat population. Significance was maintained with a hazard ratio of 0.56 (95% CI 0.34 to 0.91; $p = 0.019$) and an incidence rate ratio of 0.50 (95% CI 0.31 to 0.82; $p = 0.0057$) when restricted to a per-protocol analysis of patients who achieved 2 years' intervention.

There was limited evidence on the sensitivity of the testing strategies, because of the low disease prevalence, resulting in few cases per study, and lack of follow-up of index-test negatives to ascertain whether or not they were false negatives.

Chapter 8 Conclusions

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

Implications for service provision

Although the concept of testing endometrial cancer patients for Lynch syndrome is cost-effective using the assumptions in the model, data were sparse and were judged to be at a high risk of bias. Therefore, were this to be implemented in the NHS, some pragmatic choices may have to be made on the details of the testing and treatment pathway. These include which exact testing strategy to use, as the economic model that indicated IHC followed by methylation was underpinned by data from a study using only three out of the four target proteins. Furthermore, decisions as to whether or not to offer gynaecological surveillance, and, if so, which specific tests and at what intervals, would need to be made.

There were consistent data suggesting that testing women with endometrial cancer for Lynch syndrome will identify a significant number of women with VUSs; pathways are required to manage these women.

Suggested research priorities

We suggest two research priorities:

1. There was no RCT evidence on the effect of earlier intervention on long-term outcomes, only observational cohorts, deemed to be at a high risk of bias. In particular, little is known about the balance of benefits and harms of gynaecological cancer surveillance. RCTs would provide evidence with a lower risk of bias.
2. 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 MSI testing followed by *MLH1* promoter hypermethylation testing in women with MSI-H.

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Data-sharing statement

All available data can be obtained by contacting the corresponding author.

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Appendix 1 Literature search strategies

Clinical effectiveness

The following table presents a summary of bibliographic database searches.

Database	Date of search	Number of records
MEDLINE (via Ovid)	7 August 2019	1557
EMBASE (via Ovid)	7 August 2019	2775
The Cochrane Library	8 August 2019	36
DARE and HTA Database	8 August 2019	7
Science Citation Index and Conference Proceedings Citation Index – Science (via Web of Science)	8 August 2019	1874
PROSPERO	28 August 2019	10

DARE, Database of Abstracts of Reviews of Effects.

Total number of records from database searches: 6259.

MEDLINE (via Ovid)

Database: MEDLINE(R) ALL (via Ovid).

Date range searched: 1946 to 6 August 2019.

Date searched: 7 August 2019.

Search strategy

1. uterine neoplasms/ (40,281)
2. exp endometrial neoplasms/ (20,609)
3. ((uter* or endomet* or womb) adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)).ti,ab,kf. (66,373)
4. 1 or 2 or 3 (92,254)
5. exp Colorectal Neoplasms, Hereditary Nonpolyposis/ (4407)
6. (lynch* adj3 syndrome*).ti,ab,kf. (2951)
7. ((lynch* adj3 famil*) and (cancer* or neoplasm*)).ti,ab,kf. (360)
8. (((familial or hereditary or inherit*) adj3 (colon* or colorectal*)) and (cancer or neoplasm*)).ti,ab,kf. (4589)
9. (((hereditary or familial) adj3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)).ti,ab,kf. (3199)
10. ((hereditary adj3 (cancer or neoplasm*)) and (colon* or colorectal*)).ti,ab,kf. (2886)
11. (familial adj3 (colon* or colorectal*)).ti,ab,kf. (1169)
12. HNPCC.ti,ab,kf. (2234)
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (8122)
14. (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6).ti,ab,kf. (9664)

15. (colon* or colorectal* or lynch* or HNPCC or hereditary).ti,ab,kf. (613,827)
16. 14 and 15 (4480)
17. ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) adj3 (germline or DNA* or gene* or mutation* or deficienc*)).ti,ab,kf. (8308)
18. Amsterdam criteria.ti,ab,kf. (413)
19. 13 or 16 or 17 or 18 (14,227)
20. 4 and 19 (1557)

EMBASE (via Ovid)

Database: EMBASE Classic plus EMBASE.

Date range searched: 1947 to 6 August 2019.

Date searched: 7 August 2019.

Search strategy

1. uterus cancer/or exp endometrium cancer/or uterus carcinoma/or uterus sarcoma/ (70,395)
2. ((uter* or endomet* or womb) adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)).ti,ab,kw. (93,982)
3. 1 or 2 (117,308)
4. exp hereditary nonpolyposis colorectal cancer/ (5996)
5. (lynch* adj3 syndrome*).ti,ab,kw. (5263)
6. ((lynch* adj3 famil*) and (cancer* or neoplasm*)).ti,ab,kw. (606)
7. (((familial or hereditary or inherit*) adj3 (colon* or colorectal*)) and (cancer or neoplasm*)).ti,ab,kw. (6147)
8. (((hereditary or familial) adj3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)).ti,ab,kw. (4026)
9. ((hereditary adj3 (cancer or neoplasm*)) and (colon* or colorectal*)).ti,ab,kw. (4065)
10. (familial adj3 (colon* or colorectal*)).ti,ab,kw. (1590)
11. HNPCC.ti,ab,kw. (3206)
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (12,444)
13. (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6).ti,ab,kw. (16,365)
14. (colon* or colorectal* or lynch* or HNPCC or hereditary).ti,ab,kw. (852,547)
15. 13 and 14 (7503)
16. ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) adj3 (germline or DNA* or gene* or mutation* or deficienc*)).ti,ab,kw. (12,188)
17. Amsterdam criteria.ti,ab,kw. (627)
18. 12 or 15 or 16 or 17 (21,665)
19. 3 and 18 (2775)

Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (both via Wiley Online Library)

Date searched: 8 August 2019.

Date range searched: inception to 8 August 2019.

Search strategy

#1 MeSH descriptor: [Uterine Neoplasms] this term only (708)

#2 MeSH descriptor: [Endometrial Neoplasms] explode all trees (537)

#3 ((uter* or endomet* or womb) near/4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)):ti,ab (3139)

#4 #1 or #2 or #3 (3791)

#5 MeSH descriptor: [Colorectal Neoplasms, Hereditary Nonpolyposis] explode all trees (50)

#6 (lynch* near/3 syndrome*):ti,ab (100)

#7 ((lynch* near/3 famil*) and (cancer* or neoplasm*)):ti,ab (6)

#8 (((familial or hereditary or inherit*) near/3 (colon* or colorectal*)) and (cancer or neoplasm*)):ti,ab (118)

#9 (((hereditary or familial) near/3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)):ti,ab (48)

#10 ((hereditary near/3 (cancer or neoplasm*)) and (colon* or colorectal*)):ti,ab (51)

#11 (familial near/3 (colon* or colorectal*)):ti,ab (63)

#12 HNPCC:ti,ab (43)

#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 (227)

#14 (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6):ti,ab (173)

#15 (colon* or colorectal* or lynch* or HNPCC or hereditary):ti,ab (36,712)

#16 #14 and #15 (83)

#17 ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) near/3 (germline or DNA* or gene* or mutation* or deficienc*)):ti,ab (955)

#18 "Amsterdam criteria":ti,ab (10)

#19 #13 or #16 or #17 or #18 (1175)

#20 #4 and #19 (36)

Total: 36 –

- Cochrane Reviews (Cochrane Database of Systematic Reviews): 0.
- Cochrane Protocols (Cochrane Database of Systematic Reviews): 0.
- Trials (Cochrane Central Register of Controlled Trials): 36.

Database of Abstracts of Reviews of Effects and Health Technology Assessment Database (both via Centre for Reviews and Dissemination)

Date searched: 8 August 2019.

Date range searched: inception to 8 August 2019.

Search strategy

1. MeSH DESCRIPTOR uterine neoplasms (106)
2. MeSH DESCRIPTOR endometrial neoplasms EXPLODE ALL TREES (138)
3. ((uter* or endomet* or womb) ADJ4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)) (931)

4. #1 OR #2 OR #3 (931)
5. MeSH DESCRIPTOR Colorectal Neoplasms, Hereditary Nonpolyposis EXPLODE ALL TREES (37)
6. (lynch* ADJ3 syndrome*) (20)
7. ((lynch* ADJ3 famil*) and (cancer* or neoplasm*)) (1)
8. (((familial or hereditary or inherit*) ADJ3 (colon* or colorectal*)) AND (cancer or neoplasm*)) (37)
9. (((hereditary or familial) ADJ3 (nonpolyposis or non-polyposis)) AND (colon* or colorectal*)) (50)
10. ((hereditary ADJ3 (cancer or neoplasm*)) AND (colon* or colorectal*)) (33)
11. (familial ADJ3 (colon* or colorectal*)) (4)
12. (HNPCC) (16)
13. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 (61)
14. (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) (15)
15. (colon* or colorectal* or lynch* or HNPCC or hereditary) (3070)
16. #14 AND #15 (13)
17. ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) ADJ3 (germline or DNA* or gene* or mutation* or deficienc*)) (17)
18. (Amsterdam criteria) (6)
19. #13 OR #16 OR #17 OR #18 (68)
20. #4 AND #19 (14)

Total: 14 –

- Database of Abstracts of Reviews of Effects: 1
- HTA Database: 6
- NHS EED: 7.

Science Citation Index and Conference Proceedings Citation Index – Science (via Web of Science)

Date searched: 8 August 2019.

Date range searched: inception to 8 August 2019.

Number	Hits (*n*)	Search strategy
# 16	1874	#15 AND #1
		Indexes = SCI-EXPANDED, CPCI-S Timespan = All years
# 15	17,327	#14 OR #13 OR #12 OR #9
		Indexes = SCI-EXPANDED, CPCI-S Timespan = All years
# 14	426	TS = "Amsterdam criteria"
		Indexes = SCI-EXPANDED, CPCI-S Timespan = All years
# 13	10,712	TS = (("mismatch repair*" or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) NEAR/3 (germline or DNA* or gene* or mutation* or deficienc*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = All years
# 12	5532	#11 AND #10
		Indexes = SCI-EXPANDED, CPCI-S Timespan = All years
# 11	830,834	TS = (colon* or colorectal* or lynch* or HNPCC or hereditary)
		Indexes = SCI-EXPANDED, CPCI-S Timespan = All years

Number	Hits (*n*)	Search strategy
# 10	8611	TS = (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 9	9323	#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 8	2875	TS = HNPCC *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 7	1394	TS = (familial near/3 (colon* or colorectal*)) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 6	4493	TS = (((hereditary) near/3 (cancer or neoplasm*)) and (colon* or colorectal*)) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 5	3198	TS = (((hereditary or familial) near/3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 4	4967	TS = (((familial or hereditary or inherit*) near/3 (colon* or colorectal*)) and (cancer or neoplasm*)) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 3	434	TS = ((lynch* near/3 famil*) and (cancer* or neoplasm*)) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 2	4474	TS = (lynch* near/3 syndrome*) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*
# 1	58,489	TS = ((uter* or endomet* or womb) near/4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)) *Indexes = SCI-EXPANDED, CPCI-S Timespan = All years*

PROSPERO International Prospective Register of Systematic Reviews (via Centre for Reviews and Dissemination)

Date searched: 28 August 2019.

Date range searched: inception to 8 August 2019.

#1 MeSH DESCRIPTOR uterine neoplasms (41)

#2 MeSH DESCRIPTOR endometrial neoplasms EXPLODE ALL TREES (48)

#3 ((uter* or endomet* or womb) ADJ4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)) (231)

#4 #1 OR #2 OR #3 (256)

#5 MeSH DESCRIPTOR Colorectal Neoplasms, Hereditary Nonpolyposis EXPLODE ALL TREES (13)

#6 (lynch* ADJ3 syndrome*) (28)

#7 ((lynch* ADJ3 famil*) and (cancer* or neoplasm*)) (6)

#8 (((familial or hereditary or inherit*) ADJ3 (colon* or colorectal*)) AND (cancer or neoplasm*)) (29)

#9 (((hereditary or familial) ADJ3 (nonpolyposis or non-polyposis)) AND (colon* or colorectal*)) (24)

#10 ((hereditary ADJ3 (cancer or neoplasm*)) AND (colon* or colorectal*)) (26)

#11 (familial ADJ3 (colon* or colorectal*)) (6)

#12 (HNPCC) (17)

#13 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 (53)

#14 (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) (14)

#15 (colon* or colorectal* or lynch* or HNPCC or hereditary) (1756)

#16 #14 AND #15 (14)

#17 ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) ADJ3 (germline or DNA* or gene* or mutation* or deficienc*)) (15)

#18 (Amsterdam criteria) (3)

#19 #13 OR #16 OR #17 OR #18 (60)

#20 #4 AND #19 (10)

Cost-effectiveness

The following table presents a summary of the bibliographic database searches.

Database	Date of search	Number of records
MEDLINE (via Ovid)	28 August 2019	1105
EMBASE (via Ovid)	29 August 2019	2209
NHS EED and HTA	30 August 2019	49
Science Citation Index and Conference Proceedings Citation Index – Science (via Web of Science)	30 August 2019	1267
CEA Registry	30 August 2019	30
EconPapers (RePEc)	30 August 2019	13
ScHARRHUD	30 August 2019	8

CEA, Cost-Effectiveness Analysis; RePEc, Research Papers in Economics; ScHARRHUD, School of Health and Related Research Health Utilities Database.

Total number of records from database searches: 4681.

MEDLINE (via Ovid)

Database: MEDLINE(R) ALL (via Ovid).

Date range searched: 1946 to 27 August 2019.

Date searched: 28 August 2019.

Search strategy

1. uterine neoplasms/ (40,333)
2. exp endometrial neoplasms/ (20,699)
3. ((uter* or endomet* or womb) adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)).ti,ab,kf. (66,492)
4. 1 or 2 or 3 (92,409)
5. exp Colorectal Neoplasms, Hereditary Nonpolyposis/ (4418)
6. (lynch* adj3 syndrome*).ti,ab,kf. (2974)
7. ((lynch* adj3 famil*) and (cancer* or neoplasm*)).ti,ab,kf. (363)
8. (((familial or hereditary or inherit*) adj3 (colon* or colorectal*)) and (cancer or neoplasm*)).ti,ab,kf. (4594)
9. (((hereditary or familial) adj3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)).ti,ab,kf. (3204)
10. ((hereditary adj3 (cancer or neoplasm*)) and (colon* or colorectal*)).ti,ab,kf. (2896)
11. (familial adj3 (colon* or colorectal*)).ti,ab,kf. (1169)
12. HNPCC.ti,ab,kf. (2239)
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (8147)
14. (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6).ti,ab,kf. (9697)
15. (colon* or colorectal* or lynch* or HNPCC or hereditary).ti,ab,kf. (615,131)
16. 14 and 15 (4492)
17. ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) adj3 (germline or DNA* or gene* or mutation* or deficienc*)).ti,ab,kf. (8336)
18. Amsterdam criteria.ti,ab,kf. (412)
19. 13 or 16 or 17 or 18 (14,276)
20. exp Immunohistochemistry/ (588,192)
21. (immunohistochemistry or (IHC adj3 test*)).ti,ab,kf. (178,647)
22. Microsatellite Instability/ (2896)
23. ((microsatellite adj3 instabilit*) or (msi adj3 test*)).ti,ab,kf. (7390)
24. 20 or 21 or 22 or 23 (692,837)
25. exp Economics/ (582,592)
26. exp "Costs and Cost Analysis"/ (227,344)
27. Health Status/ (77,617)
28. exp "Quality of Life"/ (180,175)
29. exp Quality-Adjusted Life Years/ (11,281)
30. (pharmacoeconomic* or pharmaco-economic* or economic* or cost* or price or prices or pricing).ti,ab,kf. (790,706)
31. (expenditure$ not energy).ti,ab,kf. (28,328)
32. (value adj1 money).ti,ab,kf. (33)
33. budget*.ti,ab,kf. (27,980)
34. (health state* or health status).ti,ab,kf. (60,417)
35. (qaly* or ICER or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form 36 or shortform 36 or SF-36 or SF36 or SF-6D or SF6D or SF-12 or SF12 or health utilities index or HUI).ti,ab,kf. (235,497)
36. (markov or time trade off or TTO or standard gamble or SG or hrql or hrqol or disabilit* or disutilit* or net benefit or contingent valuation).ti,ab,kf. (226,798)
37. (quality adj2 life).ti,ab,kf. (262,642)
38. (decision adj2 model).ti,ab,kf. (6437)
39. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).ti,ab,kf. (58,078)
40. resource*.ti,ab,kf. (312,093)
41. (well-being or wellbeing).ti,ab,kf. (82,618)
42. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 (2,166,732)
43. 19 and 42 (880)

44. 4 and 24 and 42 (277)
45. 43 or 44 (1105)

EMBASE (via Ovid)

Database: EMBASE Classic+EMBASE.

Date range searched: 1947 to 2019 Week 34.

