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Title: *Testing strategies for Lynch syndrome in people with endometrial cancer*

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Contributions of authors

Rachel Court (Information specialist) developed the search strategy and undertook searches. Chris Stinton (Senior Research Fellow), Hannah Fraser (Research Associate), Lena Alkuhudairy (Senior Research Fellow), and James Keasley (Academic Foundation 2 doctor) conducted the clinical effectiveness systematic review, this included: screening and retrieving papers, assessing against the inclusion criteria, appraising the quality of papers and abstracting data from papers for synthesis. Chris Stinton (Senior Research Fellow) led the clinical effectiveness review. Mary Jordan (Research Fellow), Peter Auguste (Research Fellow) and Jason Madan (Professor in Health Economics) contributed to the cost-effectiveness review and undertook the health economic modelling. Dimitris Grammatopoulos (Professor of Molecular Medicine) provided clinical guidance and helped develop the model structures. Sian Taylor-Phillips (Associate Professor), led the project, and contributed to all stages for clinical and cost effectiveness. All authors were involved in writing draft and final versions of the report.

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Abstract (486 words)

Background: Lynch syndrome is an inherited genetic condition which is associated with an increased risk of cancers. NICE has recommended that people who are diagnosed with colorectal cancer are tested for Lynch syndrome. Routine testing for Lynch syndrome amongst people with endometrial cancer is not currently conducted.

Methods: We assessed the accuracy of immunohistochemistry (IHC) and microsatellite instability (MSI)-based testing strategies to identify people who are at high risk of Lynch syndrome, and the clinical and cost-effectiveness of testing for Lynch syndrome amongst people who have endometrial cancer and their biological relatives. We systematically reviewed the evidence for test accuracy of 11 predefined testing strategies. The reference standard was germline testing of normal (non-tumour) tissue for constitutional mutations in mismatch repair. 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 horizon.

Results: The clinical effectiveness search identified 3308 studies of which 38 studies of test accuracy were included, of which 7 provided full 2x2 data. There were four head-to-head test accuracy studies comparing MSI and IHC. None of these studies demonstrated a clear difference in accuracy between IHC and MSI. However other studies indicated that the specificity of IHC can 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. Test accuracy estimates used for the economic model were all taken from Lu (2007) to aid comparability across strategies. Insufficient tumour tissue being available for testing was rare, and 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.

The economic model indicated that all testing strategies vs no testing were cost effective at a willingness to pay threshold of £20,000 per QALY. IHC with MLH1 promoter hypermethylation testing was the most cost-effective testing strategy with an ICER of approximately £9,420 per QALY. The second most cost effective testing strategy was IHC testing alone, but incremental analysis produced an ICER in excess of £130,000. Results were robust across all scenario analyses, showing IHC with MLH1 hypermethylation to be the most cost-effective testing strategy. ICERs ranged from £5690 to £20,740. Scenario 8, where benefit of CRC surveillance was removed, is the only ICER which minimally exceeded UK WTP thresholds (at £20,740). Sensitivity analysis identified the main cost drivers of the ICER as the percentage of relatives accepting counselling and the prevalence of Lynch syndrome in the population. PSA analysis showed that at a willingness to pay threshold of £20,000 per QALY there is a 0.93 probability that IHC with MLH1 hypermthylation testing is cost-effective compared to no testing..

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

Scientific Summary

Background

Lynch syndrome is an inherited genetic condition. Lynch syndrome is associated with an increased risk for cancers, including colorectal, endometrial, gastric, pancreatic, and kidney cancers. Recently NICE has recommended that people who are diagnosed with colorectal cancer are tested for Lynch syndrome [DG27].

Routine testing for Lynch syndrome amongst 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 earlier treatment of cancers.

Objectives

The overall objective was to inform the NICE Diagnostic Advisory Committee (DAC) on whether testing for Lynch syndrome in people who have endometrial cancer represents a cost-effective use of NHS resources.

Research questions 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?
Sub questions
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 amongst people who have endometrial cancer, and/or their relatives?
Sub questions
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 amongst people diagnosed with endometrial cancer using IHC and MSI-based strategies compared to the current pathway for the diagnosis of Lynch syndrome?
The testing strategies investigated were as follows:

- Strategy 1: MSI testing alone (MSS: microsatellite stable, MSI: microsatellite instability, LS: Lynch syndrome)
- Strategy 2: MSI testing with MLH1 promoter hypermethylation testing
- Strategy 3: IHC-based testing (LS: Lynch syndrome)
- Strategy 4: IHC testing with MLH1 promoter hypermethylation testing
- Strategy 5: MSI testing followed by IHC testing
- Strategy 6: MSI followed by IHC testing with MLH1 promoter hypermethylation testing
- Strategy 7: IHC followed by MSI testing
- Strategy 8: IHC testing followed by MSI testing with MLH1 promoter hypermethylation testing
- Strategy 9: MSI and IHC testing
- Strategy 10: MSI and IHC 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); CENTRAL (via Wiley); Database of Abstracts of Reviews of Effects (DARE) (via Centre for Reviews and Disseminations (CRD)); Health Technology Assessment (HTA) database (via CRD); Science Citation Index and Conference Proceedings (via Web of Science); PROSPERO International Prospective Register of Systematic Reviews (via CRD). Additionally, references of included studies and relevant systematic reviews were checked and experts on the team 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 problem amplification (MLPA), long-range polymerase chain reaction (PCR), or targeted array comparative genome hybridisation (ACGH). 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 amongst people who have been diagnosed with endometrial cancer followed by colorectal or gynaecological cancer surveillance were included. Studies which only assessed the surveillance were also included for the sub-questions. Studies which 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 (QUADAS-2) tool, and the quality appraisal tool for studies of diagnostic reliability (QAREL) tool 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 at different ages, for males and females, for those without diagnosed CRC or EC and those recently diagnosed with EC. The decision tree part models all 11 testing strategies outlined above. The outcomes model simulates lifetime incidence and survival of CRC and EC for a cohort of individuals who have Lynch syndrome, from the point of discovery onwards. Costs and QALYs are discounted at a rate of 3.5% per year. Both models are conducted from a NHS and PSS perspective. The model has five states – cancer free, CRC, EC, both CRC and EC, and dead. The EC state comprises 10 ‘tunnel states’ reflecting time since incidence. The cohort can be of any age from 0 to 100, male or female, and start in any state. For this decision problem, cohorts are simulated who are cancer-free or recently diagnosed with EC, male or female, and aged in annual increments between 25 and 74. This gives 200 cohorts in total. Outcomes were not modelled for those without Lynch, on the assumption that they experience no long term costs and benefits from Lynch testing.

Data sources to inform the model were drawn from the systematic review, and previous work conducted for NICE to assess the 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 this previous work, including that for every woman recently

diagnosed with EC found to have Lynch, 6 relatives would be offered cascade testing, of whom 2.5 would be first degree relatives. Those who are found to have Lynch are offered biennial colonoscopies and (for women who are EC-free) prophylactic hysterectomy and bilateral salpingo-oophorectomy (H-BSO). Assumptions also included that biennial colonoscopies would be offered between the ages 25 and 74, with uptake rates of 100%. Prophylactic H-BSO would be offered between the ages of 25 and 70. And that uptake by age 50 would be 28% rising to 75% by age 65, and peaking at 80%. Gynaecological surveillance was assumed to reduce annual mortality in EC by 10.2% but not to reduce incidence. Aspirin chemprophylaxis would be offered to all, assuming 100% uptake, with probability of developing cancer each year reduced by a factor of 0.56 (applied equally to EC and CRC risk). Scenario analyses were used to investigate changing model inputs for test accuracy and test costs, the disultility associated with cancer, excluding the estimated benefits of gynacological survieillance and aspirin prophylaxis, and extending the colorectal screening interval to 3 years.

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 NICE and included for key question one (PETALS study, Ryan et al, University of Manchester, provided 11/12/2019). For question 1 the 45 included studies reported on approximately 10,600 participants, ranging from 12 patients to 1459 patients.

Median prevalence of Lynch syndrome across studies in unselected popualtions was [redacted]%. 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 7 provided full test accuracy data, 25 studies (28 papers) provided partial test accuracy data (incomplete 2x2 table) and 23 provided data on concordance.. The most common reason for only providing 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 was poor, with no study at low risk of bias in all domains.

Meta-analysis of test accuracy was not possible due to the small number of heterogeneous studies. Four studies provided head-to-head test accuracy data for immunohistochemistry and microsatellite instability-based testing, though the numbers of included tumours were not identical for each of the tests due to insufficient tumour tissue being available and test failures. For immunohistochemistry, there were 28 true positives, 78 false positives, 235 true negatives, and 5 false negatives; point estimates ranged from 66.7 – 100% for sensitivity, 60.9 – 83.3% for specificity. For microsatellite instability testing, there were 21 true positives, 57 false positives, 232 true negatives, and 8 false negatives; point estimates ranged from 41.7 – 100% for sensitivity, 69.2 – 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 (MSI testing alone) eight studies provided data. There were 39 true positives, and 212 false positives out of 1,402 women tested. For Strategy 3 (IHC-based testing alone) five studies provided data. There were 69 true positives, and 193 false positives out of 552 women tested. For Strategy 4 (IHC 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 (MSI and IHC testing with MLH1 promoter hypermethylation testing) six studies provided data. There were 94 true positives, and 311 false positives out of 1,627 women tested. For Strategy 11 (germline testing only) nine studies provided data, where 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 7,147 women with endomentrial 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 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 IHC with MLH1 hypermethylation test strategy for Lynch syndrome was the most cost effective testing strategy for reflex testing in EC probands and their relatives. The base case produced an ICER of £9,420 per QALY when compared against a no testing strategy, so it is cost effective at a willingness to pay threshold of £20,000 per QALY. The second most cost effective testing strategy is IHC testing alone, but pairwise analysis produces an ICER in excess of £130,000 which is well-above the accepted willingness to pay (WTP) threshold of £20,000 per QALY.

Results are robust across all scenario analyses undertaken, showing IHC with MLH1 hypermethylation to be the most cost-effective testing strategy with ICERs ranging from £5690 to £20,740. Scenario 8, where benefit of surveillance to reduce CRC incidence is removed, is the only ICER which minimally exceeds UK WTP thresholds (at £20,740). Sensitivity analysis identified the main cost drivers of the ICER as the percentage of relatives accepting counselling and the prevalence of Lynch syndrome in the population. Varying these parameters proved highly influential the ICER for IHC with hypermethylation testing remained under £20,000 per QALY throughout. PSA analysis of cost-effectiveness acceptability based on 10,000 simulations showed a 93% probability that IHC with MLH1 hypermthylation testing is cost-effective at a WTP threshold of £20,000.

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 was limited data to inform the economic model e.g.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.

Research is needed to understand

1. The effect of earlier intervention on long term outcomes, 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.
2. 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. Whilst large full test accuracy studies may be prohibitively expensive due to the low prevalence of Lynch syndrome, follow up of negative cases through disease registers could be used to determine false negative cases. Further, there is very limited data on the test accuracy of MSI testing followed by hypermethylation testing in women with MSI-H.

Word count: 2,279

Plain English Summary

Lynch syndrome is an inherited condition that is caused by a problem in our genes. People who have Lynch syndrome have a higher risk of some types of cancers (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, NICE guidance recommends testing for Lynch syndrome in people who have bowel cancer. Our aim was to investigate whether we should test for Lynch syndrome in women with womb cancer, and their relatives. We investigated two main tests, called immunohistochemistry and microsattelite 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 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. Our economic model suggested that testing women with endometrial cancer for Lynch syndrome is cost effective. The best test in our model was immunohistochemistry

followed by methylation testing. We are unsure of these results because of the low quality of evidence available.

Word count: 217

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List of Abbreviations

ACGH	Array comparative genome hybridisation
CEAC	Cost-effectiveness acceptability curves
CI	Confidence interval
CRC	Colorectal cancer
CRD	Centre for Reviews and Disseminations
CSGE	Conformation sensitive gel electrophoresis
DAC	Diagnostic Advisory Committee
DARE	Database of Abstracts of Reviews of Effects
DGGE	Denaturing gradient gel electrophoresis
DNA	Deoxyribonucleic acid
EAG	External Assessment Group
EC	Endometrial cancer
HNPCC	Hereditary non-polyposis colorectal cancer
H-SBO	Hysterectomy and bilateral salpingo-oophrectomy
HTA	Health Technology Assessment
IHC	Immunohistochemistry
LS	Lynch syndrome
LY	Life-years
MLH1	MutL homologue 1
MSH2	MutS homologue 2
MLPA	Multiplex ligation-dependent probe amplification
MMR	Mismatch Repair
MSH6	MutS homologue 6
MSI	Microsatellite instability
NGS	Next generation sequencing
NICE	The National Institute for Health and Care Excellence
NPV	Negative predictive value
QALY	Quality-adjusted life-years
QUADAS-2	Quality assessment tool for diagnostic accuracy studies
PCR	Polymerase chain reaction

PLSD	Prospective Lynch Syndrome Database
PMS2	Postmeiotic segregation increased 2
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROB 2	A revised tool to assess risk of bias in randomized trials
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
ROC	Receiver operating characteristic
SSCV	Single-Strand Conformational Variance
TAHSBO	Total abdominal hysterectomy and bilateral salpingo-ophrectomy
VUS	Variant of uncertain significance
WTP	Willingness-to-pay

Definition of terms

Cascadee	A relative of someone who presents with cancer of interest, who can be further identified as first or second degree relatives
Constitutional	Present in every cell of the body
DNA sequencing	Gene sequencing to detect point mutations and small insertions or deletions in genes. Next generation DNA sequencing (NGS) is also used for copy number variation analysis. NGS is also referred to as 'massive parallel sequencing' (MPS) or second-generation sequencing
Germline	Inherited
IHC	Immunohistochemistry is an index test performed on tumour tissue involving chemical staining of a selected panel of proteins to identify errors in these specific proteins
Lynch 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-like	People who have had a negative Germline test and negative somatic tumour testing
Lynch syndrome negative	People who have had Germline testing and a negative result obtained. These may be probands or relatives
Lynch syndrome positive	People who have had Germline testing and a positive result obtained. These may be probands or relatives
MLPA	Multiplex ligation-dependent probe amplification used to detect larger structural changes to genes (deletions, duplications or rearrangements) or NGS data can also identify structural variants
MLH1	One of the 4 proteins identified leading to diagnosis of Lynch Syndrome when a MMR error occurs in one of these at Germline level
MSH2	One of the 4 proteins identified leading to diagnosis of Lynch Syndrome when a MMR error occurs in one of these at Germline level

MSH6	One of the 4 proteins identified leading to diagnosis of Lynch Syndrome when a MMR error occurs in one of these at Germline level
PMS2	One of the 4 proteins identified leading to diagnosis of Lynch Syndrome when a MMR error occurs in one of these at Germline level
Proband	Person who presents with tumour of 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 MMR genes (i.e. inherited mutations which are present in every cell). This involves both DNA sequencing and MLPA techniques
Selected sample	A group of participants limited to only those with particular characteristics, e.g. under 50 years only, without a person/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

1. Introduction

1.1. Description of the health problem

1.1.1. 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 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 for 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 NICE has recommended that people who are diagnosed with colorectal cancer are tested for Lynch syndrome [DG27].[1] Routine testing for Lynch syndrome amongst 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 earlier treatment of cancers.[2, 3]

The External Assessment Group (EAG) assessed the accuracy of immunohistochemistry and microsatellite instability-based testing strategies to identify people who are at high risk of Lynch syndrome, and the clinical and cost-effectiveness of testing for Lynch syndrome amongst people who have endometrial cancer and their biological relatives. This will inform the NICE Diagnostic Advisory Committee (DAC) guidance on whether testing for Lynch syndrome in people who have endometrial cancer represents a cost-effective use of NHS resources.

1.2. Population and target condition

1.2.1. 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.[4] Each year in the UK, there are approximately 9,300 new cases of endometrial cancer and 2,200 endometrial cancer-related deaths.[5] 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.[5] 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%.[6] Risk factors for the development of endometrial cancer include obesity, nulliparity, early age at menarche, use of hormone-replacement therapy, and Lynch syndrome.[7-9]

1.2.2. 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.[10]

Lynch syndrome is usually caused by mutations to any one of four DNA mismatch repair (MMR) genes: MLH1 (MutL homologue 1), MSH2 (MutS homologue 2), MSH6 (MutS homologue 6), or PMS2 (postmeiotic segregation increased 2).[11] A small proportion of Lynch syndrome cases are caused by deletions to the EPCAM gene, which leads to epigenetic silencing of MSH2.[11] 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.[12] Lynch syndrome accounts for 2 - 9% of endometrial cancers.[13, 14] By the age of 75, approximately 57% of people with Lynch syndrome will have endometrial cancer.[12] The type and prevalence of cancer appears to vary according to which of the genes are affected.[12]

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

1.3. Description of technologies under assessment

Three tests areconsidered in this assessment (see section 1.6).There are two primary diagnostic tests (immunohistochemistry and microsatellite instability) and a third test, MLH1 promoter hypermethylation testing may be added to either or both of the other two. Eleven predefined testing strategies are considered, involving varying combinations of the three tests.

1.3.1. Immunohistochemistry

Immunohistochemistry (IHC) 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 section 2.3.3). IHC can detect non-functional but antibody-binding MLH1 proteins (which would be incorrectly classified as normal),[15] therefore this may lead to a false negative result.

1.3.2. Microsatellite instability testing

Microsatellites are short repeats of DNA sequence. 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 microsatellite instability (MSI). MSI testing is used to determine if there are differences in the repeat numbers between tumour and non-tumour regions in a person being tested. Various markers have been described.[16] The Bethesda guidelines identifies 5 markers (BAT25, BAT26, DS123, D17S250 and D5S346) for MSI for Lynch syndrome.[17] Typically, three classifications are derived from this approach:

- MSI-high – two or more markers show instability/more than 30% of markers show instability.
- MSI-low – 1 marker shows instability/less than 30% of markers show instability.
- MSI-stable – 0 markers show instability (also known as MSS).

Additional testing can be conducted to help rule out sporadic epigenetic silencing of MLH1 which might present as Lynch syndrome (see section 1.3.3 MLH1 promoter hypermethylation testing).

1.3.3. MLH1 promoter hypermethylation testing

Hypermethylation is an epigenetic process which 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 an MSI-H result or IHC loss in the MLH1 protein. A positive result on this test suggests 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.[18]

1.4. 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.

1.5. 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 where tumour testing is positive but no Lynch syndrome-related pathogenic variants are identified.[19, 20] This includes testing for other somatic or germline pathogenic variants (e.g. biallelic MuTYH, POLE, double somatic MMR variants).

1.6. Testing strategies

NICE has published guidance on testing for Lynch syndrome amongst people diagnosed with colorectal cancer [DG27].[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.[21] 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 below the age of 50. The 11 proposed testing pathways for the current review are outlined in figures 1 –11 below. Testing strategies include all possible combinations of index tests followed by reference standard testing.

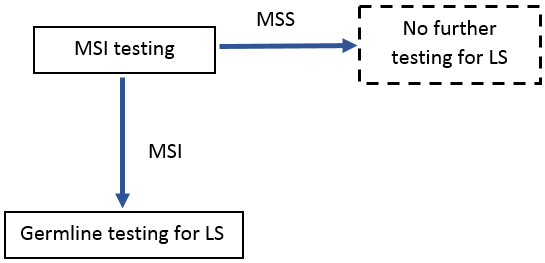


Figure 1: Strategy 1: MSI testing alone (MSS: microsatellite stable, MSI: microsatellite instability, LS: Lynch syndrome)

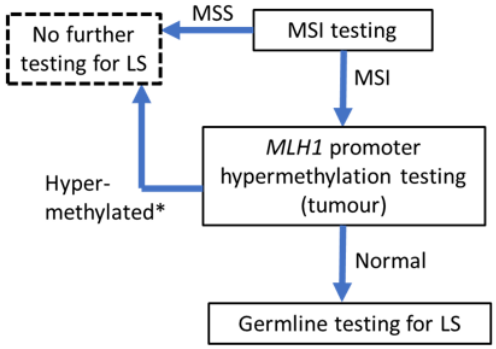


*Figure 2: Strategy 2: MSI testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)*

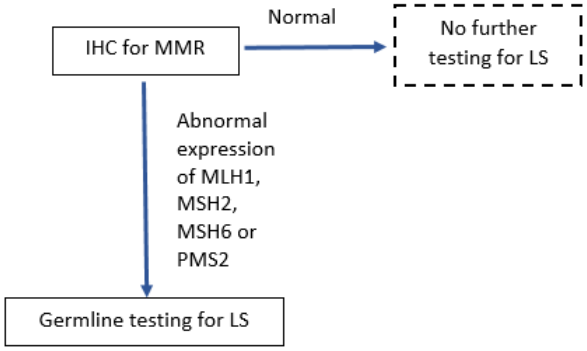


Figure 3: Strategy 3: IHC-based testing (LS: Lynch syndrome)

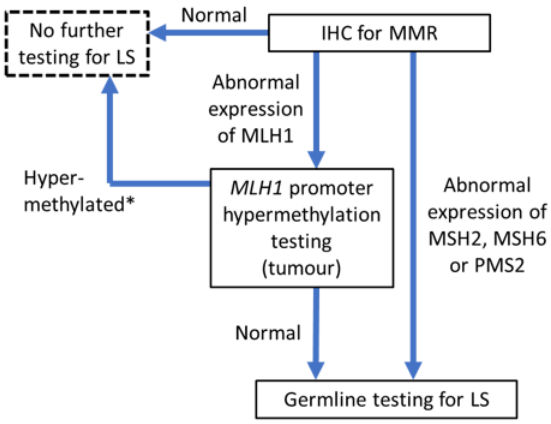


*Figure 4: Strategy 4: IHC testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)*

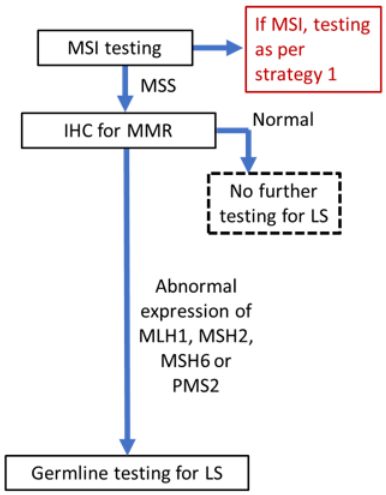


Figure 5: Strategy 5: MSI testing followed by IHC testing

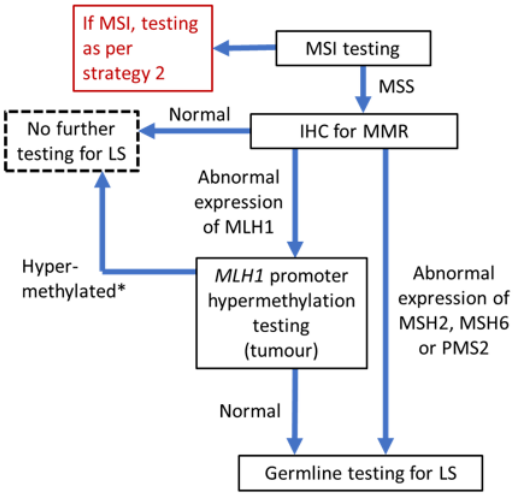


*Figure 6: Strategy 6: MSI followed by IHC testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)*

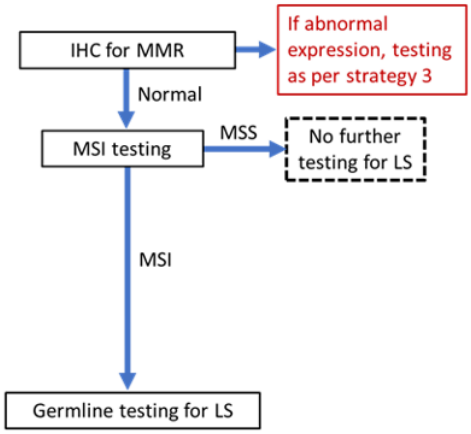


Figure 7: Strategy 7: IHC followed by MSI testing

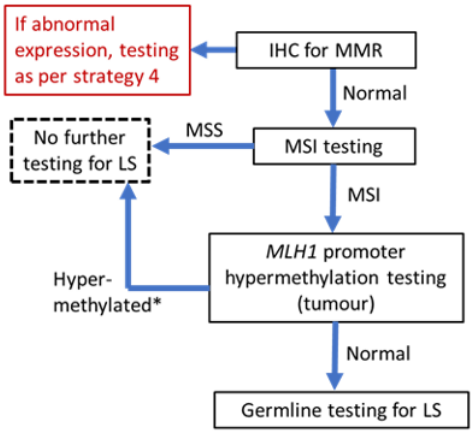


*Figure 8: Strategy 8: IHC testing followed by MSI testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)*

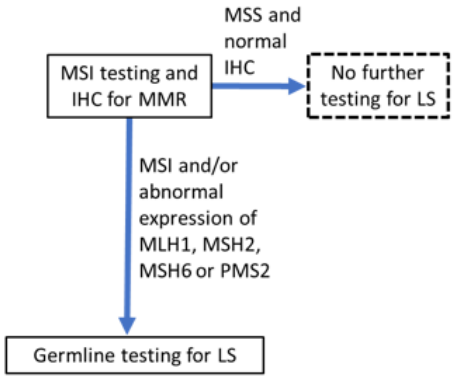


Figure 9: Strategy 9: MSI and IHC testing

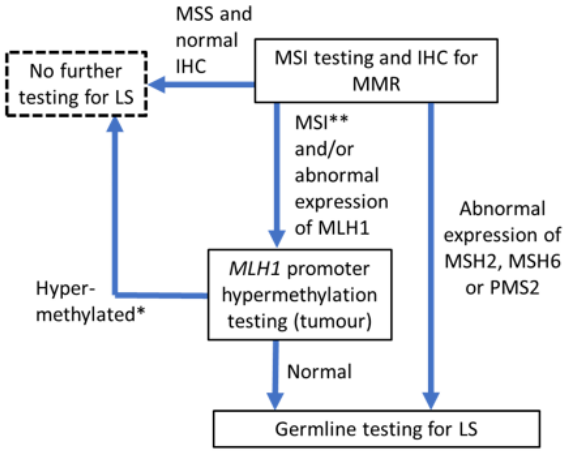


*Figure 10: Strategy 10: MSI and IHC testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome, ** MLH1 promoter hypermethylation testing not conducted after MSI if MLH1 expression on IHC is normal and abnormal expression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

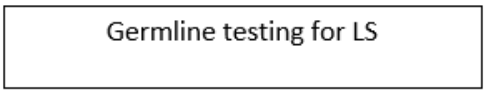


Figure 11: Strategy 11: Germline testing only

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,[22] the European HNPCC Expert group,[23] the Royal College of Obstetricians and Gynaecologists,[24] and the Manchester International Consensus Group.[20]

1.7.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 (NICE guidance DG27).[1] NHS England's National Genomic Test Directory (Testing Criteria for Rare and Inherited Disease) specifies testing criteria for inherited MMR deficiency (Lynch syndrome).[21] Affected individuals with Lynch-related cancer should meet 1 of the following criteria:

- Colorectal cancer (any age; as per NICE guidance), OR
- Lynch-related cancer (<50 years), OR
- Two Lynch-related cancers (any age, one is colorectal or endometrial), OR
- Lynch-related cancer and ≥ 1 first degree relative has Lynch-related cancer (both occurred <60 years, one is colorectal or endometrial), OR
- Lynch-related cancer and ≥ 2 relatives (first / second / third degree relatives) have Lynch-related cancer (all occurring <75 years, one is colorectal or endometrial), OR
- Lynch-related cancer and ≥ 3 relatives (first / second / third degree relatives) have Lynch-related cancer (occurring any age, one is colorectal or endometrial).

The recommended follow up care for those with CRC diagnosed with LS is outlined in the guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/ United Kingdom Cancer Genetics Group (UKCGG), NICE guidance DG27 and the NICE draft guideline on the effectiveness of aspirin in the prevent of CRC.[1, 25, 26] 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 round 97.5%.[1]

Testing for Lynch syndrome in people with endometrial cancer in the UK NHS varies nationally, with some NHS services testing all tumours and others doing no routine testing. The Manchester International Consensus Group, American College of Obstetricians and Gynecologists and ESMO clinical practice guidelines recommended a range of surveillance and preventative measures for those with gynaenacological cancers including risk-reducing total hysterectomy and bilateral salpingo-oophorectomy, individualized counselling, colorectal surveillance, lifestyle modifications, use of the combined oral contraceptive and daily asprin for those with MMR pathogenic variant carriers.[20, 27, 28]

1.8. Outcomes

The outcomes from the clinical effectiveness assessment were:

- Prevalence of Lynch syndrome, and variants of uncertain significance,
- Test accuracy

The outcome from the cost effectiveness analysis is cost per QALY for each of the 11 testing strategies in comparison to usual care. Other intermediate outcomes reported include:

- Number of probands with LS receiving LS surveillance (TP accepting)
- Number of probands with LS not receiving LS surveillance (LS positive who decline and those assumed FN although without testing cannot confirm)
- number of VUS and Lynch assumed diagnoses

2. Decision questions and objectives

The overall aim of this project was 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 the clinical (key question 2) and cost effectiveness (key question 3) of testing for Lynch syndrome amongst people who have been diagnosed with endometrial cancers. The key questions for this review are provided in the box below.