Date searched: 29 August 2019.

Search strategy

1. uterus cancer/ (20,062)
2. exp endometrium cancer/ (48,235)
3. ((uter* or endomet* or womb) adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)).ti,ab,kw. (94,282)
4. 1 or 2 or 3 (116,223)
5. exp hereditary nonpolyposis colorectal cancer/ (6076)
6. (lynch* adj3 syndrome*).ti,ab,kw. (5337)
7. ((lynch* adj3 famil*) and (cancer* or neoplasm*)).ti,ab,kw. (615)
8. (((familial or hereditary or inherit*) adj3 (colon* or colorectal*)) and (cancer or neoplasm*)).ti,ab,kw. (6160)
9. (((hereditary or familial) adj3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)).ti,ab,kw. (4028)
10. ((hereditary adj3 (cancer or neoplasm*)) and (colon* or colorectal*)).ti,ab,kw. (4083)
11. (familial adj3 (colon* or colorectal*)).ti,ab,kw. (1593)
12. HNPCC.ti,ab,kw. (3210)
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (12,545)
14. (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6).ti,ab,kw. (16,510)
15. (colon* or colorectal* or lynch* or HNPCC or hereditary).ti,ab,kw. (855,173)
16. 14 and 15 (7564)
17. ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) adj3 (germline or DNA* or gene* or mutation* or deficienc*)).ti,ab,kw. (12,290)
18. Amsterdam criteria.ti,ab,kw. (630)
19. 13 or 16 or 17 or 18 (21,837)
20. exp immunohistochemistry/(591,817)
21. (immunohistochemistry or (IHC adj3 test*)).ti,ab,kw. (285,471)
22. microsatellite instability/(12,199)
23. ((microsatellite adj3 instabilit*) or (msi adj3 test*)).ti,ab,kw. (10,785)
24. 20 or 21 or 22 or 23 (644,776)
25. exp health economics/ (829,976)
26. exp health status/ (230,300)
27. exp "quality of life"/ (475,637)
28. exp quality adjusted life year/ (24,485)
29. (pharmacoeconomic* or pharmaco-economic* or economic* or cost* or price or prices or pricing).ti,ab,kw. (1,044,110)
30. (expenditure* not energy).ti,ab,kw. (39,410)
31. (value adj2 money).ti,ab,kw. (2333)
32. budget*.ti,ab,kw. (37,547)
33. (health state* or health status).tw. (79,129)
34. (qaly* or ICER or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form 36 or shortform 36 or SF-36 or SF36 or SF-6D or SF6D or SF-12 or SF12 or health utilities index or HUI).ti,ab,kw. (342,112)

35. (markov or time trade off or TTO or standard gamble or SG or hrql or hrqol or disabilit* or disutilit* or net benefit or contingent valuation).ti,ab,kw. (331,686)
36. (quality adj2 life).tw. (411,142)
37. (decision adj2 model).tw. (9764)
38. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw. (83,448)
39. resource*.ti,ab,kw. (401,756)
40. (well-being or wellbeing).tw. (107,606)
41. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (3,041,975)
42. 19 and 41 (1824)
43. 4 and 24 and 41 (541)
44. 42 or 43 (2209)

NHS Economic Evaluation Database (via the Centre for Reviews and Disseminations)/ Health Technology Assessment database (via the Centre for Reviews and Disseminations)

Date searched: 30 August 2019.

Date range searched: inception to 8 August 2019.

Search strategy

1. MeSH DESCRIPTOR uterine neoplasms (106)
2. MeSH DESCRIPTOR endometrial neoplasms EXPLODE ALL TREES (138)
3. ((uter* or endomet* or womb) ADJ4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)) (931)
4. #1 OR #2 OR #3 (931)
5. MeSH DESCRIPTOR Colorectal Neoplasms, Hereditary Nonpolyposis EXPLODE ALL TREES (37)
6. (lynch* ADJ3 syndrome*) (20)
7. ((lynch* ADJ3 famil*) and (cancer* or neoplasm*)) (1)
8. (((familial or hereditary or inherit*) ADJ3 (colon* or colorectal*)) AND (cancer or neoplasm*)) (37)
9. (((hereditary or familial) ADJ3 (nonpolyposis or non-polyposis)) AND (colon* or colorectal*)) (50)
10. ((hereditary ADJ3 (cancer or neoplasm*)) AND (colon* or colorectal*)) (33)
11. (familial ADJ3 (colon* or colorectal*)) (4)
12. (HNPCC) (16)
13. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 (61)
14. (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) (15)
15. (colon* or colorectal* or lynch* or HNPCC or hereditary) (3070)
16. #14 AND #15 (13)
17. ((mismatch repair* or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) ADJ3 (germline or DNA* or gene* or mutation* or deficienc*)) (17)
18. (Amsterdam criteria) (6)
19. #13 OR #16 OR #17 OR #18 (68)
20. MeSH DESCRIPTOR Immunohistochemistry EXPLODE ALL TREES (248)
21. ((immunohistochemistry or (IHC adj3 test*))) (123)
22. MeSH DESCRIPTOR Microsatellite Instability (8)
23. (((microsatellite adj3 instabilit*) or (msi adj3 test*))) (22)
24. #20 OR #21 OR #22 OR #23 (294)
25. #4 AND #24 (15)
26. #19 OR #25 (75)
27. (#26) IN NHSEED, HTA (49)

HTA Database: 22.

NHS EED: 27.

Science Citation Index and Conference Proceedings Citation Index – Science (via Web of Science)

Date searched: 30 August 2019.

Date range searched: inception to 8 August 2019.

Number	Hits (*n*)	Search strategy
# 22	1267	#21 AND #20
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 21	3,347,032	TS = ("quality of life" or qol or hrql or hrqol or ("quality adjusted life" NEAR/0 year*) or qaly* or icer or cost* or economic* or pharmacoeconomic* or pharmaco-economic* or price or prices or pricing or (expenditure* not energy) or (value NEAR/1 money) or budget* or euro-qol or utilit* or disutilit* or (net NEAR/0 benefit*) or (contingent NEAR/0 valuation*) or euroqol or "euro qol" or eq5d or eq-5d or "short-form 36" or "shortform 36" or sf-36 or sf36 or sf-6d or sf6d or sf-12 or sf12 or "health utilities index" or hui or (time NEAR/0 trade*) or tto or "standard gamble" or sg or markov or (decision NEAR/1 model*) or (visual NEAR/0 analog*) or "discrete choice" or ((health* NEAR/0 year*) NEAR/0 equivalen*) or (health NEAR/0 stat*) or (willing* NEAR/1 pay) or resource* or wellbeing or well-being)
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 20	21,297	#19 OR #15
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 19	4936	#18 AND #1
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 18	203,352	#17 OR #16
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 17	14,378	TS = ((microsatellite NEAR/3 instabilit*) or (msi NEAR/3 test*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 16	190,931	TS = (immunohistochemistry or (IHC NEAR/3 test*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 15	17,441	#14 OR #13 OR #12 OR #9
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 14	426	TS = "Amsterdam criteria"
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 13	10,788	TS = (("mismatch repair*" or MMR or EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) NEAR/3 (germline or DNA* or gene* or mutation* or deficienc*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 12	5549	#11 AND #10
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 11	833,058	TS = (colon* or colorectal* or lynch* or HNPCC or hereditary)
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 10	8655	TS = (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6)
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 9	9375	#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019

Number	Hits (*n*)	Search strategy
# 8	2876	TS = HNPCC
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 7	1399	TS = (familial near/3 (colon* or colorectal*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 6	4501	TS = (((hereditary) near/3 (cancer or neoplasm*)) and (colon* or colorectal*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 5	3203	TS = (((hereditary or familial) near/3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 4	4977	TS = (((familial or hereditary or inherit*) near/3 (colon* or colorectal*)) and (cancer or neoplasm*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 3	439	TS = ((lynch* near/3 famil*) and (cancer* or neoplasm*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 2	4520	TS = (lynch* near/3 syndrome*)
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019
# 1	58,807	TS = ((uter* or endomet* or womb) near/4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*))
		Indexes = SCI-EXPANDED, CPCI-S Timespan = 1900–2019

Cost-Effectiveness Analysis Registry

Date searched: 30 August 2019.

Date range searched: inception to 8 August 2019.

- Basic search: Methods: Lynch Syndrome (10)
- Basic search: Methods: hereditary non-polyposis (1) (0 unique)
- Basic search: Methods: Endometrial (24) (20 unique)

Total: 30.

EconPapers (Research Papers in Economics)

Date searched: 30 August 2019.

Date range searched: inception to 8 August 2019.

"lynch syndrome" OR "hereditary non-polyposis" OR "hereditary nonpolyposis" OR HNPCC OR "familial non-polyposis" OR "familial nonpolyposis" OR "familial colorectal" OR "hereditary colorectal" OR "familial colon" OR "hereditary colon" OR (("mismatch repair" or MMR or EPCAM* or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6) AND (germline or DNA or gene or genetic or genetics or mutation* or deficienc*)) OR "Amsterdam criteria" OR ((endometri* OR uter* OR womb) AND (microsatellite OR MSI OR immunohistochemistry OR IHC)) (13)

School of Health and Related Research Health Utilities Database

Date searched: 30 August 2019.

Date range searched: inception to 8 August 2019.

(lynch* OR familial OR hereditary OR mismatch repair or MMR or EPCAM* or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6 or amsterdam criteria) OR ((endometri* OR uter* OR womb) and (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)) (8)

Appendix 2 Data extraction and quality appraisal forms

Data extraction form for clinical effectiveness studies

Name of first reviewer: *Name of second reviewer:*

Study details	
Study ID (Endnote ref)	
First author surname and year of publication	
Country	
Study design	
Study setting	
Number of centres	
Time period/study duration	
Follow up period	
Funding	
Competing interests	
Answers which part of interest 1. All 2. More than 10% don't get reference standard 3. Concordance only 4. 2 cancers	
Aim of the study	
Description of study format (study design/set up)	
Patient selection	
Inclusion criteria:	
Exclusion criteria:	

Study flow	
Item	
Number of people screened for eligibility	
Number of eligible people	
Number of people included in study	
People excluded from the study, number and reason(s)	
Strategies the study relates to (1-10)	

Baseline characteristics	
Item	
Age mean (SD) Median (range)	
Ethnicity	
Any previous/concurrent cancers? Type No. (%)	
Any information regarding relatives and their history	
Any people included with known lynch syndrome	
Comments	

Testing methods	
Tumour testing	
IHC	
Age at specimens collection	
Method of IHC testing	
List proteins IHC performed on (e.g. MLH1, MSH2, MSH6, PMS2)	
Description of how positive and negative staining has been defined	
Description of quality assurance (name guidance used)	
Test undertaken blind to other tests?	
MSI	
MSI primers used	
Method of MSI testing	
Source for control tissue (e.g. blood/normal endometrium tissue from patient, pooled normal tissue)	
Markers (specify which markers were used, e.g. original Bethesda)	
Description of how MSI-High, MSI-Low and MSI-Stable were defined	

Threshold pre-specified (y/n)	
Test undertaken blind to other tests?	
Data management	
Description of quality assurance (can name guidance used)	
Testing method – MLH1 Promoter hypermethylation	
Method of MLH1 promoter hypermethylation testing	
Test undertaken blind to other tests?	
Description of quality assurance (can name guidance used)	
Germline testing	
Sequencing/next-generation sequencing	
Where DNA obtained from	
Genes analysed	
Method of germline testing (e.g. how DNA extracted, equipment used)	
Test undertaken blind to other tests?	
Description of quality assurance (can name guidance used)	

MLPA	
Where DNA obtained from	
Genes analysed	
Method of germline testing	
Test undertaken blind to other tests?	
Description of quality assurance (can name guidance used)	
Other eligible reference standards (array-based comparative genomic hybridization or long-range PCR, specify which)	
Where DNA obtained from	
Genes analysed	
Method of germline testing	
Test undertaken blind to other tests?	
Description of quality assurance (can name guidance used)	
MLH1 Promoter hypermethylation testing	**As a reference standard test, in non-tumour tissue. Not an official reference standard!**
Where DNA obtained from	
Method of germline testing	

Test undertaken blind to other tests?	
Description of quality assurance (can name guidance used)	

Number receiving index test(s) and reference standard(s)	
Number receiving IHC	
Number excluded from IHC, with reason(s)	
Number receiving MSI	
Number excluded from MSI testing, with reason(s)	
Number receiving MLH1 promoter hypermethylation testing	
Number excluded from MLH1 promoter hypermethylation testing, with reason(s)	
Number receiving sequencing (specify if sequencing/next-generation sequencing)	
Number excluded from sequencing, with reason(s) ***Make a note of the number refusing germline testing**	
Number receiving MLPA	
Number excluded from MLPA, with reason(s)	

Number receiving (specify other applicable reference standard here)	
Number excluded from (other reference standard), with reason(s)	

Outcomes – whole sample/complete testing strategy	
Provide brief description of testing strategy that paper provides results for:	
Outcome	
Lynch diagnoses, n/N (%)	
TP	
TN	
FP	
FN	
Sensitivity, % (95% CI)	
Specificity, % (95% CI)	
PPV, % (95% CI)	
NPV, % (95% CI)	
Likelihood ratios	
Diagnostic odds ratios	
ROC curves	
Test failures, n/N (%)	
Indeterminate results, n/N (%)	
Time from index test given to test result	
Time from test (specify) given to diagnosis	

Concordance between IHC and MSI • n/N (%) agreement/concordance • n/N (%) disagreement/discordance • Kappa (specify type, e.g. unweighted)	
Types/frequencies of Lynch syndrome genetic mutations (MLH1, MSH2, MSH6, PMS2)	
Other Lynch-like variants, n	
Paper definition (e.g. variants of unknown clinical significance, presumed Lynch)	
Characteristics of other Lynch syndrome variants (e.g. family history, IHC results and discordant cases between the two index tests)	
Notes/comments (anything at all, but make a note if paper reports on use of more than one MSI panel)	

Outcomes – whole sample/testing strategy using few than the standard 4 proteins (any combination – repeat table as required)	
(Specify which proteins included in IHC)	
Outcome	
Lynch diagnoses, n/N (%)	
TP	
TN	
FP	
FN	
Sensitivity, % (95% CI)	
Specificity, % (95% CI)	
PPV, % (95% CI)	
NPV, % (95% CI)	
Likelihood ratios	
Diagnostic odds ratios	
ROC curves	
Test failures, n/N (%)	
Indeterminate results, n/N (%)	Indeterminate results, n/N (%)
Time from index test given to test result	
Time from test (specify) given to diagnosis	
Concordance between IHC and MSI • n/N (%) agreement/concordance • n/N (%) disagreement/discordance • Kappa (specify type, e.g. unweighted)	
Characteristics of discordant cases	

Types/frequencies of Lynch syndrome genetic mutations (MLH1, MSH2, MSH6, PMS2)	
Other Lynch-like variants, n	
Paper definition (e.g. variants of unknown clinical significance, presumed Lynch)	
Characteristics of other Lynch syndrome variants (e.g. family history, IHC results and discordant cases between the two index tests)	
Notes/comments	

Outcomes - whole sample/pre-specified subgroups				
Outcome	Age subgroups		Prior LS-cancer subgroup	
	<70	>70	Prior LS cancer	No prior LS cancer
Lynch diagnoses, n/N (%)				
TP				
TN				
FP				
FN				
Sensitivity, % (95% CI)				
Specificity, % (95% CI)				
PPV, % (95% CI)				
NPV, % (95% CI)				

Likelihood ratios				
Diagnostic odds ratios				
ROC curves				
Test failures, n/N (%)				
Indeterminate results, n/N (%)				
Time from index test given to test result				
Time from test (specify) given to diagnosis				
IHC/MSI concordance • n/N (%) agreement/concordance • n/N (%) disagreement/discordance • Kappa (specify type, e.g. unweighted)				
Other Lynch-like variants, n				
Paper definition (e.g. variants of unknown clinical significance, presumed Lynch)				
Characteristics of other Lynch syndrome variants (e.g. family history, IHC results and discordant cases between the two index tests)				
Notes/comments				

Authors' comments & conclusion
Reviewer's comments & conclusion

Quality appraisal tools for clinical effectiveness studies

QUADAS-2 tool reproduced with permission from the University of Bristol.[35]

First author surname and year of publication:

Name of first reviewer: *Name of second reviewer:*

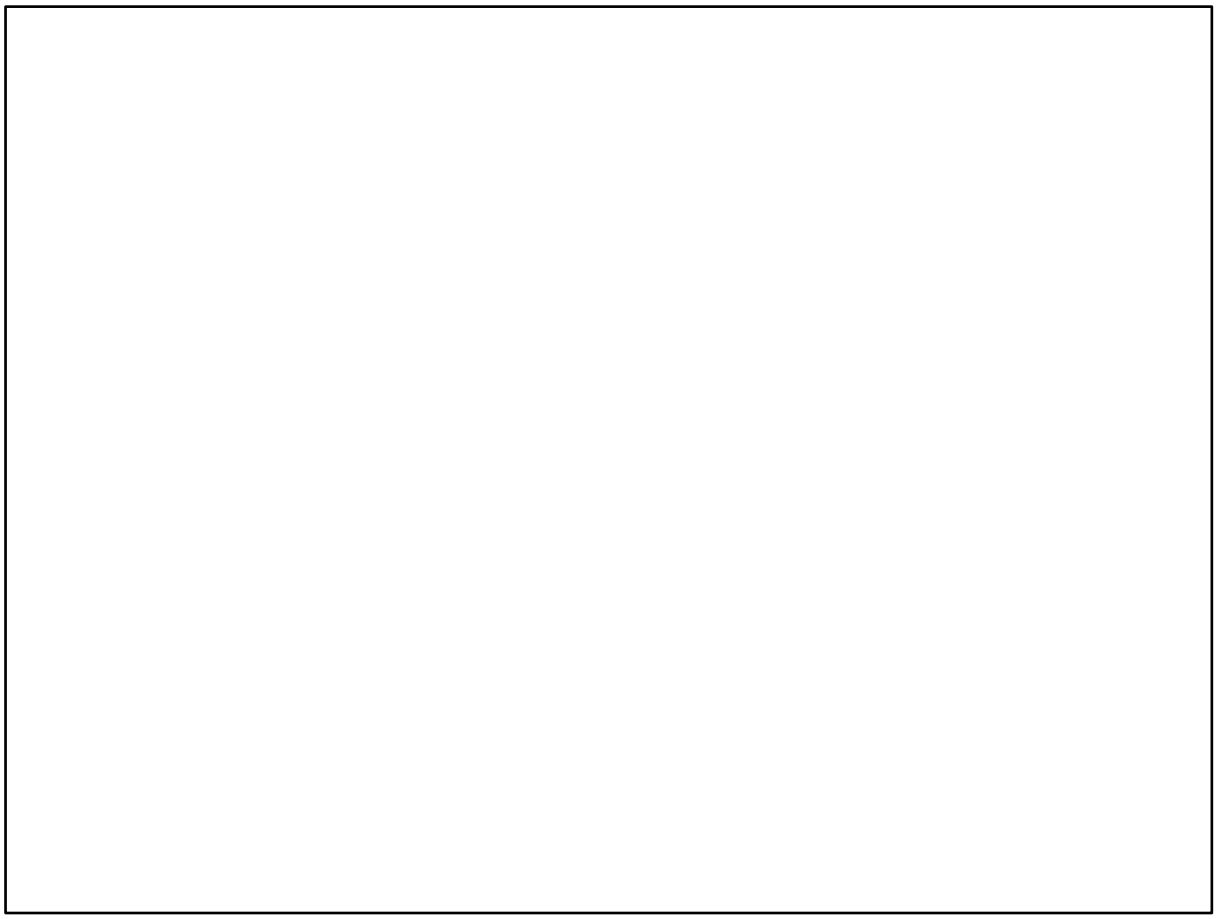
Date completed: *Date completed:*

Phase 1: State the review question:

What are the test accuracy, test failure rates, and time to diagnosis of IHC and MSI-based strategies for detecting Lynch syndrome in people who have a diagnosis of endometrial cancer?

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Reference standard and target condition:

Phase 2: Draw a flow diagram for the primary study



Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection:	
+ Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear
+ Was a case-control design avoided?	Yes/No/Unclear
+ Did the study avoid inappropriate exclusions?	Yes/No/Unclear
Could the selection of patients have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
Is there concern that the included patients do not match the review question?	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 2: INDEX TEST(S) **If more than one index test was used, please complete for each test.** **A. Risk of Bias**	
Describe the index test and how it was conducted and interpreted:	
+ Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/No/Unclear
+ Were thresholds pre-specified?	Yes/No/Unclear
+ Were quality assurances measures in place?	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 3: REFERENCE STANDARD **If more than one reference standard was used, please complete for each test.** **A. Risk of Bias**	
Describe the reference standard and how it was conducted and interpreted:	
+ Is the reference standard likely to correctly classify the target condition?	Yes/No/Unclear
+ Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 4: FLOW AND TIMING **A. Risk of Bias**	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):	
Describe the time interval and any intervention between index tests(s) and reference standard:	
+ Did all patients receive a reference standard?	Yes/No/Unclear
+ Did all patients receive the same reference standard?	Yes/No/Unclear
+ Were all patients included in the analysis?	Yes/No/Unclear
Could the patient flow have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**

DOMAIN 5: ROLE OF SPONSOR **A. Risk of Bias**	
+ Did the funding source/sponsor play no role in design of study, interpretation of results and publication?	Yes/No/Unclear
Could the funding source have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**

Modified QUADAS-2 and guidance notes

Parts of this section have been reproduced with permission from the University of Bristol.[36]

For each of the domains, risk of bias should be rated as 'low' if all signaling questions are answered with 'yes'. If one or more signaling question is answered with 'no' the risk of bias should be rated as 'high'. If none of the signaling question is answered 'no' and at least one question is answered with 'unclear', the risk of bias should be judged 'unclear'.

Domain 1: Patient selection

A. Risk of bias

Guidance:

Was a consecutive or random sample of people with endometrial cancer enrolled?

This question should only be answered 'yes' if the study clearly states that people with endometrial cancer were recruited consecutively or randomly. This question should be answered 'no' if the study clearly states that people with endometrial cancer were not recruited consecutively or randomly.

Was a case-control design avoided?

We would expect prospective cohort designs. Therefore, if the study is a case-control study this question should be answered with 'no'.

Did the study avoid inappropriate exclusions?

If the study excludes potential participants inappropriately (e.g. because they are difficult to diagnose, have had a previous or have a synchronous malignancy, or because of their age) or if >10% of participants are excluded either with or without specifying reasons, the exclusions should be considered as inappropriate. This cut-off has been determined pragmatically.

B. Concerns regarding applicability

Guidance:

For applicability concerns to be low, the study participants should be comparable to the eligible UK population (e.g. in terms of age range and ethnicity). If testing for Lynch syndrome in people with endometrial cancer is introduced in the UK, no age restrictions are

anticipated. Therefore, any study that limits participants by age will be considered to have high applicability concerns.

The setting of the study might have an impact on the applicability of the study results to general practice in terms of feasibility, if the equipment or standards of the study setting are unlikely to be met by the routine laboratory carrying out the tests in clinical practice in the UK. Some of the technologies used in the studies might not be feasible to be carried out in routine laboratories. It needs to be decided how applicable the results of these studies are to routine practice but also whether the index test is likely to be carried out in routine laboratories or in a few specialised centers.

Domain 2: Index test

The main sources of bias introduced by conducting and interpreting the index test are blinding, defining the threshold, the subjectivity of tests, and lack of quality assurance. If the reference standard is carried out before the index test (e.g. in case-control studies) it is important to blind personnel to the results of the reference standard. The QUADAS-2 tool requires a threshold to be pre-specified in the methods in order to avoid adjustment of the threshold according to the test outcome. There is some subjectivity involved in interpreting immunohistochemistry results. Tumours that show an absence of nuclear staining are rated as being 'negative' for the expression of the particular protein(s). Tumours that show nuclear staining are rated as being 'positive' for the expression of the particular protein(s). However, the amount and intensity of staining is important, and different studies have used different amounts and intensity of staining to indicate positive/negative expression of proteins. Factors that can affect the conduct of testing and accuracy of interpretation include pathologist experience, adequacy of biopsy sample (tumour content of >30% has been suggested for MSI and MHL1 promoter hypermethylation testing, e.g. to avoid false negative results), and the type of control sample (e.g. blood or normal tissue from matched-control).

A. Risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

The studies need to report blinding clearly in order to answer this question with 'yes'.

Were thresholds pre-specified?

For this question to be answered 'yes' the study needs to mention the threshold used (e.g. microsatellite instability-based testing rated as 'positive' if 30% or more microsatellite markers show instability; immunohistochemistry rated as negative if unequivocal absence of staining or if <10% of the tumor is stained) and clearly state that it was specified before the start of the study. If the study reports adjustment to the threshold and reports results according to adjusted thresholds this question should be answered with 'no'.

Were quality assurances measures in place?

For this question to be answered 'yes' studies should indicate that the laboratories performing the index tests participate in an accredited quality assessment/control scheme, e.g. UK-National External Quality Assessment Scheme, Nordic immunohistochemical Quality Control, Clinical Laboratory Improvement Amendments programme. This question should be answered 'no' for studies that do not mention quality assurance being in place.

B. Concerns about applicability

Concerns about applicability will be low for studies that conduct and interpret index tests in accordance to best practice guidelines and via laboratories that are participating in quality assurance programmes. Applicability concerns will be high for studies not adhering to these standards, for example those that use experimental/research-only methods for index testing.

Domain 3: Reference standard

There is no single test that is used to identify all cases of Lynch syndrome. Lynch syndrome is diagnosed on the basis of constitutional mutations (i.e. mutations that are present in every cell) in MMR genes. This involves sequencing to detect point mutation, small insertions or deletions in these genes, and techniques such as multiplex ligation-dependent probe amplification to detect larger structural changes (i.e. deletions, duplications or rearrangements) to genetic sequences that could be missed by sequencing alone.

A. Risk of bias

Is the reference standard likely to correctly classify the target condition?

This question will be answered with 'yes' for studies that use (1) sequencing to detect point mutations in combination with (2) multiplex ligation-dependent probe amplification, next-generation copy number, long-range PCR or targeted array comparative genome hybridisation to detect larger rearrangements or for dosage analysis. The process of conducting testing for constitutional mutations and interpretation of mutations should be carried out in accordance to best practice guidelines (e.g. Association for Clinical Genetic Services Best Practice Guidelines for Genetic Testing and Diagnosis of Lynch Syndrome, American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories) in appropriately accredited laboratories (e.g. according to the UK Accreditation Service, the Clinical Laboratory Improvement Amendments). If studies use other reference standards or do not use methods to detect both point mutations and detect larger structural abnormalities together the question should be answered as 'no'. If studies do not report the testing standard performed and the accreditation of the testing laboratories, n the question should be answered as 'unclear.

Were the reference standard results interpreted without knowledge of the results of the index test?

This question should be answered with 'yes' if blinding of the index result is explicitly stated.

B. Concerns about applicability

Applicability concerns for the reference standard will be low if Lynch syndrome is diagnosed by germline testing for constitutional mutations in MMR genes by sequencing (as a minimum). It will be high if any other non-applicable reference standard (see protocol) is used (in the absence of sequencing), or if >10% of those reported as having Lynch syndrome have genetic variants of unknown clinical significance, Lynch-like syndrome, or 'presumed' Lynch syndrome (other terms are used and need to be assessed on a case-by-case basis) and their data cannot be excluded from our analyses. This threshold has been determined pragmatically.

Domain 4: Flow and Timing

A. Risk of bias

Did all participants receive a reference standard?

This question can only be answer with 'yes' if the all participants undergo germline testing using at least one of the reference standards mentioned above. The question should be answered with 'unclear' if the study provides no information on how controls were identified in case-control studies and risk of bias should be classed as 'high'.

Did all participants receive the same reference standard?

This question should be answered with 'no' if people received different reference standards, including if people with a positive tumour test result received a different reference standard to people with a negative tumour test result. This question should be answered with 'unclear' if a list of reference standards is given but no report is made of which people received which reference standard(s).

Were all participants included in the analysis?

If inconclusive or intermediate results or participants lost to follow up are not considered in the analysis the question should be answered with 'no' and the risk of bias considered 'high'. If studies report a clinical experience and base test accuracy estimates on interim results and not all people were followed up, the question should be answered with 'no' and the risk of bias should be classed as 'high'.

Domain 5: Role of sponsor

Studies that are sponsored by companies that manufacture the index tests might be biased if the company has influence on the study design, conduct, interpretation of results and decision to publish.

A. Risk of bias

Did the funding source/sponsor play no role in the design of study, interpretation of results, and publication?

The study needs to clearly state that sponsors played no role in order to answer this question with ’yes’. Equally, to answer the question with ‘no’ the study needs to clearly state sponsor involvement.

Data extraction for economic evaluation studies

Date:

Study ID:

Name of first reviewer:

Name of second reviewer:

Table X:

Study details	
Study title	
First author	
Co-authors	
Source of publication Journal yy;vol(issue):pp	
Language	
Publication type	
Inclusion criteria/study eligibility/PICOS	
Population	
Intervention(s)	
Comparator(s)	
Outcome(s)	
Study design	
Methods	
Target population and subgroups	
Setting and location	
Study perspective	
Comparators	
Time horizon	
Discount rate	
Outcomes	
Measurement of effectiveness	

Measurement and valuation of preference based outcomes	
Resource use and costs	
Currency, price date and conversion	
Model type	
Assumptions	
Results	
Study parameters	
Incremental costs and outcomes	
Characterising uncertainty	
Discussion	
Study findings	
Limitations	
Generalisability	
Other	
Source of funding	
Conflicts of interest	
Comments	
Authors conclusion	
Reviewer's conclusion	

Assessment	Studies				
Title					
Abstract					
Introduction					
Background and objectives					
Methods					
Target population and subgroups					
Setting and location					
Study perspective					
Comparators					
Time horizon					
Discount rate					
Choice of health outcomes					
Measurement of effectiveness					
Measurement and valuation of preference-based outcomes					
Estimating resources and costs					
Currency, price date, and conversion					
Choice of model					
Assumptions					
Analytical methods					

Assessment	Studies				
Results					
Study parameters					
Incremental costs and outcomes					
Characterising uncertainty					
Discussion					
Study findings					
Limitations					
Generalizability					
Other					
Source of funding					
Conflicts of interest					

Philips' criteria		Studies			
Structure					
1.	Is there a clear statement of the decision problem?				
2.	Is the objective of the model specified and consistent with the stated decision problem?				
3.	Is the primary decision maker specified?				
4.	Is the perspective of the model stated clearly?				
5.	Are the model inputs consistent with the stated perspective?				
6.	Has the scope of the model been stated and justified?				
7.	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?				
8.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?				
9.	Are the sources of the data used to develop the structure of the model specified?				
10.	Are the causal relationships described by the model structure justified appropriately?				
11.	Are the structural assumptions transparent and justified?				
12.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?				
13.	Is there a clear definition of the options under evaluation?				

Philips' criteria		Studies			
14.	Have all feasible and practical options been evaluated?				
15.	Is there justification for the exclusion of feasible options?				
16.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?				
17.	Is the time horizon of the model sufficient to reflect all important differences between the options?				
18.	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?				
19.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?				
20.	Is the cycle length defined and justified in terms of the natural history of disease?				
21.	Are the data identification methods transparent and appropriate given the objectives of the model?				
22.	Where choices have been made between data sources are these justified appropriately?				
23.	Has particular attention been paid to identifying data for the important parameters of the model?				
24.	Has the quality of the data been assessed appropriately?				

Philips' criteria		Studies			
25.	Where expert opinion has been used are the methods described and justified?				
26.	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?				
27.	Is the choice of baseline data described and justified?				
28.	Are transition probabilities calculated appropriately?				
29.	Has a half-cycle correction been applied to both costs and outcomes?				
30.	If not, has the omission been justified?				
31.	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?				
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?				
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?				
34.	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?				
35.	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis				
36.	Are the costs incorporated into the model justified?				
37.	Has the source for all costs been described?				
38.	Have discount rates been described and justified given the target decision maker?				

Philips' criteria		Studies			
39.	Are the utilities incorporated into the model appropriate?				
40.	Is the source of utility weights referenced?				
41.	Are the methods of derivation for the utility weights justified?				
42.	Have all data incorporated into the model been described and referenced in sufficient detail?				
43.	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)				
44.	Is the process of data incorporation transparent?				
45.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?				
46.	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?				
47.	Have the four principal types of uncertainty been addressed?				
48.	If not, has the omission of particular forms of uncertainty been justified?				
49.	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?				
50.	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?				
51.	Has heterogeneity been dealt with by running the model separately for different sub-groups?				