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?

Sub questions

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 amongst people who have endometrial cancer, and/or their relatives?

Sub questions

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 amongst people diagnosed with endometrial cancer using IHC and MSI-based strategies compared to the current pathway for the diagnosis of Lynch syndrome*?*

3. Methods

3.1. 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 sub questions:

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 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?)

2. 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 of Diagnostic Test Accuracy[29] and the NICE Diagnostic Assessment Programme manual.[30]

3.1.1. Identification and selection of studies

3.1.1.1. Search strategy

The search strategy comprised the following main elements:

1) Searching of electronic bibliographic databases,
2) Contacting experts in the field, and
3) 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, 10] and scoping searches (personal communication, D Barnes, NICE, 2019). 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: Literature search strategies. Searches were conducted in the following databases, from inception: MEDLINE All (via Ovid); Embase (via Ovid); Cochrane Database of Systematic Reviews (via Wiley); CENTRAL (via Wiley); Database of Abstracts of Reviews of Effects (DARE) (via Centre for Reviews and Disseminations (CRD)); Health Technology Assessment (HTA) database (via CRD); Science Citation Index and Conference Proceedings (via Web of Science); PROSPERO International Prospective Register of Systematic Reviews (via CRD). Additionally, references of included studies and relevant systematic reviews were checked and experts on the team consulted.

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

3.1.1.2. Study eligibility criteria

Studies that satisfy the following criteria were included:

Population	All test accuracy questions People with endometrial cancer with no known diagnosis of Lynch syndrome

Target condition	<u>All test accuracy questions</u> Lynch syndrome
Intervention	<u>All test accuracy questions</u> 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	<u>All test accuracy questions</u> Genetic verifications of constitutional mutations in the MMR genes through: sequencing with or without multiplex ligation-dependent probe amplification. 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 for genetic testing and diagnosis of Lynch syndrome, i.e. array-based comparative genomic hybridization, and long-range PCR.[31]
Comparator	<u>Key question</u> No reflex testing <u>Sub questions 1a and 1b</u> 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 <u>Sub question 2</u> No reflex testing

Outcome	Key question Test accuracy, detection rate, sensitivity and specificity, predictive values, likelihood ratios, diagnostic odds ratios, receiver operating characteristic (ROC) curves and numbers of true positive, false positive, true negative, 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 1. Time from test being conducted to test result being given, and/or 2. Time from test being conducted to diagnosis being given Sub question 1a Concordance between IHC and MSI (fractions, kappa, % agreement) Sub question 1b Any available characteristics of the population or tumours, including family history, and results of germline testing Sub question 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, randomised controlled trials, cohort studies and case-control studies. Head-to-head (direct comparison) studies were prioritised Sub questions 1a and b 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 Sub question 2 All study designs were included, including randomised controlled trials, 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 provide numerical data and sufficient detail on methodology to enable assessment of study quality/risk of bias. Further, 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

Papers that fulfil 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 where more than 10% of the sample do 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 the English language. Studies using index tests other than those specified in the inclusion criteria. 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 that are at higher risk of Lynch syndrome because of the different risk profile). If sufficient head-to-head studies are identified that can provide meaningful analysis, other study designs were excluded.

3.1.1.3. Review strategy

Two reviewers (CS, 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, 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 have be documented, including the reasons for their exclusion.

3.1.2. Extraction and study quality

3.1.2.1. Data extraction strategy

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

3.1.2.2. Assessment of study risk of bias

The risk of bias of test accuracy studies were assessed using a modified QUADAS-2.[32] Two reviewers (CS, 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.[32] The results of each risk of bias item are presented in table and graph form.

3.1.3. 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, i.e. individuals who are index test positive (at higher risk for the disease or condition) receive the reference standard, while individuals who are index test negative do not receive the reference standard. While this approach accurately reflects how tests are used in clinical practice it leads to partial verification bias (also called detection bias or work-up 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.[33] 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, i.e. true positives, false positives, true negative, false negatives, sensitivity, specificity, positive predicitive values, and negative predictive values. For 'partial' test accuracy studies, we present results only for those test accuracy metrics that relate to participants who have received both the index test and reference standard, i.e. true positives, false positives, and positive predicitive values. Further, 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 positive predictive value upwards, we only included studies in which at least 95% of women who were eligible for germline testing

(those who were index test positive) received it. The sensitivity, specificity, positive predictive- and negative predicitive estimates 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 were calculated using Wilson's continuity correction.[34]

Test accuracy results are presented for testing strategies 1 – 10, comparing the index tests to 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, i.e. (1a) IHC alone, then (1b) IHC *plus MLH1* promoter hypermethylation testing, (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 MSI-L and MSI-H patients. Subgroup analysis was not conducted for the different combinations of microsatellite markers due to the small number of studies and the wide range of panels used. Our main analysis assumed MSI low are test negative. Due to insufficient data we did not conduct subgroup analyses of test accuracy by (1) age (under vs over 70 years) or (2) amongst 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"). A narrative summary of the evidence is presented because meta-analysis was not possible due to 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 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. Due to 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 for genetic testing and diagnosis of Lynch syndrome, i.e. array-based comparative genomic hybridization, and long-range PCR.[31] 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 sub-analysis, 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 are used. Due to the small number of studies using alternative tests, we did not compare the results of these multi-stage reference standards to the results of germline testing for MLH1, MSH2, MSH6, and PMS2 using sequencing with or without MLPA.

3.1.4. Quality assessment strategy for test accuracy studies

Quality assessment of eligible test accuracy studies was undertaken with a tailored Quality Assessment of Diagnostic Accuracy Studies – 2 (QUADAS-2) tool. Methodological quality was assessed by two independent reviewers. Disagreements were resolved by consensus or use of a third reviewer.

Modifications to tailor the QUADAS-2 form to the research question in terms of the risk of bias assessment were as follows (see Appendix 2 for 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 quality assurance measures are in place.

3.2. Methods for assessing clinical effectiveness

Key question 2

What are the benefits and harms of testing for Lynch syndrome amongst people who have endometrial cancer, and/or their relatives?

Sub questions

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?

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.[30] We conducted a literature search to identify end-to-end studies of testing for Lynch syndrome amongst 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 section 4) were employed to address this question. The sub-questions are designed to identify the benefits and harms of the two main surveillance strategies which would be employed after identification with Lynch syndrome.

Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[35] and the NICE Diagnostic Assessment Programme manual.[30]

3.2.1. Identification and selection of studies

3.2.1.1. Search strategy

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

3.2.1.2. Study eligibility criteria

Studies that satisfy the following criteria were <u>included</u>:

Population	<u>Key question</u> People with endometrial cancer with no known diagnosis of Lynch syndrome, and/or their relatives <u>Sub questions 1 and 2</u> People with endometrial cancer who have also been diagnosed with Lynch syndrome, and/or their relatives
Target condition	<u>Key question</u> Lynch syndrome <u>Sub question 1</u> Colorectal cancer

	Sub question 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 hybridization, 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 colorectal cancer 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 hybridization, 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 colorectal cancer 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 hybridization, 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 colorectal cancer or gynaecological cancers Sub question 1 Surveillance/testing for colorectal cancer Sub question 2 Surveillance/testing for gynaecological cancers (endometrial, ovarian, cervical, vaginal and vulval)
Comparator	Key question No testing for Lynch syndrome Sub questions 1 and 2 No surveillance/testing
Outcome	Key question Mortality Morbidity

	Type and number of Lynch syndrome-related cancers Health-related quality of life using validated tools Anxiety using validated tools Depression using validated tools Change in patient management Number of cascade tests on first/second-degree relatives 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 <u>Sub question 1</u> Colorectal cancer incidence Number of interventions related to surveillance for Lynch syndrome-related cancers Number of risk reducing interventions for Lynch syndrome-related cancer Colorectal cancer-related mortality Colorectal cancer-related morbidity Health-related quality of life using validated tools Anxiety using validated tools Depression using validated tools Change in patient management <u>Sub question 2</u> 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) Health-related quality of life using validated tools Anxiety using validated tools Depression using validated tools Change in patient management
Study design	<u>All questions</u> Randomised controlled trials Controlled trials
Publication type	<u>All questions</u> 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. Further, only data on outcomes that have not been reported in peer-reviewed full text papers was extracted and reported.
Language	All questions English

Papers that fulfil 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 where more than 10% of the sample do 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 the English language. Studies using index tests other than those specified in the inclusion criteria.

3.2.1.3. Review strategy

Two reviewers (CS, 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, 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) when required.

3.2.2. Extraction and study quality

3.2.2.1. Data extraction strategy

No studies met the inclusion criteria so no data extraction took place.

3.2.2.2. Assessment of study risk of bias

We planned to assess the risk of bias using the Cochrane revised tool to assess risk of bias in randomized trials (RoB 2)[36] and the Cochrane risk of bias in non-randomized studies of interventions (ROBINS-I) tool.[37] No studies were included so no risk of bias assessment took place.

3.2.3. Methods of analysis/synthesis

No studies were identified which met the inclusion criteria so no data synthesis was undertaken.

3.3. Methods for assessing Cost effectiveness

Key question 3

What is the cost-effectiveness of testing for Lynch syndrome amongst people diagnosed with endometrial cancer using immunohistochemistry and microsatellite instability-based strategies compared to the current pathway for the diagnosis of Lynch syndrome?

3.3.1. Review of existing cost-effectiveness models

3.3.1.1. 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 studies (HRQoL) 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/cost/HRQoL, or endometrial cancer and testing and economic/cost/HRQoL. 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: Literature search strategies

The following databases were searched, from inception: MEDLINE All (Ovid); Embase (via Ovid); National Health Service Economic Evaluation Database (NHS EED) and HTA database (via CRD); Science Citation Index and Conference Proceedings Science (via Web of Science); Cost-Effectiveness Analysis (CEA) registry; EconPapers (Research Papers in Economics (RePEc)); 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.

3.3.1.2. 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:-

- Microsatellite instability-based testing (with/without MLH1 promoter hypermethylation testing) followed by germline testing
- Immunohistochemistry (with/without MLH1 promoter hypermethylation testing) followed by germline testing
- Combination of microsatellite instability-based testing and immunohistochemistry (with/without promoter hypermethylation) 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 (ICER) e.g. cost per quality-adjusted life year (QALY) gained).

Study design:

- Studies comprising an economic evaluation (cost analysis, cost-consequence 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 Language
- Abstracts (only if they are companion publications to full text included studies)
- Only humans

3.3.1.3. Methods

The search was run by our information specialist (RC). Sifting was undertaken by 2 reviewers. MJ lead the review sifting abstract and titles of all identified studies while CS, JK, HF and LK acted as second reviewers. Results between 1st and respective 2nd reviewer were then compared and anomalies resolved through discussion or where this was not possible by recourse to the full team of reviewers. Full text of the result of the first sift were obtained and screened using the same process.

3.3.1.4. Data extraction

Information was extracted by one reviewer using a pre-piloted data extraction form 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 (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness current, assumptions and analytical methods), results (study parameters, base-case and sensitivity analysis results), discussion (study findings, limitations of the models and generalisability), other (source of funding and conflicts of interests), overall reviewer comments and conclusions (author's and reviewer's). 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.

3.3.1.5. Quality assessment

The reporting quality of the studies included in the systematic review was assessed against the Consolidated Health Economic Reporting Standards (CHEERS)[38] and the Philips' checklist,[39] respectively.

The economic evaluations were appraised against a framework for best practice for reporting economic evaluation studies developed by the CHEERS task force. [38] 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 the criteria have been clearly reported. Additionally, the models were critically appraised against a framework for best practice for reporting decision-analytical models developed by Philips et al.[39] 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 the criteria have been clearly reported (see Appendix 6: Quality assessment for the completed assessment of studies included in the systematic review).

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.

3.3.1.6. Data synthesis

Information extracted from the included studies was summarised and presented in Table 11. Due 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.

3.3.2. 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 for women newly diagnosed with EC, to offer testing to relatives of those thereby identified with Lynch, and to offer interventions to those identified with Lynch (probands and cascadees) aimed at reducing the risk of them developing (further) Lynch 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 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, compared with not knowing this. The impact occurs due to various risk reduction and surveillance interventions which can be offered once it is know that a person has Lynch. The costs and consequences of these interventions need to be modelled from the point at which they are offered, over the lifetime of the recipient.

We adopted a modular approach involving two sub-models, 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 EC from the point at which an individual is identified with Lynch, until their death (from CRC, EC, or other causes). 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 might be identified, as a table. This table

became an input for the decision tree model, hence integrating the two sub-models in a unified model.

Construction of the model involved consulting the previous Health Technology Assessment (HTA) report undertaken by Snowsill and colleagues comparing diagnostic strategies to identify Lynch syndrome in people with colorectal cancer.[10] This also comprised two separate stages, a diagnostic 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. Additionally, data and the modelling approach used by Snowsill in his cost-effectiveness analysis of reflex testing for LS in women with endometrial cancer[40] was drawn upon, 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 Excel, and a subsequent Markov cohort state transition model, in R software package, to estimate the long-term benefits accrued through risk reduction and surveillance measures for both CRC and EC as a result of LS identification and cascade testing of relatives.

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

The model is described in greater detail below.

3.3.2.1. Diagnostic decision tree

This section of the model estimates the number of EC probands and their relatives diagnosed with Lynch syndrome using the 11 strategies for inclusion within this review against the comparative strategy of no reflex testing. Figure 12 shows an overview of the testing pathway modelled for EC 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 LS or who are assumed to have LS.

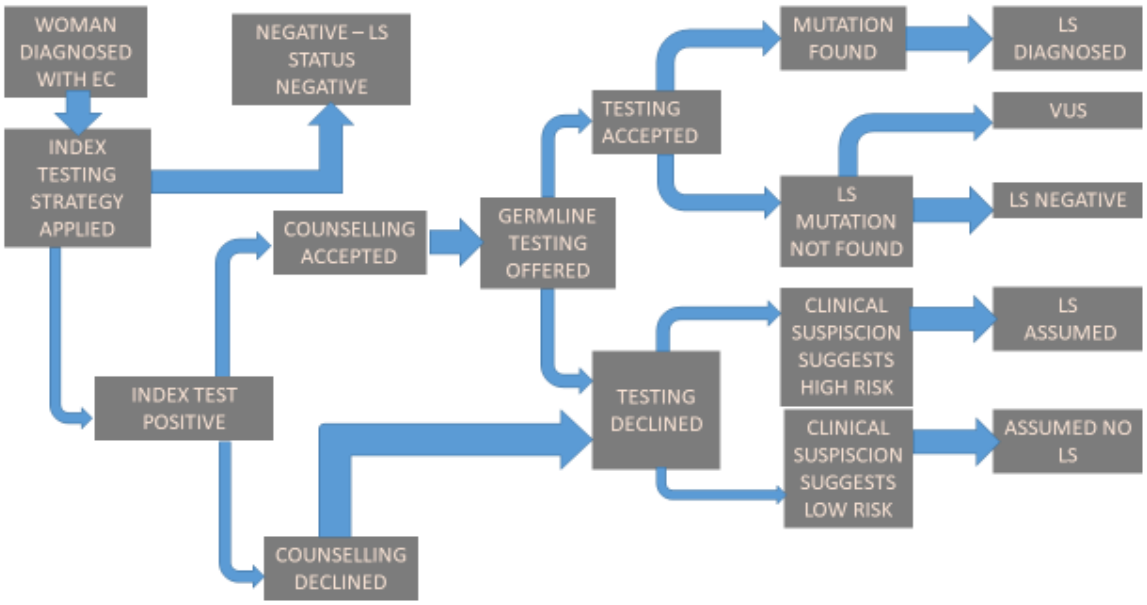


Figure 12: Overview of diagnostic model for probands

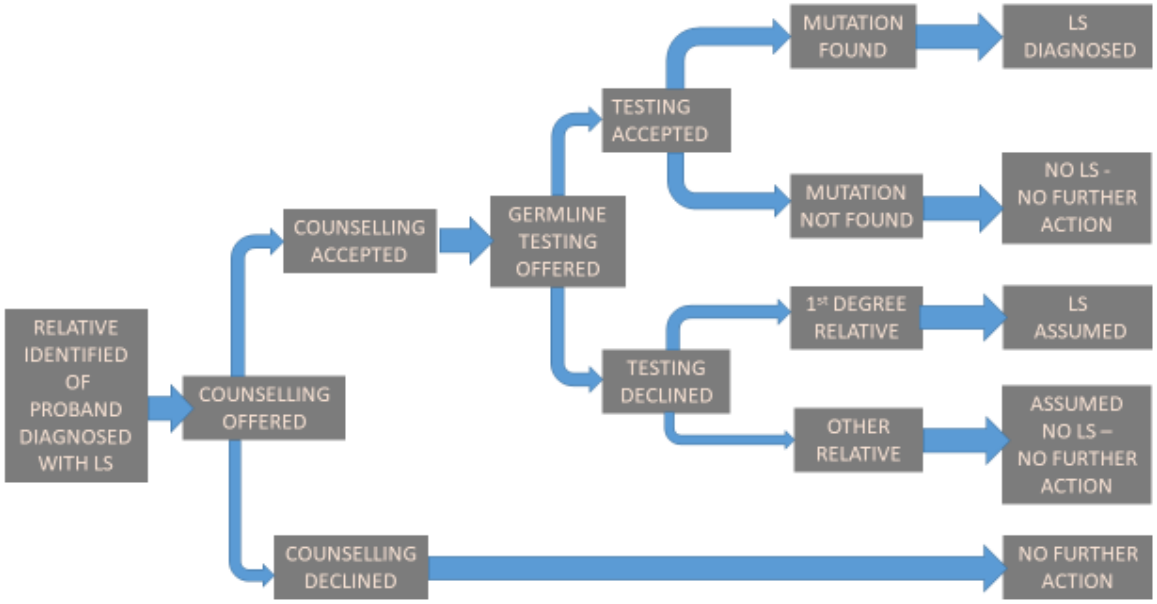


Figure 13: Overview of testing and management pathway for relatives of probands

Probands with EC enter the model and are assigned to one of the 11 diagnostic strategies under assessment. Their path through the model is dependent upon the result of the index test (combination of tests in the strategy) 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, LS status is confirmed.

Probands with a positive index 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 LS mutation negative except for a specified proportion who are Assumed LS based on clinical suspicion.

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

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 EC probands.

Diagnostic strategies for probands

Strategies modelled within the diagnostic component are:

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 for Lynch syndrome-related mutations
6. MSI followed by IHC plus *MLH1* hypermethylation then germline for Lynch syndrome-related mutations
7. IHC followed by MSI then germline for Lynch syndrome-related mutations
8. IHC followed by MSI plus *MLH1* hypermethylation then germline 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* hypermethylation testing then germline for Lynch syndrome-related mutations

11. Germline testing for Lynch syndrome-related mutations

These strategies are compared against no testing for Lynch syndrome-related mutations and fully incremental analysis performed to report outcomes as an ICER 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 LS and offered LS 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 LS 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 LS receiving LS surveillance and the number of probands with LS not receiving LS surveillance. As EC probands are considered not to be at risk of further EC, only female relatives of EC probands who are diagnosed with LS are offered risk reducing interventions for EC.

Probands who test negative for a pathogenic mutation on index tesing are diagnosed with sporadic EC and continue with standard EC management. They are neither offered surveillance nor is cascade tesing pursued with their relatives.

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

Probands with positive index results on tumour tissue and negative germline results are considered LS negative, but in a proportion of these clinical suspicion of LS remains. Similarly, despite negative results for currently identified pathogenic mutations for LS germline testing may detect other mutation variances on these genes. These Variations of Uncertain Significance (VuS) may be later identified as pathogenic for LS or not, in which 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 VuS is non-pathogenic for LS and management is then downgraded to that of non-LS 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 assumed.

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

Diagnostic strategies for relatives

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

Outcomes of diagnostic model for relatives

Relatives who test positive for a pathogenic mutation at germline testing are diagnosed with LS and offered LS 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 LS and no further surveillance measures are offered.

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

Outcomes of diagnostic model for relatives

Relatives who test positive for a pathogenic mutation at germline testing are diagnosed with LS and offered LS 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 LS and no further surveillance measures are offered.

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

Outcomes of diagnostic model summary

- number of probands with LS receiving LS surveillance (TP accepting)
- number of probands without LS receiving LS surveillance (FP accepting)
- number of probands without LS who do not receive LS surveillance (delineated as those identified as LS positive who decline surveillance and those diagnosed LS negative. (FP declining and TN not offered)
- number of VUS and Lynch assumed diagnoses

3.3.2.2. 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-related cancers. We use these models to predict the benefit of being identified with Lynch through cascade testing by simulating incidence and mortality with, and without, surveillance and risk reduction measures, which we assume are adopted once Lynch 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, sex, and previous Lynch 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 below).

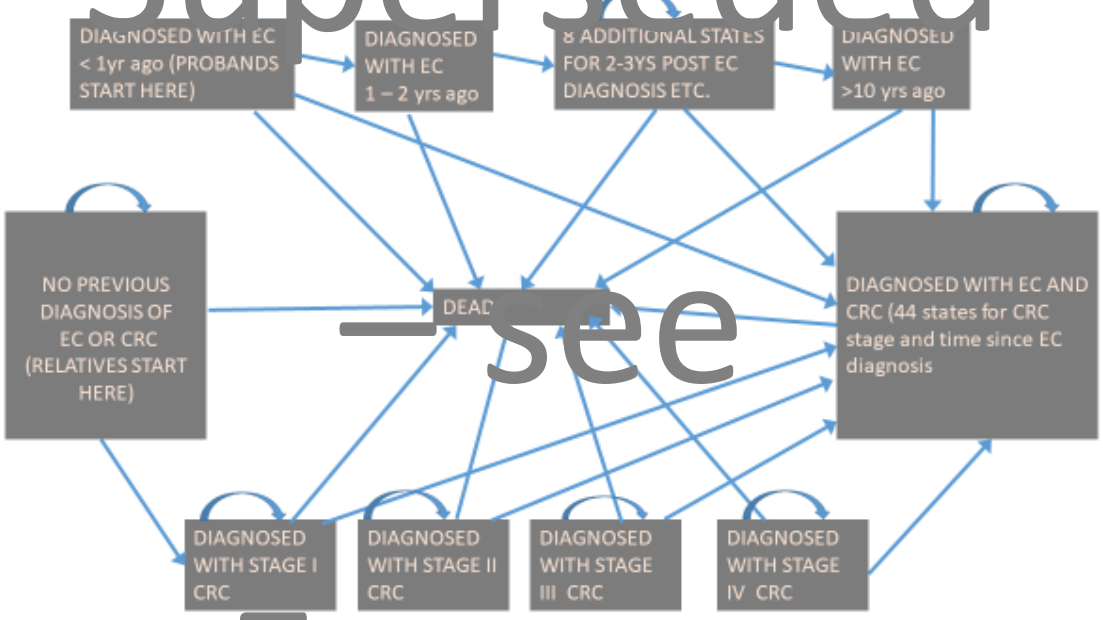


Figure 14: : Overview of Long term model diagram

The model has five states – cancer free, CRC, EC, both CRC and EC, and dead. The EC state comprises 10 ‘tunnel states’ reflecting time since incidence of EC. 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, male or female, and start in any state. The state for women who have both EC and CRC therefore has

4 sub-states, each with 10 tunnel states. For this decision problem, we simulate cohorts who are cancer-free or recently diagnosed with EC, male or female, and aged in annual increments between 25 and 74. This gives 200 cohorts in total. We do not model outcomes for those without Lynch, on the assumption that they experience no long term costs and benefits from Lynch testing.

For the comparator, we assume that, as the person is unaware of their Lynch status, no surveillance or risk reduction measures are offered. We model age-related annual incidence of CRC and EC. For CRC, we further assume that incidence is gene-dependent. In line with Snowsill et al,[40] we assume that this incidence has a lognormal distribution. Previous work in this field has drawn on data on individuals with Lynch who benefit from colonoscopic surveillance. We follow that work in assuming that, based on Jarvinen et al.,[41] surveillance reduces incidence with a hazard ratio of 0.387. We apply this to the lognormal distritubion to derive the incidence rates illustrated below.

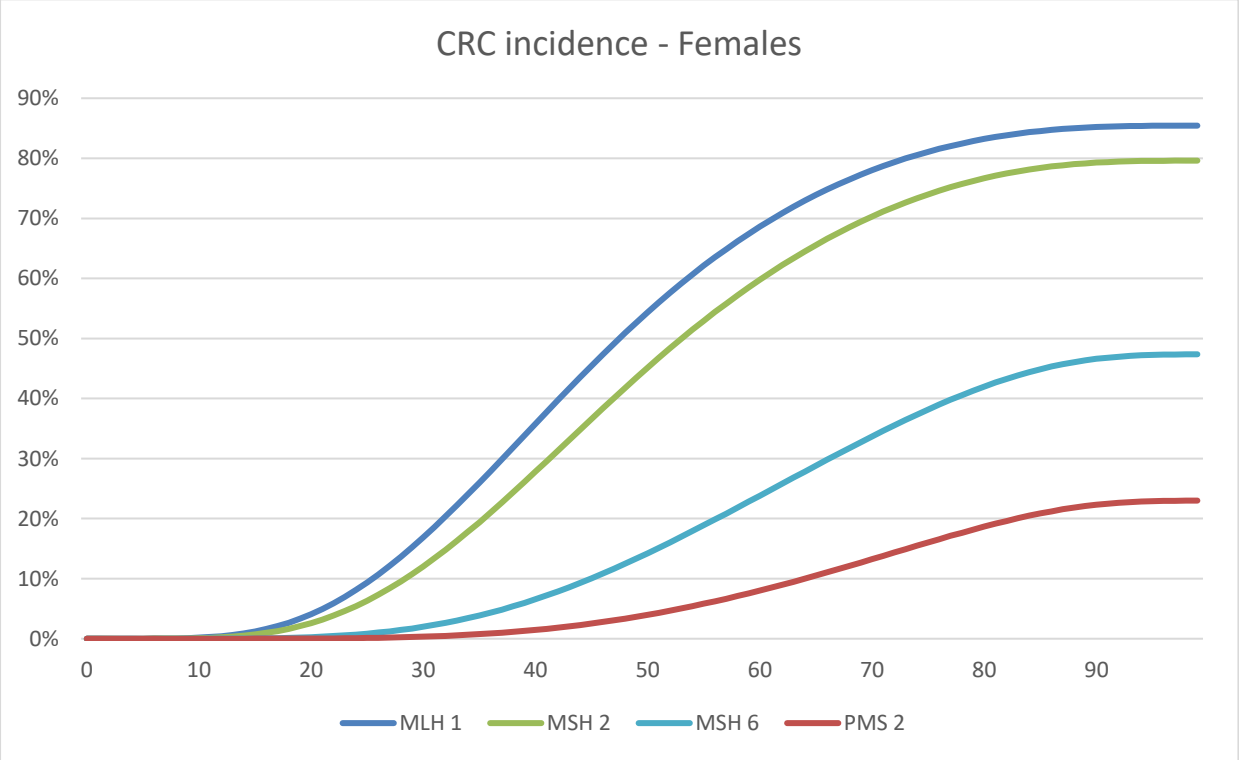


Figure 15:Modelled cumulative incidence of CRC in females with Lynch Syndrome, assuming no surveillance

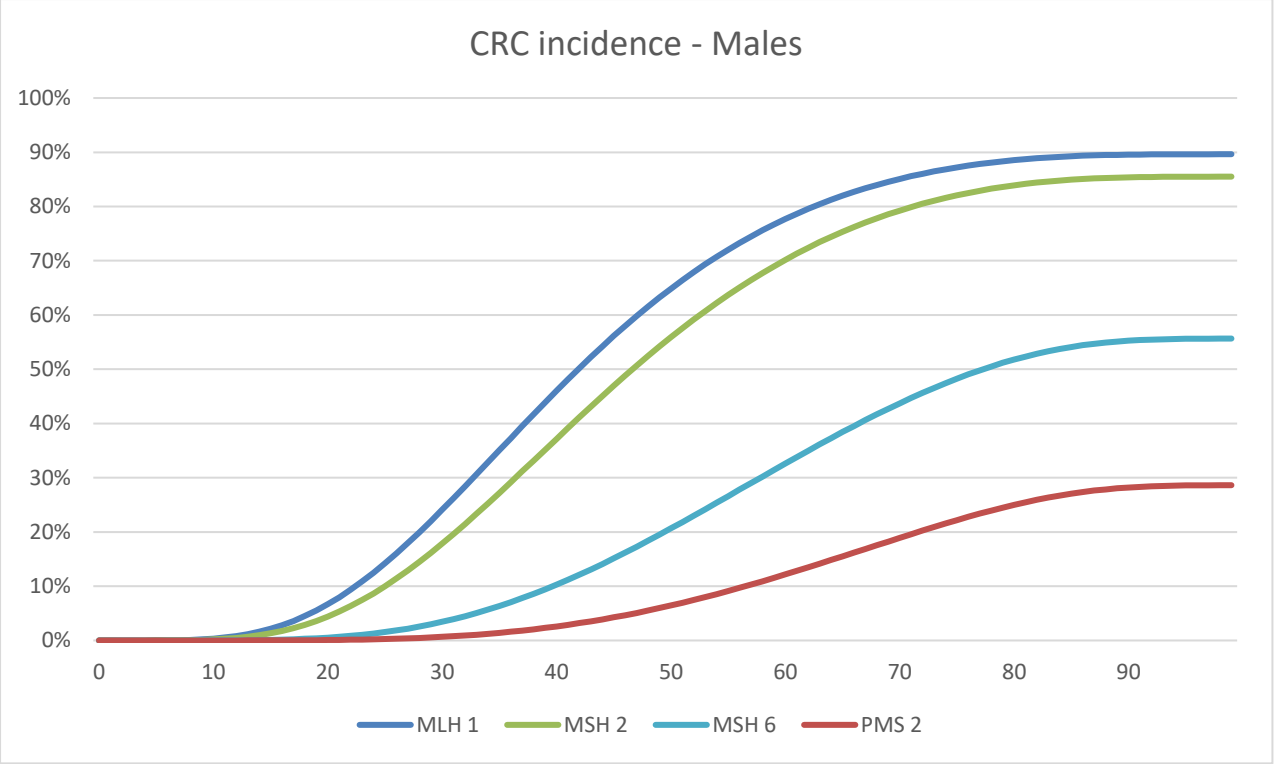


Figure 16: Modelled cumulative incidence of CRC in males with Lynch Syndrome, assuming no surveillance.