Philips' criteria		Studies			
52.	Are the methods of assessment of parameter uncertainty appropriate?				
53.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?				
54.	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?				
55.	Are any counterintuitive results from the model explained and justified?				
56.	If the model has been calibrated against independent data, have any differences been explained and justified?				
57.	Have the results been compared with those of previous models and any differences in results explained?				
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear					

Appendix 3 Excluded studies with rationale

Reference	Reason for exclusion
Question 1	
1. Abbaszadegan MR, Asadzadeh H, Rastin F, Dadkhah E. Microsatellite instability in young women with endometrioid type endometrial cancer. *Iran J Public Health* 2009;**38**:24–30	No reference standard
2. Adams R, Geiersbach K, Tripp S, Samowitz W. Unusual immunohistochemistry staining patterns encountered in cancers screened for Lynch syndrome. *Lab Invest* 2015;**1**:144A	Not enough information to quality appraise – abstract
3. Adán-Merino L, Aldeguer-Martínez M, Alonso-Gamarra E, Valentín-Gómez F, Zaera-De la Fuente C, Martín-Chávarri S. Diagnosis and clinical behavior in patients with Lynch-like syndrome. *Rev Gastroenterol Mex* 2018;**83**:470–4	Wrong population
4. Adar T, Rodgers LH, Shannon KM, Yoshida M, Ma T, Mattia A, *et al.* Enhancing the identification of Lynch syndrome through universal screening of both endometrial and colon cancers. *Gastroenterology* 2017;**152**(Suppl. 1):S178	Not enough information to quality appraise – abstract
5. Affolter K, Wilson A, Samowitz W, Geiersbach K. Base pair changes in assessing microsatellite instability and correlation to mismatch repair status by immunohistochemistry. *Lab Invest* 2013;**1**:141A	Not enough information to quality appraise – abstract
6. Aguirre E, Mele M, Tuset N, Velasco A, Tarragona J, Sampayo M, *et al.* Screening for Lynch syndrome among endometrial cancer patients less than 60 years. *Ann Oncol* 2016;**27**:296–312	Not enough information to quality appraise – abstract
7. Alenda C, Egoavil C, Soto JL, Castillejo A, Barbera VM, Roman MJ, *et al.* Prevalence of Lynch syndrome among unselected endometrial cancer patients. *Lab Invest* 2012;**1**:258A	Not enough information to quality appraise – abstract
8. AlHilli MM, Carr CE, Priyadarshini A, Radeva M, Marquard J. Predictors of Lynch syndrome and clinical outcomes among universally screened endometrial cancer patients. *Gynecol Oncol* 2017;**145**(Suppl. 1):92	Not enough information to quality appraise – abstract
9. Al-Nourhji O, Zhang G, Zou Y, Biscotti CV, Rose P, Yang B. PD-L1 frequently expressed in endometrial carcinoma associated with mismatch-repair deficiency. *Lab Invest* 2017;**97**(Suppl. 1):273A	Not enough information to quality appraise – abstract
10. Andrade C, Mengatto M, Vieira M, Cadamuro M, Palmero E, Oliveira J, *et al.* Screening endometrial cancer for Lynch syndrome in a Brazilian public health care system cancer center. *Gynecol Oncol* 2013;**130**:e100	Not enough information to quality appraise – abstract
11. Anonymous. Uterine cancer could be harbinger of other cancers. An inherited mutation – Lynch syndrome – may lead to higher risk. *Duke Med Health News* 2006;**12**:9–10	Editorial
12. Anonymous. Abstracts presented for the 40th annual meeting of the Society of Gynecologic Oncologists. *Gynecol Oncol* 2009;**112**(Suppl. 1)	Not enough information to quality appraise – abstract
13. Anonymous. StatBite: Lynch syndrome increases the risk of various cancers. *J Natl Cancer Inst* 2010;**102**:1383	Not enough information to quality appraise – abstract

Reference	Reason for exclusion
14. Avila M, Alvarado M, Axtell AE, Goff J, Funston JR, Lentz SE. Universal immunohistochemistry testing in endometrial cancer tumors maximizes Lynch syndrome identification among affected individuals. *Gynecol Oncol* 2019;**154**:e13	Not enough information to quality appraise – abstract
15. Ayme A, Arcioni S, Membrez V, Feilchenfeldt J, Fonteneau L, Viassolo V, *et al.* Systematic screening for Lynch syndrome in a cohort of colorectal and endometrial cancer patients in Switzerland: the SYSSYL study. *Fam Cancer* 2017;**16**(1 Suppl. 1):S116	Not enough information to quality appraise – abstract
16. Backes FJ, Hampel H, Backes KA, Vaccarello L, Lewandowski G, Bell JA, *et al.* Are prediction models for Lynch syndrome valid for probands with endometrial cancer? *Fam Cancer* 2009;**8**:483–7	Not test accuracy
17. Backman AS, Walton-Bernstedt S, Bjork J. A large proportion of Lynch syndrome patients still undergo genetic screening first in connection with their diagnosis of cancer. *Gastroenterology* 2016;**1**:S364	Not enough information to quality appraise – abstract
18. Baker T, Deihimi S, Martin LP, Hall MJ, Hampel H, El-Deiry WS. Variable DNA mismatch repair-associated gene profiles in colorectal versus uterine cancers. *J Clin Oncol* 2017;**35**(Suppl. 1)	Not enough information to quality appraise – abstract
19. Ballester VR, Carrera R, Blazquez C, Casalots A, Ramos MC, Vazquez J, *et al.* Universal screening for Lynch Syndrome detection. *Virchows Arch* 2016;**469**(Suppl. 1):S202	Not enough information to quality appraise – abstract
20. Banno K, Susumu N, Hirao T, Yanokura M, Hirasawa A, Aoki D, *et al.* Identification of germline MSH2 gene mutations in endometrial cancer not fulfilling the new clinical criteria for hereditary nonpolyposis colorectal cancer. *Cancer Genet Cytogenet* 2003;**146**:58–65	Ineligible reference standard
21. Banno K, Susumu N, Yanokura M, Hirao T, Iwata T, Hirasawa A, *et al.* Association of HNPCC and endometrial cancers. *Int J Clin Oncol* 2004;**9**:262–9	Review
22. Barinoff J, Lange J, Brandi C, Schulze C, Riener MO, Aulmann S, *et al.* HNPCC related endometrial carcinoma: management in the clinical routine. *Int J Gynecol Cancer* 2016;**26**(Suppl. 3):125	Not enough information to quality appraise – abstract
23. Bartley AN, Luthra R, Saraiya D, Broaddus RR. Discordance between molecular and immunohistochemical analyses for Lynch syndrome assessment. *Lab Invest* 2011;**1**:144A	Not enough information to quality appraise – abstract
24. Bartosch C, Relvas S, Jeronimo C, Lopes JM. Evaluation of mismatch repair (MMR) protein immunohistochemical expression in endometrial carcinomas. *Virchows Arch* 2013;**463**:311–12	Not enough information to quality appraise – abstract
25. Bats A, Rossi L, Buecher B, Borghese B, Douay-Hauser N, Lecuru F. Clinico-pathological characteristics of endometrial cancer in Lynch syndrome. *Int J Gynecol Cancer* 2013;**1**:73	Not enough information to quality appraise – abstract
26. Batte BA, Bruegl AS, Daniels MS, Ring KL, Dempsey KM, Djordjevic B, *et al.* Consequences of universal MSI/IHC in screening endometrial cancer patients for Lynch syndrome. *Gynecol Oncol* 2014;**134**:319–25	Authors contacted due to unclear reporting. Authors could not confirm information around testing
27. Beneder C, Vorburger SA, Balli M, Mueller MD. [Is a screening according to the Lynch syndrome meaningful for young patients with endometrium carcinoma.] *Geburtshilfe und Frauenheilkunde* 2008;**68**:431	Foreign-language paper

Reference	Reason for exclusion
28. Bennett J, Pesci A, ,Badrinarain J, Da Silva A, Oliva E. Mismatch repair protein expression in endometrioid carcinoma of the ovary: incidence and clinicopathologic associations in 77 cases. *Lab Invest* 2017;**97**(Suppl. 1):276A	Not enough information to quality appraise – abstract
29. Benshushan A, Gazit N, Goldberg Y, Peretz T, Zik A. Genetics of endometrial cancer is greater than previously estimated in the our local population. *Int J Gynecol Cancer* 2017;**27**(Suppl. 4):100	Not enough information to quality appraise – abstract
30. Billingsley CC, Cohn D, Mutch DG, Broaddus R, Ramirez N, Lankes H, *et al.* Clinical implications for MSI, *MLH1* methylation analysis and IHC in Lynch screening for endometrial cancer patients: an analysis of 940 endometrioid endometrial cancer cases from the GOG 0210 study. *Gynecol Oncol* 2015;**137**:4–5	Not enough information to quality appraise – abstract
31. Bohiltea RE, Radoi V, Turcan N, Cirstoiu MM. National genetic screening for endometrial cancer. *Gineco.eu* 2016;**12**:15–18	No primary data. Not enough information to quality appraise
32. Boyd J, Kohler MF, Berchuck A, Watson P, Lynch HT, Risinger JI. Microsatellite instability in sporadic endometrial carcinomas and those associated with HNPCC. *Am J Hum Genet* 1993;**53**:22	Not enough information to appraise – abstract
33. Brodsky AL, Lee J, Asgari S, Fehniger J, Levine DA, Pothuri B. Genetic counselor involvement with abnormal immunohistochemistry results improves genetic testing in patients with endometrial cancer. *Gynecol Oncol* 2019;**154**(Suppl. 1):282–3	Not enough information to quality appraise – abstract
34. Bruegl A, Djordjevic B, Broaddus R. Lynch syndrome screening criteria: a new approach to identifying patients at risk via clinical history and pathology (CHiP) criteria. *Gynecol Oncol* 2012;**1**:S85–6	Not enough information to quality appraise – abstract
35. Bruegl A, Djordjevic B, Fellman B, Urbauer D, Luthra R, Broaddus R. Screening by young age and family history of colon cancer misses the majority of endometrial cancer patients with Lynch syndrome. *Lab Invest* 2013;**1**:267A	Not enough information to quality appraise – abstract
36. Bruegl A, Djordjevic B, Fellman B, Urbauer D, Luthra R, Lu K, *et al.* A population-based study to evaluate SGO criteria for the identification of Lynch syndrome among endometrial cancer patients. *Gynecol Oncol* 2013;**130**:e28	Not enough information to quality appraise – abstract
37. Bruegl A, Daniels M, Broaddus RR. Does universal tissue testing provide universal answers? Clinical challenges associated with tumor screening for Lynch syndrome associated endometrial cancer. *Lab Invest* 2017;**97**(Suppl. 1):277A	Not enough information to quality appraise – abstract
38. Bruegl AS, Djordjevic B, Urbauer DL, Westin SN, Soliman PT, Lu KH, *et al.* Utility of *MLH1* methylation analysis in the clinical evaluation of Lynch syndrome in women with endometrial cancer. *Curr Pharm Des* 2014;**20**:1655–63	Not enough information to quality appraise – abstract
39. Bruegl AS, Djordjevic B, Batte B, Daniels M, Fellman B, Urbauer D, *et al.* Evaluation of clinical criteria for the identification of Lynch syndrome among unselected patients with endometrial cancer. *Cancer Prev Res* 2014;**7**:686–97	No reference standard
40. Bruegl AS, Djordjevic B, Urbauer DL, Westin SN, Soliman PT, Lu KH, *et al.* Utility of *MLH1* methylation analysis in the clinical evaluation of Lynch syndrome in women with endometrial cancer. *Curr Pharm Des* 2014;**20**:1655–63	No reference standard

Reference	Reason for exclusion
41. Bruegl AS, Djordjevic B, Westin SN, Soliman PT, Brandt AC, Daniels MS, *et al.* An alternative approach to identify women at risk for colorectal cancer. *J Clin Oncol* 2012;**30**(15 Suppl. 1)	Not enough information to quality appraise – abstract
42. Bruegl A, Westin S, Djordjevic B, Broaddus R. Common screening criteria for Lynch syndrome: who are we missing? *Gynecol Oncol* 2012;**125**:S195	Not enough information to quality appraise – abstract
43. Bruegl AS, Djordjevic B, Fellman BM, Urbauer DL, Luthra R, Lu KH. Poor performance of published clinical screening criteria for the population-based identification of endometrial cancer patients with Lynch syndrome. *Cancer Res* 2013;**73**(8 Suppl. 1). 104th annual meeting of the American Association for Cancer Research (AACR)	Not enough information to quality appraise – abstract
44. Bruegl AS, Djordjevic B, Rajyalakshmi L, Lu KH, Sun CC, Broaddus R. Cost analysis comparing universal tumor testing to clinically based criteria in the evaluation of endometrial adenocarcinomas for Lynch syndrome. *Gynecol Oncol* 2014;**1**:45	No reference standard
45. Bruegl AS, Djordjevic B, Urbauer D, Westin SN, Soliman PT, Lu KH, *et al.* Can clinical criteria reliably distinguish between sporadic and Lynch syndrome-associated endometrial carcinomas with immunohistochemical loss of MLH1? *Cancer Prev Res* 2012;**5**(Suppl. 1)	Not enough information to quality appraise – abstract
46. Bruegl AS, Ring KL, Daniels M, Fellman BM, Urbauer DL, Broaddus RR. Clinical challenges associated with universal screening for Lynch syndrome-associated endometrial cancer. *Cancer Prev Res* 2017;**10**:108–15	Abstract only. Associated full paper included
47. Buchanan DD, Clendenning M, Jayasekara H, Joo JE, Wong EM, Southey MC, *et al.* Double somatic mutations as a cause of tumor mismatch repair deficiency in population-based colorectal and endometrial cancer with Lynch-like syndrome. *Cancer Res* 2017;**77**(Suppl. 1)	Not enough information to quality appraise – abstract
48. Burks RT, Kessis TD, Cho KR, Hedrick L. Microsatellite instability in endometrial carcinoma. *Oncogene* 1994;**9**:1163–6	No reference standard. Not lynch testing
49. Busmanis I, Chew I. MSI and mucinous differentiation in uterine endometrioid carcinoma. *Virchows Arch* 2011;**1**:S230	Not enough information to quality appraise – abstract
50. Busmanis I, Lim T, Tan MH. MSI in an Asian series of primary uterine endometrioid carcinoma. *Virchows Arch* 2013;**463**:307–8	Not enough information to quality appraise – abstract
51. Cadoo KA, Tran C, DeLair D, Arnold AG, Ashraf A, Jewell EL, *et al.* Clinical characterization of DNA mismatch repair deficiency (MMR-D) in endometrial cancer (EC). *J Clin Oncol* 2016;**34**(Suppl. 15)	Not Lynch syndrome. No reference standard. Not enough information to quality appraise – abstract
52. Calkins SM, Karnezis AN, Conrad PG, Chen LM, Rabban JT. Lynch syndrome screening tests in uterine cancer patients > 50 years depends on clinical and tumor morphology criteria: evidence against universal testing. *Lab Invest* 2012;**1**:262A	Not enough information to quality appraise – abstract
53. Carvalho SD, Pardal J. Universal Lynch syndrome screening in endometrial cancer: two years of experience. *Virchows Arch* 2018;**473**(Suppl. 1):s70	Not enough information to quality appraise – abstract
54. Catasus L, Machin P, Matias-Guiu X, Prat J. Microsatellite instability in endometrial carcinomas: clinicopathologic correlations in a series of 42 cases. *Hum Pathol* 1998;**29**:1160–4	No reference standard

Reference	Reason for exclusion
55. Cederquist K, Emanuelsson M, Göransson I, Holinski-Feder E, Müller-Koch Y, Golovleva I, Grönberg H. Mutation analysis of the MLH1, MSH2 and MSH6 genes in patients with double primary cancers of the colorectum and the endometrium: a population-based study in northern Sweden. *Int J Cancer* 2004;**109**:370–6	More than 10% wrong population
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Question two	
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17. Salyer C, Lentz S, Dontsi M, Armstrong MA, Butt A, Hoodfar E, *et al.* Comparison of effectiveness of two strategies to identify Lynch syndrome in women with endometrial cancer. *Gynecol Oncol* 2019;**154**:e12–13	Intervention, comparator, outcome and study design not relevant
18. Nebgen D, Lu K, Chisholm G, Sun C, Earles T, Soletsky B, Lynch P. Lynch Syndrome – combined endometrial and colon cancer screening results. *Fam Cancer* 2019;**18**:S1–88	Participant, comparator and study design not relevant
19. Crawford R, Newcombe B, Bolton H, Ngu SF, Freeman S, Addley H, *et al. The Ten Year Experience of a Regional Specialist Gynaecology Cancer Genetics Clinic with Lynch Syndrome.* The European Society of Gynaecological Oncology 20th International Meeting, Vienna, 4–7 November 2017	Not enough information to quality appraise – abstract
20. Adar T, Rodgers LH, Shannon KM, Yoshida M, Ma T, Mattia A, *et al.* A tailored approach to BRAF and MLH1 methylation testing in a universal screening program for Lynch syndrome. *Mod Pathol* 2017;**30**:440–7	Participant not relevant
21. Hartnett E, Stuckey A, Danilack V, McCourt C. Evaluation of universal immunohistochemistry screening for diagnosing Lynch syndrome in endometrial cancer patients at a tertiary care center. *Gynecol Oncol* 2015;**139**:599	Comparator, outcomes and study design not relevant
22. Mutch DG, Powell MA, Schmidt A, Broaddus R, Ramirez N, Tritchler D, *et al.* Clinicopathologic features associated with defective DNA mismatch repair (MMR): a GOG 0210 cohort study of 1041 endometrioid endometrial cancer cases. *Gynecol Oncol* 2015;**137**:20–21	Intervention, comparator, study design not relevant
23. Fu L, Sheng JQ, Li XO, Jin P, Mu H, Han M, *et al.* Mismatch repair gene mutation analysis and colonoscopy surveillance in Chinese Lynch syndrome families. *Cell Oncol* 2013;**36**:225–31	Participant and study design not relevant