For EC, we source incidence data from the Prospective Lynch Syndrome Database, recently published in Genetics in Medicine.[42] This database reported gene-based risk of cancer based on 6350 individuals with Lynch. Risks are reported at age 25, 40, 50, 60,70 and 75. We fitted a piecewise linear model to these data. The cumulative lifetime incidence of EC in the absence of preventative measures implied by this assumption is illustrated below.

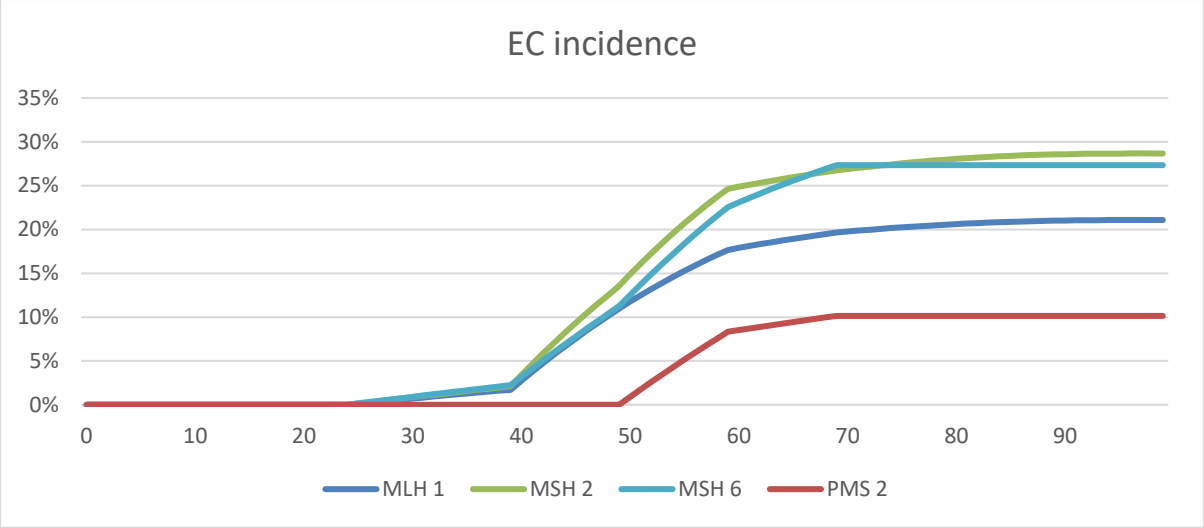


Figure 17: Modelled cumulative incidence of endometrial cancer in females with Lynch Syndrome.

For CRC, we assume that the proportion presenting in stages I to IV are 18.8%, 48.8%, 21.3% and 11.3% respectively. We assume a one-off cost of treatment, dependent on age and stage at diagnosis.

Table 1: Table of one-off whole diease treatment costs of CRC by age and stage

	STAGE I	STAGE II	STAGE III	STAGE IV
0-49	£8,754.12	£8,740.53	£14,489.51	£11,704.91
50-59	£5,712.39	£7,015.84	£9,691.73	£8,443.68
60-69	£4,623.22	£5,351.77	£7,259.39	£6,508.89
70-79	£3,177.62	£3,454.61	£4,485.25	£4,365.04
80+	£1,379.75	£1,545.95	£1,560.59	£806.95

We assume CRC mortality is stage dependent with transition probabilities of 0.009, 0.035, 0.098 and 0.543 for stages I to IV respectively.[40]

For EC, we assume a one-off treatment cost of £6,510, in line with previous work.[10] We draw on CRUK reported statistics on EC mortality,[43] and assume these are the same for those with Lynch syndrome as those without. We assume that the those who have one Lynch 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 apply an age-dependent transition probability for mortality from other causes. All those still alive in the model are assigned an age-

dependent quality-of life utility weighting using accepted methodology by Ara,[44] except that those with CRC stage 4 are assigned a utility of 0.178 as modelled by Snowsill.[10]
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 CAPP2 trial[118] 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 EC and CRC risk).
CRC surveillance: We assume that individuals known to have Lynch Syndrome have biennial colonoscopies from age 25 (or age at identification of Lynch if later) until age 74. We assume the cost of colonoscopy is £325.00.[45] We assume that 100,000 colonoscopies result in 8.3 deaths, 40 perforations, and 55 bleeding events requiring hospital treatment (of which 40 are mild, 10 are moderate, and 5 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 propotions 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 EC: We assume that women with Lynch can opt for hysterectomy and oophorectomy (hysterectomy with bilateral salpingo-oophorectomy, H-BSO), and that this elimitates their risk of EC. We assume that the uptake of this increases with age, as shown below. The cost of this is assumed to be £3,428.

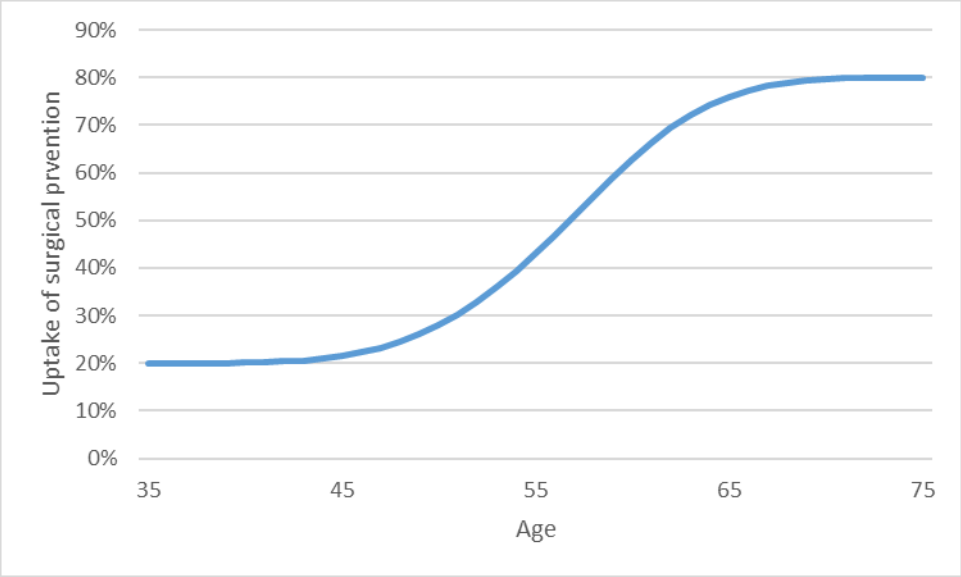


Figure 18: Uptake of surgical prophylaxis

Gynaecological surveillance: We assume that women who have not had surgical prophylaxis undergo annual surveillance to detect EC. 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. This does not affect the incidence of EC , but reduces mortality by 10.2%.

3.3.3. Parameters

Parameter input values for both diagnostic and long-term components of the model were sourced from literature obtained during the clinical and cost-effectiveness systematic literature review process, with the best available evidence used to inform the base case. Where suitable input parameters were not obtained, targeted searches were undertaken and individual publications critiqued. Additional information was also provided by clinical experts within the field. Discussion and critique of the sources of each parameter is detailed in the results section 6.4.1.

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

Each year:

Transition occurs from all states into the death state based on annual mortality rates for all causes other than CRC or EC. Death from the respective cancer state is accounted for in

further transition from CRC, based on stage, and from EC based on length of time they have spent in the EC state. Transitions from all states to death based on all cause mortality. Further transitions from CRC or CRC+EC to death based on stage (CRC) or dwell time in state (EC).

Survivors in the EC or EC and CRC states at the end of each cycle move into the next tunnel state or remain in the final tunnel state prior to death).All those in EC or EC+CRC state who survive move to the next tunnel state (or stay in tunnel state 10)
Quality of life score are 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 the 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 QoL score based on their age.
Those who move into 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 ameliorating measures, and once assuming measures are applied (since the model starts at the age at which an individual would be identified with Lynch 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 above. It is assumed that the costs of aspirin, as a cheap OTC medication, are not borne by the NHS.

The outputs from the model were the incremental costs and QALYs resulting from the addition of Lynch cancer ameliorating measures. These were calculated separately by sex, for those cancer-free and those recently diagnosed with EC, and for ages 25-74 in one year intervals. These results provide an estimate of the benefit of Lynch 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 numbers in, and moving between, each state. These allowed life years gained, cancers avoided, and cancer deaths prevented, to be calculated.

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, and that the mean age of probands was 49. 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 recently diagnosed aged 49 with EC 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.

3.3.4. 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 they originated from the described source. Further, the reviewer constructed an alternative version of the diagnostic model in Tree Age (rather than Excel) so cross checking of results could also be carried out.

3.3.5. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis 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 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; 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 which could be used as an input table for the pay-off nodes for probands and relatives with Lynch in the decision tree model when it was run stochastically, producing PSA outputs which reflected joint uncertainty across the two models.

3.3.6. Sensitivity Analysis

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

3.3.7. Scenario Analyses

Alternative analyses were conducted for the following scenarios:

1. Strategy level test accuracy obtained from (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019)
2. Costs of testing obtained from (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019)
3. Strategy level test accuracy obtained from (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019) and costs of testing obtained from Ryan et al. (2019)[46]
4. Disutility due to cancer inflated
5. Gynaecological surveillance excluded
6. Three-year colonoscopy surveillance
7. Excluding benefit from Aspirin
8. Excluding HR reducing incidence of CRC due to surveillance

3.3.8. Assumptions in base case

- MSI-H results are treated as a positive indicator of LS while MSI-L results are treated as a negative
- The sensitivity of MSI and IHC testing did not depend on which MMR gene is mutated
- The average number of relatives per proband was 6 (2.5 of whom were first-degree relatives).
- Colorectal surveillance colonoscopies occurred every 2 years starting age 25 and stopping at 75

- Surveillance colonoscopies are effective immediately upon commencement of surveillance and ineffective immediately after discontinuation (i.e., no lag time)
- Disutility is only applied to people with stage IV colorectal cancer.
- EC not modelled for women without Lynch syndrome-causing mutations
- Treatment for EC assumed to be total abdominal H-BSO ± chemotherapy ± radiotherapy
- Survival of endometrial cancer not affected by Lynch syndrome status
- Surveillance for EC comprises annual review with GP with 10% of women attending referred for invasive gynaecological surveillance consisting of gynaecological examination, transvaginal ultrasound, endometrial biopsy and 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 (TAHBSO) eliminates risk of EC
- Prophylactic hysterectomy (TAHBSO) is offered to all female relatives with no age restrictions

4. Clinical Effectiveness Results

4.1. Clinical effectiveness results

4.1.1. Search results

Figure 19 is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram that illustrates the study selection process for the clinical effectiveness review. The search identified 6259 records though database and other searches. Following duplicate removal, we screened 3308 records of which 2968 were excluded by their titles and abstracts, leaving 340 full texts assessed for eligibility for inclusion in the review. 296 papers were subsequently excluded leaving 44 papers.[13, 14, 47-88] All 44 papers were relevant for key question one 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 was that there was no eligible reference standard in the studies or that too little information was included to enable quality appraisal. One additional unpublished study, the PETALS study, was provided by NICE and included for key question one (personal communication, Ryan et al, University of Manchester, 11/12/2019). The full list of excluded studies with reasons for exclusion can be found in Appendix 4: Table of excluded studies with rationale.

For key question two, on the clinical effectiveness benefits and harms of testing for Lynch syndrome amongst 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 pre-defined inclusion criteria as stated in the protocol (5.1.2). No studies were identified that were relevant for key question two on the clinical effectiveness benefits and harms of testing for Lynch syndrome amongst people who have endometrial cancer, and/or their relatives. The most common reason for exclusion of clinical effectiveness studies at this stage were study design (not RCTs). The full list of excluded studies with reasons for exclusion can be found in Appendix 4: Table of excluded studies with rationale

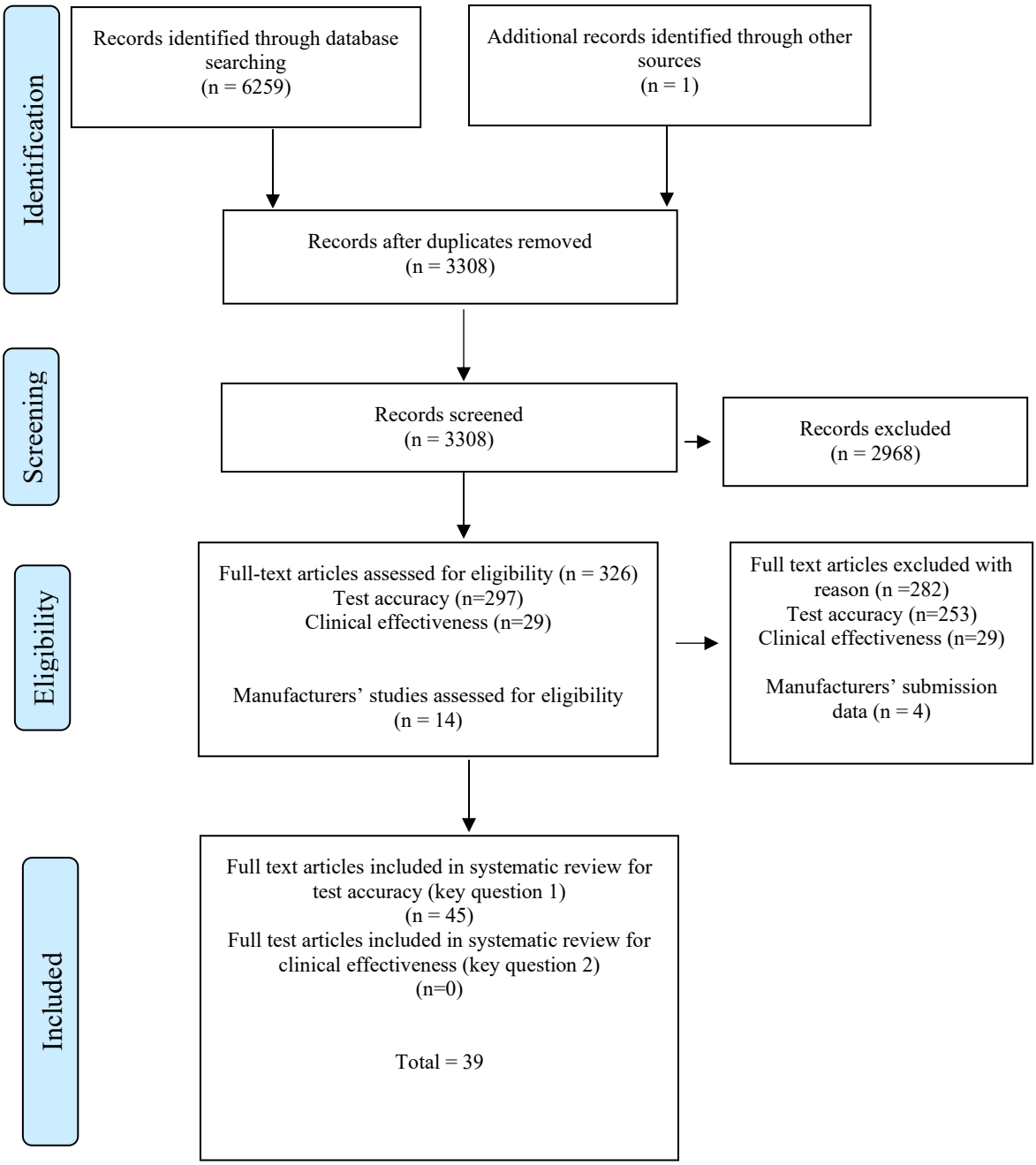


Figure 19: PRISMA flow diagram showing selection for clinical effectiveness review

4.2.Study characteristics

Characteristics of the 45 studies included in the clinical effectiveness review are described in Table 2. '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.

Table 2: Characteristics of the included studies

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Anagnostopoulos 2017[47]	England	Cohort (prospective and retrospective)	Hospital/ cancer registry	Jan 2005-Sept 2012	Prevalence	35	Selected	Median 45 (31-49) years	NR	NR	Not extractable	MSI and IHC	Sequencing and MLPA
Backes 2009[48]	USA	Clinical experience and prospective cohort (MMR proteins only)	Hospital and University medical centre	April 2007end date not reporter	Prevalence	140	Unselected	Mean 60.5 (30-91) years	NR	13 reported, unclear whether from whole sample: 5 ovarian 1 pancreatic 3 colon 2 endometrial 2 urinary tract	NR for whole sample	IHC	Large rearranegment and deletion testing. Full gene analysis and sequencing

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Baldinu 2002[49]/ Strazzullo 2003[83]*	Italy	Prospective cohort	University	1989-1997	Partial test accuracy, prevalence	116	Selected	Median 64 (35-88) years	NR	NR	excluded if they had first- or second-degree relatives with HNPCC	MSI and IHC	denaturing high-performance liquid chromatography and sequencing
Berends 2003[50]	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, staretgy 11 prevalence and concordance	58	Selected	Median 45 (27-49) years	NR	13/38 (22.4%)	22/58 (37.9%) cancer diagnosis in 1st degree relatives	MSI and IHC	DGGEand sequencing
Bruegl 2017[51]	USA	Prospective cohort	Cancer centre	Aug 2012-2014	Concordance and prevalence	203	Unselected but adult only	Mean 61.3 years	For 381 (retrospective sample):	NR	NR for whole sample	MSI, IHC and MLH1 promoter	NGS and MLPA

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
								Median 61 (23-86) years	Caucasian 265 (70%) African–American 34 (9%) Hispanic 66 (17%) Asian 14 (4%) Native American 2 (1%)			hypermethylation testing	
Buchanan 2014[52]/ Nagle 2018[72]	Australia	Prospective cohort	Cancer registries	Jul 2005-Dec 2013	Test accuracy by proteins and prevalence	1459 (698 from Nagle)	Selected	IHC tested, mean = 61.8 years (27.1 – 79.9)	NR	65/702 (9.3%)	1st degree relatives Colorectal cancer, n = 98 (14%) Endo cancer, n	IHC and MLH1 promoter hypermethylation testing	Unspecified germline testing and MLPA

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
											= 36 (5.1%)		
Carnevali 2017[53]/ Libera 2017[64]	Italy	Retrospective cohort	Hospital	1994-2014	Concordance and prevalence	88 (74 in Carnevali)	Selected	Carnevali mean 51.04 Median 49 (27-75) years Libera 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 2019[54]	China	Prospective cohort	Hospital	Dec 2017-Aug 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 years Median 55 (31-82) years	NR	0 – excluded	14/111 (12.6%) Amsterdam II criteria, 2 met Bethesda criteria	IHC, MSI and MLH1 promoter hypermethylation testing	NGS and Sanger sequencing

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Dillon 2017[55]	Lebanon	Retrospective cohort	Hopsital	May 2015-Dec 2016	Prevalence	233	Unselected	Median 63 (30-90) years	NR	NR for whole population	NR	IHC and MLH1 promoter hypermethylation testing	NGS
Dudley 2015[56]/Mas-Moya 2015[66]	USA	Propsective cohort and cross-sectional	Hospital	Jan 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 2013[57]	Spain	Retrospective cohort	Hospital	2004-2009	Concordance and prevalence	173	Unselected	Mean 63.3 years (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 reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Ferguson 2014[58]	Canada	Prospective cohort	Hospital	Jul 2010-June 2011	Prevalence ,strategy 11 and concordance	117	Selected	Median 61 (26-91) years	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 2015[59]	USA	Propsective cohort	Hospital	2003-2007	Strategy 10,concordance and prevalence	1043	Selected after 2007	Mean 62 (25-100) years	White, n = 848 (90.4%) African American, n= 55 (5.9%) Asian,	NR	938/1043 (90%) had Lynch associated cancers	MSI, IHC and MLH1 promoter hypermethylation testing	NGS

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
									n = 17 (1.8%) Other, n = 7 (0.7%) Unknown/ not specified, n = 11 (1.2%)				
Goodfellow 2003[60]	USA	Prospective cohort	University hospitals	NR	Prevalence	441	Unclear	Median 64.6 (26-92) years	NR	NR for whole sample	NR for whole sample	MSI and MLH1 promoter hypermethylation testing	SSCV and sequencing
Hampel 2006[13]	USA	Retrospective cohort	Hospital	Jan 1999-Dec 2003	Strategy 6, prevalenceconcordance	543	Unselected	Mean 60.9 (17-94) years	95% Caucasian	NR	NR	MSI and MLH1 promoter hypermethylation testing	Sequencing and MLPA
Kato 2016[61]/ Takahashi 2017[85]	Japan	Retrospective cohort	Hospital	Jan 2003-Dec 2013	Prevalence	360	Selected	Median 59 (28-89) years	360/360 (100%) Asian	30/348 (8.6%) personal history of	Family history of LS-related	IHC and MLH1 promoter	PCR, sequencing and MLPA

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
										Lynch (Takahashi)	cancer, n = 147/348 (42.4%) Family history of colorectal cancer, n = 42/348 (12.1%) Family history of stomach cancer, n = 91/348 (26.1%) (Takahashi)	hypermethylation testing	

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Latham 2019[62]	USA	Retrospective Cohort	Hospital	Jan 2014-Jun 2017	Strategy 1 and prevalence	525	Unclear	Median 55-60 years across all MSI groups	NR for whole sample	NR	NR	MSI and IHC	NGS
Leenen 2012[63]	Netherlands	Prospective cohort	Hospital/ academic medical centre	May 2007-Sept 2009	Prevalence	179	Selected	Median 61 years (IQR 57-66)	NR	NR	NR	MSI, IHC and MLH1 promoter hypermethylation testing	Sequencing and MLPA
Lin 2016[65]	USA	Prospective cohort	Medical centre	Jul 2009-Dec 2013	Prevalence	76	Selected	Mean 55 (23-95) years	NR	7/76 (9.2%) concurrant ovarian cancer	NR	IHC and MLH1 promoter hypermethylation testing	NR
Lu 2007[14]	USA	Prospective cohort	Gynaecologic oncology clinics	Jan 2000 end date NR	Complete test accuracy, MSI only (MSI-H vs MSI-L/MSS), IHC only, test	100	Selected	Mean 41.6 Median 43	NR	12/100 (12%) 2 Colon	21/100 (21%) LS related cancer in	MSI, IHC and MLH1 promoter hypermethylation testing	Sequencing and unclear further testing for

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
					accuracy by proteins, strategy 1, strategy 3, strategy 4, strategy 10, strategy 11 and prevalence			(24-49) years		9 synchronous ovarian 1 brain	at least 1 first degree relative		large deletions
Masuda 2012[67]	Japan	Prospective cohort study	NR	Jan 2000-Jul 2002	Concordance	36	Selected	NR overall Median 44.4 (34.2-54.6) years LUS group 59.48 (55.8-63.1) years Non-LUS group	Asian	NR	1 had a family history of cancer	MSI, IHC and MLH1 promoter hypermethylation testing	NA

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
McConechy 2015[68]	Canada	Retrospective cohort study	Tissue Biobank Repository	NR	Concordance	157	Unselected	Mean 62.6 years	NR	NR	NR	MSI, IHC and MLH1 promoter hypermethylation testing	NA
Mercado 2012[69]	USA	Retrospective cohort study	Hospitals	NR	Strategy 1, strategy 3, prevalence	129	Selected	Median 63 (38-89) years	94 (73%) Caucasian 1(1%) Hispanic 1 (1%) Asian 2 (2%) other	34 (27%) CRC 6 (5%) adenoma 33(26%) other Lynch 37 (29%) Multiple LS	115/129 (89%) CRC 48/129 (37%) EC 67 (52%) Other LS cancer	MSI, IHC	Denaturing high performance liquid chromatography and sequencing
Millar 1999[70]	Canada	Retrospective cohort	Cancer registry	1971-1996	Strategy 11, prevalence	40	Selected	NR	NR	40/40 (100%) all synchronous endometrial and colorectal	4/40 (10%) met Amsterdam criteria	MSI	SSCV then PCR and sequencing

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
										cancer patients			
Modica 2007[71]	USA	Retrospective cohort	Cancer centre	1992-2003	Concordance	90	Selected	Mean 63.8 years Median 63 (37-86) years	NR	NR	Yes unclear	MSI and IHC	NA
Najdawi 2017[73]	Australia	Propsective Cohort (clinical experience study)	Hospital	Aug 2012-Dec 2016	Prevalence	124	Selected	Mean 64.5 (31-93) years	NR	Synchronous uterine and ovarian, n = 1/124 (0.8%)	NR for whole sample	IHC and MLH1 promoter hypermethlyation testing	Sequencing and MLPA
Ollikainen 2005[74]	Finland	Cohort (retrospective and prospective)	Hospital	1986-1997	Strategy 1, Strategy 4, Strategy 10 and prevalence	23	Selected	Mean 62 years Median 61 (32-81) years	NR	2/23 (9%) breast cancer	23/23 (100%) family history of EC	MSI, IHC and MLH1 promoter hypermethylation testing	Sequencing and MLPA

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Pecorino 2017[75]	Italy	Prospective cohort	Hospital	2007-2014	Concordance	41	Selected	Mean 44.4 years (32-50)	NR	Unclear	Unclear	MSI and IHC	NA
Planck 2002[76]	Sweden	Retrospective cohort	Population based Cancer Registry	1958-1998	Concordance	36	Selected	Mean 47 years (37-61)	NR	36/36 (100%) adenocarcinoma of the large bowel and uterine corpus	NR	MSI and IHC	NA
Ring 2016[77]	USA	Prospective cohort	Hospital	NR	Complete test accuracy, prevalence, strategy 11	381	Unselected adult only	Mean 61 years at diagnosis	Caucasian n = 265 (70%) African–American n = 34 (9%) Hispanic n = 66 (17%) Asian n = 14 (4%)	NR	NR for whole sample	MSI, IHC and MLH1 promoter hypermethylation testing	NGS and MLPA

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
									Native American n = 2 (1%)				
Rubio 2016[78]	Spain	Retrospective and prospective cohort	Hospital	3 years NR	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 (personal communication, Ryan et al, University of	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Manchester, 11/12/2019)											[redacted]		
Salvador 2019[79]	USA	Retrospective cohort study	Laboratory/ hospital	2016-2018	Complete test accuracy, strategy 10, strategy 11, prevalence	237	Selected	NR for EC patients alone	NR for EC patients alone	NR for EC sample alone	NR for EC sample alone	MSI, IHC and MLH1 promoter hypermethylation testing	NGS and MLPA
Sarode 2019[80]	USA	Retrospective cohort (including prospective analysis of tissue)	Hospital	Sept 2011-Aug 2013	Strategy 4 and prevalence	99	Selected	NR for whole sample	NR for whole sample	NR for EC patients	NR for whole sample	IHC and MLH1 promoter hypermethylation testing	ACGH, long-range PCR, MLPA

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
Shin 2015[81]	South Korea	Retrospective cohort study	Hospital	Jan 2004-Dec 2013	Strategy 9, synchronous cancers and prevalence	12	Selected	Median 52.5 years at diagnosis	NR	12/12 (100%) EC and CRC. 4/12 (33.3%) additional bladder, cervical or gastric cancer	NR for whole sample	MSI and IHC	Sequencing and PCR
Stelloo 2017[82]	Netherlands	Retrospective cohort study	Radiation centres	NR	Concordance	686	Selected	Mean 69 years (41-88)	NR	NR	NR	MSI, IHC and MLH1 promoter hypermethylation testing	NA
Svampane 2014[84]	Latvia	Retrospective cohort	Hospital	Jan 2006-Apr 2010	Prevalence	704	Unselected	Range 30-80 years	NR	NR	19 women with family history of HNPCC (meeting	IHC	Sequencing

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
											Amsterdam I or II criteria)		
Tian 2019[86]	China	Propsective cohort	Cancer centre	Jan 2014-Jul 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%) LS related tumour in a first degree relative	IHC	Sequencing, NGS and MLPA
Wang 2017[87]	USA	Retrospective cohort study	University medical centre	June 2012-Jan 2015	Concordance	402	Unclear	Median 61 (30-86) years	NR	NR	NR	MSI and IHC	NA
Yoon 2008[88]	Korea	Prospective cohort	Hospital	Jan 1996-Dec 2004	Prevalence and strategy 10	113	Selected	NR	NR	NR	4 women met Amsterdam II criteria for	MSI, IHC and MLH1 promoter methylation testing	Sequencing

Study reference	Country	Study design	Study setting	Time period	Outcomes	Sample size included	Selected / unselected sample	Age Mean Median (range	Ethnicity	Previous /concurrent cancers	Relatives	Index test(s)	Reference standard tests(s)
											HNPCC, 1 of whom had a sister with endo and colorectal cancer		

ACGH = Array Comparative Genomic Hybridisation; CSGE = conformation sensitive gel electrophoresis ; DGGE = denaturing gradient gel electrophoresis; HNPCC = Hereditary nonpolyposis colorectal cancer; IHC = immunohistochemistry testing; MLH1-PM = MLH1 promoter methylation; MLPA =multiplex Ligation-dependent Probe Amplification; MSI = microsatellite instability testing; NA = not applicable; NGS = next-generation sequencing; NR = Not reported; SSCV = single strand conformational variant

4.2.1. Population

The 45 included papers included approximately 10,600 participants, ranging from 12 [81] to 1459 patients.[52] The results of 5 studies were reported in more than one paper.[49, 52, 53, 56, 61, 64, 66, 72, 83, 85] These papers have been reported together (i.e. 2 papers are combined into 1 study) in Table 2 and throughout this report. Only two studies took place in the United Kingdom (UK) (one published[47] and the PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019)), with the majority taking place in the United States (15/45; 33%) and Europe (11/45; 24%). However, ethnicity was largely unreported (32/45; 71%). Several studies included age as an inclusion criterion, often limiting patients to 50 years and under for inclusion in the study.[14, 47, 50, 75] In the remainder of studies, ages ranged from 17 to 100.[13, 59] Only 24% of studies (10/41) were in unselected populations, meaning all patients in particular settings were included over the study time period, without any restrictions by age, cancer histology or family history. 2 studies have been classified as unselected populations but limited to all adults (all those over 18 years).[51, 77]

44% (18/41) of studies reported on patients who had a previous or concurrent cancers. The number of patients included across the studies who had a history of cancer ranged from 0-100.[54, 70, 76, 81] 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%.[50, 73, 86] The types of cancer reported were ovarian, pancreatic, colon, endometrial, urinary tract, brain, breast, skin, bladder, cervical and gastric cancers.