Reference	Reason for exclusion
24. Abstracts of the 13th International Meeting on Psychosocial Aspects of Hereditary Cancer (IMPAHC), Sydney, NSW, 7–8 March 2013. *Fam Cancer* 2013;**12**(Suppl. 1):1–22	Conference preceedings. No relevant data
25. Lu K, Chen L, Lynch H, Munsell M, Cornelison T, Boyd-Rogers S, *et al.* A prospective, multicenter randomized study of oral contraceptive versus Depo-Provera for the prevention of endometrial cancer in women with Lynch syndrome. *Gynecol Oncol* 2013;**116**:S4–5	Participant, intervention, outcome and study design not relevant
26. Wang Y, Xue F, Broaddus RR, Tao X, Xie SS, Zhu Y. Clinicopathological features in endometrial carcinoma associated with Lynch syndrome in China. *Int J Gynecol Cancer* 2009;**19**:651–6	Intervention, comparator and study design not relevant
27. Järvinen HJ. Endoscopic surveillance in hereditary nonpolyposis colorectal cancer. *Tech Gastrointest Endosc* 2006;**8**:110–13	Participant and study design not relevant
28. Macrae F. *A Randomised Double Blind Dose Non-inferiority Trial of a Daily Dose of 600 mg versus 300 mg versus 100 mg of Enteric Coated Aspirin as a Cancer Preventive in Carriers of a Germline Pathological Mismatch Repair Gene Defect. Lynch Syndrome. Project 3 in the Cancer Prevention Programme (CaPP3)*. URL: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617000804381 (accessed 2 January 2020)[98]	Participants and comparator not relevant
29. Arber N. *A Randomised Double Blind Dose Non-inferiority Trial of a Daily Dose of 600 mg Versus 300 mg Versus 100 mg of Enteric Coated Aspirin as a Cancer Preventive in Carriers of a Germline Pathological Mismatch Repair Gene Defect. Lynch Syndrome.* URL: https://clinicaltrials.gov/ct2/show/nct02497820 (accessed 2 January 2020)[99]	Participants and comparator not relevant

Appendix 4 Study characteristics of included studies

Characteristics of included clinical effectiveness studies

Study and year	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected/ unselected sample	Age (years) (range)	Ethnicity	Previous/ concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Anagnostopoulos *et al.*[51] 2017	England	Cohort (prospective and retrospective)	Hospital/ cancer registry	January 2005–September 2012	Prevalence	35	Selected	Median 45 (31–49)	NR	NR	Not extractable	MSI and IHC	Sequencing and MLPA
Backes *et al.*[52] 2009	USA	Clinical experience and prospective cohort (MMR proteins only)	Hospital and university medical centre	April 2007; end date not reported	Prevalence	140	Unselected	Mean 60.5 (30–91)	NR	13 reported, unclear whether or not from whole sample: • 5 ovarian • 1 pancreatic • 3 colon • 2 endometrial • 2 urinary tract	NR for whole sample	IHC	Large rearrangement and deletion testing. Full gene analysis and sequencing
Baldinu *et al.*[53] 2002/Strazzullo *et al.*[87] 2003	Italy	Prospective cohort	University	1989–97	Partial test accuracy and prevalence	116	Selected	Median 64 (35–88)	NR	NR	Excluded if they had first- or second-degree relatives with HNPCC	MSI and IHC	Denaturing high-performance liquid chromatography and sequencing
Berends *et al.*[54] 2003	The Netherlands	Retrospective and prospective cohort	Cancer registry	Before 1989–2000	Complete test accuracy, MSI only (MSI-H vs. MSI-L/MSS), IHC only, strategy 1, strategy 3, strategy 11, prevalence and concordance	58	Selected	Median 45 (27–49)	NR	13/38 (22.4%)	22/58 (37.9%) cancer diagnosis in first-degree relatives	MSI and IHC	DGGE and sequencing
Ring *et al.*[81] 2016	USA	Prospective cohort	Cancer centre	August 2012–14	Concordance and prevalence	203	Unselected but adult only	• Mean: 61.3 • Median: 61 (23–86)	For 381 (retrospective sample): • White 265 (70%) • African American 34 (9%) • Hispanic 66 (17%) • Asian 14 (4%) • Native American 2 (1%)	NR	NR for whole sample	MSI, IHC and *MLH1* promoter hypermethylation testing	NGS and MLPA

Study and year	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected/ unselected sample	Age (years) (range)	Ethnicity	Previous/ concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Buchanan *et al.*[56] 2014/Nagle *et al.*[76] 2018	Australia	Prospective cohort	Cancer registries	July 2005–December 2013	Test accuracy by proteins and prevalence	1459 (698 from Nagle *et al.*[76])	Selected	IHC tested, mean 61.8 (27.1–79.9)	NR	65/702 (9.3%)	First-degree relatives • CRC, *n* = 98 (14%) • Endo cancer, *n* = 36 (5.1%)	IHC and *MLH1* promoter hypermethylation testing	Unspecified germline testing and MLPA
Carnevali *et al.*[57] 2017/Libera *et al.*[68] 2017	Italy	Retrospective cohort	Hospital	1994–2014	Concordance and prevalence	88 (74 in Carnevali *et al.*[57])	Selected	Carnevali *et al.*:[57] • Mean: 51.04 • Median: 49 (27–75) Libera *et al.*:[68] NR	NR	3/74 (4%) ovarian cancer	16/61 (31.1%) met Amsterdam criteria	MSI, IHC and *MLH1* promoter hypermethylation testing	Sanger sequencing and MLPA
Chao *et al.*[58] 2019	China	Prospective cohort	Hospital	December 2017–August 2018	• Complete test accuracy, MSI only (MSI-H vs. MSI-L/MSS), IHC only, • Strategies 1, 3, 10 and 11 • Concordance and prevalence	111	Selected	• Mean: 55.7 • Median: 55 (31–82)	NR	0 – excluded	14/111 (12.6%) Amsterdam II criteria;[93] two met Bethesda criteria	IHC, MSI and *MLH1* promoter hypermethylation testing	NGS and Sanger sequencing
Dillon *et al.*[59] 2017	Lebanon	Retrospective cohort	Hospital	May 2015–December 2016	Prevalence	233	Unselected	Median 63 (30–90)	NR	NR for whole population	NR	IHC and *MLH1* promoter hypermethylation testing	NGS
Dudley *et al.*[60] 2015/ Mas-Moya *et al.*[70] 2015	USA	Prospective cohort and cross-sectional	Hospital	January 2008–May 2014	Strategy 10 and prevalence	215	Unselected	NR for whole sample	NR	NR	NR	IHC, MSI and *MLH1* promoter hypermethylation testing	Sequencing
Egoavil *et al.*[61] 2013	Spain	Retrospective cohort	Hospital	2004–9	Concordance and prevalence	173	Unselected	Mean 63.3 (29–90)	NR	• 26/173 (15%) synchronous • 23/173 history of cancer	• 38 met Bethesda criteria • 4 met Amsterdam criteria • 86 unknown • 45 no family history	MSI, IHC and *MLH1* promoter hypermethylation testing	PCR, sequencing and MLPA

Study and year	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected/ unselected sample	Age (years) (range)	Ethnicity	Previous/ concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Ferguson *et al.*[62] 2014	Canada	Prospective cohort	Hospital	July 2010–June 2011	Prevalence, strategy 11 and concordance	117	Selected	Median 61 (26–91)	NR	Excluded patient with ovarian primary tumour	• 16/61 (15.2%) met Ontario Ministry of Health • 7/61 (6.6%) Amsterdam II • 8/61 (7.6%) SGO	MSI and IHC	Sequencing and MLPA
Goodfellow *et al.*[63] 2015	USA	Prospective cohort	Hospital	2003–7	Strategy 10, concordance and prevalence	1043	Selected after 2007	Mean 62 (25–100)	• White, *n* = 848 (90.4%) • African American, *n* = 55 (5.9%) • Asian, *n* = 17 (1.8%) • Other, *n* = 7 (0.7%) • Unknown/not specified, *n* = 11 (1.2%)	NR	938/1043 (90%) had Lynch syndrome-associated cancers	MSI, IHC and *MLH1* promoter hypermethylation testing	NGS
Goodfellow *et al.*[64] 2003	USA	Prospective cohort	University hospitals	NR	Prevalence	441	Unclear	Median 64.6 (26–92)	NR	NR for whole sample	NR for whole sample	MSI and *MLH1* promoter hypermethylation testing	SSCV and sequencing
Hampel *et al.*[15] 2006	USA	Retrospective cohort	Hospital	January 1999–December 2003	Strategy 6, prevalence and concordance	543	Unselected	Mean 60.9 (17–94)	95% white	NR	NR	MSI and *MLH1* promoter hypermethylation testing	Sequencing and MLPA
Kato *et al.*[65] 2016/Takahashi *et al.*[89] 2017	Japan	Retrospective cohort	Hospital	January 2003–December 2013	Prevalence	360	Selected	Median 59 (28–89)	360/360 (100%) Asian	30/348 (8.6%) personal history of Lynch syndrome (Takahashi *et al.*[89])	• Family history of Lynch syndrome-related cancer: 147/348 (42.4%) • Family history of CRC: 42/348 (12.1%) • Family history of stomach cancer: 91/348 (26.1%) (Takahashi *et al.*[89])	IHC and *MLH1* promoter hypermethylation testing	PCR, sequencing and MLPA

Study and year	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected/ unselected sample	Age (years) (range)	Ethnicity	Previous/ concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Latham *et al.*[66] 2019	USA	Retrospective cohort	Hospital	January 2014–June 2017	Strategy 1 and prevalence	525	Unclear	Median 55–60 across all MSI groups	NR for whole sample	NR	NR	MSI and IHC	NGS
Leenen *et al.*[67] 2012	The Netherlands	Prospective cohort	Hospital/ academic medical centre	May 2007–September 2009	Prevalence	179	Selected	Median 61 (IQR 57–66)	NR	NR	NR	MSI, IHC and *MLH1* promoter hypermethylation testing	Sequencing and MLPA
Lin and Hecht[69] 2016	USA	Prospective cohort	Medical centre	July 2009–December 2013	Prevalence	76	Selected	Mean 55 (23–95)	NR	7/76 (9.2%) concurrent ovarian cancer	NR	IHC and *MLH1* promoter hypermethylation testing	NR
Lu *et al.*[16] 2007	USA	Prospective cohort	Gynaecologic oncology clinics	January 2000; end date NR	Complete test accuracy, MSI only (MSI-H vs. MSI-L/MSS), IHC only, test accuracy by proteins, strategy 1, strategy 3, strategy 4, strategy 10, strategy 11 and prevalence	100	Selected	• Mean: 41.6 • Median: 43 (24–49)	NR	12/100 (12%) • Colon, $n = 2$ • Synchronous ovarian, $n = 9$ • Brain, $n = 1$	21/100 (21%) Lynch syndrome-related cancer in at least one first-degree relative	MSI, IHC and *MLH1* promoter hypermethylation testing	Sequencing and unclear further testing for large deletions
Masuda *et al.*[71] 2012	Japan	Prospective cohort study	NR	January 2000–July 2002	Concordance	36	Selected	NR overall • LUS group: median 44.4 (34.2–54.6) • Non-LUS group: median 59.48 (55.8–63.1)	Asian	NR	One had a family history of cancer	MSI, IHC and *MLH1* promoter hypermethylation testing	NA
McConechy *et al.*[72] 2015	Canada	Retrospective cohort study	Tissue biobank repository	NR	Concordance	157	Unselected	Mean 62.6	NR	NR	NR	MSI, IHC and *MLH1* promoter hypermethylation testing	NA

Study and year	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected/ unselected sample	Age (years) (range)	Ethnicity	Previous/ concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Mercado *et al.*[73] 2012	USA	Retrospective cohort study	Hospitals	NR	Strategy 1, strategy 3 and prevalence	129	Selected	Median 63 (38–89)	• 94 (73%) white • 1 (1%) Hispanic • 1 (1%) Asian • 2 (2%) other	• 34 (27%) CRC • 6 (5%) adenoma • 33 (26%) other Lynch syndrome • 37 (29%) multiple Lynch syndrome	• 115/129 (89%) CRC • 48/129 (37%) endometrial cancer • 67 (52%) other Lynch syndrome cancer	MSI, IHC	Denaturing high-performance liquid chromatography and sequencing
Millar *et al.*[74] 1999	Canada	Retrospective cohort	Cancer registry	1971–96	Strategy 11 and prevalence	40	Selected	NR	NR	40/40 (100%) all synchronous endometrial and CRC patients	4/40 (10%) met Amsterdam criteria	MSI	SSCV then PCR and sequencing
Modica *et al.*[75] 2007	USA	Retrospective cohort	Cancer centre	1992–2003	Concordance	90	Selected	• Mean: 63.8 • Median: 63 (37–86)	NR	NR	Yes	MSI and IHC	NA
Najdawi *et al.*[77] 2017	Australia	Prospective cohort (clinical experience study)	Hospital	August 2012–December 2016	Prevalence	124	Selected	Mean 64.5 (31–93)	NR	Synchronous uterine and ovarian, 1/124 (0.8%)	NR for whole sample	IHC and *MLH1* promoter hypermethylation testing	Sequencing and MLPA
Ollikainen *et al.*[78] 2005	Finland	Cohort (retrospective and prospective)	Hospital	1986–97	Strategy 1, strategy 4, strategy 10 and prevalence	23	Selected	• Mean: 62 • Median: 61 (32–81)	NR	2/23 (9%) breast cancer	23/23 (100%) family history of endometrial cancer	MSI, IHC and *MLH1* promoter hypermethylation testing	Sequencing and MLPA
Pecorino *et al.*[79] 2017	Italy	Prospective cohort	Hospital	2007–14	Concordance	41	Selected	Mean 44.4 (32–50)	NR	Unclear	Unclear	MSI and IHC	NA
Planck *et al.*[80] 2017	Sweden	Retrospective cohort	Population-based cancer registry	1958–98	Concordance	36	Selected	Mean 47 (37–61)	NR	36/36 (100%) adenocarcinoma of the large bowel and uterine corpus	NR	MSI and IHC	NA

Study and year	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected/ unselected sample	Age (years) (range)	Ethnicity	Previous/ concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Ring *et al.*[81] 2016	USA	Prospective cohort	Hospital	NR	Complete test accuracy, prevalence and strategy 11	381	Unselected adult only	Mean 61 at diagnosis	• White, *n* = 265 (70%) • African American, *n* = 34 (9%) • Hispanic, *n* = 66 (17%) • Asian, *n* = 14 (4%) • Native American, *n* = 2 (1%)	NR	NR for whole sample	MSI, IHC and *MLH1* promoter hypermethylation testing	NGS and MLPA
Rubio *et al.*[82] 2016	Spain	Retrospective and prospective cohort	Hospital	3 years	Complete test accuracy, MSI only (MSI-H vs. MSI-L/MSS), MSI only (MSI-H/L vs. MSS), IHC only, strategy 1, strategy 3, strategy 11, prevalence and concordance	103	Selected	NR	NR	• Colon, *n* = 20 (19.4%) • Ovary, *n* = 14 (13.6%) • Skin, *n* = 4 (3.9%)	64/99 (65%) available histories	MSI and IHC	CSGE sequencing, MLPA
PETALS study (Dr Neil AJ Ryan, personal communication)	UK	Prospective and retrospective cohort study	Gynaecology cancer centre	2 years	Strategy 1, strategy 3, strategy 4, prevalence and concordance	Confidential information has been removed	Unselected	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	MSI, IHC and *MLH1* promoter hypermethylation testing	Long-range PCR, NGS and MLPA
Salvador *et al.*[83] 2019	USA	Retrospective cohort study	Laboratory/ hospital	2016–18	Complete test accuracy, strategy 10, strategy 11 and prevalence	237	Selected	NR for endometrial cancer patients alone	NR for endometrial cancer patients alone	NR for endometrial cancer sample alone	NR for endometrial cancer sample alone	MSI, IHC and *MLH1* promoter hypermethylation testing	NGS and MLPA
Sarode and Robinson[84] 2018	USA	Retrospective cohort (including prospective analysis of tissue)	Hospital	September 2011–August 2013	Strategy 4 and prevalence	99	Selected	NR for whole sample	NR for whole sample	NR for endometrial cancer patients	NR for whole sample	IHC and *MLH1* promoter hypermethylation testing	ACGH, long-range PCR and MLPA

Study and year	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected/ unselected sample	Age (years) (range)	Ethnicity	Previous/ concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Shin *et al.*[85] 2015	Republic of Korea	Retrospective cohort study	Hospital	January 2004–December 2013	Strategy 9, synchronous cancers and prevalence	12	Selected	Median 52.5 at diagnosis	NR	• 12/12 (100%) endometrial cancer and CRC • 4/12 (33.3%) additional bladder, cervical or gastric cancer	NR for whole sample	MSI and IHC	Sequencing and PCR
Stelloo *et al.*[86] 2017	The Netherlands	Retrospective cohort study	Radiation centres	NR	Concordance	686	Selected	Mean 69 (41–88)	NR	NR	NR	MSI, IHC and *MLH1* promoter hypermethylation testing	NA
Svampane *et al.*[88] 2014	Latvia	Retrospective cohort	Hospital	January 2006–April 2010	Prevalence	704	Unselected	Range 30–80	NR	NR	19 women with family history of HNPCC (meeting Amsterdam I or II criteria)	IHC	Sequencing
Tian *et al.*[90] 2019	China	Prospective cohort	Cancer centre	January 2014–July 2017	Prevalence, IHC only, strategy 3 and strategy 11	198	Selected	NR in whole sample	Chinese	• 44/196 (22.4%) multiple primary tumour • 20 CRC • 6 ovarian	47/196 (24%) Lynch syndrome-related tumour in a first-degree relative	IHC	Sequencing, NGS and MLPA
Wang *et al.*[91] 2017	USA	Retrospective cohort study	University medical centre	June 2012–January 2015	Concordance	402	Unclear	Median 61 (30–86)	NR	NR	NR	MSI and IHC	NA
Yoon *et al.*[92] 2008	Republic of Korea	Prospective cohort	Hospital	January 1996–December 2004	Prevalence and strategy 10	113	Selected	NR	NR	NR	Four women met Amsterdam II criteria for HNPCC, one of whom had a sister with endometrial cancer and CRC	MSI, IHC and *MLH1* promoter hypermethylation testing	Sequencing

ACGH, array comparative genomic hybridisation; CSGE, conformation-sensitive gel electrophoresis; DGGE, denaturing gradient gel electrophoresis; LUS, lower uterine segment; NA, not applicable; NR, not reported; SSCV, single-strand conformational variance.