4.2.2. Index tests

9 studies (11 papers) included immunohistochemistry only,[48, 52, 55, 61, 65, 66, 72, 73, 80, 84, 86] 3 studies included microsatellite instability-based testing only,[13, 60, 70] 28 studies (31 papers, including the unpublished PETALS study) included both tests,[14, 47, 49-51, 53, 54, 56-59, 62-64, 67-69, 71, 74-79, 81-83, 85, 87, 88] and 24 studies (29 papers, including the unpublished PETALS study) included MLH1 promoter methylation testing in combination with IHC or MSI testing (MSI and MLH1 promoter methylation testing n=2; IHC and MLH1 promoter methylation testing n=6; MSI, IHC and MLH1 promoter.methylation testing n=16)[13, 14, 51-57, 59-61, 63-68, 72-74, 77, 79, 80, 82, 83, 85, 88]

4.2.3. Comparator and Reference Standard

The reference standards considered appropriate in this review were sequencing in combination with multiplex ligation-dependent problem amplification (MLPA), long-range polymerase chain reaction (PCR), or targeted array comparative genome hybridisation (ACGH). Of the 33 studies (36 papers) which 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.[13, 14, 47, 48, 51, 53-55, 57-59, 61-64, 73, 74, 77-79, 81, 84-86]

2 studies (3 papers) only reported sequencing and did not report any details on the method of sequencing.[56, 66, 88]

One study did not mention sequencing but used ACGH, PCR and MLPA in combination.[80] 2 studies (3 papers) did not report clearly the methods of germline testing.[52, 65, 72]

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, by Goodfellow et al and Millar et al used Single-Strand Conformational Variance (SSCV).[60, 70] The studies by Berends et al., Rubio et al. and Mercado et al. used denaturing gel electrophoresis[50, 78] and the study reported across two papers by Baldinu et al. and Strazzullo et al. used denaturing high-performance liquid chromatography.[49, 83]

4.2.4. Outcomes

Data on the number of Lynch syndrome diagnoses amongst women with endometrial cancer was reported in thirty-two studies (including the unpublished PETALS study).[13, 14, 47-55, 57-60, 62, 63, 65, 66, 73, 74, 77-81, 84-86, 88] Four studies provided head-to-head test accuracy data for immunohistochemistry and microsatellite instability-based testing.[14, 50, 54, 78] Complete test accuracy data was provided by five studies for immunohistochemistry,[14, 50, 54, 78, 86] four studies for microsatellite instability-based testing[14, 50, 54, 78] and four studies for immunohistochemistry, microsatellite instability-based testing, and MLH1 promoter methylation testing.[14, 54, 77, 79] An additional nine studies provided partial test accuracy data (true positives, false positives, and positive predictive values) in which only women who tested positive on index tests were considered for germline testing.[14, 50, 54, 59, 62, 74, 78, 86, 88]

Concordance between immunohistochemistry and microsatellite instability-based testing was assessed in twenty-three studies.[13, 14, 47, 50, 51, 54, 57-59, 63, 64, 67, 68, 71, 74-78, 81-83, 87]

4.2.5. Setting

The majority of the patients in the included studies were recruited from hospitals (26/41, 63%).[13, 47, 48, 53-64, 66, 73-75, 77-80, 84, 85, 88] 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.[67]

4.2.6. Study design

All the studies within this review had a cohort design. 39% studies (16/41) were prospective cohort studies, 46% were retrospective (19/41) 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 and Lynch-like syndrome groups.[56, 66]

4.3. Quality considerations of included studies

4.3.1. QUADAS

In the proposed testing strategies, 1 – 10 (below) only women who test 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 negative predictive values from these studies due to 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, positive and negative predictive values and have been defined here as full test accuracy data studies. There were 41 studies (45 papers) identified, of which 7 provided full test accuracy data (as all participants received both the index test and reference standard),[14, 50, 51, 54, 78, 79, 86] 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)[13, 47-49, 51-53, 55-60, 62-66, 69, 70, 72-74, 80, 81, 84, 85, 88] and 23 studies (including the PETALS study) provided data on concordance.[14, 47, 50, 51, 54, 57, 59, 63, 64, 67, 68, 71, 74-76, 78, 82, 83, 87]

The studies providing test accuracy information were appraised using the QUADAS-2 tool and the 7 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) tool. There were 16 studies (16 papers, including the PETALS study) which reported both test accuracy and concordance and were appraised using both tools.[13, 14, 47, 50, 51, 54, 57-60, 63, 64, 74, 78, 81]

4.3.1.1. Quality considerations of included studies – complete test accuracy studies

The assessment of risk of bias and applicability for the 7 complete test accuracy studies using the QUADAS-2 tool are summarised in Table 3 and *Figure 20*.[14, 50, 51, 54, 78, 79, 86] Six of the 7 studies included both MSI and IHC index tests, and 4 included additional MLH1 promoter hypermethylation testing.[14, 51, 54, 79] 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 2 or more domains for 5 studies (71%).[50, 51, 54, 78, 86] One study was at high risk of bias in 1 domain,[86] and the remaining study was unclear in the majority of domains (5/7 domains, 71%).[14] No study was at low risk of bias in all domains.

In 71% of studies (5/7), there was a high risk of bias in patient selection (domain 1: patient selection).[50, 51, 54, 78, 86] 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 whether there was bias in how patients had been selected.[14] There was only one study in which there was low risk of bias in the patient selection, which consecutive enrolment of patients in a cohort study, with no exclusions.[79]

6 out of 7 studies were head-to-head studies, testing patients using both MSI and IHC index tests, with 1 test using IHC alone.[86] In all studies, for both tests (6/6 MSI, 7/7 IHC, 100%), the risk of bias was unclear due to a lack of information around blinding between index test and reference standard results, whether thresholds were pre-specified or determined pragmatically and whether the laboratories performing the index tests participate in an accredited quality assessment/control scheme (domain 2: index tests). 4/7 studies also undertook MLH1 promoter hypermethylation testing, all of which lacked information on blinding and quality assessment so were also rated unclear.[14, 51, 54, 86]

Unclear reporting was common in the reference standard domain (domain 3: reference standard). In all studies there was not enough information to determine whether the results of germline testing (reference standard) were determined without knowledge of the MSI and IHC test results (index tests). Additionally, for many of the studies it was unclear whether the reference standard used would correctly identify Lynch syndrome (5/7, 71%), because of a lack of information being presented about the testing methods used and/or whether quality assurance was in place.[50, 51, 54, 78, 79] 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 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. One study used sequencing alongside denaturing gradient gel electrophoresis which is not a recognised reference standard for the purpose of this study.[50] 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, 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).[50, 51, 54, 78, 79]

The flow of patients through the study was rated at high risk of bias in 57% of studies (4/7, domain 4: flow and timing).[50, 54, 78, 86] Three of the studies did not include all patients in their analysis,[54, 78, 86] and 1 study did not give all patients the same reference standard, sequencing was only given to those with aberrant band patterns using denaturing gradient gel electrophoresis.[50] The remaining 3 studies had a low risk of bias with all patients receiving the reference standard, all patients receiving the same reference standard and all patients included in the analysis.[14, 51, 79]

The role of the sponsor was low in 4 of the 7 studies (domain 6: role of the sponsor).[14, 50, 54, 78] In 2 studies multiple authors were employed by genetics companies who funded the studies.[51, 79] In 1 study the funding was not specified.[86]

Applicability of study findings for complete test accuracy studies

The applicability of study findings was assessed in regards 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 6 of the 7 studies (86%; domain 1: patient selection).[14, 50, 51, 54, 78, 86] In one study there was not enough information to determine whether the population was comparable to the review question.[79] Based upon 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 6 studies, the populations were not ethnically comparable to the UK and/or limited by age. None of the 7 studies were 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.[51, 54] 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%).[14, 50, 78] Only 4 of the studies reported on MLH1 promoter hypermethylation testing, of those 50% (2/4) had high applicability concerns,[51, 54] and 50% did not report enough information to make a judgement.[14, 79]

Only 1 study was rated as having high 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.[50] The remainder were all of low concern, bar 1 study which did not report enough information for the raters to make a determination of applicability.[86]

Table 3. Judgement of risk of bias and applicability of included complete test accuracy studies

Study	RISK OF BIAS							APPLICABILITY CONCERNS				
	Patient Selection	**Index Test - MSI**	**Index test - IHC**	**Index test – MLH1 PM testing**	**Reference test**	**Flow & Timing**	**Role of sponsor**	**Patient Selection**	**Index Test - MSI**	**Index test - IHC**	**Index test – MLH1 PM testing**	**Reference Standard**
Berends 2003[50]	High	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Unclear	NA	High
Chao 2019[54]	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Low	Low	low	Low
Lu 2007[14]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Unclear	Unclear	Unclear	Low
Ring 2016[51]	High	Unclear	Unclear	Unclear	Unclear	low	high	High	Low	low	low	Low
Rubio 2016[78]	High	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Unclear	NA	Low
Salvador 2019[79]	Low	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	Unclear	Unclear	Unclear	Low
Tian 2019[86]	High	NA	Unclear	NA	Unclear	High	Unclear	High	NA	Unclear	NA	Unclear

NA: Not applicable

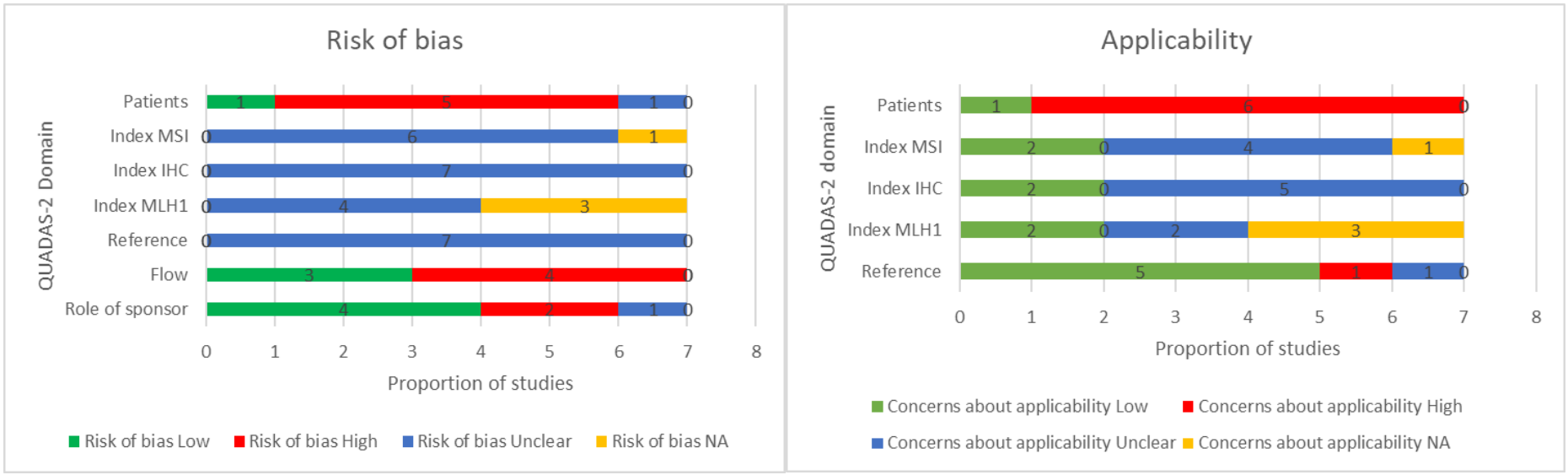


Figure 20: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included complete test accuracy studies

4.3.1.2. 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 **Error! Reference source not found.** and *Figure 20*.[13, 47-49, 51-53, 55-60, 62-66, 69, 70, 72-74, 80, 81, 84, 85, 88] 16 studies included both MSI and IHC index tests (62%; 16/26), 1 study reported only MSI[60] and 9 studies reported only IHC.[48, 55, 65, 70, 72, 73, 80, 84, 85] 17 (20 papers, including the PETALS study) included the additional MLH1 promoter hypermethylation testing.[13, 47, 51-53, 55-57, 59, 60, 63-66, 72, 73, 80, 85, 88] All index tests have been reported separately.

Risk of bias for partial test accuracy studies

There were 2 domains with high risk of bias. The first was patient selection (domain 1: patient selection) with 62% (16/26) of studies rated as high risk of bias.[13, 47, 49, 52, 53, 58-60, 63-65, 69, 70, 72-74, 84, 88] As per the full test accuracy papers this was because studies had strict inclusion criteria (such as age, previous/synchronous cancers or family history) which excluded many of the suitable population. The second domain with a large proportion of high risk of bias studies was the flow and timing of studies, with 100% (26/26) rated high risk of bias. In these studies, not all patients were given the reference standard. Usually only those believed to have the disease based upon the index test result. The role of the sponsor was low in all studies bar 4 in which not enough information was provided to make a determination.[49, 59, 62, 69]

In all other domains, the majority of the studies were rated as unclear due to 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; 22/26, 85% domain 3: Reference standard).

The only domain with a low risk of bias was domain 5: the role of the sponsor, with 85% (22/26) of studies rated low. The remaining 4 studies did not report enough information to judge the risk of bias surrounding sponsor involvement.[49, 59, 62, 69]

Applicability of study findings for partial test accuracy studies

There were applicability concerns in 1 domain. 50% (13/26) of studies had high 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.[13, 47, 51, 53, 63-65,

[69, 70, 74, 80, 81, 85, 88] The only other domain with a high risk of bias was regarding the reference standard (domain 3: reference standard). 12% of studies (3/26) were high risk of bias for the reference standard, with differing methods of germline testing than was recognised in this review. Two of the studies primarily used single-strand conformational variant analysis and the remaining study used array-based comparative genomic hybridization/long-range PCR.[60, 70, 80] All other studies were considered low risk as they provided sequencing followed by PCR or MLPA. The majority of index test ratings were unclear, with little information describing whether 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; 10/17, 59% domain 2: index test MLH1 promoter hypermethylation testing).

Table 4: Judgement of risk of bias and applicability of included partial test accuracy studies

Study	Risk of bias							Applicability concerns				
	Patient selection	Index test - MSI	Index test- IHC	Index test - MLH1 PMT	Reference test	Flow & Timing	Role of sponsor	Patients	Index test - MSI	Index test- IHC	Index test - MLH1 PMT	Reference
Anagnostopulos 2017[47]	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Unclear	Unclear	Low
Backes 2009[48]	Low	NA	Unclear	NA	Unclear	High	Low	Unclear	NA	Unclear	NA	Unclear
Baldinu 2002[49]	High	Unclear	Unclear	NA	Unclear	High	Unclear	Unclear	Unclear	Unclear	NA	Low
Bruegl 2017[51]	Low	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Low	Unclear	Low
Buchanan 2014[52]/Nagle 2018[72]	High	NA	Unclear	Unclear	Unclear	High	Low	Unclear	NA	Unclear	Unclear	Low
Dillon 2017[55]	Low	NA	Unclear	Unclear	Unclear	High	Low	Unclear	NA	Unclear	Unclear	Low
Egoavil 2013[57]	Low	Unclear	Unclear	Low	Unclear	High	Low	Unclear	Unclear	Unclear	Low	Low
Ferguson 2014[58]	High	Unclear	Unclear	NA	Unclear	High	Low	Unclear	Unclear	Unclear	NA	Low
Goodfellow 2003[60]	High	Unclear	NA	Unclear	High	High	Low	Unclear	Unclear	NA	Unclear	High
Goodfellow 2015[59]	High	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Hampel 2006[13]	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Unclear	Unclear	Low
Latham 2019[62]	Unclear	Unclear	Unclear	NA	Unclear	High	Unclear	Unclear	Unclear	Unclear	NA	Low
Leenen 2012[63]	High	Unclear	Unclear	Low	Unclear	High	Low	High	Unclear	Unclear	Low	Low
Libera 2017[64]/	High	Unclear	Unclear	Low	Unclear	High	Low	High	Unclear	Unclear	Low	Low

Study	Risk of bias							Applicability concerns				
	Patient selection	Index test - MSI	Index test- IHC	Index test - MLH1 PMT	Reference test	Flow & Timing	Role of sponsor	Patients	Index test - MSI	Index test- IHC	Index test - MLH1 PMT	Reference
Carnevali 2017[53]												
Lin 2016[65]	High	NA	Unclear	Unclear	Unclear	High	Low	High	NA	Unclear	Unclear	Unclear
Mas Moya 2015[66]/ Dudley 2015[56]	Low	Unclear	Unclear	Low	Unclear	High	Low	Unclear	Unclear	Unclear	Low	Low
Mercado 2012[69]	High	Unclear	Unclear	NA	High	High	Unclear	High	Unclear	Unclear	NA	Unclear
Millar 1999[70]	High	NA	Unclear	NA	High	High	Low	High	NA	Unclear	NA	High
Najdawi 2017[73]	High	NA	Unclear	Low	Unclear	High	Low	Unclear	NA	Unclear	Low	Low
Ollikainen 2005[74]	High	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Low	NA	Low
PETALS study, (personal communication, Ryan et al., University of Manchester, 11/12/2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarode 2018[80]	Unclear	NA	Low	Unclear	High	High	Low	High	NA	Low	Low	High
Shin 2015[81]	Unclear	Unclear	Unclear	NA	Unclear	High	Low	High	Unclear	Unclear	NA	Low
Svampane 2014[84]	High	NA	Unclear	NA	Unclear	High	Low	Unclear	NA	Unclear	NA	Low
Takahashi 2017[85]	Unclear	NA	High	Unclear	Unclear	High	Low	High	NA	Unclear	Unclear	Low
Yoon 2008[88]	High	Unclear	Unclear	Unclear	Unclear	High	Low	High	Unclear	Unclear	Unclear	Low

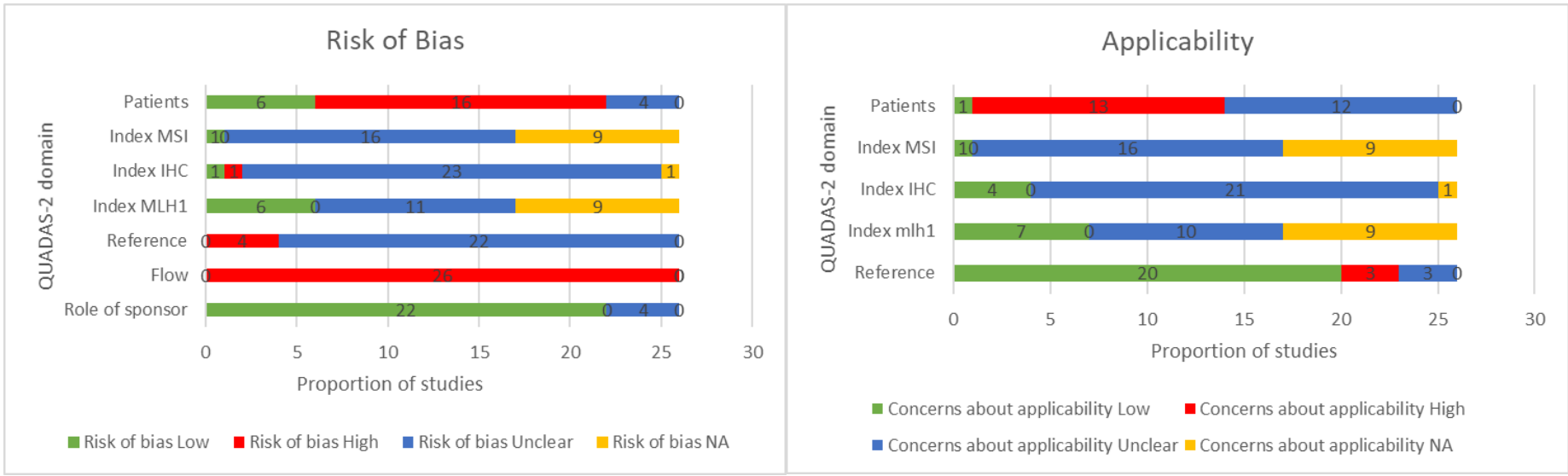


Figure 21: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included partial test accuracy studies

4.3.2. QAREL

Twenty-three studies (including the unpublished PETALS study) provided data on concordance.[13, 14, 47, 50, 51, 54, 57-59, 63, 64, 67, 68, 71, 74-76, 78, 81-83, 87] These studies were appraised using the QAREL tool. Two of the questions in the QAREL tool were deemed not applicable for 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 Figure 22 and Table 5.

In general the quality of the included studies was poor, with only one study (the unpublished PETALS study) having more than 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).[13, 14, 47, 50, 51, 57, 58, 63, 64, 67, 68, 74-76, 78, 81-83] The studies were not comparable to clinical practice in the UK, with populations selected based upon 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.[51, 57] 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 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).[13, 14, 47, 50, 51, 54, 58, 63, 64, 67, 68, 71, 74-76, 78, 81-83]

There was a consistent lack of reporting regarding blinding across the studies. In 83% of studies (19/23) it was unclear whether blinders were rated to the findings of other raters (question 3), in 90% of studies (21/23) it was unclear whether blinders were rated to their own findings (question 4), in 65% of studies (11/17, 6 studies were concordance only studies with no reference standard so this question was not applicable) it was unclear whether blinders were rated to the results from the reference standard (question 5) and in 96% (22/23, including the PETALS study) studies it was unclear whether blinders were rated to patient's clinical information (question 6) .[14, 47, 50, 51, 54, 57, 59, 63, 64, 67, 68, 71, 74-76, 78, 83, 87]

Additionally, there was a lack of reporting on how the tests were undertaken, meaning it could not be determined whether the order of the testing varied (question 8; 19/23, including the PETALS study, 83%),[13, 14, 47, 50, 51, 54, 57-59, 63, 64, 67, 68, 74, 76, 78, 81, 83] or if tests have been conducted according to best practice guidelines/via laboratories that are participating in quality assurance programmes (question 10; 21/23, 91%).[13, 14, 47, 50, 51, 54, 57-59, 63, 64, 67, 68, 71, 74-76, 78, 81-83]

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 intra-class correlations, or between categorical/ordinal data with kappas).[13, 14, 47, 50, 51, 54, 57-59, 63, 64, 67, 71, 74-76, 78, 81, 83, 87]

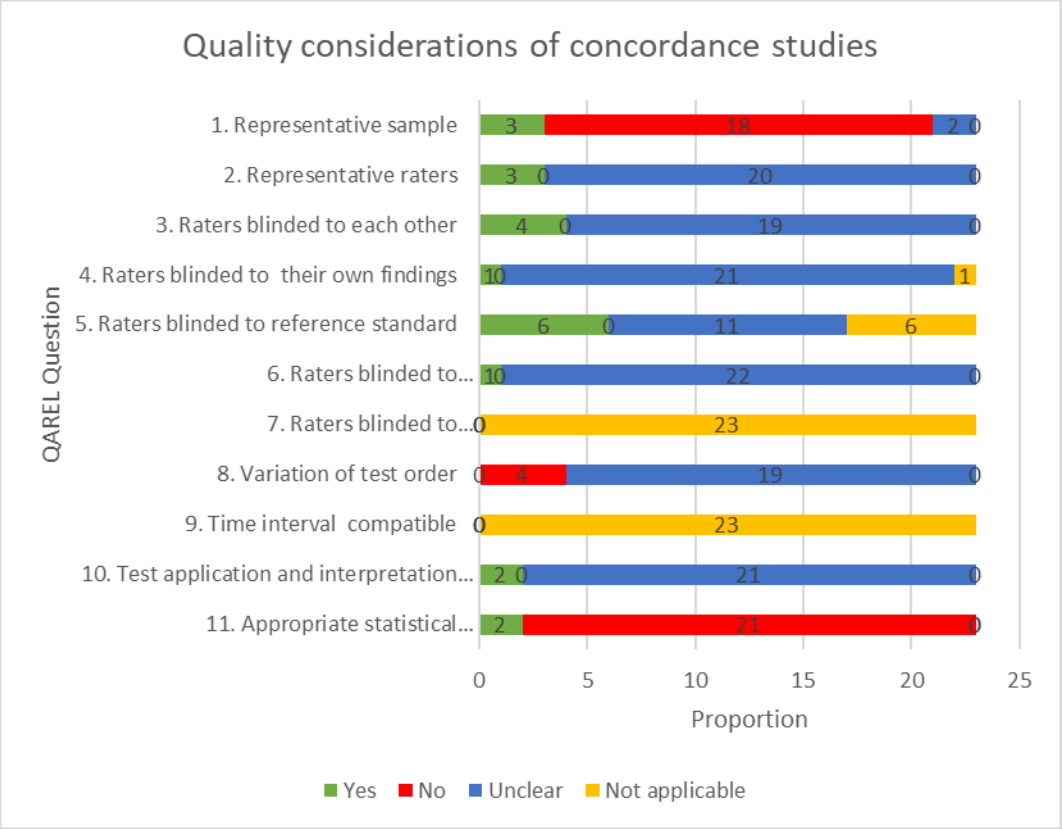


Figure 22. Quality appraisal of included studies according to QAREL criteria

Table 5 Judgement of quality using the QAREL tool for concordance studies

Study	Representative sample	Representative raters	Raters blinded to each other	Raters blinded to their own findings	Raters blinded to reference standard	Raters blinded to clinical information	Raters blinded to additional cues	Variation of test order	Time interval compatible	Test application and interpretation	Appropriate statistical measures
Anagnostopoulos 2017[47]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Berends 2003[50]	No	Unclear	Yes	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Bruegl 2017[51]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Chao 2019[54]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Egoavil 2013[57]_	Yes	Yes	Yes	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Ferguson 2014[58]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Goodfellow 2015[59]	No	Yes	Unclear	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Hampel 2006[13]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Leenen 2012[63]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Libera 2017[64]	No	Unclear	Unclear	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Lu 2007[14]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Masuda 2012[67]	No	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	NA	Unclear	No

Study	Representative sample	Representative raters	Raters blinded to each other	Raters blinded to their own findings	Raters blinded to reference standard	Raters blinded to clinical information	Raters blinded to additional cues	Variation of test order	Time interval compatible	Test application and interpretation	Appropriate statistical measures
McConechy 2015[68]	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	NA	Unclear	Yes
Modica 2007[71]	No	Unclear	Unclear	Yes	NA	Unclear	NA	No	NA	Unclear	No
Ollikainen 2005[74]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Pecorino 2017[75]	No	Unclear	Unclear	Unclear	NA	Unclear	NA	No	NA	Unclear	No
Planck 2017[76]	No	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	NA	Unclear	No
Rubio 2016[78]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shin 2015[81]	No	Unclear	Unclear	Unclear	Yes	Unclear	NA	Unclear	NA	Unclear	No
Stelloo 2017[82]	No	Unclear	Unclear	Unclear	Unclear	Yes	NA	No	NA	Unclear	Yes
Strazzullo 2003[83]	No	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	No
Wang 2017[87]	Unclear	Yes	Yes	NA	NA	Unclear	NA	No	NA	Yes	No

NA: Not applicable

4.4. Assessment of test accuracy

Number of Lynch syndrome diagnoses

Thirty-three studies provided data on Lynch syndrome diagnoses.[13, 14, 47-55, 57-60, 62, 63, 65, 66, 69, 73, 74, 77-81, 84-86, 88] including one unpublished study, the PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019). Full details of the number of women identified with LS and variants of uncertain significance/Lynch-like syndrome, and the types and frequencies of mutations are reported in Table 6. Across all thirty-two studies, 349 cases of LS were identified from 7367 women tested. The reported prevalence of LS ranged from 0% (0 out of 140 women tested, in a clinical experience study from the USA which included all women undergoing hysterectomies at two hospitals) to 62%.[69]

The prevalence of LS was typically lower in studies that recruited unselected samples of women (median [redacted]%, range 0 – 5.3%) than in studies of selected samples of women (median 7.5, range 0.9 –62%). The prevalence of LS in two UK studies were [redacted] women tested, including [redacted] women with known LS) in an unselected sample of women (PETALS study) and 8.5% (3 out of 35 women tested) in a selected sample of women under 50 years.[47] The types and frequencies of MMR gene mutations varied between studies. Combining data from all studies, variants in MSH2 were the most common (38.6% of LS cases), followed by MSH6 (30.4% of LS cases), MLH1 (23.6% of LS cases), and PMS2 7.3% of LS cases). One study did not report which of the MMR were mutated,[79] and 10 studies did not assess all four MMR genes.[14, 49, 50, 60, 70, 74, 78, 81, 84, 88] MHL1 and MSH2 were not assessed in one study,[60] MSH6 was not assessed in 3 studies,[49, 70, 81] and PMS2 was not assessed in 10 studies.[14, 49, 50, 60, 70, 74, 78, 81, 84, 88] Combining data from studies of unselected samples of women, variants in MSH6 were the most common (39.1% of LS cases), followed by MSH2 (32.2% of LS cases), MLH1 (19.5% of LS cases), and PMS2 (9.2% of LS cases). Combining data from studies of selected samples of women, variants in MSH2 were the most common (42.1% of LS cases), followed by MSH6 (25.7% of LS cases), MLH1 (25.4% of LS cases), and PMS2 (6.8% of LS cases).

Eighty-nine variants of uncertain significance were reported in 10 studies (including the PETALS study), ranging from 2 – 15 cases per study.[13, 14, 50-54, 57, 59, 78, 86] In one study [redacted] of the variants of uncertain significance were identified in women who were [redacted]

Nine women were reported to have Lynch-like syndrome from 2 studies, ranging from 3 – 6 cases per study.[55, 66]

Table 6. Prevalence

Prevalence[1]									
Study	**Country**	**Sample size**	**LS prevalence, n (%)**	**Gene variant (number)**				**Variants of uncertain significance**	**Notes**
				MLH1	**MSH2**	**MSH6**	**PMS2**		
Unselected samples									
Backes (2009) [48]	USA	140	0 (0%)	0	0	0	0	None reported	-
Bruegl (2017) [51]	USA	213	7 (3.3%)	3	0	2	2	2	
Buchanan (2014) [52]/Nagle (2018) [72]	Australia	702	22 (3.1%)	3	8	10	1	4	Only included women with IHC data (702/1,459 women with EC)
Dillon (2017) [55]	Lebanon	233	5 (2.1%)	1	2	2	0	3 Lynch-like	-
Dudley (2015) [56]/ Mas-Moya (2016) [66]	USA	215	11 (5.1%)	3	5	1	2	6 Lynch-like	-
Egoavil (2013) [57]	Spain	173	8 (4.6%)	1	3	3	1	2	-
Hampell (2006) [13]	USA	543	10 (1.8%)	1	3	6	0	13	-

Prevalence[1]									
Study	**Country**	**Sample size**	**LS prevalence, n (%)**	**Gene variant (number)**				**Variants of uncertain significance**	**Notes**
				MLH1	**MSH2**	**MSH6**	**PMS2**		
PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019)	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Svampane (2014) [84]	Latvia	113	6 (5.3%)	3	3	2	NA	None reported	2 women had germline mutations in both MLH1 and MSH2
Selected samples									
Anagnostopoulos (2017) [47]	England	35	3 (8.5%)	0	2	1	0	None reported	Only included women diagnosed with EC under 50 years

Prevalence[1]									
Study	**Country**	**Sample size**	**LS prevalence, n (%)**	**Gene variant (number)**				**Variants of uncertain significance**	**Notes**
				MLH1	**MSH2**	**MSH6**	**PMS2**		
Baldinu (2002) [49]/Strazzullo (2003) [83]	Italy	116	1 (0.9%)	1	0	NA	NA	None reported	Assessed only for MLH1 and MSH2
Berends (2003) [50]	Netherlands	58	5 (8.6%)	1	3	1	NA	3	Initial reference standard was denaturing gradient gel electrophoresis
Carnevali (2017) [53] /Libera (2017) [64]	Italy	61	22 (36.1%)	7	8	5	2	6	Only included women with suspected LS on the basis of clinical criteria
Chao (2019) [54]	China	93	6 (6.5%)	1	2	3	0	14	-
Ferguson (2014) [58]	Canada	118	7 (5.9%)	4	1	2	0	None reported	-
Goodfellow (2015) [59]	USA	1002	22 (2.2%)	2	7	10	3	2	-
Leenen (2012)[63]	Netherlands	179	7 (3.9%)	0	0	6	1	None reported	Only includes women under 70 years

Prevalence[1]									
Study	**Country**	**Sample size**	**LS prevalence, n (%)**	**Gene variant (number)**				**Variants of uncertain significance**	**Notes**
				MLH1	**MSH2**	**MSH6**	**PMS2**		
Lin (2016) [65]	USA	74	3 (4.21%)	1	0	2	0	None reported	Study included 2 women with known LS (I have excluded these from the sample
Lu (2007) [14]	USA	100	9 (9%)	1	7	1	NA	11 VUS	
Mercado(2012) [69]	USA	129	80(62%)	31	40	9	0	0	-
Millar (1999) [70]	Canada	40	7 (17.5%)	1	6	NA	NA	None reported	All women had EC and CC Only MLH1 and MSH2 assessed
Najdawi (2017) [73]	Australia	124	3 (2.4%)	0	1	0	2	None reported	Only including women undergoing surgery with curative intent
Ollikainen (2005) [74]	Finland	23	2 (8.9%)	0	1	1	NA	None reported	-

Prevalence[1]									
Study	**Country**	**Sample size**	**LS prevalence, n (%)**	**Gene variant (number)**				**Variants of uncertain significance**	**Notes**
				MLH1	**MSH2**	**MSH6**	**PMS2**		
Ring (2016) [77]	USA	365	21 (6.0%)	3	7	6	6	25	Includes 2 two EPCAM-MSH2 variants
Rubio (2016) [78]	Spain	103	14 (13.6%) Prior LS cancer, 5/14 (35.71%) No prior LS cancer, 9/14 (64.3%)	1	2	6	NA	4	-
Salvador (2019)[79]	USA	296	51 (17.3%)	NR	NR	NR	NR	NR	Mixed EC/CC sample. Only partial data extractable for EC
Sarode (2019) [80]	USA	99	4 (4.0%)	1	0	3	0	None reported	-

Prevalence[1]									
Study	**Country**	**Sample size**	**LS prevalence, n (%)**	**Gene variant (number)**				**Variants of uncertain significance**	**Notes**
				MLH1	**MSH2**	**MSH6**	**PMS2**		
Shin (2015) [81]	South Korea	12	3 (25%)	2	1	NA	NA	None reported	All women had EC and CC Only MLH1 and MSH2 assessed
Takahasi (2017) [85]/Kato (2016) [61]	Japan	360	10 (2.8%)	3	4	2	1	2 VUS 15 Lynch-like	Overlapping, but not identical populations
Tian (2019) [86]	China	198	45 (22.7%)	10	20	11	4	15 VUS	-
Yoon (2008) [88]	Korea	113	5 (4.4%)	1	2	6	NA	None reported	1 woman diagnosed with LS did not meet MSI/IHC referral criteria but was offered germline as met HNPCC criteria
Sample selection unclear									
Goodfellow (2003) [60]	USA	441	7 (1.6%)	NA	NA	7	NA	None reported	Only MSH6 investigated

Prevalence[1]									
Study	**Country**	**Sample size**	**LS prevalence, n (%)**	**Gene variant (number)**				**Variants of uncertain significance**	**Notes**
				MLH1	**MSH2**	**MSH6**	**PMS2**		
									Sample included 5 women with known MSH2 germline mutations
Latham (2019) [62]	USA	525	7 (1.3%)	2	1	3	1	None reported	Nonstandard approach to MSI, no MSI-L

CC = colorectal cancer; EC = endometrial cancer; LS = Lynch syndrome; NA = not applicable; VUS = variant of uncertain significance

The methods, 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. Full details of test accuracy are reported in Table 7 and details of test failures and indeterminate results are reported in Table 9. 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 immunohistochemistry and microsatellite instability-based testing, though the numbers of included tumours were not identical for each of the tests due to insufficient tumour tissue being available and test failures.[14, 50, 54, 78] Three studies had a larger number of results for IHC than MSI: 102 vs 83,[54] 99 vs 95,[14] and 94 vs 83.[78] One study had a larger number of results for MSI than IHC: 57 vs 51.[50] All four studies comprised selected samples of women. Two studies excluded women over 50 years old,[14, 50] one study excluded women with recurrent or synchronous cancers,[54] and one study excluded women (1) without a personal/family history of Lynch syndrome or (2) who were over 50 years old.[78] Two studies included an ineligible reference standard (conformational-sensitive gel electrophoresis/denaturing gradient gel electrophoresis) as part of their diagnostic process.[50, 78] Three of the studies were at high risk of bias.[50, 54, 78] The remaining study had an unclear risk of bias, as insufficient information was presented on which to make an assessment.[14] All four studies had high applicability concerns. (see 4.3.1.1 "Risk of bias for complete test accuracy studies" and "Applicability of study findings for complete test accuracy studies" for further details)

For immunohistochemistry, there were 28 true positives, 78 false positives, 235 true negatives, and 5 false negatives; point estimates ranged from 66.7 – 100% for sensitivity, 60.9 – 83.3% for specificity, 14.3 – 37.5% for positive predictive values, and 95.2 – 100% for negatives predictive values. For microsatellite instability testing, there were 21 true positives, 57 false positives, 232 true negatives, and 8 false negatives; point estimates ranged from 41.7 – 100% for sensitivity, 69.2 – 89.9% for specificity, 20 – 33.3% for positive predictive values, and 88.7 – 100% for negative predictive values. There was were no statistically

significant differences (on the basis of confidence intervals) between MSI and IHC on any of the four tests accuracy metrics.

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

Immunohistochemistry alone

Five studies provided test accuracy data for immunohistochemistry.[14, 50, 54, 78, 86] All five studies comprised selected samples of women. Two studies excluded women over 50 years old,[14, 50] one study excluded women with recurrent or synchronous cancers,[54] one study excluded women (1) without a personal/family history of Lynch syndrome-related cancer or (2) who were over 50 years old ,[78] and one study excluded women who were (1) over 50 years old, (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.[86] Four studies assessed all four MMR proteins,[50, 54, 78, 86] and one study assessed MHL1, MSH2, and MSH6.[14] There were 69 true positives, 193 false positive, 243 true negatives, and 6 false negatives in the five included studies. The most commonly affected gene was MSH2 (34/69 cases of LS, 49.3%), followed by MSH6 (18/69 cases of LS, 26.1%), MLH1 (14/69 cases of LS, 20.3%), and PMS2 (3/69 cases of LS, 4.3%). PMS2 was only assessed in 2 studies.[54, 86] In total, 33 variants of uncertain significance were identified in the five studies (median = 4; 3 to 11 cases per study). The point estimates ranged from 66.7 – 100% for sensitivity, 6.5 – 83.3% for specificity, 14.3 - 37.5% for positive predictive value, and 88.9 – 100% for negative predictive value (see Figure 23). With the exception of positive predictive value in the study by Tian (2019),[86] confidence intervals 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.

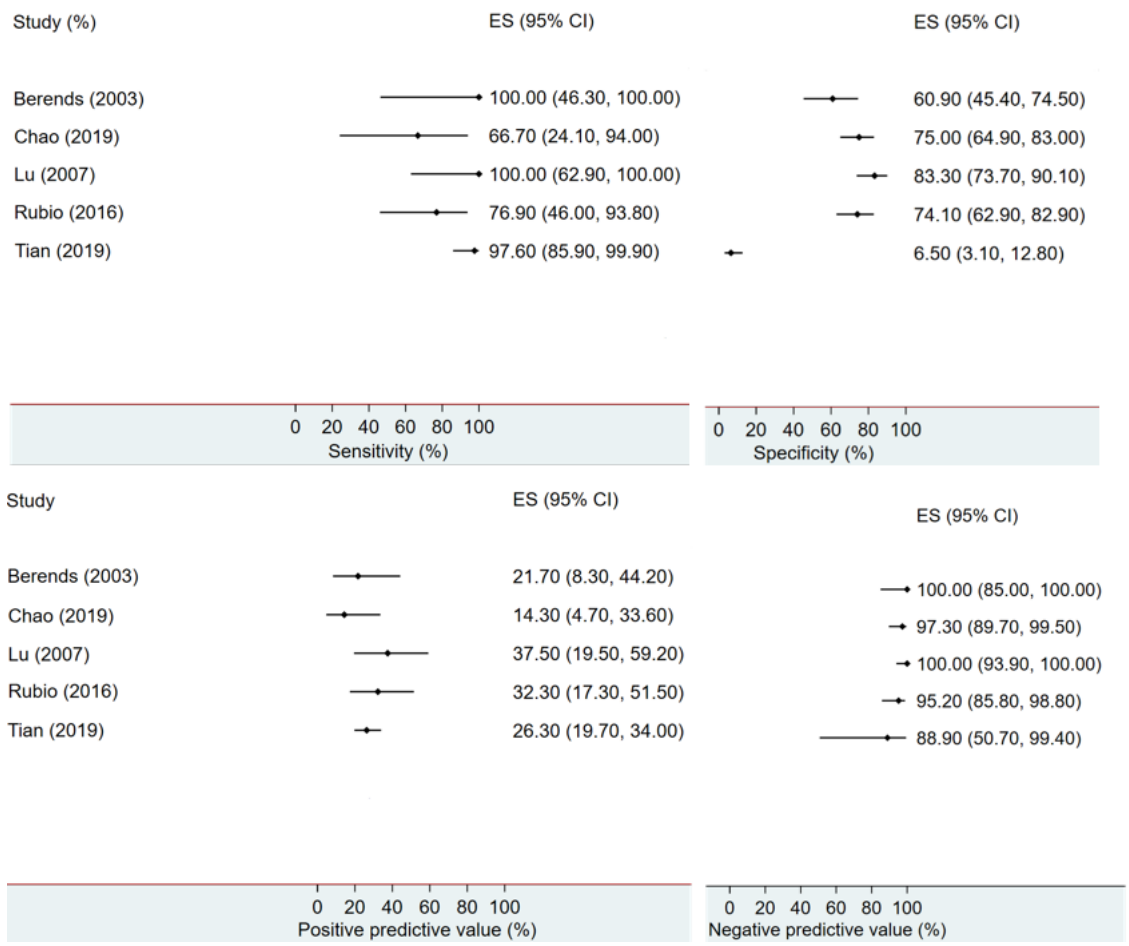


Figure 23: Sensitivity, specificity, positive predictive value, and negative predictive value of immunoistochemistry for Lynch syndrome

Test failures were reported for 0 – 1% of tumours for immunohistochemistry (1 out of 522 tumours). No indeterminate results were reported. Testing was not conducted in 0 – 16.2% for participants (57 out of 372 tumours) for immunohistochemistry, due to insufficient tumour tissue (or unspecified reasons).

From the five studies, one presented data in sufficient detail to estimate test accuracy by individual proteins.[14] This study reported on MLH1, MSH2 and MSH6 in 99 patients. True positives were determined by the individual protein tests 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% - 49.3%) for MLH1, 66.7% (95% CI 30.9% - 91.0 %) for MSH6, and 77.8% (95% CI 40.2% - 96.1%) for MSH2. Specificity was 87.8% (95% CI 79.2% - 93.2%) for MLH1, 95.6% (95% CI 88.4% -

98.6%) for MSH6, and 95.7% (95% CI 88.6% - 98.6%) for MSH2. PPV was 7.7% (95% CI 0.4% - 37.9%) for MLH1, 60.0% (95% CI 27.4% - 86.3%) for MSH6, and 63.6% (95% CI 31.6% - 87.6%) for MSH2. NPV was 90.7% (82.0% - 95.6%) for MLH1, 96.6% (95% CI 89.8% - 99.1%) for MSH6, and 97.6% (95% CI 91.0% - 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 to only 4 for MSH2 and MSH6.

In the other four studies, information on IHC result by individual protein was only presented for those with a germline mutation in three studies,[50, 78, 86] while in the remaining study eight IHC cases were not reported and there were discrepancies between values reported in the text and table.[54]

Secondary analysis of test accuracy in which variants of uncertain significance were considered germline positive was possible for two studies.[14, 50, 54, 78] Estimates of test accuracy were as follows: sensitivity 100.0% (95% CI 59.8 - 100.0%), specificity 62.8 (95% CI 46.7 - 76.6%), positive predictive value 33.3% (95% CI 16.4 - 55.3%), negative predictive value 100.0% (95% CI 84.5 - 100.0%),[50] sensitivity 90.0% (95% CI 66.9 - 98.2%), specificity 75.6% (95% CI 64.7 - 84.1%), positive predictive value 47.4% (95% CI 31.3 - 64.0%), negative predictive value 96.9% (95% CI 88.2 - 99.5%),[54] sensitivity 100.0% (95% CI 80.0 - 100.0%), specificity 83.5% (95% CI 73.1 - 90.6%), positive predictive value 60.6% (95% CI 42.2 - 76.6%), negative predictive value 100.0% (95% CI 93.1 - 100.0%),[14] sensitivity 82.4% (55.8 - 95.3%), specificity 75.3% (64.0 - 84.1%), positive predictive value 42.4% (26.0 - 60.6%), negative predictive value 95.1% (85.4 - 98.7%).[78] These were similar to estimates in which variants of uncertain significance were consider to be germline negative.

Microsatellite instability-based testing alone

Four studies provided test accuracy data for microsatellite.[14, 50, 54, 78] All four studies comprised selected samples of women. Two studies excluded women over 50 years old,[14, 50] one study excluded women with recurrent or synchronous cancers,[54] and one study excluded women (1) without a personal/family history of Lynch syndrome or (2) who were over 50 years old.[78] Three different panels of markers were used in the four studies; only two studies

used the same panel of markers.[14, 78] Using microsatellite instability: high (2 or more unstable markers) as a cut off, 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 LS, 61.9%), followed by MSH6 (4/21 cases of LS, 19%) and MLH1 (4/21 cases of LS, 19%). PMS2 was only assessed in 1 study; there were no cases of LS with a PMS2 mutation.[54] In total, 29 variants of uncertain significance were identified in the four studies (median = 7; 3 to 12 cases per study). Point estimates ranged from 41.7 – 100% for sensitivity, 69.2 – 89.9% for specificity, 20 – 89.9% for positive predictive value, and 88.7 – 100% for negative predictive value (see figure X2). One of the included studies reported data that allowed us to calculate test accuracy using microsatellite instability: high or low (1 or more unstable marker) as a cut off. There were 5 true positives, 17 false positives, 54 true negatives, and 7 false negatives.[78] The most commonly affected gene was MSH2 (3/5 cases of LS, 60.0%), followed by MSH6 (1/5 cases of LS, 20%) and MLH1 (1/5 cases of LS, 20%). PMS2 was not assessed. Three variants of uncertain significance were identified. Test accuracy metrics were similar to those reported using microsatellite instability: high as a cut off: sensitivity was 41.7%, specificity was 76.1%, positive predictive value was 22.7%, and negative predictive value was 88.5%. Using a cut-off of 1 or more stable marker, changed the status of 1 index test result from true negative to false positive.

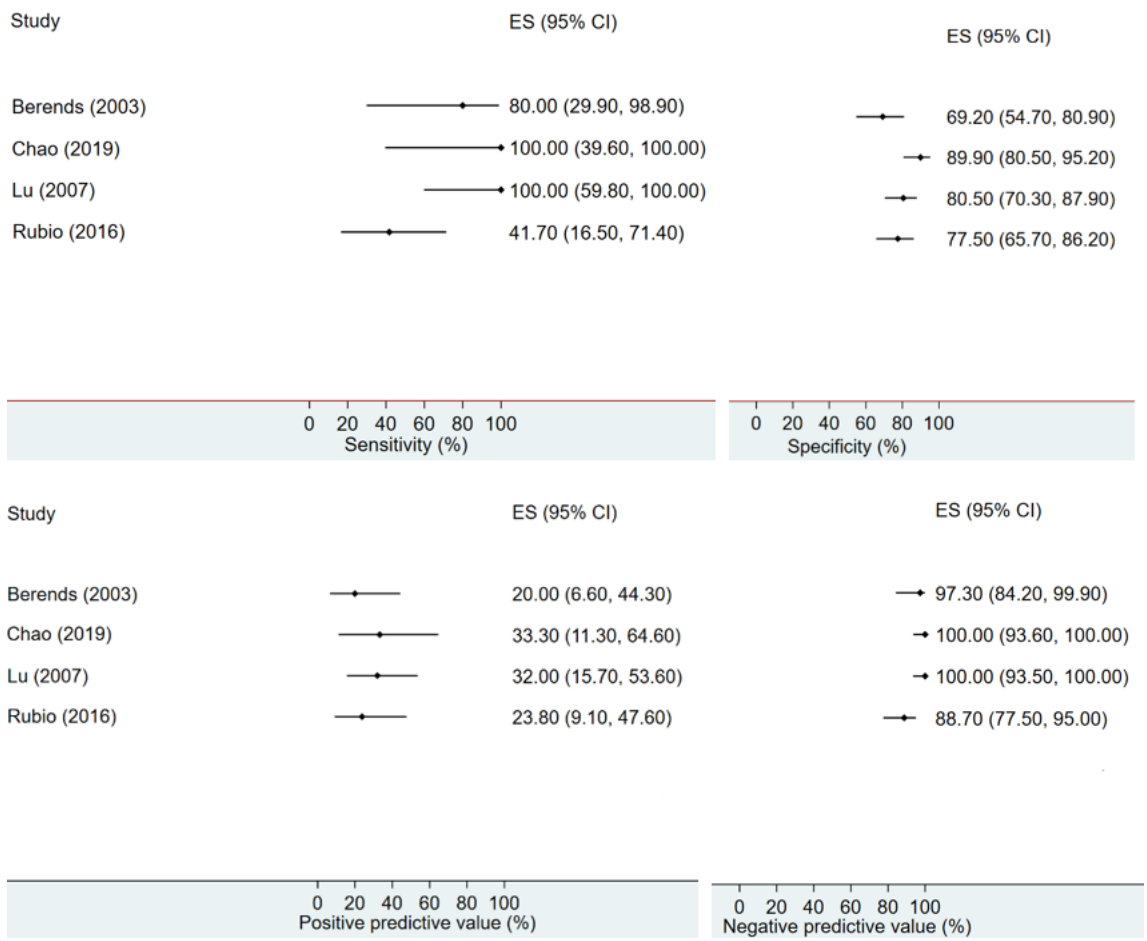


Figure 24: Sensitivity, specificity, positive predictive value, and negative predictive value of microsatellite instability-based testing for Lynch syndrome

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

Secondary analysis of test accuracy in which variants of uncertain significance were considered germline positive was possible for two studies.[14, 50, 54, 78] Estimates of test accuracy were as follows: sensitivity 87.5% (95% CI 46.7 - 99.3%), specificity 69.4% (95% CI 54.4 - 81.3%), positive predictive value 31.8% (95% CI 14.7 - 54.9%), negative predictive value 97.1% (95% CI 83.4 - 99.9%);[50] sensitivity 100.0% (95% CI 75.9 - 100.0%), specificity 91.0% (95% CI 80.9 - 96.3%), positive predictive value 72.7% (95% CI 49.6 - 88.4%), negative predictive value 100.0% (95% CI 92.6 - 100.0%);[54] Sensitivity 100.0%

(95% CI 79.1 - 100.0%), specificity 80.3% (95% CI 69.2 - 88.2%), positive predictive value 55.9% (95% CI 38.1 - 72.4%), negative predictive value 100.0% (95% CI 92.6 - 100.0%);[14] sensitivity 53.3% (95% CI 27.4 - 77.7%), specificity 76.5% (95% CI 64.4 - 85.6%), positive predictive value 33.3% (95% CI 16.4 - 55.3%), negative predictive value 88.1% (95% CI 76.5 - 94.7%).[78] These were similar to estimates in which variants of uncertain significance were consider to be germline negative.