Characteristics of included health economics studies

Study and country	Aim of the study	Study characteristics (study design, perspective, setting)	Intervention/comparator	Outcome(s)	Model type	Health states	Results (base-case and sensitivity analyses)
Resnick *et al.*[101] 2009, USA	To assess the cost-effectiveness of screening strategies for diagnosing Lynch syndrome among newly diagnosed endometrial cancer patients	Model-based cost-effectiveness analysis, undertaken from the viewpoint of the third-party payer	Amsterdam criteria (full gene sequencing for women with endometrial cancer who meet the revised Amsterdam criteria), sequence all (full gene sequencing for all women with endometrial cancer), sequence for all women aged < 60 years with endometrial cancer and IHC/single gene strategy (IHC for all women with endometrial cancer after gene sequencing)	Cost per additional Lynch syndrome case detected	Decision tree structure	Lynch positive, Lynch negative, *MSH6* deletion (Lynch positive), *MSH2* deletion (Lynch positive), *MSH2* deletion (Lynch negative)	In comparison to the Amsterdam criteria strategy, IHC/single gene strategy was more costly but detected more Lynch syndrome cases from the hypothetical cohort of 40,000 women with endometrial cancer, equating to an ICER of approximately US$13,800 per Lynch syndrome case detected. The ICER was sensitive to the cost of full gene sequencing
Kwon *et al.*[102] 2011, USA	To assess the cost-effectiveness to compare the benefits and costs of each testing strategy	Model-based economic analysis, societal perspective	• Amsterdam II criteria • Endometrial cancer at < 50 years of age with at least one first-degree relative • Endometrial cancer at < 50 years of age (IHC triage) • Endometrial cancer at < 60 years of age (IHC triage) • Endometrial cancer at any age with at least one first-degree relative (IHC triage) • All endometrial cancers, any age (IHC triage)	Cost per life-year gained	Markov Monte Carlo simulation model, with annual cycle lengths	Well, at risk of CRC, CRC – unscreened, CRC – screened and dead	IHC triage of women at any age, with at least one first-degree relative with a Lynch syndrome-associated cancer – when compared with at age < 50 years, at least one first-degree relative had a mean incremental cost of US$22 and expected to yield an additional 0.00263 life-years, which equated to an ICER of approximately US$9,100 per life-year gained. Results from the sensitivity analysis showed that the ICER was robust to changes made to model input parameters

Study and country	Aim of the study	Study characteristics (study design, perspective, setting)	Intervention/comparator	Outcome(s)	Model type	Health states	Results (base-case and sensitivity analyses)
Breugl *et al.*[103] 2014, USA	To assess the cost-effectiveness of universal tissue testing versus the SGO 5–10% clinical criteria[105] for identifying Lynch syndrome in a cohort of unselected women with endometrial cancer	Cost-effectiveness analysis, third-party payer	SGO 5–10% critical criteria vs. universal tissue testing	Cost per probable Lynch syndrome	NA	*NA*	The SGO 5–10% clinical criteria strategy identified 15 women diagnosed as probable Lynch syndrome; the universal tissue testing strategy identified 43 women with probable Lynch syndrome
Goverde *et al.*[104] 2016, the Netherlands	To assess the cost-effectiveness of routine screening for Lynch syndrome among endometrial cancer patients aged $\leq$ 70 years	Cost-effectiveness analysis	MSI; IHC for *MLH1*, *MSH2*, *MSH6* and *PMS2* protein expression; and the revised Bethesda guidelines	Cost per life-years gained based on the number of Lynch syndrome cases identified among probands and their relatives	NA	NA	Routine screening of endometrial cancer patients aged $\leq$ 70 years, compared with screening endometrial cancer patients aged $\leq$ 50 years, resulted in an ICER of approximately €5300 per life-year gained. Sensitivity analysis results showed that the health benefits (life-years gained) per female relative had the greatest impact on the ICER

Study and country	Aim of the study	Study characteristics (study design, perspective, setting)	Intervention/comparator	Outcome(s)	Model type	Health states	Results (base-case and sensitivity analyses)
Snowsill *et al.*[43] 2019, UK	To identify the relative cost-effectiveness of reflex testing for Lynch syndrome in women with endometrial cancer in the NHS	Model-based cost-effectiveness analysis, NHS and PSS perspective	• Reflex testing with MMR IHC followed by referral for Lynch syndrome diagnostic mutation testing • IHC alone • Reflex testing with MSI followed by referral to genetic counselling for Lynch syndrome diagnostic mutation testing • MSI • Direct referral to genetic counselling for Lynch syndrome diagnostic mutation testing • No testing for Lynch syndrome	Cost per QALY	Decision tree and Markov model, with monthly cycle lengths	• Decision tree (actual Lynch syndrome, actually sporadic) • Markov component [no CRC, CRC (stages 1–4) and dead]	Testing with IHC with methylation was the most cost-effective strategy, with an ICER of approximately £14,200 per QALY. The IHC-alone strategy was the most effective and the most costly, but the results did not reach cost-effectiveness when compared with IHC with methylation, with an ICER of approximately £129,000 per QALY Authors stated that the PSA results were in line with the deterministic results. From the 1000 iterations, there was a 0.36 probability that IHC with methylation was cost-effective at a WTP threshold of £20,000 per QALY. The ICER was sensitive to the age of the proband and the effectiveness of colonoscopy in reducing CRC incidence. When using the effectiveness results from Arrigoni *et al.*[106] for reducing the incidence of CRC, none of the testing strategies was cost-effective

NA, not applicable.

Appendix 5 Test accuracy results

Prevalence of Lynch syndrome

Study (first author and year)	Country	Sample size (*n*)	Lynch syndrome prevalence, *n* (%)	Gene variant (*n*)				VUSs	Notes
				MLH1	*MSH2*	*MSH6*	*PMS2*		
Unselected samples									
Backes *et al.* 2009[52]	USA	140	0 (0)	0	0	0	0	None reported	–
Bruegl *et al.* 2017[55]	USA	213	7 (3.3)	3	0	2	2	2	
Buchanan *et al.* 2014[56]/Nagle *et al.* 2018[76]	Australia	702	22 (3.1)	3	8	10	1	4	Only included women with IHC data (702/1459 women with endometrial cancer)
Dillon *et al.* 2017[59]	Lebanon	233	5 (2.1)	1	2	2	0	3 Lynch like	–
Dudley *et al.* 2015[60]/Mas-Moya *et al.* 2016[70]	USA	215	11 (5.1)	3	5	1	2	6 Lynch like	–
Egoavil *et al.* 2013[61]	Spain	173	8 (4.6)	1	3	3	1	2	–
Hampel *et al.* 2006[15]	USA	543	10 (1.8)	1	3	6	0	13	–
PETALS study (Dr Neil AJ Ryan, personal communication)	UK	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Svampane *et al.* 2014[88]	Latvia	113	6 (5.3)	3	3	2	NA	None reported	Two women had germline mutations in both *MLH1* and *MSH2*

Study (first author and year)	Country	Sample size (*n*)	Lynch syndrome prevalence, *n* (%)	Gene variant (*n*)				VUSs	Notes
				MLH1	*MSH2*	*MSH6*	*PMS2*		
Selected samples									
Anagnostopoulos *et al.* 2017[51]	England	35	3 (8.5)	0	2	1	0	None reported	Only included women diagnosed with endometrial cancer aged < 50 years
Baldinu *et al.* 2002[53]/Strazzullo *et al.* 2003[87]	Italy	116	1 (0.9)	1	0	NA	NA	None reported	Assessed only for *MLH1* and *MSH2*
Berends *et al.* 2003[54]	The Netherlands	58	5 (8.6)	1	3	1	NA	3	Initial reference standard was denaturing gradient gel electrophoresis
Carnevali *et al.* 2017[57]/Libera *et al.* 2017[68]	Italy	61	22 (36.1)	7	8	5	2	6	Only included women with suspected Lynch syndrome on the basis of clinical criteria
Chao *et al.* 2019[58]	China	93	6 (6.5)	1	2	3	0	14	–
Ferguson *et al.* 2014[62]	Canada	118	7 (5.9)	4	1	2	0	None reported	–
Goodfellow *et al.* 2015[63]	USA	1002	22 (2.2)	2	7	10	3	2	–
Leenen *et al.* 2012[67]	The Netherlands	179	7 (3.9)	0	0	6	1	None reported	Only includes women aged < 70 years
Lin *et al.* 2016[69]	USA	74	3 (4.21)	1	0	2	0	None reported	Study included two women with known Lynch syndrome (these have been excluded from the sample)

Study (first author and year)	Country	Sample size (*n*)	Lynch syndrome prevalence, *n* (%)	Gene variant (*n*)				VUSs	Notes
				MLH1	*MSH2*	*MSH6*	*PMS2*		
Lu *et al.* 2007[16]	USA	100	9 (9)	1	7	1	NA	11 VUS	–
Mercado *et al.* 2012[73]	USA	129	80 (62)	31	40	9	0	0	–
Millar *et al.* 1999[74]	Canada	40	7 (17.5)	1	6	NA	NA	None reported	All women had endometrial cancer and CRC. Only *MLH1* and *MSH2* assessed
Najdawi *et al.* 2017[77]	Australia	124	3 (2.4)	0	1	0	2	None reported	Only including women undergoing surgery with curative intent
Ollikainen *et al.* 2005[78]	Finland	23	2 (8.9)	0	1	1	NA	None reported	–
Ring *et al.* 2016[81]	USA	365	21 (6.0)	3	7	6	6	25	Includes two *EPCAM-MSH2* variants
Rubio *et al.* 2016[82]	Spain	103	14 (13.6) • Prior Lynch syndrome cancer: 5/14 (35.71) • No prior Lynch syndrome cancer: 9/14 (64.3)	1	2	6	NA	4	–
Salvador *et al.* 2019[83]	USA	296	51 (17.3)	NR	NR	NR	NR	NR	Mixed endometrial cancer/CRC sample. Only partial data extractable for endometrial cancer
Sarode *et al.* 2019[84]	USA	99	4 (4.0)	1	0	3	0	None reported	–

Study (first author and year)	Country	Sample size (*n*)	Lynch syndrome prevalence, *n* (%)	Gene variant (*n*)				VUSs	Notes
				MLH1	*MSH2*	*MSH6*	*PMS2*		
Shin *et al.* 2015[85]	Republic of Korea	12	3 (25)	2	1	NA	NA	None reported	All women had endometrial cancer and CRC. Only *MLH1* and *MSH2* assessed
Takahasi *et al.* 2017[89]/Kato *et al.* 2016[65]	Japan	360	10 (2.8)	3	4	2	1	2 VUSs; 15 Lynch like	Overlapping, but not identical, populations
Tian *et al.* 2019[90]	China	198	45 (22.7)	10	20	11	4	15 VUSs	–
Yoon *et al.* 2008[92]	Republic of Korea	113	5 (4.4)	1	2	6	NA	None reported	One woman diagnosed with Lynch syndrome did not meet MSI/IHC referral criteria, but was offered germline as she met HNPCC criteria
Sample selection unclear									
Goodfellow *et al.* 2003[64]	USA	441	7 (1.6)	NA	NA	7	NA	None reported	Only *MSH6* investigated. Sample included five women with known *MSH2* germline mutations
Latham *et al.* 2019[66]	USA	525	7 (1.3)	2	1	3	1	None reported	Non-standard approach to MSI, no MSI-L

NA, not applicable.

Concordance between immunohistochemistry and microsatellite instability-based testing

Study (first author and year)	Country	Sample size in analysis (*n*)	MSI threshold[a]	Agreement, *n*/*N* (%)	Disagreement, *n*/*N* (%)	Kappa (95% CI)	Notes
Anagnostopoulos *et al.* 2017[51]	England	32	NR	30/32 (93.75)	2/32 (6.25)	0.86 (0.66 to 1.00)	Kappa calculated by CS using GraphPad (GraphPad Software, Inc., San Diego, CA, USA)
Berends *et al.* 2003[54]	The Netherlands	51	MSI-H	36/51 (70.6)	15/51 (29.4)	0.403 (0.155 to 0.651)	Kappa calculated by CS using GraphPad
Bruegl *et al.* 2017[55]	USA	197	MSI-H (three unstable markers)	190/197 (96.4)	7/197 (3.6)	0.91 (0.84 to 0.98)	Kappa calculated by CS using GraphPad
			MSI-H/L (one or more unstable markers)	187/197 (94.9)	10/197 (5.1)	0.87 (0.80 to 0.95)	
Chao *et al.* 2019[58]	China	77	MSI-H	73/77 (94.8)	4/77 (5.2)	0.803 (0.616 to 0.989)	Kappa calculated by CS using GraphPad
Egoavil *et al.* 2013[61]	Spain	173	MSI-H	156/173 (90.2)	17/173 (9.8)	0.77 (0.67 to 0.87)	Kappa calculated by CS using GraphPad
Ferguson *et al.* 2014[62]	Canada	117	MSI-H	111/117 (94.9)	6/117 (5.1)	0.866 (0.762 to 0.969)	Kappa calculated by CS using GraphPad
Goodfellow *et al.* 2015[63]	USA	934	MSI-H	907/934 (97.1)	27/934 (2.9)	0.94 (0.91 to 0.96)	Kappa calculated by CS using GraphPad
			MSI-H/L	893/934 (95.6)	41/934 (4.4)	0.91 (0.88 to 0.93)	Kappa calculated by CS using GraphPad
Hampel *et al.* 2006[15]	USA	211	NA	See 'Notes' column	See 'Notes' column	Not calculable	IHC conducted only for women with MSS results: • Agreement – 202/211 (95.7%) • Disagreement – 9/127 (4.3%)
Leenen *et al.* 2012[67]	The Netherlands	179	MSI-H	179/179 (100)	0/179 (0)	1.00 (1.00 to 1.00)	Kappa calculated by CS using GraphPad