Immunohistochemistry and microsatellite instability based testing, with MLH1 promoter methylation testing

Four studies provided test accuracy data for immunohistochemistry and microsatellite instability-based testing, where a lack of expression on immunohistochemistry without MLH1 methylation *or* microsatellite instability:high (2 or more unstable markers) test was considered index test positive.[14, 54, 77, 79] The circumstances under which MLH1-PM 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),[14, 79] in one study methylation testing was conducted in women who had IHC MLH1 loss only.[54] In the remaining paper, the circumstances under which MLH1-PM was conducted was not reported.[77] Three studies comprised selected samples of women,[14, 54, 79] and one study comprised an unselected sample of women.[77] One study excluded women over 50 years old,[14] one study excluded women with recurrent or synchronous cancers,[54] 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.[79] Each study used a different panel of MSI markers. There were 85 true positives, 307 false positives, 448 true negatives, and 4 false negatives. Two studies reported the gene variants in LS cases.[14, 54] The most commonly affected gene was MSH2 (9/15 cases of LS, 60%), followed by MSH6 (4/15 cases of LS, 26.7%), MLH1 (2/15 cases of LS, 13.3%), and PMS2 (0/15 cases of LS, 0%). PMS2 was only assessed in 1 study.[54] In two studies, 25 variants of uncertain significance were identified (median = 12.5; 11 to 14 cases per study).[14, 54] One study did not report variants of uncertain significance.[79] In the remaining study, 25 variants of uncertain significance were identified but the study did not report whether the participants had had index testing.[77] Point estimates ranged from 90.5 – 100% for sensitivity, 2.6 – 90.7% for specificity, 18.3 - 37.3% for positive predictive values, and 75.0 – 100% for negative predictive values (see figure X3). In the study with an unselected sample of women, there were 19 true positives, 32 false

positives, 312 true negatives, and 2 false negatives.[77] Comparing confidence intervals, there was no statistically significant difference in sensitivity, positive predictive values, or negative predictive values between the studies with selected versus unselected samples, but specificity was significantly higher for the study with an unselected sample (90.5%, 95% CI 87.0 – 93.5%) than those with selected samples (6.6%, 95% CI 3.9 – 10.7%; 72.4%, 95% CI 61.6 – 81.2%; 73.6%, 95% CI 63.2 – 82.1%)

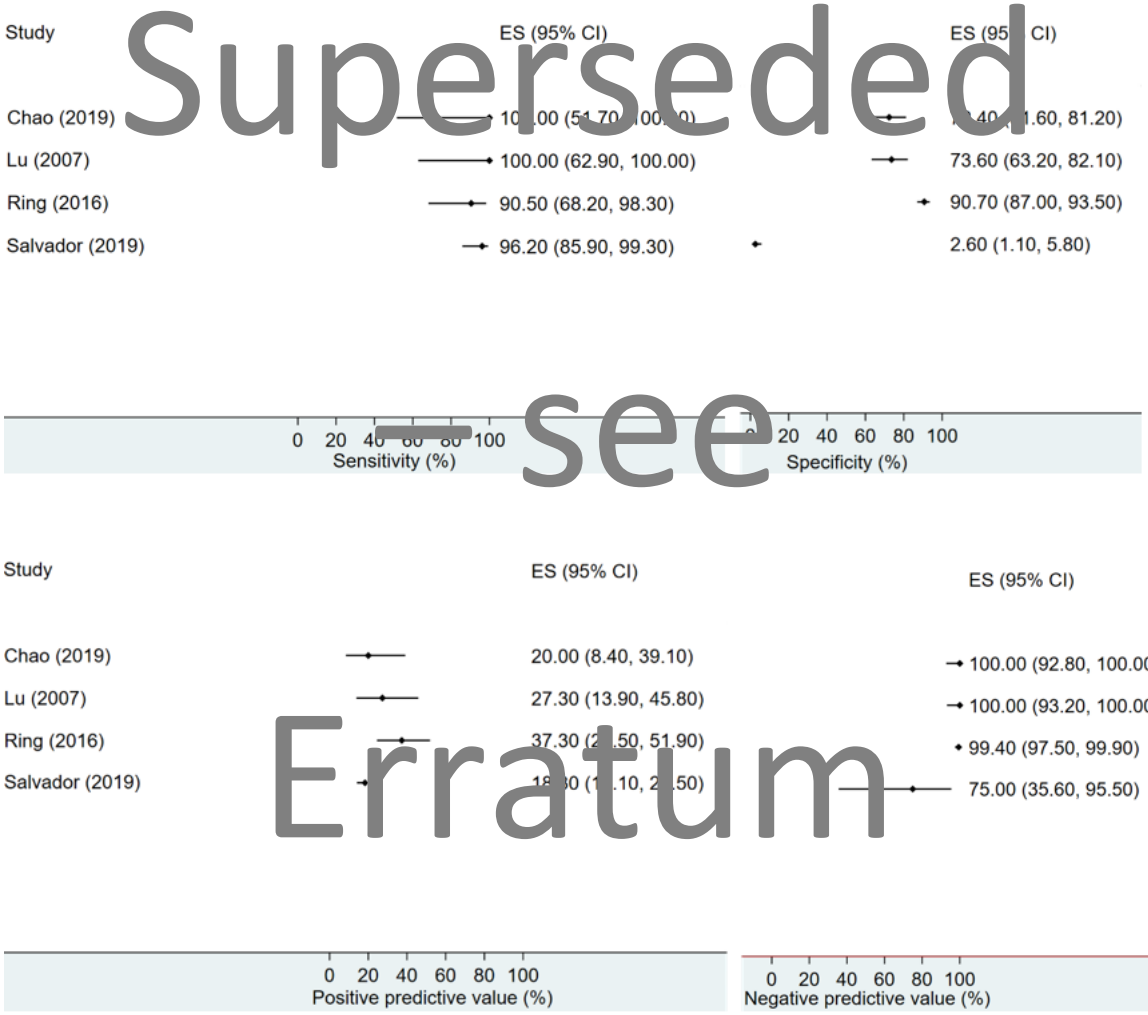


Figure 25: Sensitivity, specificity, positive predictive value, and negative predictive value of immunohistochemistry, microsatellite instability-based testing, and MLH1 promoter methylation testing for Lynch syndrome

Two studies reported the results of MLH1 promoter hypermethylation testing.[14, 54] Twelve out of 13 tumours (92.3%),[14] and 12 out of 15 tumours (80%) were hypermethylated.[54]

Data on test failures, indeterminate results, or lack of testing was reported in full for two studies.[14, 54] One study did not report any data on test failures, indeterminate results, or lack of testing,[77] and one study did not provide this data for MLH1 promoter hypermethylation testing.[79] Test failures were reported for 0 – 1% of tumours for immunohistochemistry (1 out of 567 tumours). No test failures were reported for microsatellelite instability-based testing or MLH1 promoter hypermethylation testing. No indeterminate results were reported of any of the three tests. Testing was not conducted in 0 – 8.1% for participants (9 out of 576 tumours) for immunohistochemistry, and 0.5 – 25.2% of participants (39 out of 372 tumours) for microsatellite instability-based testing due to insufficient tumour tissue (or unspecified reasons). There were no reported instances where MLH1 promoter hypermethylation testing could not be carried out.

Secondary analysis of test accuracy in which variants of uncertain significance were considered germline positive was possible for two studies.[14, 54] Estimates of test accuracy were as follows: Sensitivity 100.0% (95% CI 80.0 - 100.0%), specificity 86.3% (95% CI 75.8 - 92.9%), positive predictive value 66.7% (95% CI 47.1 - 82.1%), negative predictive value 100.0% (92.8 - 100.0%); [54] sensitivity 100.0% (80.0 - 100.0%), specificity 78.8% (67.9 - 86.8%), positive predictive value 54.1% (37.1 - 70.2%), negative predictive value 100.0% (92.8 - 100.0%).[14] These were similar to estimates in which variants of uncertain significance were consider to be germline negative with the except of positive predictive value for Chao et al,[54] which was higher when variants of uncertain significance were considered to be germline positive (66.7%, 95% CI 47.1 - 82.1% versus 20.0%, 95% CI 8.4% - 39.1%).

Concordance between immunohistochemistry and microsatellite instability-based testing

Twenty-three studies, including the unpublished PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019), provided data on concordance between immunohistochemistry and microsatellite instability-based testing.[13, 14, 47, 50, 51, 54, 57-59, 63, 64, 67, 68, 71, 74-76, 78, 81-83, 87] Twenty studies provided complete concordance data (agreement/disagreement between IHC positive/negative and IHC negative), and 3 studies provided partial concordance data (IHC only conducted for MSI:H tumours,[83] MSI only conducted for women with IHC loss,[75] IHC only conducted for women with MSS results[13]). Full details of concordance are reported in Table 10. 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 adisgreement being 31.8%), median kappa 0.84 (range 0.32 – 0.97). Kappa values were calculated by the reviewers.

Few studies examined characteristics of discordant cases. Four studies reported that MLH1 promoter hypermethyation was common in discordant cases: 50% (1 out of 2 cases),[67] 75% (3 out of 4 cases),[8] 80% (4 out of 5 cases),[51] and 83% (10/12 cases).[82] Six of the 13 concordance studies reported on the characteristics of discordant cases of MSI and IHC testing.[13, 14, 47, 51, 59, 68, 81] In 2 of these 6 studies it was possible to determine germline results for the discordant cases.[14, 51] Bruegl et al found 5.1% disagreement, with 7/197 discordant cases.[51] Of these 7 only 1 was found to have a germline mutation and this was in MSH6 variant. Likewise, Goodfellow et al found the only discordant case with a germline mutation was in the MSH6 variant.[59] Whereas, Lu et al found that of the 5 discordant cases, all were germline mutation negative.[14]

Across 3 studies, 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.[14, 51, 68]

For one study, discordance was associated with the classification of MSI-L cases. When MSI-L cases were grouped with MSS cases, there were 2 discordant cases, whilst when MSI-H or MSI-L were grouped together and compared to MSS, there were no cases of discordance between MSI and IHC testing results.[47]

It was possible to calculate the average age for discordant cases in three studies.[13, 47, 81] In Anagnostopoulos et al, discordant cases (n=2) had a median age of 39.5 years, which was lower than the overall median in the sample of 48 years. Whilst Shih et al and Hampel et al found no real difference in age between discordant cases and the whole sample. Shih et al found 2 discordant cases with a mean age of 55 years at diagnosis for EC cancer and 52.5 years for CRC, compared to the overall sample mean age of 52.5 years for EC cancer and 54.5 years for CRC and Hamel et al found a mean age of 60.5 years in discordant cases, compared to the overall mean of 60.9 years in the whole sample.

There was 1 study which reported on the comorbidities of other cancers in discordant cases. All cases in the study had a history of both EC and CRC. They found 1 of the 2 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. Further details on concordance are provided in Table 10.

Table 7. Complete test accuracy

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
MSI, IHC, and MLH1-PM											
Chao (2019) [54]	93	IHC (MLH1, MSH2, MSH6, PMS2) Negative staining of any of MMR protein MSI MSI-H:≥ 2 instable markers	NGS, Sange[illegible] sequencing	6	24	63	0	100.0% (51.7% - 100.0%)	72.4% (61.6% - 81.2%)	20.0% (8.4% - 39.1%)	100.0% (92.8% - 100.0%)

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Lu (2007) [14]	100	IHC (MHL1, MSH2, MSH6) Loss of protein expression MSI MSI-H:≥ 2 instable markers	Sequencing, unspecified test for large deletions	9	24	67	0	100.0% (62.9% - 100.0%)	73.6% (63.2% - 82.1%)	27.3% (13.9% - 45.8%)	100.0% (93.2% - 100.0%)
Ring (2016) [77]	365	IHC (MLH1, MSH2, MSH6, PMS2) Complete absence of	MLPA, NGS	19	32	312	2	90.5% (68.2%, 98.3%)	90.7% (87.0%, 93.5%)	37.3% (24.5%, 51.9%)	99.4% (97.5%, 99.9%)

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
		MMR protein expression <u>MSI</u> MSI:H, but cut off not reported									
Salvador (2019) [79]	296	<u>IHC</u> (MLH1, MSH2, MSH6, PMS2) Cut off not reported <u>MSI</u> MSI-H:≥ 2 instable markers	MLPA, NGS	51	227	6	2	96.2% (85.9% - 99.3%)	2.6% (1.1 - 5.8%)	18.3% (14.1% - 23.5%)	75.0% (35.6 - 95.5%) %)

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
MSI only (MSI:H vs MSI:L/MSS)											
Berends (2003) [50]	57	MSI MSI-H ≥2 unstable markers	DGGE, sequencing, MLPA	4	16	36	1	80% (2[illegible].9-98.[illegible]%)	69.2% (5[illegible].7-80.[illegible]%)	20% (6.6-44.3%)	97.3% (84.2-99.9%)
Chao (2019) [54]	83	MSI MSI-H:≥ 2 instable markers	NGS, Sanger sequencing	4	8	71	0	100.0% (39.6% - 100.0%)	89.9% (80.5% - 95.2%)	33.3% (11.3% - 64.6%)	100.0% (93.6% - 100.0%)
Lu (2007) [14]	95	MSI MSI-H:≥ 2 instable markers	Sequencing, unspecified test for large deletions	8	17	70	0	100.0% (59.8% - 100.0%)	80.5% (70.3% - 87.9%)	32.0% (15.7% - 53.6%)	100.0% (93.5% - 100.0%)

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Rubio (2016) [78]	83	MSI MSI-H, number of markers not specified	CSGE, sequencing, MLPA	5	16	55	7	41.7% (16.5-71.4%)	77.5% (65.7-86.2%)	23.8% (9.1-47.6%)	88.7% (77.5-95%)
MSI only (MSI:H/L vs MSS)											
Rubio (2016) [78]	83	MSI MSI-H/L, number of markers not specified	CSGE, sequencing, MLPA	5	17	54	7	41.7% (16.5-71.4%)	76.1% (64.2-85.1%)	22.7% (8.7-45.8%)	88.5% (77.2-94.9%)
IHC only											
Berends (2003) [50]	51	IHC (MLH1, MSH2, and MSH6) Absence of detectable	DGGE, sequencing, MLPA	5	18	28	0	100% (46.3-100%)	60.9% (45.4-74.5%)	21.7% (8.3-44.2%)	100% (85-100%)

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
		nuclear staining of cancer cells									
Chao (2019) [54]	102	IHC (MLH1, MSH2, MSH6, PMS2) Negative staining of any of MMR protein	NGS, Sanger sequencing	4	24	75	2	66.7% (24.1% - 94.0%)	75.0% (64.9% - 83.0%)	14.3% (4.7% - 33.6%)	97.3% (89.7% - 99.5%)
Lu (2007) [14]	99	IHC (MHL1, MSH2, MSH6)	Sequencing, unspecified test for large deletions	9	15	75	0	100.0% (62.9% - 100.0%)	83.3% (73.7% - 90.1%)	37.5% (19.5% - 59.2%)	100.0% (93.9% - 100.0%)

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
		Loss of protein expression									
Rubio (2016) [78]	94	IHC Cut off not reported	CSGE sequencing, MLPA	1	2	60	3	76.9 % (46-93.8%)	74.1% (62.9-82.9%)	32.3% (17.3-51.5%)	95.2% (85.8-98.8%)
Tian (2019) [86]	165	IHC Cut off not reported	Sequencing/NGS, MLPA	41	115	8	1	97.6% (85.9 - 99.9)	6.5% (3.1 - 12.8%)	26.3% (19.7 - 34.0%)	88.9% (50.7 - 99.4%)

ACGH = Array Comparative Genomic Hybridisation; CC = colorectal cancer; CI = confidence interval; CSGE = conformation sensitive gel electrophoresis ; DGGE = denaturing gradient gel electrophoresis; EC = endometrial cancer ;MLH1-PM = MLH1 promoter methylation; MLPA =multiplex Ligation-dependent Probe Amplification; MMR = mismatch repair; NA = not applicable; NGS = next-generation sequencing; NPV = negative predictive value; PPV = positive predictive value; SSCV = single strand conformational variant

4.4.1. Testing pathways under review - Partial test accuracy studies

In the proposed testing strategies, 1 – 10 (below) 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 negative predictive values from these studies due to a lack of follow up of women who were negative on the index tests. Studies in which full text accuracy could be extracted/calculated have already been reported above (see section 4.4) , so here we report results from any studies (full or partial test accuracy) which report on numbers of true positive and false positive results for each strategy. Full details of all the strategies are provided in Table 8.

There is a risk that the likelihood that someone receives 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 and those who do not have the disease do not get the reference standard. This biases positive predictive value upwards. Therefore, we only included studies in which at least 95% of women who were eligible for germline testing (those who were index test positive) received it.

Strategy 1: MSI testing alone

Eight studies, including the unpublished PETALS study (Ryan et al, University of Manchester, 11/12/2019), provided test accuracy data for this strategy.[14, 50, 54, 62, 69, 74, 78]
Six studies comprised selected samples of women,[14, 50, 54, 69, 74, 78] one study provided insufficient information on which to make an assessment of sample selection type, (Latham) and one study comprised an unselected sample of women.(Ryan, University of Manchester, 2019) Two studies excluded women over 50 years old,[14, 50] one study excluded women with recurrent or synchronous cancers,[54] one study only included women with a family history of EC cancers,[74] and one study excluded women (1) without a personal/family history of Lynch syndrome-related cancer or (2) who were over 50 years old.[69, 78]
There were 39 true positives, and 212 false positives out of 1,402 women tested. The most commonly affected gene was MSH2 (18/39 cases of LS, 46.2%), followed by MSH6 (11/39 cases of LS, 28.2%), MLH1 (8/39 cases of LS, 20.5%), and PMS2 (2/39 cases of LS, 5.1%). PMS2 was only assessed in 4 out of the 8 studies (including the PETALS study).[54, 62, 69] In total, 11 variants of uncertain significance were identified in the seven studies (median = 2; 0

to 3 cases per study). Point estimates for positive predictive values ranged from 5.9 - 66.7% (see figure Figure 26). Test failures were reported in the PETALS study for [redacted] of tumours for MSI testing ([redacted] out of [redacted] tumours tested). None of the other studies reported test failures. No study reported indeterminate results.No testing was conducted in 0 – 25.2% of participants (54 out of 994 tumours) due to insufficient tumour tissue.

Figure 26: Positive predictive value of microsatellite instability-based testing for Lynch syndrome

Strategy 2: MSI testing with MLH1 promoter hypermethylation testing

No studies were identified that examined this strategy.

Strategy 3: IHC-based testing alone

Six studies provided test accuracy data for this strategy.[14, 50, 54, 69, 78, 86] All six studies comprised selected samples of women,[14, 50, 54, 69, 78, 86] Two studies excluded women over 50 years old,[14, 50] one study excluded women with recurrent or synchronous cancers,[54] one study excluded women (1) without a personal/family history of Lynch syndrome-related cancer or (2) who were over 50 years old,[78] and one study excluded women who (1) were over 50 years old, (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.[69, 86] 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 LS, 49.3%), followed by MSH6 (18/69 cases of LS, 26.1%), MLH1 (14/69 cases of LS, 20.3%), and PMS2 (3/69 cases of LS, 3%). PMS2 was only assessed in 3 out of the 6 studies.[54, 69, 86] In total, 22 variants of uncertain significance were identified in the seven studies (median = 3; 2 to 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 LS, 50%), followed by MLH1 (31/80 cases of LS, 38.8%), and MSH6 (9/81 cases of LS, 11.2%).[69] Point estimates for positive predictive values ranged from [redacted] – 37.5% in the studies reported on all 4 MMR genes (see Figure 27), [14, 50, 54 78 86] and 77.4 – 84.6% in the study that reported each gene separately.[69] No test failures or indeterminate results were reported. No testing was conducted in 0 – 16.2% of participants (57 out of 644 tumours) due to insufficient tumour tissue.

Figure 27: Positive predictive value of immunohistochemistry for Lynch syndrome

Strategy 4: IHC testing with MLH1 promoter hypermethylation testing

Three studies provided test accuracy data for this strategy. (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019)[14, 74] Two studies comprised selected samples of women.[14, 74] One study excluded women over 50 years old,[14] and one study only included women with a family history of EC cancers.[74] One study was conducted in an unselected sample of women with endometrial cancer. (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019) There were 27 true positives, and 49 false positives out of 622 women tested. The most commonly affected gene was MSH2 (12/27 cases of LS, 44.4%) followed by MSH6 (10/27 cases of LS, 37%), MLH1 (3/27 cases of LS, 11.1%), and PMS2 (2/27 cases of LS, 7.4%). Only one study assessed PMS2, (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019). In total, 9 variants of uncertain significance were identified in the three studies (median = 2; 0 to 7 cases per study). Point estimates for positive predictive values ranged from 20.0 - [redacted]% (see figure X6). All three studies reported the results of MLH1 promoter hypermethylation testing. One out of 7 tumours (14.3%),[74] 12 out of 13 tumours (92.3%),[14] and [redacted](PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019) were hypermethylated. Test failures were reported in one studies, in which 13 out of 500 IHC failed (but were all successful on retesting), and [redacted]_MLH1-PM tests failed multiple times. (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019) No other test failures or indeterminate results were reported, and all tumours had sufficient tissue for testing.

Figure 28: Positive predictive value of immunohistochemistry with MLH1 promoter hypermethylation testing for Lynch syndrome

Strategy 5: MSI testing followed by IHC testing

No studies were identified that examined this strategy.

Strategy 6: MSI followed by IHC testing with MLH1 promoter hypermethylation testing

No studies were identified that examined this strategy.

Strategy 7: IHC followed by MSI testing

No studies were identified that examined this strategy.

Strategy 8: IHC testing followed by MSI testing with MLH1 promoter hypermethylation testing

No studies were identified that examined this strategy.

Strategy 9: MSI and IHC testing

No studies were identified that examined this strategy.

Strategy 10: MSI and IHC testing with MLH1 promoter hypermethylation testing

Six studies provided test accuracy data for this strategy.[14, 54, 59, 74, 79, 88] All six studies comprised selected samples of women.[14, 54, 59, 74, 79, 88] One study excluded women with recurrent or synchronous cancers,[54] one study excluded women who were not considered

suitable candidates for surgery, had prior retroperitoneal surgery, or prior pelvic or abdominal radiation therapy, or who were pregnant,[59] one study excluded women over 50 years old (Lu), one study only included women with a family history of EC cancers,[74] one study included an unselected sample of women but did not report data on women with uninformative MMR results or without prior tumour testing,[79] and one study only included women who answered questions about family/personal history of cancer and who had tumour and normal tissue available for analysis were included.[88] Four panels of markers were used in the six studies; the studies by Berends at al.[50] and Ollikainen et al.[74] used the same 5 marker panel, and the studies by Lu et al,[14] and Rubio et al.[78] used the same 6 marker panel. There were 94 true positives, and 311 false positives out of 1,627 women tested. Five studies reported the affected genes.[14, 54, 59, 74, 88] The most commonly affected gene was MSH2 (19/43 cases of LS, 44.2%), followed by MSH6 (16/43 cases of LS, 37.2%), MLH1 (5/43 cases of LS, 11.6%), and PMS2 (3 out of 43 cases of LS, 7.0%. Only 2 studies assessed PMS2.[54, 59]) Five studies reported details of variants of uncertain significance.[14, 54, 59, 74, 88] In total, 18 variants of uncertain significance were identified (median = 2; 0 to 14 cases per study). Point estimates for positive predictive values ranged from 18.3 - 43.1% (see Figure 29). Five studies reported the results of MLH1 promoter hypermethylation testing.[14, 54, 59, 74, 88] 14.3 – 92.3% of tumours were hypermethylated (368 out of 516 tumours).

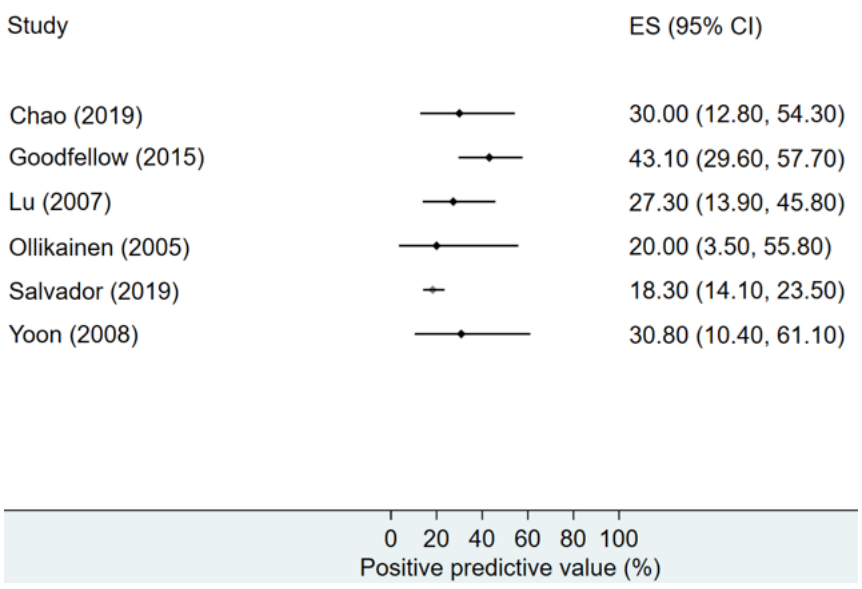


Figure 29: Positive predictive value of MSI and IHC testing with MLH1 promoter hypermethylation testing for Lynch syndrome

Test failures (Table 9) were reported for 0 – 8.1% of tumours for immunohistochemistry (13 out of 1686 tumours), none for microsatellelite instability-based testing, and 0 – 3.7% (39 out of 1163 tumours) for MLH1 promoter hypermethylation testing. No indeterminate results were reported of any of the three tests. No testing was conducted in 0 – 8.1% of participants (9 out of 1686 tumours) for immunohistochemistry, 0 – 25.2% of participants (28 out of 1163 tumours) for microsatellite instability-based testing, and 0% (out of 173 tumours – number of tumours tested not reported for two studies[79, 88]) for MLH1 promoter hypermethylation testing due to insufficient tumour tissue.

Strategy 11: Germline testing only

Nine studies provided data on germline only testing, where women were offered the reference standard(s) irrespective of the result of index tests.[14, 50, 54, 58, 70, 77-79, 86] Lynch syndrome was identified in 166 out of 1375 (12.1%) women tested. (median = 9, 5 to 51 cases of LS per study). In total, 47 variants of uncertain significance were identified (median = 3; 0 to 15 cases per study).

Table 8 Partial test accuracy

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Strategy 1: MSI testing alone											
Berends (2003) [50]	57	MSI MSI-H≥2 unstable markers	DGGE, sequencing, MLPA	4	16	NA	NA	NA	NA	20.0% (6.6% - 44.3%)	NA
Chao (2019) [54]	83	MSI MSI-H:≥ 2 instable markers	NGS, Sanger sequencing	4	8	NA	NA	NA	NA	33.3% (11.3% - 64.6%)	NA
Latham (2019) [62]	525	MSI MSIsensor scores ≥ 10	NGS	7	112	NA	NA	NA	NA	5.9% (2.6% - 12.2%)	NA
Lu (2007) [14]	95	MSI MSI-H:≥ 2 instable markers	Sequencing, unspecified test for large deletions	8	17	NA	NA	NA	NA	32.0% (15.7% - 53.6%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Mercado (2012) [69]	24	MSI MSI-H:≥ 2 instable markers	DHPLC, sequencing	15	5	NA	NA	NA	NA	75% (50.6 - 90.4%)	NA
Ollikainen (2005) [74]	23	MSI MSI-H:≥ 2 instable markers	Sequencing & MLPA	2	1	NA	NA	NA	NA	66.7% (12.5 - 98.2%)	NA
PETALS study, (personal communication, Ryan et al., University of Manchester, 11/12/2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rubio (2016) [78]	83	MSI MSI-H, number of	CSGE, sequencing, MLPA	5	16	NA	NA	NA	NA	23.8% (9.1-47.6%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
		markers not specified									
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
Strategy 3: IHC alone											
Study ID	**Number tested**	**IHC cut off**	**Reference standard**	**2x2 table**				**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
				TP	**FP**	**TN**	**FN**				
Berends (2003) [50]	51	IHC Absence of detectable nuclear staining of cancer cells	DGGE, sequencing, MLPA	5	18	NA	NA	NA	NA	21.7% (8.3%, 44.2%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Chao (2019) [54]	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% - 33.6%)	NA
Lu (2007) [14]	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% - 59.2%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Mercado[69]	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	75.0% (54.8 - 88.6%) MSH6 = 77.4% (58.5 - 89.7%) PMS2 = 81.8% (59.0 - 94.0%)	NA
PETALS study, (personal communication, Ryan et al., University of Manchester, 11/12/2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Rubio (2016) [78]	94	IHC Cut off not reported	CSGE, sequencing, MLPA	10	21	NA	NA	NA	NA	32.3% (17.3% - 51.5%)	NA
Tian (2019) [86]	165	IHC Cut off not reported	Sequencing/NGS, MLPA	41	115	NA	NA	NA	NA	26.3% (19.7 - 34.0%)	NA
Strategy 4: IHC with MLH1 promoter hypermethylation testing											
Lu (2007) [14]	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% - 59.2%)	NA
Ollikainen (2005) [74]	23	IHC (MLH1, MSH2, MSH6) Cut off not reported	Sequencing & MLPA	2	8	NA	NA	NA	NA	20.0% (3.5 - 55.8%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
PETALS study, (personal communication, Ryan et al., University of Manchester, 11/12/2019)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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											
Study ID	**Number tested**	**Index test and cut off**	**Reference standard**	**2x2 table**				**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
				TP	**FP**	**TN**	**FN**				
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											
Study ID	**Number tested**	**Index test cut offs**	**Reference standard**	**2x2 table**				**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
				TP	**FP**	**TN**	**FN**				

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
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											
Study ID	**Number tested**	**Index test cut offs**	**Reference standard**	**2x2 table**				**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
				TP	**FP**	**TN**	**FN**				
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
Strategy 10: MSI and IHC testing with MLH1 promoter hypermethylation testing											
Study ID	**Number tested**	**Index test cut offs**	**Reference standard**	**2x2 table**				**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
				TP	**FP**	**TN**	**FN**				
Chao (2019) [54]	77	IHC (MLH1, MSH2, MSH6, PMS2) Negative staining of	NGS, Sanger sequencing	6	14	NA	NA	NA	NA	30.0% (12.8% - 54.3%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
		any of MMR protein MSI MSI-H:≥ 2 instable markers									
Goodfellow (2015) [59]	1002	IHC (MLH1, MSH2, MSH6, plus PMS2 in subset Cut off not reported MSI MSI-H:≥ 2 instable markers	NGS	22	29	NA	NA	NA	NA	43.1% (29.6% - 57.7%)	

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Lu (2007) [14]	100	IHC (MHL1, MSH2, MSH6) Loss of protein expression MSI MSI-H:≥ 2 instable markers	Sequencing, unspecified test for large deletions	9	24	NA	NA	NA	NA	27.3% (13.9% - 45.8%)	NA
Ollikainen (2005) [74]	23	IHC (MLH1, MSH2, MSH6) Cut off not reported MSI	Sequencing & MLPA	2	8	NA	NA	NA	NA	20.0% (3.5 - 55.8%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
		MSI-H:≥ 2 instable markers									
Salvador (2019) [79]	296	IHC (MLH1, MSH2, MSH6, PMS2) Cut off not reported MSI MSI-H:≥ 2 instable markers	MLPA, NGS	51	227	NA	NA	NA	NA	18.3% (14.1% - 23.5%)	NA
Yoon (2008) [88]	113	MSI MSI-H:≥ 2 instable markers	Sequencing	4	9	NA	NA	NA	NA	30.8% (10.4% - 61.1%)	NA

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
		IHC (MHL1, MSH2, MSH6) No evidence of expression									

Study ID	Number tested	Index test and cut off	Reference standard	2x2 table				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
				TP	FP	TN	FN				
Strategy 11: Germline only											
Study ID	**Number tested**	**Reference standard**		**Number of Lynch syndrome diagnoses (%)**				**Notes**			
Berends (2003) [50]	57	DGGE, sequencing, MLPA		5 (8.8%)				Initial reference standard was denaturing gradient gel electrophoresis (followed, in case of aberrant band patterns, by direct sequencing of independently amplified PCR products)			
Chao (2019) [54]	111	NGS and Sanger sequencing		6 (5.4%)				-			
Ferguson (2014) [58]	89	Sequencing, MLPA		7/89 (7.9%)				-			
Millar(1999)[70]	40	SSCV, sequencing		7 (17.5%)				All of the women included had EC and CC			
Lu (2007) [14]	100	Sequencing, unspecified test for large deletions		9 (9%)				-			
Ring (2016) [77]	381	MLPA, NGS		22 (5.8%)				2 women diagnosed with Lynch syndrome had mutations in EPCAM than extended into MSH2			
Rubio (2016)[78]	103	CSGE, sequencing, MLPA		14 (13.6%)				-			
Salvador (2019) [79]	296	NGS, MLPA, ACGH		51 (17.3%)				-			
Tian (2019) [86]	198	Sequencing, NGS, MLPA		45 (22.7%)				-			

ACGH = Array Comparative Genomic Hybridisation; CC = colorectal cancer; CI = confidence interval; CSGE = conformation sensitive gel electrophoresis ; DGGE = denaturing gradient gel electrophoresis; DHPLC = Denaturing high performance liquid chromatography; EC = endometrial cancer; MLH1-PM = MLH1 promoter methylation; MLPA =multiplex Ligation-dependent Probe Amplification; MRM MMR = mismatch repair; NA = not applicable; NGS = next-generation sequencing; NPV = negative predictive value; PPV = positive predictive value; SSCV = single strand conformational variant

Table 9. Test failures and indeterminate test results

Study	**IHC test failures, n/N (%)**	**IHC indeterminate results, n/N (%)**	**MSI test failures, n/N (%)**	**MSI indeterminate results, n/N (%)**	**MLH1-PM test failures, n/N (%)**	**MLH1-PM indeterminate results, n/N (%)**	**Reference standard test failures, n/N (%)**	**Reference standard indeterminate results, n/N (%)**	**Notes**
Anagnostopoulos (2017) [47]	0/35 (0%)	0/35 (0%)	0/35 (0%)	0/35 (0%)	0/2 (0%)	0/2 (0%)	0/9 (0%)	0/9 (0%)	Only included women with both IHC and MSI data
Backes (2009) [48]	0/140 (0%)	0/140 (0%)	NA	NA	NA	NA	0/2 (0%)	0/2 (%)	-
Baldinu (2002[49])/ Strazzullo (2003) [83]	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

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Berends (2003) [50]	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 (2017) [51]	NR	NR	NR	NR	NR	NR	0/11 (0%)	0/11 (0%)	"Insufficient tissue to perform the evaluation" given as one of group of reason for lack of index test. Number not reported
Buchanan (2014) [52]/Nagle (2018) [72]	0/702 (0%),	0/702 (0%), see note 1	NA	NA	NR See note 2	NR See note 2	0/170 (0%)	0/170 (0%)	1. Only included

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
	see note 1								women with IHC results 2. Offered only to women with MMR deficient + sufficient tumour tissue or random sample of MMR proficient

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Carnevali (2017) [53] /Libera (2017)[64]	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 LS
Chao (2019) [54]	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 (2017) [55]	0/233 (0%)	0/233 (0%)	NA	NA	0/51 (0%)	0/51 (0%)	0/8 (0%)	0/8 (0%)	Insufficient tumour tissue: MLH1-PM = 1/51
Egoavil (2013) [57]	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	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Ferguson (2014) [58]	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 (2003) [60]	NA	NA	0/441 (0%)	0/441 (0%)	0/137 (0%)	0/137 (0%)	0/7 (0%)	0/7 (0%)	-
Goodfellow (2015) [59]	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%)	-
Hampell (2006) [13]	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. Only reported for women offered germline testing

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
									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

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
									insufficient DNA
Kato (2016) [61]/Takahashi (2017) [85]	0/360 (0%)	0/360 (0%)	NA	NA	NA	NA	0/27 (0%)	0/27 (0%)	IHC, 12 specimens not available
Latham (2019) [62]	NR	NR	0/525 (0%)	0/525 (0%)	NA	NA	0/119 (0%)	0/119 (0%)	For 1 women diagnosed with LS, IHC was 'not available'. No further details.
Leenen (2012) [63]	0/179 (0%)	0/179 (0%)	0/179 (0%)	0/179 (0%)	0/42 (0%)	0/42 (0%)	0/10 (0%)	0/10 (%)	4 IHC not conducted because no

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
									tumour tissue available
Lin (2016) [65]	0/74 (0%)	2/74 (2.6%)	NA	NA	0/14 (0%)	0/14 (0%)	0/3 (0%)	0/3 (0%)	
Lu (2007) [14]	1/100 (1%)	0/100 (0%)	0/100 (0%)	0/100 (0%)	0/100 (0%)	0/100 (0%)	0/100 (0%)	0/100 (0%)	5 MSI not conducted because of insufficient tumour tissue
Mas-Moya (2016) [66]/Dudley (2015) [56]	0/215 (0%)	0/215 (0%)	0/215 (0%)	0/215 (0%)	NR	NR	0/17 (0%)	0/17 (0%)	-
Masuda (2012) [67]	0/36 (0%)	0/36 (0%)	0/36 (0%)	0/36 (0%)	NR	NR	NA	NA	Concordance only

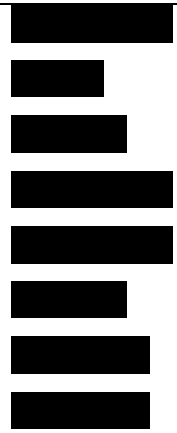
Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
McConechy (2015) [68]	0/89 (0%%)	0/89 (0%)	0/89 (0%)	0/89 (0%)	NA	NA	NA	NA	Insufficient tumour tissue: IHC, n = 2/157, MSI, n = 0/157 (68 insufficient normal tissue)
Mercado (2012) [69]	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

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
									reported for IHC refers to the largest sample of women in the study. The denomitor for germline refers to all women who received germline testing.
Millar (1999) [70]	NA	NA	0/40 (0%)	0/40 (0%)	NA	NA	0/40 (0%)	0/40 (0%)	
Modeca (2007) [71]	0/90 (0%)	5/90 (5.6%)	0/90 (0%)	0/90 (0%)	NA	NA	NA	NA	Concordance only

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Najdawi (2017) [73]	0/124 (0%)	0/124 (0%)	NA	NA	0/26 (0%)	0/26 (0%)	0/9 (0%)	0/9%)	2 IHC not conducted because of insufficient tumour material
Ollikainen (2005) [74]	0/23 (0%)	1/23 (4.5%)	0/23 (0%)	0/23 (0%)	0/6 (0%)	0/6 (0%)	0/10 (0%)	0/10 (%)	Only includes women with a family history of EC Table 2 says 1 IHC not determined. No further details.

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Pecorino (2017) [75]	0/41 (0%)	0/41 (%)	0/19 (0%)	0/19 (0%)	NA	NA	NA	NA	MSI was only conducted for women who had loss on IHC
Planck (2002) [76]	0/30 (0%)	2/30 (6.6%)	0/30 (0%)	1/30 (3.3%)	NA	NA	NA	NA	All women had CC and EC
Ring (2016) [77]	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	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Rubio (2016) [78]	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, (personal communication,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Ryan et al., University of Manchester, 11/12/2019)									
Salvador (2019) [79]	NR	NR	NR	NR	NR	NR	0/296 (0%)	0/296 (0%)	Mixed EC/CC sample. Only partial data extractable for EC
Sarode (2019) [80]	0/99 (0%)	4/99 (4%)	NA	NA	NR	NR	NR	NR	-

Study	IHC test failures, n/N (%)	IHC indeterminate results, n/N (%)	MSI test failures, n/N (%)	MSI indeterminate results, n/N (%)	MLH1-PM test failures, n/N (%)	MLH1-PM indeterminate results, n/N (%)	Reference standard test failures, n/N (%)	Reference standard indeterminate results, n/N (%)	Notes
Shin (2015) [81]	0/8 (0%)	0/8 (0%)	0/12 (%)	0/12 (%)	NA	NA	0/3 (0%)	0/3 (%)	All women had CC and EC
Stelloo (2017) [82]	0/696 (0%)	18/696 (2.6%)	NR	NR	NA	NA	NA	NA	168 women excluded without reason
Svampane (2014) [84]	2/111 (1.8%)	0/111 (0%)	NA	NA	NA	NA	0/8 (0%)	0/8 (0%)	No cancer tissue found, 2/113
Tian (2019) [86]	NR	NR	NA	NA	NA	NA	0/198 (0%)	0/198 (0%)	32 IHC results not available, not details given
Wang (2017) [87]	0/78 (0%)	0/78 (0%)	0/78 (0%)	0/78 (0%)	NA	NA	NA	NA	Concordance only
Yoon (2008) [88]	0/113 (0%)	0/113 (0%)	0/113 (0%)	0/113 (0%)	NR	NR	0/16 (0%)	0/16 (0%)	-

EC = endometrial cancer; LS = Lynch syndrome; MLH1-PM = MLH1 promoter methylation; NA = not applicable; NR = not reported

Table 10. Concordance between immunohistochemistry and microsatellite instability-based testing

Study	Country	Sample size in analysis	MSI threshold[a]	Agreement n/N (%)	Disagreement n/N (%)	Kappa (95% CI)	Notes
Anagnostopoulos (2017) [47]	England	32	NR	30/32 (93.75%)	2/32 (6.25%)	0.86 (95% CI 0.66 to 1.00)	Kappa calculated by CS using GraphPad
Berends (2003) [50]	Netherlands	51	MSI:H	36/51 (70.6%)	15/51 (29.4%)	0.403 (0.155 - 0.651)	Kappa calculated by CS using GraphPad
Bruegl (2017) [51]	USA	197	MSI:H (3 unstable markers) MSI:H/L (1 or more unstable markers)	190/197 (96.4%) 187/197 (94.9%)	7/197 (3.6%) 10/197 (5.1%)	0.91 (95% CI 0.84 to 0.98) 0.87 (95% CI 0.80 - 0.95)	Kappa calculated by CS using GraphPad
Chao (2019) [54]	China	77	MSI:H	73/77 (94.8%)	4/77 (5.2%)	0.803 (0.616 – 0.989	Kappa calculated by CS using GraphPad
Egoavil (2013) [57]	Spain	173	MSI:H	156/173 (90.2%)	17/173 (9.8%)	0.77 (0.67 - 0.87)	Kappa calculated by CS using GraphPad

Study	Country	Sample size in analysis	MSI threshold[a]	Agreement n/N (%)	Disagreement n/N (%)	Kappa (95% CI)	Notes
Ferguson (2014) [58]	Canada	117	MSI:H	111/117 (94.9 %)	6/117 (5.1%)	0.866 (0.762 - 0.969)	Kappa calculated by CS using GraphPad
Goodfellow (2015) [59]	USA	934	MSI:H MSI:H/L	907/934 (97.1%) 893/934 (95.6%)	27/934 (2.9%) 41/934 (4.4%)	0.94 (0.91 – 0.96) 0.91 (0.88 – 0.93)	Kappa calculated by CS using GraphPad Kappa calculated by CS using GraphPad
Hampell (2006) [13]	USA	211	NA	See notes	See notes	Not calculable	IHC only conducted for women with MSS results. Agreement, 202/211 (95.7%) Disagreement, 9/127 (4.3%)
Leenen (2012) [63]	Netherland	179	MSI:H	179/179 (100%)	0/179 (0%)	1.00 (1.00 – 1.00)	Kappa calculated by CS using GraphPad

Study	Country	Sample size in analysis	MSI threshold[a]	Agreement n/N (%)	Disagreement n/N (%)	Kappa (95% CI)	Notes
Libera (2017) [64]	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 - 1.00) 2. 0.72 (0.57 - 0.88)	1. Borderline MSI = MSI:H 2. Borderline MSI = MSS Kappa calculated by CS using GraphPad
Lu (2007) [14]	USA	100	MSI:H	89/94 (94.9%)	5/94 (5.3%)	0.858 (0.738 - 0.979)	Kappa calculated by CS using GraphPad
Masuda (2012) [67]	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 - 1.000) 0.769 (0.354 - 1.000)	MHL1 only 36 women in study, concordance data only available for 9 Kappa calculated by CS using GraphPad
McConechy (2015) [68]	Canada	89	MSI:H	83/89 (93.3%)	6/89 (6.7%)	0.837 (0.711 - 0.963)	Kappa calculated by CS using GraphPad

Study	Country	Sample size in analysis	MSI threshold[a]	Agreement n/N (%)	Disagreement n/N (%)	Kappa (95% CI)	Notes
Modeca (2007) [71]	USA	85	MSI:H	74/85 (87.1%)	11/85 (12.9%)	0.739 (0.596 - 0.883)	Samples selected for equal representation of MSI:H and MSS
Ollikainen (2005) [74]	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 – 0.624) 0. 621 (0.310 – 0.932)	Kappa calculated by CS using GraphPad
Pecorino (2017) [75]	Italy	19	NA	See notes	See notes	Not calculable	MSI only conducted for women with IHC loss Agreement, 6/19 (31.6%) Disagreement, 13/19 (68.4%)
PETALS study, (personal communication, Ryan et al., University of	UK	[redacted]	MSI:H MSI:H/L	[redacted]	[redacted]	[redacted]	Kappa calculated by CS using GraphPad

Study	Country	Sample size in analysis	MSI threshold[a]	Agreement n/N (%)	Disagreement n/N (%)	Kappa (95% CI)	Notes
Manchester, 11/12/2019)							
Planck (2002) [76]	Sweden	28	MSI:H/L	20/28 (71.4%)	8/28 (28.6%)	0.44 (0.15 - 0.74)	All women had EC and CC Kappa calculated by CS using GraphPad
Rubio (2016) [78]	Spain	103	NR	?/? (86.06%)	?/? (13.92%)	Not calculable	% agreement reported in the paper but no details enabling checking or any further calculations
Shin (2015) [81]	South Korea	12	MSI:H	6/8 (75%)	2/8 (25%)	Not calculated	All women had EC and CC Only MLH1 and MSH2 assessed
Stelloo (2017) [82]	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 – 0.973) 0.942 (0.913 - 0.971)	In paper, agreement = 94%, kappa = 0.854; 95% CI 0.811–0.897). Unclear how reached. Kappa in this table calculated by CS using GraphPad

Study	Country	Sample size in analysis	MSI threshold[a]	Agreement n/N (%)	Disagreement n/N (%)	Kappa (95% CI)	Notes
Strazzullo (2003) [83] (same population as Baldinu, 2002) [49]	Italy	31	MSI:H	See notes	See notes	Not calculated	IHC only conducted for MSI:H tumours Agreement, 18/31 (58.1%) Disagreement, 13/31 (41.9%)
Wang (2017) [87]	USA	78	MSI:H	77/78 (98.7%)	1/78 (1.3%)	0.965 (0.896 - 1.000)	Kappa calculated by CS using GraphPad

CC = colorectal cancer; CI = confidence intervals; EC = endometrial cancer; MSI: = microsatellite instability; n = numerator; N = denominator; NR = not reported

[a] MSI:H refers to 2 or more unstable markers unless otherwise specified

Decline rates

33 studies reported on index test and germline testing. There were approximately 8825 patients included across these 32 studies. 6 studies (7 papers, including the PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019)) reported on the number of declines at baseline, prior to testing.[13, 51, 52, 58, 70, 72, 84] Across 5 of the 6 studies there were 1089 people who declined or failed to respond to the study invite out of approximately 5503 invited, (incomplete reporting of denominator). From the remaining study there were 14 who failed to provide insurance to enable testing, declined or there was insufficient tumour sample, but it unspecified how many precisely were declines.[51] 7 studies reported no declines at baseline.[57, 60, 61, 63, 73, 85, 86, 88]

7 studies, including the PETALS study, reported on the numbers declining genetic counselling.[47, 57, 58, 63, 70, 73] 30 patients out of 100 patients offered, declined genetic counselling.

15 studies (16 papers, including the PETALS study) reported on the number declining germline testing.[14, 47, 48, 51, 56-59, 63, 65, 66, 73, 77-79] Across these 15 studies, 76 patients declined germline testing out of 1124 patients offered the test. Additionally in two studies (including the PETALS study),[57] 4 patients died prior to germline testing, 3 were lost to follow up and 3 were already known carriers for LS.

4.5. Assessment of studies of clinical effectiveness (key question 2)

No eligible studies were identified which reported on the clinical effectiveness (benefits and harms) of testing for Lynch syndrome amongst people who have endometrial cancer, and/or their relatives. Most studies were excluded for multiple reasons. The most common reasons for exclusion were studies which were not RCTs (and so subject to greater risk of bias), and/or which did not have any relevant outcomes. A further limitation was that most studies were in the broader Lynch syndrome population, rather than those who had endometrial cancer, which limits applicability to our question. Reasons for exclusion are given in Appendix 4: Table of excluded studies with rationale.

Some of the excluded studies are as follows. These were all considered for inclusion in the economic model alongside other sources. De Jong et al.[89] describe reducing time trends in colorectal mortality, which they associate with increasing surveillance for Lynch syndrome over time. These time trends are subject to confounding. Jarvinen et al. 2009[90] in an observational cohort, compared Lynch-mutation positive relatives (who were offered colorectal and endometrial surveillance) to 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 likely underpowered with very wide confidence intervals, and biased due to the differences in risk profile between groups at baseline. Jarvinen et al. 2000 found screening Lynch syndrome patients for colorectal cancer was associated with a reduction in colorectal cancer.[41] However, patients were not randomly allocated, they self-selected into screened and unscreened groups so this study is subject to selection bias. Hereditary nonpolyposis colorectal cancer registry studies describe womens outcomes after endometrial cancer surveillance, for example in Denmark[91] and Finland.[92] 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[93] and Israel.[94] These ongoing RCTs do not yet have any results available.

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

The estimates used for prevalence, LS 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 section 4.6.

4.6.1. Prevalence

Prevalence

For our health economic model, we incorporated data from the nine studies (reported in 11 papers) that assessed prevalence of LS in unselected samples of women with endometrial cancer; these studies were the most applicable to our population of interest, i.e. they did not limit on the basis of age, or prior cancers. The median prevalence of LS in these papers (including the PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019)) was [redacted]% (0 – 5.3%).[13, 48, 51, 52, 55-57, 66, 72, 84] This was used in our base case as overall prevalence of LS in EC.

Ryan et al also systematically reviewed the evidence on prevalence of Lynch syndrome in endometrial cancer patients.[95] Few studies undertook germline testing in all women with endometrial cancer so they took a stepwise approach to estimation. They conducted a series of meta-analyses of test positivity of IHC (MLH-1 specific and across all proteins) MSI, and methylation. They combined data from these seperate 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 in germline testing, in a population which 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 combination of data from a large number of studies, but made assumptions about the equivalence of different populations, and was inclusive of studies which did not exactly represent the population or test of interest.

Both reviews suggest a figure for overall prevalence around the 3% level [redacted] ([redacted] out of [redacted] women tested, including [redacted] women with known LS) present in their sample.

A higher base case prevalence of 3.91% obtained through random effects meta-analysis of results from fifteen studies was used by Snowsill (2019). However, when studies at risk of bias due to high dropout (≥ 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 EC 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.,[95] subgroup analysis of studies that did not use a tumor triage stage but proceeded directly to germline testing, also found a higher proportion of LS carriers of 6%. We have therefore conducted sensitivity analysis using an increased overall prevalence figure of 6.5%.

Prevalence by individual gene

Four studies retrieved in our systematic review (including the PETALS study (personal communication, Ryan et al, University of Manchester, 11/12/2019) assessed all four MMR genes (MLH1, MSH2, MSH6, and PMS2) using sequencing plus MLPA as a reference standard in unselected sample of women with endometrial cancer.[13, 51, 57] Data from the four studies were combined to produce prevalence estimates of MMR genes amongst women diagnosed with LS of: MLH1 [redacted]%, MSH2 [redacted]%, MSH6 [redacted]%, and PMS2 [redacted]%. When studies from our review with unselected samples were also included, which had all 4 genes, and any reference standard (n=8), results were: MLH1 16.1%, MSH2 31.7%, MSH6 40.5% and PMS2 10.1%. The model by Snowsill et al (2019)[40] produced figures of MLH1 16.9%, MSH2 24.6%, MSH6 47.7% and 10.8%. Figures do not vary substantially despite differing methodology to elicit data, although our combined estimates inflate the proportion of MHS2 and whilst 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 our systematic literature review, with median values

for all 0%. This is likely explained by testing protocols within laboratories where where tumours with insufficient samples were not tested. However, some test failures did occur with the range greater for MSI (0 - 43.3%) than IHC (0 – 11.8%), and MLH1 promoter hypermethylation 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 PSA.

4.6.2. Diagnostic accuracy

Initially we attempted to identify the bests 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 [14] to ensure considetency across strategies, to aid comparison between strategies. We undertook sensitivity analyses using estimates from the PETALS study and Snowsill.[40]

Best test accuracy per strategy approach

While we found 45 papers describing at least partial test accuracy, only 7 gave full test accuracy from which we could extract 2x2 tables. Seven studies provided complete test accuracy data (i.e. sensitivity, specificity, positive predictive values, and negative predictive values) [14, 50, 54, 77-79, 86]. None was conducted in the UK, and most of these only covered a small subset of the strategies, so meta-analysis within each strategy was not possible due to the small number of heterogeneous studies. We identified the 'best' (most applicable, least biased) study from this group. The rationale for each is outlined below. Overall, data from Chao 2010[54] was considered best for strategies 1 and 3, but did not provide data for many of the other strategies. Lu[14] provided data for more strategies, but for some strategies there were no data available.

Strategy 1: MSI testing alone: Four studies provided data for this strategy.[14, 50, 54, 78] Chao [54] was considered to provide the best data as it included an unselected sample of women with endometrial cancer, although it was not conducted in a country with comparable demographics to the UK, and had very few cases of Lynch syndrome, with an incomplete head-to head design.

Strategy 3: IHC alone:Five studies provided data for this strategy.[14, 50, 54, 78, 86] Chao [54] was considered to provide the best data as it included an unselected sample of women with

endometrial cancer, although it was not conducted in a country with comparable demographics to the UK.
Strategy 4, 5, 7 and 9: No study directly assessed these strategies. One study (comprising a selected sample of women aged 50 years and younger) presented sufficient data for us to estimate test accuracy data for this testing strategy.[14] In this study immunohistochemistry, microsatellite instability-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,ad 9

Strategy 10: MSI and IHC testing with MLH1 promoter hypermethylation testing: Four studies provided data for this strategy.[14, 54, 77, 79] Two studies were excluded from consideration as they included a selected sample of women (<50 years at diagnosis),[14] or data were not extractable for the whole sample.[79] The best accuracy data was considered to come from combinng 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 comparable demographics to the UK, one conducted in China and one in the USA.[54, 77]

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 due to differences between studies rather than tests. For example whilst Chao was considered the best evidence for IHC and MSI accuracy, there were only 4 cases of Lynch syndrome for IHC and 6 for MSI, so within 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. Further, Chao did not give

information for the pathways including hypermethylation testing, so accuracy of strategies with and without hypermethylation testing would be logically inconsistent.

Consistent test accuracy estimates from Lu [14]

The base case estimates for test accuracy used in the model are all from Lu.[14] 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 both a small sample, and 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 hypermethylation testing, particularly those which were MSI-H. Further it did not include the PMS2 protein in the IHC testing panel.

Test accuracy data was extracted for strategies 1, 3, 4, 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 was very low levels of missing data for these strategies. Where data was missing on the pathway in question we excluded the case, where we could follow the whole strategy for that patient we included them, even if there was missing data elsewhere. There was also incomplete data for hypermethylation after IHC, but of the 13 MLH1 deficient tumours through IHC testing so potentially eligible for hypermethylation testing, 12 had hypermethylation 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 methylation testing for MSI-H affecting strategies 2, 6, 8, 10. Overall of the 25 cases which tested MSI-H, only 13 tested MSI status, and all 13 were in patients without a germline mutation (two were in variants of uncertain significance). Excluding these would have excluded all patients with the disease. There is some evidence from an Australian study on the accuracy of methylation testing in cases demonstrating MLH1/PMS2 IHC loss, of 127 cases, 111 were hypermethylated, all of which were germline MLH1 negative. However, accuracy of methylation testing in MSI-H cases, beyond those that also have IHC MLH1 loss is not known, so a conservative estimate was considered appropriate.[52] 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 94 and 95 total respectively) where hypermethylation results were assumed. This is because these strategies start with MSI-based testing then hypermethylation of cases where instability is detected. For strategy 8 this method of estimation was applied to 3 out of 98 cases, and 4 of 94 cases for strategy 10. Test accuracy estimates should be viewed with extreme caution (in particular strategy 2, 6, 8, 10).

Strategy 1: MSI testing alone

	Germline +ve	Germline -ve	Totals
Index test +ve	8	17	25
Index test –ve	0	70	70
Totals	8	87	95

Sensitivity: 100.0% (95% CI 63.06 - 100%)

Specificity: 80.46% (95% CI 70.57 - 88.19%)

Strategy 2: MSI testing with MLH1 promoter hypermethylation testing

	Germline +ve	Germline -ve	Totals
Index test +ve	5	3	8
Index test –ve	3	84	87
Totals	8	87	95

Sensitivity: 62.50% (95% CI 24.49 - 91.48%)

Specificity: 96.55% (95% CI 90.25 - 99.28%%)

Strategy 3: IHC-based testing alone

	Germline +ve	Germline -ve	Totals
Index test +ve	9	15	24
Index test –ve	0	75	75
Totals	9	90	99

Sensitivity: 100.0% (95% CI 66.37 - 100%)

Specificity: 83.33% (74.00 - 90.36%)

Strategy 4: IHC testing with MLH1 promoter hypermethylation testing

	Germline +ve	Germline -ve	Totals
Index test +ve	8	3	11
Index test –ve	0	87	87
Totals	8	90	98

Sensitivity: 100.0% (95% CI 63.06 - 100%)

Specificity: 96.67% (90.57 - 99.31%)

Strategy 5: MSI testing followed by IHC testing

	Germline +ve	Germline -ve	Totals
Index test +ve	8	19	27
Index test –ve	0	68	68
Totals	8	87	95

Sensitivity: 100.0% (95% CI 63.06 - 100%)

Specificity: 78.16% (68.02 - 86.31%)

Strategy 6: MSI followed by IHC testing with MLH1 promoter hypermethylation testing

	Germline +ve	Germline -ve	Totals
Index test +ve	5	4	9
Index test –ve	3	83	86
Totals	8	87	95

Sensitivity: 62.50% (95% CI 24.49 - 91.48%)

Specificity: 95.40% (95% CI 88.64 - 98.73%)

Strategy 7: IHC followed by MSI testing

	Germline +ve	Germline -ve	Totals
Index test +ve	9	18	27
Index test –ve	0	68	68
Totals	9	86	95

Sensitivity: 100.0% (95% CI 66.37 - 100%)

Specificity: 79.07% (68.95 - 87.10%)

Strategy 8: IHC testing followed by MSI testing with MLH1 promoter hypermethylation testing

	Germline +ve	Germline -ve	Totals
Index test +ve	8	5	13
Index test –ve	0	81	81
Totals	8	86	94

Sensitivity: 100.0 (95% CI 63.06 - 100%%)

Specificity: 94.19% (86.95 - 98.09%)

Strategy 9: MSI and IHC testing

	Germline +ve	Germline -ve	Totals
Index test +ve	8	18	26
Index test –ve	0	68	68
Totals	8	86	94

Sensitivity: 100.0 (95% CI 63.06 - 100%)

Specificity: 79.07% (68.95 - 87.10%)

Strategy 10: MSI and IHC testing with MLH1 promoter hypermethylation testing

	Germline +ve	Germline -ve	Totals
Index test +ve	8	5	13
Index test –ve	0	81	81
Totals	8	86	94

Sensitivity: 100.0% (95% CI 63.06 - 100.00%)

Specificity: 94.19% (86.95 - 98.09%%)

4.6.2.1. Sensitivity analyses

Due to uncertainties in the base case a sensitivity analysis was performed, using data from a large as yet unpublished UK based study. (personal communication, Ryan et al, University of Manchester, 11/12/2019) [redacted]

[redacted]

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 an abstract only or irrelevant study population. The literature search identified five studies (Resnick et al., 2009; Kwon et al., 2011; Bruegl et al., 2014; Goverde et al., 2016; Snowsill et al., 2019)[40, 96-99] which 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 30.