Study (first author and year)	Country	Sample size in analysis (*n*)	MSI threshold[a]	Agreement, *n/N* (%)	Disagreement, *n/N* (%)	Kappa (95% CI)	Notes
Libera *et al.* 2017[68]	Italy	71	MSI-H	1. 68/71 (95.8) 2. 61/71 (85.9)	1. 3/71 (4.2) 2. 10/71 (10.1)	1. 0.91 (0.82 to 1.00) 2. 0.72 (0.57 to 0.88)	1. Borderline MSI = MSI-H 2. Borderline MSI = MSS Kappa calculated by CS using GraphPad
Lu *et al.* 2007[16]	USA	100	MSI-H	89/94 (94.9)	5/94 (5.3)	0.858 (0.738 to 0.979)	Kappa calculated by CS using GraphPad
Masuda *et al.* 2012[71]	Japan	9	MSI-H MSI-H/L	7/9 (77.8) 8/9 (88.9)	2/9 (22.2) 1/9 (11.1)	0.526 (0.016 to 1.000) 0.769 (0.354 to 1.000)	• *MHL1* only • 36 women in study; concordance data available for nine only • Kappa calculated by CS using GraphPad
McConechy *et al.* 2015[72]	Canada	89	MSI-H	83/89 (93.3)	6/89 (6.7)	0.837 (0.711 to 0.963)	Kappa calculated by CS using GraphPad
Modica *et al.* 2007[75]	USA	85	MSI-H	74/85 (87.1)	11/85 (12.9)	0.739 (0.596 to 0.883)	Samples selected for equal representation of MSI-H and MSS
Ollikainen *et al.* 2005[78]	Finland	22	MSI-H MSI-H/L	15/22 (68.2) 18/22 (81.8)	7/22 (31.8) 4/22 (18.2)	0.319 (0.014 to 0.624) 0. 621 (0.310 to 0.932)	Kappa calculated by CS using GraphPad
Pecorino *et al.* 2017[79]	Italy	19	NA	See 'Notes' column	See 'Notes' column	Not calculable	MSI conducted only for women with IHC loss: • Agreement – 6/19 (31.6%) • Disagreement – 13/19 (68.4%)
PETALS study, (Dr Neil AJ Ryan, personal communication)	UK	Confidential information has been removed	MSI-H MSI-H/L	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Kappa calculated by CS using GraphPad
Planck *et al.* 2002[80]	Sweden	28	MSI-H/L	20/28 (71.4)	8/28 (28.6)	0.44 (0.15 to 0.74)	• All women had endometrial cancer and CRC • Kappa calculated by CS using GraphPad

Study (first author and year)	Country	Sample size in analysis (*n*)	MSI threshold[a]	Agreement, *n/N* (%)	Disagreement, *n/N* (%)	Kappa (95% CI)	Notes
Rubio *et al.* 2016[82]	Spain	103	NR	NR/NR (86.06)	NR/NR (13.92)	Not calculable	Percentage of agreement is reported in the paper, but no details are provided to enable checking or any further calculations
Shin *et al.* 2015[85]	Republic of Korea	12	MSI-H	6/8 (75)	2/8 (25)	Not calculated	• All women had endometrial cancer and CRC • Only *MLH1* and *MSH2* assessed
Stelloo *et al.* 2017[86]	The Netherlands	696	• MSI-H • MSI-H/L	658/672 (97.9) 663/678 (97.8)	14/672 (2.1) 15/678 (2.2)	0.944 (0.915 to 0.973) 0.942 (0.913 to 0.971)	• In paper, agreement = 94%, kappa = 0.854 (95% CI 0.811 to 0.897). Unclear how these values were reached • Kappa in this table calculated by CS using GraphPad
Strazzullo *et al.* 2003;[87] same population as Baldinu *et al.* 2002[53]	Italy	31	MSI-H	See 'Notes' column	See 'Notes' column	Not calculated	IHC conducted only for MSI-H tumours: • Agreement – 18/31 (58.1%) • Disagreement – 13/31 (41.9%)
Wang *et al.* 2017[91]	USA	78	MSI-H	77/78 (98.7)	1/78 (1.3)	0.965 (0.896 to 1.000)	Kappa calculated by CS using GraphPad

CS, Chris Stinton; NA, not applicable; NR, not reported.
a MSI-H refers to two or more unstable markers unless otherwise specified.

Test failures and indeterminate results in index test

Study (first author and year)	IHC, *n/N* (%)		MSI, *n/N* (%)		*MLH1* promoter hypermethylation, *n/N* (%)		Reference standard, *n/N* (%)		Notes
	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	
Anagnostopoulos *et al.* 2017[51]	0/35 (0)	0/35 (0)	0/35 (0)	0/35 (0)	0/2 (0)	0/2 (0)	0/9 (0)	0/9 (0)	Included only women with both IHC and MSI data
Backes *et al.* 2009[52]	0/140 (0)	0/140 (0)	NA	NA	NA	NA	0/2 (0)	0/2 (0)	–
Baldinu *et al.* 2002[53]/Strazzullo *et al.* 2003[87]	0/39 (0)	0/39 (0)	0/39 (0)	12/39 (30.8)	NA	NA	0/9 (0)	0/9 (0)	Assessed for *MLH1* and *MSH2* only
Berends *et al.* 2003[54]	0/51 (0)	0/51 (0)	0/57 (0)	0/57 (0)	NA	NA	0/58 (0)	0/58 (0)	Insufficient tumour tissue: IHC, 7/58; MSI, 1/58
Bruegl *et al.* 2017[55]	NR	NR	NR	NR	NR	NR	0/11 (0)	0/11 (0)	'Insufficient tissue to perform the evaluation' given as one of group of reasons for lack of index test. Number not reported
Buchanan *et al.* 2014[56]/Nagle *et al.* 2018[76]	0/702 (0), see note 1	0/702 (0), see note 1	NA	NA	NR, see note 2	NR, see note 2	0/170 (0)	0/170 (0)	1. Included only women with IHC results 2. Offered only to women with MMR deficiency and sufficient tumour tissue or random sample of MMR proficient
Carnevali *et al.* 2017[57]/Libera *et al.* 2017[68]	0/71 (0)	0/71 (0)	0/71 (0)	13/71 (18.3)	NA	NA	0/28 (0)	0/28 (0)	All women met clinical criteria for Lynch syndrome
Chao *et al.* 2019[58]	0/102 (0)	0/102 (0)	0/102 (0)	0/102 (0)	0/14 (0)	0/14 (0)	0/111 (0)	0/111 (0)	Insufficient tumour tissue: IHC = 9/111; MSI = 28/111
Dillon *et al.* 2017[59]	0/233 (0)	0/233 (0)	NA	NA	0/51 (0)	0/51 (0)	0/8 (0)	0/8 (0)	Insufficient tumour tissue: *MLH1* promoter hypermethylation = 1/51
Egoavil *et al.* 2013[61]	0/173 (0)	0/173 (0)	0/173 (0)	0/173 (0)	0/44 (0)	0/44 (0)	0/19 (0)	0/19 (0)	–

Study (first author and year)	IHC, *n/N* (%)		MSI, *n/N* (%)		*MLH1* promoter hypermethylation, *n/N* (%)		Reference standard, *n/N* (%)		Notes
	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	
Ferguson *et al.* 2014[62]	0/118 (0)	0/118 (0)	0/117 (0)	0/117 (0)	NA	NA	0/89 (0)	0/89 (0)	Insufficient tumour tissue: MSI, 1/118
Goodfellow *et al.* 2003[64]	NA	NA	0/441 (0)	0/441 (0)	0/137 (0)	0/137 (0)	0/7 (0)	0/7 (0)	–
Goodfellow *et al.* 2015[63]	3/1043 (0.3)	0/1043 (0)	0/1043 (0)	0/1043 (0)	39/1,043 (0.3)	0/1043 (3.7)	2/53 (3.8)	0/53 (0)	–
Hampel *et al.* 2006[15]	15/127 (11.8) See note 1	0/543 (0)	0/543 (0)	0/543 (0)	See note 2	0/118 (0)	See note 2	0/118 (0)	1. Reported only for women offered germline testing 2. MLPA *MLH1/MSH2*, 11 failed; MLPA *MSH6/PMS2*, 14 failed 3. MLPA *MLH1* and *MSH2* test, 6 had insufficient DNA; *MSH6/PMS2*, 7 had insufficient DNA
Kato *et al.* 2016[65]/ Takahashi *et al.* 2017[89]	0/360 (0)	0/360 (0)	NA	NA	NA	NA	0/27 (0)	0/27 (0)	IHC, 12 specimens not available
Latham *et al.* 2019[66]	NR	NR	0/525 (0)	0/525 (0)	NA	NA	0/119 (0)	0/119 (0)	For one woman diagnosed with Lynch syndrome, IHC was 'not available'. No further details
Leenen *et al.* 2012[67]	0/179 (0)	0/179 (0)	0/179 (0)	0/179 (0)	0/42 (0)	0/42 (0)	0/10 (0)	0/10 ()	Four IHC tests not conducted because no tumour tissue available
Lin *et al.* 2016[69]	0/74 (0)	2/74 (2.6)	NA	NA	0/14 (0)	0/14 (0)	0/3 (0)	0/3 (0)	–
Lu *et al.* 2007[16]	1/100 (1)	0/100 (0)	0/100 (0)	0/100 (0)	0/100 (0)	0/100 (0)	0/100 (0)	0/100 (0)	Five MSI tests not conducted because of insufficient tumour tissue
Mas-Moya *et al.* 2016[70]/Dudley *et al.* 2015[60]	0/215 (0)	0/215 (0)	0/215 (0)	0/215 (0)	NR	NR	0/17 (0)	0/17 (0)	–

Study (first author and year)	IHC, *n/N* (%)		MSI, *n/N* (%)		*MLH1* promoter hypermethylation, *n/N* (%)		Reference standard, *n/N* (%)		Notes
	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	
Masuda *et al.* 2012[71]	0/36 (0)	0/36 (0)	0/36 (0)	0/36 (0)	NR	NR	NA	NA	Concordance only
McConechy *et al.* 2015[72]	0/89 (0)	0/89 (0)	0/89 (0)	0/89 (0)	NA	NA	NA	NA	Insufficient tumour tissue: IHC, 2/157, MSI, 0/157 (68 insufficient normal tissue)
Mercado *et al.* 2012[73]	0/74 (0)	0/74 (0)	0/24 (0)	0/24 (0)	NA	NA	0/80 (0)	0/80 (0)	IHC results reported by protein in paper, with different numbers of women tested for each protein. The denominator reported for IHC refers to the largest sample of women in the study. The denominator for germline refers to all women who received germline testing
Millar *et al.* 1999[74]	NA	NA	0/40 (0)	0/40 (0)	NA	NA	0/40 (0)	0/40 (0)	–
Modica *et al.* 2007[75]	0/90 (0)	5/90 (5.6)	0/90 (0)	0/90 (0)	NA	NA	NA	NA	Concordance only
Najdawi *et al.* 2017[77]	0/124 (0)	0/124 (0)	NA	NA	0/26 (0)	0/26 (0)	0/9 (0)	0/9)	Two IHC tests not conducted because of insufficient tumour material
Ollikainen *et al.* 2005[78]	0/23 (0)	1/23 (4.5)	0/23 (0)	0/23 (0)	0/6 (0)	0/6 (0)	0/10 (0)	0/10 ()	Includes only women with a family history of endometrial cancer. Table 2 in the Ollikainen 2005[78] paper says one IHC not determined. No further details are provided in the Ollikainen 2005[78] paper
Pecorino *et al.* 2017[79]	0/41 (0)	0/41 ()	0/19 (0)	0/19 (0)	NA	NA	NA	NA	MSI was conducted only for women who had loss on IHC
Planck *et al.* 2002[80]	0/30 (0)	2/30 (6.6)	0/30 (0)	1/30 (3.3)	NA	NA	NA	NA	All women had CRC and endometrial cancer
Ring *et al.* 2016[81]	0/365 (0)	0/365 (0)	0/365 (0)	0/365 (0)	NR	NR	0/381 (0)	0/381 (0)	• MSI, 2/365 insufficient tumour • Germline, 66/447 insufficient DNA

Study (first author and year)	IHC, *n/N* (%)		MSI, *n/N* (%)		*MLH1* promoter hypermethylation, *n/N* (%)		Reference standard, *n/N* (%)		Notes
	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	Test failures	Indeterminate results	
Rubio *et al.* 2016[82]	NR	NR	NR	NR	NA	NA	0/103 (0)	0/103 (0)	• IHC: 9/103 (8.7%) not conducted; reasons not reported • MSI: 20/103 (19.4%) not conducted; reasons not reported
PETALS study, (Dr Neil AJ Ryan, personal communication)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed. IHC had incomplete staining (women with incomplete loss were referred for germline testing)
Salvador *et al.* 2019[83]	NR	NR	NR	NR	NR	NR	0/296 (0)	0/296 (0)	Mixed endometrial cancer/ CRC sample. Only partial data extractable for endometrial cancer
Sarode *et al.* 2019[84]	0/99 (0)	4/99 (4)	NA	NA	NR	NR	NR	NR	–
Shin *et al.* 2015[85]	0/8 (0)	0/8 (0)	0/12 (0)	0/12 (0)	NA	NA	0/3 (0)	0/3 (0)	All women had CRC and endometrial cancer
Stelloo *et al.* 2017[86]	0/696 (0)	18/696 (2.6)	NR	NR	NA	NA	NA	NA	168 women excluded without reason
Svampane *et al.* 2014[88]	2/111 (1.8)	0/111 (0)	NA	NA	NA	NA	0/8 (0)	0/8 (0)	No cancer tissue found, 2/113
Tian *et al.* 2019[90]	NR	NR	NA	NA	NA	NA	0/198 (0)	0/198 (0)	32 IHC results not available; no details given
Wang *et al.* 2017[91]	0/78 (0)	0/78 (0)	0/78 (0)	0/78 (0)	NA	NA	NA	NA	Concordance only
Yoon *et al.* 2008[92]	0/113 (0)	0/113 (0)	0/113 (0)	0/113 (0)	NR	NR	0/16 (0)	0/16 (0)	–

NA, not applicable; NR, not reported.

Appendix 6 Quality assessment of included studies

Quality assessment of included economic evaluation studies

Assessment	Study and year				
	Resnick *et al.*[101] 2009	Kwon *et al.*[102] 2011	Bruegl *et al.*[103] 2014	Goverde *et al.*[104] 2016	Snowsill *et al.*[43] 2019
Title	Yes	Yes	Yes	Yes	Yes
Abstract	Yes	Yes	Yes	Yes	Yes
Introduction					
Background and objectives	Yes	Yes	Yes	Yes	Yes
Methods					
Target population and subgroups	Yes	Yes	Yes	Yes	Yes
Setting and location	Yes	Yes	Yes	Yes	Yes
Study perspective	Yes	Yes	Yes	Yes	Yes
Comparators	Yes	Yes	Yes	Yes	Yes
Time horizon	Yes	Yes	NA	Yes	Yes
Discount rate	Yes	Yes	NA	Yes	Yes
Choice of health outcomes	Yes	Yes	Yes	Yes	Yes
Measurement of effectiveness	Yes	Yes	Yes	Yes	Yes
Measurement and valuation of preference-based outcomes	Yes	NA	NA	NA	Unclear
Estimating resources and costs	Yes	Yes	Yes	Yes	Yes
Currency, price date and conversion	Yes	Yes	Yes	Yes	Yes
Choice of model	Yes	Yes	NA	NA	Yes
Assumptions	Yes	Yes	Yes	Yes	Yes
Analytical methods	Yes	Yes	Yes	Yes	Yes
Results					
Study parameters	Yes	Yes	Yes	Yes	Yes
Incremental costs and outcomes		Yes	Yes	Yes	Yes
Characterising uncertainty	Yes	Yes	Yes	Yes	Yes
Discussion					
Study findings	Yes	Yes	Yes	Yes	Yes
Limitations	Yes	Yes	Yes	Yes	Yes
Generalisability	Yes	NR	NR	Yes	No
Other					
Source of funding	Yes	Yes	Yes	Yes	Yes
Conflicts of interest	Yes	Yes	Yes	Yes	Yes

NA, not applicable; NR, not reported.

Number	Philips' criteria	Studies		
		Resnick *et al.*[101] 2009	Kwon *et al.*[102] 2011	Snowsill *et al.*[43] 2019
Structure				
1.	Is there a clear statement of the decision problem?	Yes	Yes	Yes
2.	Is the objective of the model specified and consistent with the stated decision problem?	Yes	Yes	Yes
3.	Is the primary decision-maker specified?	Yes	Yes	Yes
4.	Is the perspective of the model stated clearly?	Yes	Yes	Yes
5.	Are the model inputs consistent with the stated perspective?	Yes	No	Yes
6.	Has the scope of the model been stated and justified?	Yes	No	Yes
7.	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes	Yes	Yes
8.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Yes	Yes
9.	Are the sources of the data used to develop the structure of the model specified?	Yes	Yes	Yes
10.	Are the causal relationships described by the model structure justified appropriately?	Yes	Yes	Yes
11.	Are the structural assumptions transparent and justified?	Yes	Yes	Yes
12.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Yes	Yes	Yes
13.	Is there a clear definition of the options under evaluation?	Yes	Yes	Yes
14.	Have all feasible and practical options been evaluated?	No	No	No
15.	Is there justification for the exclusion of feasible options?	No	Yes	Yes
16.	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Yes	Yes	Yes
17.	Is the time horizon of the model sufficient to reflect all important differences between the options?	No	Yes	Yes
18.	Are the time horizon of the model and the duration of treatment described and justified?	No	Yes	Yes
19.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes	Yes	Yes
20.	Is the cycle length defined and justified in terms of the natural history of disease?	NA	Yes	Yes
Data				
21.	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes	Yes
22.	When choices have been made between data sources, are these justified appropriately?	No	No	No
23.	Has particular attention been paid to identifying data for the important parameters of the model?	Unclear	Unclear	No
24.	Has the quality of the data been assessed appropriately?	Unclear	Unclear	Unclear
25.	When expert opinion has been used, are the methods described and justified?	No	NA	Yes
26.	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Yes	Yes	Yes

Number	Philips' criteria	Studies		
		Resnick *et al.*[101] 2009	Kwon *et al.*[102] 2011	Snowsill *et al.*[43] 2019
27.	Is the choice of baseline data described and justified?	Yes	Yes	Yes
28.	Are transition probabilities calculated appropriately?	NA	Unclear	Yes
29.	Has a half-cycle correction been applied to both costs and outcomes?	NA	No	Yes
30.	If not, has the omission been justified?	No	No	NA
31.	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	NA	NA	Yes
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	NA	NA	Yes
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?	NA	NA	Yes
34.	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	NA	NA	NA
35.	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	NA	NA	NA
36.	Are the costs incorporated into the model justified?	Yes	Yes	Yes
37.	Has the source for all costs been described?	Yes	Yes	Yes
38.	Have discount rates been described and justified given the target decision-maker?	Yes	Yes	Yes
39.	Are the utilities incorporated in the model appropriate?	NA	NA	Yes
40.	Is the source of utility weights referenced?	NA	NA	Yes
41.	Are the methods of derivation for the utility weights justified?	NA	NA	Yes
42.	Have all data incorporated in the model been described and referenced in sufficient detail?	Yes	No	Yes
43.	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Yes	Yes	Yes
44.	Is the process of data incorporation transparent?	No	No	Yes
45.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	NA	NA	Yes
46.	If data have been incorporated as distributions, is it clear that second-order uncertainty is reflected?	NA	NA	Yes
47.	Have the four principal types of uncertainty been addressed?	No	No	Yes
48.	If not, has the omission of particular forms of uncertainty been justified?	No	No	NA
49.	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	No	Yes
50.	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	No	Yes
51.	Has heterogeneity been dealt with by running the model separately for different subgroups?	No	Yes	Yes
52.	Are the methods of assessment of parameter uncertainty appropriate?	Yes	Yes	Yes

Number	Philips' criteria	Studies		
		Resnick *et al.*[101] 2009	Kwon *et al.*[102] 2011	Snowsill *et al.*[43] 2019
53.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Yes	Yes	Yes
54.	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	No	No	Yes
55.	Are any counterintuitive results from the model explained and justified?	NA	NA	NA
56.	If the model has been calibrated against independent data, have any differences been explained and justified?	Yes	NA	Yes
57.	Have the results been compared with those of previous models and any differences in results explained?	Yes	Yes	Yes

NA, not applicable.

Appendix 7 Health economic results

Model input parameters: colorectal cancer surveillance supporting information

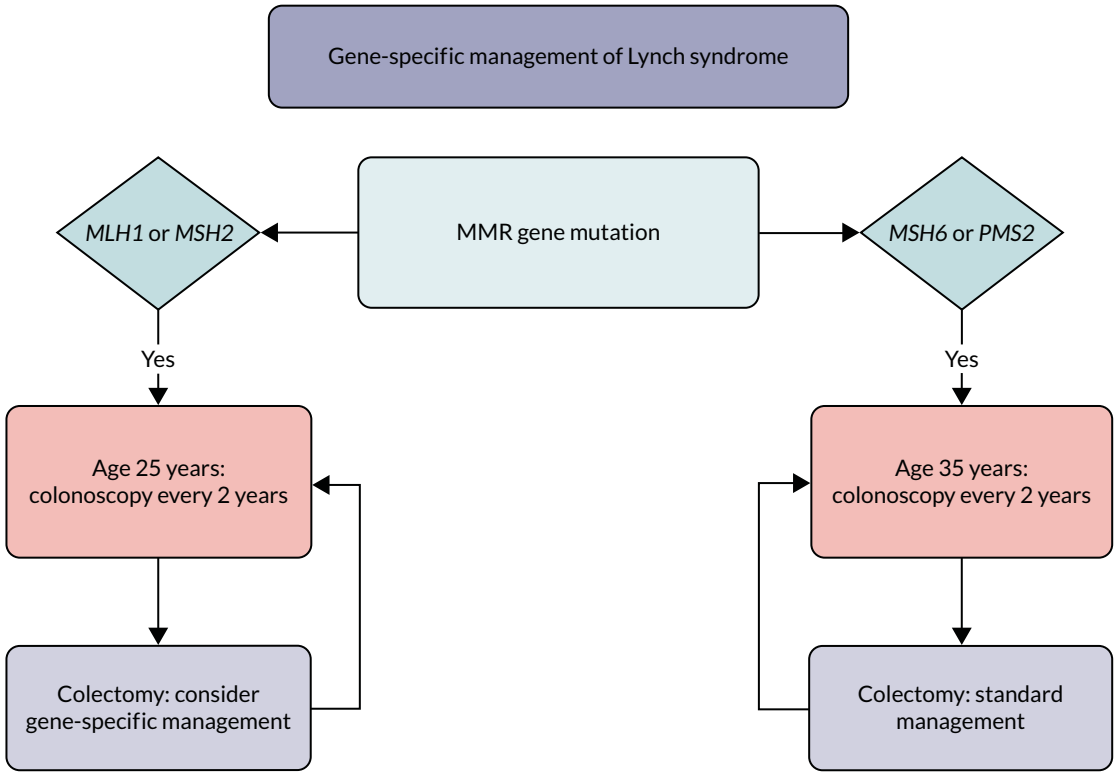

FIGURE 34 Gene-specific management of Lynch syndrome. Reproduced from Monahan *et al.*[27] © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ. This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/. Minor amendments have been made for journal style.

Additional scenario analyses

Scenario analysis 4

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER (£)
No testing	0	–	0.0000	–	–
MSI with *MLH1* methylation	520	520	0.0522	0.0522	Extendedly dominated
IHC with *MLH1* methylation	630	630	0.0832	0.0832	7570
MSI followed by IHC with *MLH1* methylation	720	90	0.0523	−0.0309	Dominated
IHC	790	70	0.0849	0.0017	41,180
MSI	840	50	0.0853	0.0004	125,000
IHC followed by MSI with *MLH1* methylation	870	30	0.0835	−0.0018	Dominated
MSI and IHC with *MLH1* methylation	890	20	0.0853	0.0000	Dominated
IHC followed by MSI	1026	186	0.0854	0.0001	Extendedly dominated
MSI followed by IHC	1029	189	0.0856	0.0003	630,000
MSI and IHC	1070	41	0.0854	−0.0002	Dominated
Germline testing	1160	31	0.0828	−0.0028	Dominated

Scenario analysis 5

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER (£)
No testing	0	–	0	–	–
MSI with *MLH1* methylation	510	510	0.0413	0.0413	Extendedly dominated
IHC with *MLH1* methylation	620	620	0.0659	0.0659	9410
MSI followed by IHC with *MLH1* methylation	710	90	0.0414	−0.0245	Dominated
IHC	780	160	0.0671	0.0012	133,330
MSI	830	50	0.0673	0.0002	250,000
IHC followed by MSI with *MLH1* methylation	860	30	0.0661	−0.0012	Dominated
MSI and IHC with *MLH1* methylation	880	50	0.0661	−0.0012	Dominated
IHC followed by MSI	1010	180	0.0675	0.0002	900,000
MSI followed by IHC	1020	10	0.0675	0.0000	Dominated
MSI and IHC	1060	50	0.0675	0.0000	Dominated
Germline testing	1150	140	0.0656	−0.0019	Dominated

Scenario analysis 6

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER (£)
No testing	0	–	0	–	–
MSI with *MLH1* methylation	475	475	0.0415	0.0415	Extendedly dominated
IHC with *MLH1* methylation	570	570	0.0662	0.0662	8610
MSI followed by IHC with *MLH1* methylation	680	110	0.0416	−0.0246	Dominated
IHC	730	160	0.0674	0.0012	133,330
MSI	770	40	0.0677	0.0003	133,330
IHC followed by MSI with *MLH1* methylation	800	30	0.0665	−0.0012	Dominated
MSI and IHC with *MLH1* methylation	830	60	0.0665	−0.0012	Dominated
IHC followed by MSI	959	189	0.0678	0.0001	Extendedly dominated
MSI followed by IHC	963	193	0.0679	0.0002	965,000
Germline testing	1000	37	0.0660	−0.0019	Dominated
MSI and IHC	1000	0	0.0678	−0.0001	Dominated

Scenario analysis 7

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALYs	Incremental QALYs	ICER (£)
No testing	0	–	0	–	–
MSI with *MLH1* methylation	530	530	0.0351	0.0351	Extendedly dominated
IHC with *MLH1* methylation	660	660	0.0560	0.0560	11,790
MSI followed by IHC with *MLH1* methylation	730	70	0.0352	−0.0208	Dominated
IHC	810	150	0.0570	0.0010	150,000
MSI	860	50	0.0572	0.0002	250,000
IHC followed by MSI with *MLH1* methylation	890	30	0.0562	−0.0010	Dominated
MSI and IHC with *MLH1* methylation	910	50	0.0562	−0.0010	Dominated
IHC followed by MSI	1048	188	0.0573	0.0001	Extendedly dominated
MSI followed by IHC	1052	195	0.0574	0.0002	975,000
MSI and IHC	1090	38	0.0573	−0.0001	Dominated
Germline testing	1190	138	0.0558	−0.0016	Dominated

Probabilistic sensitivity analysis distributions and approach

The following tables summarise the distributions used for all model parameters. A two-stage bootstrapping approach was taken to combine uncertainty in the diagnostic and long-term models for the PSA. First, the long-term model was run probabilistically in R. This generated a set of jointly sampled (to allow for correlation between outcomes for relatives and probands) values for costs and QALYs for probands and relatives reflecting uncertainty in these parameters. The values were stored as a table and then used as a sampling frame in the diagnostic model. This meant that, for each PSA run, the number of probands and relatives identified by testing was sampled probabilistically, and then the costs and QALYs attributable to a proband and a relative were sampled from the table of PSA values generated from the long-term model. The resulting total costs and QALYs reflected uncertainty in all parameters across the two models, and were used to generate the PSA results reported.

Model input parameters required

Variable	Base-case value	Distribution	Parameters
Test accuracy			
Sensitivity IHC with *MLH1* methylation		Fixed	
Specificity IHC with *MLH1* methylation	–	Beta	$\alpha = 56.10$, $\beta = 1.93$
Costs (£, 2018/19 prices)			
GP visit	39.00	Log-normal	$\mu = 3.66$, $\sigma = 0.10$
IHC test	210.00	Log-normal	$\mu = 5.35$, $\sigma = 0.10$
MMR proband	755.00	Log-normal	$\mu = 6.63$, $\sigma = 0.10$
MMR relative	165.00	Log-normal	$\mu = 5.11$, $\sigma = 0.10$
Offer counselling	28.25	Log-normal	$\mu = 3.34$, $\sigma = 0.10$
Pre-test proband	642.19	Log-normal	$\mu = 6.46$, $\sigma = 0.10$
Post-test proband	141.44	Log-normal	$\mu = 4.95$, $\sigma = 0.10$
Pre-test relative	514.13	Log-normal	$\mu = 4.95$, $\sigma = 0.10$
Post-test relative	141.44	Log-normal	$\mu = 6.24$, $\sigma = 0.10$
CRC incidence, log-normal parameters			
Constant (female with *MLH1* and no previous CRC)	4.306	Multivariate normal	Mu = (4.306, 0.100, 0.531, 0.863, –0.118, –0.230)
Standard deviation	0.567		See *Variance–covariance matrix used for colorectal cancer incidence in probablistic sensitivity analysis*
Coefficient for			
MSH2	0.100		
MSH6	0.531		
PMS2	0.863		
Male	–0.118		
Previous cancer	–0.230		

Variable	Base-case value	Distribution	Parameters
CRC mortality			
Stage I	0.0090	Log-normal	$\mu = -4.26$, $\sigma = 0.054$
Stage II	0.0345	Log-normal	$\mu = -2.95$, $\sigma = 0.014$
Stage III	0.0977	Log-normal	$\mu = -1.91$, $\sigma = 0.009$
Stage IV	0.5440	Log-normal	$\mu = -0.42$, $\sigma = 0.357$
Aspirin incidence rate ratio	0.5800	Log-normal	$\mu = -0.55$, $\sigma = 0.288$
CRC surveillance hazard ratio for incidence	0.3870	Uniform	0.387, 1.000
CRC stage at presentation *Without surveillance*			
Stage I	68.5%	Dirichlet	29.5, 4.5, 5.5, 3.5
Stage II	10.5%		
Stage III	12.7%		
Stage IV	8.12%		
With surveillance			
Stage I	18.8%	Dirichlet	7.5, 19.5, 8.5, 4.5
Stage II	48.7%		
Stage III	21.2%		
Stage IV	11.3%		
CRC treatment costs			
CRC treatment costs	See *Table 3*	Gamma	Param1 = 25, Param2 = see *Param2 values for Gamma distribution giving uncertainty around colorectal cancer treatment costs in probabilistics sensitivity analysis*
Endometrial cancer incidence[a] *Gene*			
MLH1 by age (years)			
25	0	Fixed	Not applicable
40	0.019	Beta	$\alpha = 3.4$, $\beta = 173.6$
50	0.147	Beta	$\alpha = 39.1$, $\beta = 226.6$
60	0.273	Beta	$\alpha = 62.7$, $\beta = 166.9$
70	0.352	Beta	$\alpha = 57.5$, $\beta = 105.9$
75	0.370	Beta	$\alpha = 48.9$, $\beta = 83.3$
MSH2 by age (years)			
25	0	Fixed	Not applicable
40	0.023	Beta	$\alpha = 2.8$, $\beta = 119.1$
50	0.175	Beta	$\alpha = 32.5$, $\beta = 153.2$
60	0.380	Beta	$\alpha = 58.4$, $\beta = 95.3$
70	0.465	Beta	$\alpha = 54.4$, $\beta = 62.6$
75	0.489	Beta	$\alpha = 44.2$, $\beta = 46.17$

Variable	Base-case value	Distribution	Parameters
MSH6 by age (years)			
25	0	Fixed	Not applicable
40	0.023	Beta	$\alpha = 0.1$, $\beta = 4.8$
50	0.126	Beta	$\alpha = 2.8$, $\beta = 19.7$
60	0.283	Beta	$\alpha = 10.7$, $\beta = 27.2$
70	0.411	Beta	$\alpha = 17.4$, $\beta = 24.9$
75	0.411	Beta	$\alpha = 13.7$, $\beta = 19.7$
PMS2 by age (years)			
25	0	Fixed	Not applicable
40	0	Fixed	Not applicable
50	0	Fixed	Not applicable
60	0.093	Beta	$\alpha = 0.5$, $\beta = 5.2$
70	0.128	Beta	$\alpha = 1.0$, $\beta = 6.7$
75	0.128	Beta	$\alpha = 1.0$, $\beta = 6.8$

a As cumulative incidence cannot decrease, the values used in each PSA run were set at the maximum of the sampled value and the value sampled at the previous age. This meant that the annual incidence rates sampled at each run could never be negative.

Variance–covariance matrix used for colorectal cancer incidence in probabilistic sensitivity analysis

0.0048610	0.0024265	0.00306302	-2.84316×10^{-5}	−0.001366422	−0.001293855	0.001470131
0.002426593	0.016159274	0.006487453	−0.000390521	−0.00359213	−0.000760428	0.005271669
0.003063026	0.006487453	0.110071236	−0.000804802	−0.006512378	-2.36405×10^{-5}	0.009192278
-2.84316×10^{-5}	−0.000390521	−0.000804802	0.005788262	0.003564862	−0.003063665	−0.001316882
−0.001366422	−0.00359213	−0.006512378	0.003564862	0.009596563	−0.003612567	−0.006267887
−0.001293855	−0.000760428	-2.36405×10^{-5}	−0.003063665	−0.003612567	0.003639508	0.001641483
0.001470131	0.005271669	0.009192278	−0.001316882	−0.006267887	0.001641483	0.010196606

Param2 values for Gamma distribution giving uncertainty around colorectal cancer treatment costs in probabilistics sensitivity analysis

350.1648682	349.6213287	579.5803466	468.1965605
228.4956424	280.6336233	387.6690935	337.7470812
184.9288611	214.0709403	290.3755235	260.355419
127.1046208	138.1844644	179.4098447	174.6016107
55.1901643	61.83807046	62.42342068	32.27788397

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