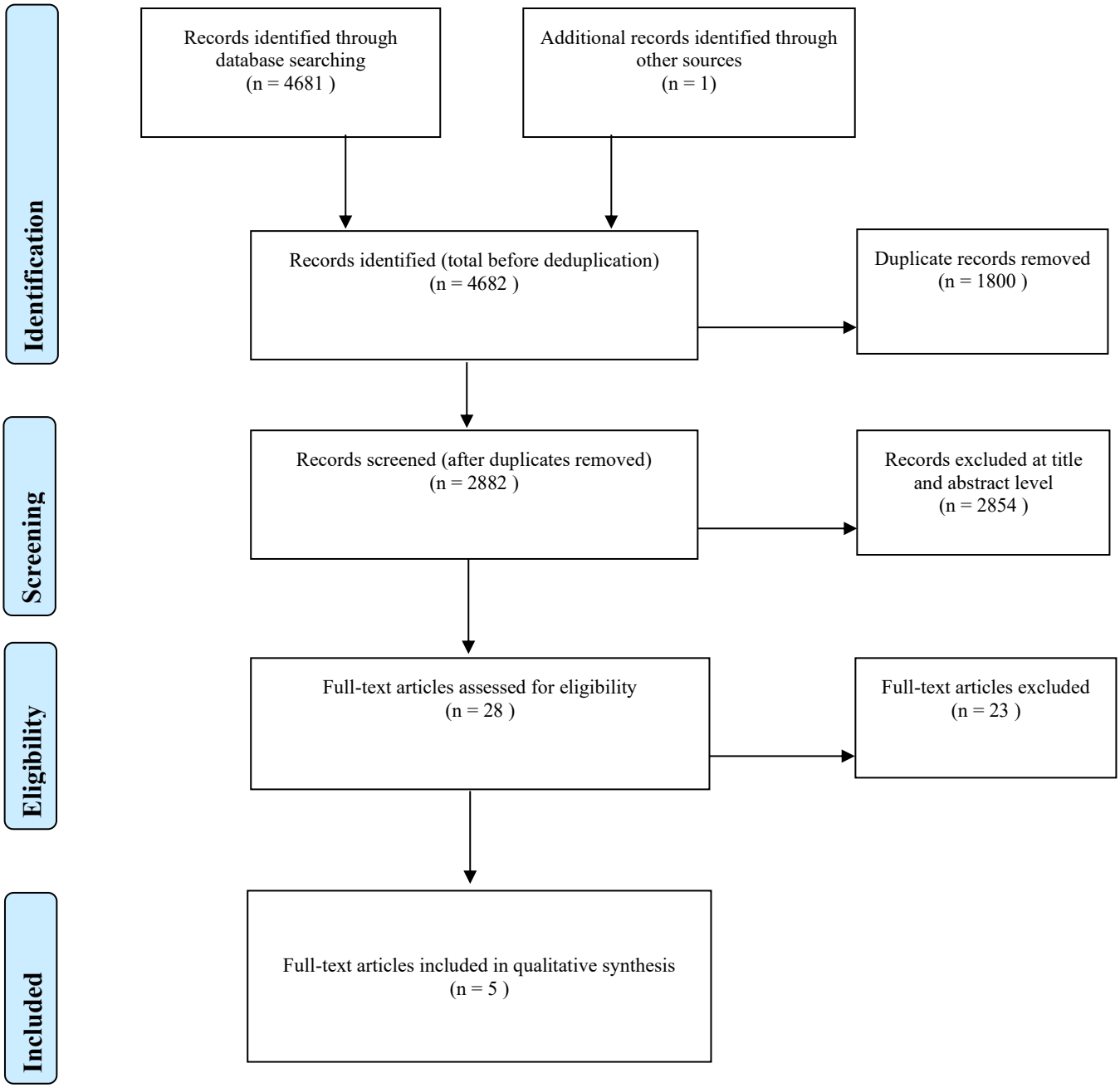


Figure 30: Flow diagram of economic model review

5.1.1. 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., 2009[96]

Resnick et al. (2009)[96] 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 endometrial cancer patients would take whilst 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 (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 < 60 years with endometrial cancer and, immunohistochemistry/single gene strategy (immunohistochemistry for all women with endometrial cancer after gene sequencing). After testing, women were categorised as Lynch positive or Lynch negative. With the immunohistochemistry and sequencing testing strategy, women were categorised as MLH1 over 60 years, MLH1 under 60 years of age or 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 were required to populate the model, and this was obtained from published sources. Clinical information included the probability of fulfilling the Amsterdam criteria, 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 immunohistochemistry results. Resource use and costs were required for genetic consultation, full genetic sequencing, immunohistochemistry, 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 incremental cost-effectiveness ratio (ICER) expressed as cost per additional Lynch syndrome case detected. Authors undertook scenario analysis around the cost of full gene sequencing.

The base-case deterministic results showed that immunohistochemistry/single-gene when compared to the Amsterdam testing strategy had an ICER of approximately of 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 immunohistochemistry 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. Though 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 case remains unanswered. Additionally, the authors acknowledged that the testing strategy genotyping for the screening of mismatch repair 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., 2011[97]

Kwon et al. (2011)[97] 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 now receiving one of the following testing strategies endometrial cancer younger than 50 years with at least one first-degree relative with a LS associated cancer, endometrial cancer younger than 50 years (IHC triage), endometrial cancer younger than 60 years (IHC triage), endometrial cancer at any age with at least one first-degree relative with a LS associated cancer (IHC triage), all endometrial cancers and any age (IHC triage) compared to Amsterdam II criteria. Authors have outlined and justified why they have excluded testing strategies that include microsatellite instability.

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

for genetic counselling, gene sequencing, immunohistochemistry for mismatch repair proteins, colonoscopy, and colorectal cancer treatment costs. Details of the 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 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 healthcare provider were included in the economic analysis; hence, reflecting a narrower perspective (third-party provider).

Deterministic results showed that immunohistochemistry triage of women of any age, with at least one first-degree relative with LS associated cancer when compared to age < 50 years and at least one first-degree relative had an incremental cost-effectiveness ratio (ICER) of approximately US$9,100 per life-year gained. Also, results were reported on the number of women who would undergo immunohistochemistry and, subsequently the women diagnosed with Lynch syndrome and those who further developed colorectal cancer. 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 made the authors concluded that immunohistochemistry triage of women of any age, with at least one first-degree relative was the most cost-effective testing strategy when compared to using the Amsterdam II criteria.

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. Second, it is unclear what assumptions are being made about the colorectal cancer 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., 2014[98]

Authors undertook an economic analysis alongside a clinical study to assess the cost-effectiveness of universal tissue testing (immunohistochemistry for all and MLH1 methylation analysis when indicated) versus the Society of Gynaecologic Oncology 5-10% clinical criteria (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, 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 and in 2012 prices. The economic analyses included hospital and healthcare professional costs associated with identifying women with probable Lynch syndrome. Costs included initial genetic counselling and follow-up visits, immunohistochemistry for MLH1, MSH2, MSH6 and PMS2, MLH1 promoter methylation assay for tumours with loss of MLH1, and single germline mutation testing.

Under the SGO 5-10% clinical criteria, 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 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 to identify Lynch syndrome in women diagnosed with endometrial cancer, this strategy is likely to miss some cases when compared to a strategy of using a universal tumour-testing strategy (immunohistochemistry for DNA mismatch repair 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 and cost-effectiveness about different strategies that can be used to identify and diagnose women (and their first-degree relatives) with Lynch syndrome. While the analysis adds to the existing literature, there are some concerns that may question the transferability and robustness of these results. First, as acknowledged by the authors, all potentially relevant strategies have not been included in the analysis, and this is common in clinical trials. Second, the authors assumed that there is 100% genetic counselling referral rate for endometrial cancer patients meeting the SGO 5-10% criteria, but referral rates are likely to be between 17% and 48%. Third, 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, it was unclear about the resource quantity used to derive costs, 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., 2016[99]

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

The analysis required clinical and cost information. Clinical parameters included acceptance of prophylactic gynaecological surgery, complication rate following colonoscopy, lifetime risk of developing colorectal cancer for Lynch syndrome carriers and reduction in colorectal cancer risks by Lynch syndrome surveillance. Resource use and costs included microsatellite instability analysis, genetic counselling and germline mutation analysis, immunohistochemistry and MLH1 hypermethylation, which were derived using micro-costing methodology. All costs were reported in Euros and reported 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 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 microsatellite instability, immunohistochemistry and MLH1 hypermethylation was cost-effective when compared to screening up to the age of 50 years, with an ICER of approximately €5,300 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 microsatellite, immunohistochemistry and MLH1 hypermethylation for Lynch syndrome in people diagnosed with endometrial cancer up to the age of 70 years was the most cost-effective strategy compared to an age cut-off 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., 2019[40]

Authors conducted an economic analysis by using a decision-tree structure with Markov nodes to assess the cost-effectiveness of different testing strategies (microsatellite with methylation, direct mutation testing, immunohistochemistry with methylation, microsatellite alone, immunohistochemistry 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, and probable Lynch syndrome. Following diagnosis, women received colorectal cancer surveillance.

The model required clinical information (natural history, epidemiology, health-related quality of life, 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 personal social service (PSS) perspective, with all costs reported in UK pounds sterling and 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 horizon, with the results presented in terms of an incremental cost-effectiveness ratio (ICER) expressed as cost per quality adjusted life-year (QALY). An ICER at or below the £20,000 per QALY willingness-to-pay threshold was cost-effective. Several one-way sensitivity analyses, including probabilistic sensitivity analyses were undertaken based on the cost per QALY.

The base-case deterministic results showed that the immunohistochemistry with methylation was the most cost-effective strategy with an ICER of approximately £14,200 per QALY. The immunohistochemistry alone strategy yielded the most QALYs and was most costly, but the results did not reach cost-effectiveness when compared to immunohistochemistry with methylation, with an ICER of approximately £129,000 per QALY. PSA results showed that there was a 0.36 probability that immunohistochemistry with methylation was the most-cost-effective strategy at a willingness-to-pay threshold. One-way sensitivity analysis results showed that the ICER was sensitive to the age of the proband and the effectiveness of colonoscopy in reducing colorectal cancer incidence. Scenario analysis results showed that using the effectiveness of colonoscopic surveillance to reduce the colorectal cancer incidence derived from information obtained from Arrigoni et al., 2005, none of the testing strategies were 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 of colorectal cancer screening to probands. 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. Additionally, the model was sensitive to some model input parameters. Specific attention in the form of systematic reviews around these key parameters with detail critique between sources would improve the transparency in the selection of model inputs.

Table 11: Summary characteristics of the health economic models comparing different screening strategies to identify Lynch Syndrome in women diagnosed with endometrial cancer

Study (First author, year, 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 analysis)**
Resnick et al., 2009, USA[96]	To assess the cost-effectiveness of screening strategies for diagnosing Lynch Syndrome among newly diagnosed endometrial	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 < 60 years with endometrial cancer and, immunohistochemistry/single gene strategy	Cost per additional Lynch syndrome case detected	Decision tree structure	Lynch positive, Lynch negative, MSH6 deletion (Lynch positive), MSH2 deletion (Lynch positive), MSH2	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

Study (First author, year, 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 analysis)
	cancer patients		(immunohistochemistry for all women with endometrial cancer after gene sequencing			deletion (Lynch negative)	US$13,800 per Lynch syndrome case detected. The ICER was sensitive to the cost of full gene sequencing.
Kwon et al., 2011, USA[97]	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 younger than 50 years with at least 1 first-degree relative • Endometrial cancer younger than 50 years (IHC triage) • Endometrial cancer younger than 60 years (IHC triage)	Cost per life-year gained	Markov Monte Carlo simulation model, with annual cycle lengths	Well, at risk of colorectal cancer, colorectal cancer-unscreened, colorectal cancer-	IHC triage of women any age, with at least one first-degree relative with a LS associated cancer when compared to age < 50, at least one first-degree relative had a mean

Study (First author, year, 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 analysis)
			• Endometrial cancer at any age with at least 1 first-degree relative (IHC triage) • All endometrial cancers, any age (IHC triage)			screened and dead	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 (First author, year, 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 analysis)
Breugl et al., 2014, USA[98]	To assess the cost-effectiveness of universal tissue testing versus the Society of Gynaecologic Oncology 5-10% clinical criteria for identifying Lynch syndrome in	Cost-effectiveness analysis, third-party payer,	Society of Gynaecologic Oncology 5-10% critical criteria versus universal tissue testing	Cost per probable Lynch syndrome	Not applicable	Not applicable	SGO 5-10% clinical criteria strategy would identify 15 women diagnosed as probable Lynch syndrome compared to the universal tissue testing strategy that identified 43 women with probable Lynch syndrome.

Study (First author, year, 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 analysis)
	a cohort of unselected women with endometrial cancer						
Goverde et al., 2016, The Netherlands[99]	To assess the cost-effectiveness of routine screening for Lynch syndrome in endometrial cancer patients up to	Cost-effectiveness analysis	Microsatellite instability, 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	Not applicable	Not applicable	Routine screening endometrial cancer patients up to 70 years compared to screening endometrial cancer patients up to 50 years resulted in an ICER of approximately €5,300 per life-year gained.

Study (First author, year, 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 analysis)
	70 years of age			probands and their relatives			Sensitivity analysis results showed that the health benefits (life-years gained) per female relative had the greatest impact to the ICER.
Snowsill et al., 2019, UK[40]	To identify the relative cost-effectiveness of reflex testing for Lynch syndrome in	Model-based cost-effectiveness analysis, NHS and PSS perspective	• Reflex testing with MMR IHC followed by referral for Lynch syndrome diagnostic mutation testing • Immunohistochemistry alone • Reflex testing with Microsatellite instability followed by referral to genetic counselling for LS diagnostic mutation testing • Microsatellite instability	Cost per QALY	Decision tree and Markov model, with monthly cycle lengths	Decision tree (Actual Lynch syndrome, actually sporadic)	Testing with immunohistochemistry with methylation was the most cost-effective strategy with an ICER of approximately £14,200 per QALY.

Study (First author, year, 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 analysis)
	women with endometrial cancer in the NHS		• Direct referral to genetic counselling for LS diagnostic mutation testing • No testing for Lynch syndrome			Markov component (No colorectal cancer, colorectal cancer (stages 1-4), and dead)	The immunohistochemistry alone strategy was the most effective and the most costly, but the results did not reach cost-effectiveness when compared to immunohistochemistry with methylation, with an ICER of approximately £129,000 per QALY.

Study (First author, year, 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 analysis)
							Authors stated that the PSA results were in line with the deterministic results. From the 1000 iterations, there was a 0.36 probability that immunohistochemistry with methylation was cost-effective at a willingness-to-pay threshold of £20,000 per QALY. The ICER was sensitive to the age of the proband

Study (First author, year, 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 analysis)
							and the effectiveness of colonoscopy in reducing colorectal cancer incidence. When using the effectiveness results from Arrigoni et al., 2005 for reducing the incidence of colorectal cancer, none of the testing strategies were cost-effective.
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; NHS, National Health Service; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life-years							

5.1.2. Characteristics of included studies

Table 2 summarises the characteristics of the studies included in this systematic review. Three economic analyses were undertaken in the USA,[96-98] one in The Netherlands[99] and one in the UK.[40] Three studies[40, 96, 97] undertook a model-based economic analysis, and the remaining two studies[98, 99] 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[96] used a decision tree structure, one a Markov model structure[97] and the other[40] 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. Of note 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[97] from the societal perspective; however, the costs included did not reflect a societal viewpoint. All analyses except Snowsill et al. (2019)[40] reported their results in terms of natural units. Snowsill et al. (2019)[40] reported an incremental cost-effectiveness ratio (ICER) expressed as cost per QALY. All studies attempted one-way sensitivity analysis and/or scenario analysis. One study (Snowsill et al., 2019) undertook probabilistic sensitivity analysis.[40]

Three studies included the benefit to probands by reduction to the incidence of colorectal cancer.[40, 97, 99] 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.[40, 97, 99]

Quality assessment of the modelling methods and economic analyses

Structure

The structures of the models included were of satisfactory quality. Studies clearly stated their decision problem or research questions, the viewpoint of their analysis, the objectives of the models and economic analyses, which were coherent with the decision problem. Only one study (Snowsill et al., 2019)[40] 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. Where appropriate, all studies were conducted over a lifetime 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 complexed, and in general their model structures followed the screening → diagnosis → surveillance → treatment pathway. In general, authors assessed testing strategies that included immunohistochemistry (with/without MLH1 methylation) followed by germline testing, microsatellite instability (with/without methylation) followed by germline testing, direct mutation testing, using the SOG 5-10% clinical criteria, Amsterdam II criteria, Bethesda guidelines or a no testing strategy, confirmatory diagnosis by use of germline testing was included in all analyses. Studies that included risk-reducing interventions, surveillance to reduce the incidence of colorectal cancer was considered. Other risk-reduction interventions (surgery, chemoprevention, and aspirin) were not included. Authors have alluded to this as limitation and have provided reasonable justification for not including. Goverde et al. (2016) included costs associated with gynaecologic surveillance for relatives.[99]

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. Additionally, it was not clear if quality appraisal of these studies were undertaken. Information to populate the economic models were mainly obtained 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) and resource use and costs (testing strategy, colonoscopic surveillance for probands and relatives, treatment of colorectal cancer, 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 colorectal cancer, endometrial cancer mortality, and colorectal cancer mortality. The prevalence of Lynch syndrome was required in all studies. Prevalence was reported by age of the proband[96, 97] and overall prevalence.[40, 98, 99] All studies reported the references for individual studies, but only Snowsill et al. elaborated on the methods used to estimate the prevalence.[40] The distribution of gene mutation status was reported in all studies. In general, studies reported gene mutation status for the overall population,[97-99] older/younger than 60 years[96] and by a given age.[40] The lifetime risk of colorectal cancer was required in three studies.[40, 97, 99] Both Kwon et al. and Goverde et al. provided estimates for lifetime risk of colorectal cancer, where information was obtained from the literature.[97, 99] However, Kwon et al. provided lifetime risk of colorectal cancer by mutation status and in the absence or presence of screening.[97] Goverde et al. provided estimates for Lynch syndrome carriers only.[99] These two studies did not elaborate on the methods used to combine/pool the results from individual studies that reported lifetime risk of developing colorectal cancer. Conversely, Snowsill et al. provided details about the methods used to estimate the lifetime risk of colorectal cancer.[40] All economic analyses undertaken over a lifetime horizon included mortality. People were subjected to endometrial cancer mortality, colorectal cancer mortality and age and gender-

specific mortality according to their respective locations. Snowsill et al. derived transition probabilities for the risk of colorectal cancer mortality for people with/without Lynch syndrome and by stage of the cancer.[40] However, it was unclear if stage-specific risks of colorectal cancer 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[40] clearly stated the methodology used to derive pooled estimates, where appropriate. Additionally, it was unclear about the assumptions 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. Additionally, studies included the health benefit to women with Lynch syndrome and their first-degree relatives.[40, 97, 99] Economic analyses that included colonoscopic surveillance estimated the effectiveness/impact of surveillance on the incidence of colorectal cancer and mortality.[40, 97, 99]

One study[40] reported their results in terms of quality adjusted life-years (QALYs). Snowsill et al. elaborated on the assumptions made, with justification about how utility values were estimated. First, baseline utility values were estimated from age and gender-specific population values. Second, it was assumed that there was no disutility associated with people with stage I-III colorectal cancer. People with stage IV colorectal cancer had their utility scaled by 0.79, as opposed to 1.00 for stage I-III colorectal cancer. 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[97] 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, colorectal cancer screening and treatment of

colorectal cancer. 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[40, 96, 97, 99] included 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 where multiple sources of information was available to assess the impact to 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 diagrams 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 'worse-case' analyses were not undertaken. Snowsill et al. (2019) explored heterogeneity, as well as undertook probabilistic sensitivity analysis.[40] Additionally, 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 due to the heterogonous 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 the appendices.

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 that undertook a model-based economic analysis and two studies 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.

Our 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.[100] To increase the transparency of the economic analyses and the confidence/robustness of the results, guidelines[38, 39] 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[40, 96, 98] clearly provided definitions for people with Lynch syndrome, probable 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[97] stating 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 a 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[97] 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. re-iterates that analysts should provide justification for the choice of model type and present an illustrative model structure.[39]

Information required to parameterise the economic analyses included clinical and cost information. Despite all studies providing the sources of inputs, little information is 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. provides 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. elaborated on the methods used to synthesise the evidence for prevalence and sensitivity and specificity.[40] Deriving point estimates (as well as their confidence/credible intervals) should follow acceptable methods for synthesising the evidence.[39] 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 where more than one source of information is available, or more so, when an input is a key driver to the economic analysis.

Snowsill et al. [40] were the exception as the detailed outline of model structure for the diagnostic component could easily be followed with explanations and supplementary material available to support the use, 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.[39, 100] 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 'worse case' scenario), and probabilistic sensitivity analysis.[101]

Our systematic review highlighted that none of the economic analyses undertook a value of information analysis. Value of information can be used to provide a framework for analysing uncertainty within 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 (EVPI), which represents the monetary value of obtaining perfect information to eliminate uncertainty for key parameters and thus, the overall decision-making process.[102] If the costs of obtaining further information exceeds the EVPI, there is little justification for undertaking further research.[102]

The economic analyses, more specifically those using an economic model to assess different strategies to identify Lynch syndrome in women with endometrial cancer is limited to three studies. Though research in this area can be seen 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 colorectal cancer, and 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, where 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 colorectal cancers averted in probands, cases of endometrial cancers avoided in first degree relatives, life-years gained) and costs per QALY, 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. Our systematic review provides detail about the conduct of each economic analysis, as well as a reporting quality assessment for each study. Also, 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 MJ and JK independently. However, data extraction and reporting quality appraisal was undertaken by

PA and cross-checked by MJ. Second, we have not provided details with 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 limits the transparency, robustness and hence, the transferability of these results to a specific setting/jurisdiction. Though the transferability of economic results may present challenges due to 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, be clear about the methods used to synthesis 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.[40] achieved these key quality indicators, and as the most recent and geographically relevant (UK setting), established a comprehensive reference model upon which to build our modelling approach.

6. Economic Model

6.1. Discussion of model input parameters

Whilst none of the cost-effectiveness studies retrieved in our systematic review answered the decision problem in full, the model by Snowsill and colleagues[40] proved particularly useful in terms of structure and sourcing of relevant model inputs. This work, in combination with

previous reviews of Lynch syndrome testing in CRC[10, 103] was drawn upon to inform our modelling approach. Parameters are discussed for each section of the model in order; diagnostic decision tree, long term CRC and long term EC 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 within 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 section 4.6 of this report.

Additionally, a parameter for the proportion of relatives tested who have positive LS mutations of 44% (40.7 – 47.4 95% CI) was taken from a random effects meta-analysis of studies conducted by Snowsill et al.[103]

Diagnostic mutation testing

92.5% of probands are expected to attend genetic counselling following positive index test results, irrespective of testing strategy. This figure is elicited from clinical expert (IMF) range 90-95% in Snowsill et al. (2014)[103] and independently corroborated more recently by clinical expert (Demetra Georgiou, Principal genetic counsellor, London North West University Healthcare NHS Trust, 13th December 2019). Of those attending genetic counselling, 95% are assumed to undergo genetic testing based on expert opinion (Demetra Georgiou, Principal genetic counsellor, London North West University Healthcare NHS Trust, 13th December 2019), supported by a rate of 90% assumed by Snowsill et al. [10] in their review. Unpublished data by Crosbie et al, (Crosbie, Acceptability manuscript, 19th July 2019) supports a high acceptability of genetic testing in EC 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 [redacted]

For strategy 11, where probands do not undergo an initial tumour test, the acceptance of genetic testing is assumed to be less than in strategies where a positive initial test has been performed. This assumption was made in the Snowsill[40] 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 were investigated further in one-way sensitivity analysis where the proportion of probands accepting genetic counselling and the proportion accepting genetic testing was 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 impacts on proportions of relatives accepting counselling and testing. Similarly, where patient-directed contact is ultimately reliant upon the individual charactersitics of the proband it is difficult to assess the influence a female-only cohort of probands exerts over relatives with a syndrome which 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 that are identified through cascade testing and are assumed to be contactable was set at 6 per proband, in line with recent CRC review[10] based on data from Snowsill, 2014[103] which was updated using Manchester regional Lynch syndrome registry results[104] and unpublished data provided by Ian Frayling within previous work.[10, 103]

It was assumed all 6 relatives made contact with their GP, with cost of GP contact attributed, and of these 77.5% were assumed to pursue referral to a genetic counsellor based on findings of a systematic literature review of uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome by Menko and colleagues.[105] Of those attending genetic counselling, 76.7% were assumed to undergo predictive testing as reported by Barrow et al.[104] This figure is the recorded proportion at 12 years after relatives are informed of their 'at risk' status which, whilst 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.[106] found up to 97% of relatives underwent predictive testing (median 8.6 years (range 1-12 years) and clinical expert opinion suggests almost 90% of relatives who attend genetic counselling pursue testing at some point (Demetra Georgiou, Principal genetic counsellor, London North West University Healthcare NHS Trust, 13th December 2019).

To explore the impact of relative uptake further, sensitivity analysis was undertaken to vary the proportion of relatives accepting genetic counselling and proportion accepting genetic testing from 50% to 100%. Additionally, the number of relatives identified per proband was decreased from 6 in the base case to 3 and then increased to 12 to assess sensitivity to measure.

CRC incidence

Age-related annual incidence of CRC is sourced from the modelling work of Snowsill et al.[40] Gene specific data from the Prospective Lynch Syndrome Database (PLSD)[2, 12, 107] was used against which to fit parametric, non-parametric and flexible spline models, with best fit resulting from the lognormal model which we replicated in our long term model. By applying a hazard ratio of 0.387 as used by Snowsill[10] it was assumed this would counter any benefits associated with CRC surveillance.

This served as our baseline incidence data for CRC incidence in LS positive individuals who had not been identified and proceeded along the natural history pathway without risk reduction measures.

A more recent publication from the PLSD has been published since this work,[42] which builds on earlier work by adding a newly recruited cohort of LS individuals to increase the size of the database from 2823 pathogenic mutation carriers to 6350 in total. The new cohort of 3727 were used to validate findings reported previously,[2, 12, 107] before merger of the two datasets occurred, which found cumulative risk for CRC for each of the four affected genes did not differ significantly from the original ($P>0.05$).

The figures used by Snowsill[10] were therefore considered to be valid and had been considered appropriate for use by NICE in the recent DG 27 for Lynch syndrome in CRC.[1]

CRC 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 into cancer and to detect any tumours promptly so CRC can be diagnosed at an earlier stage thereby improving outcomes.

Similarly to Snowsill,[10] we apply a hazard ratio of 0.387 from Jarvinnen to estimate beneficial impact 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 HR of 0.387 was used in our base case.

To reflect the considerable uncertainty around this parameter we conducted a scenario analysis where it was assumed CRC surveillance had no impact on CRC incidence (see scenario analysis 8).

Guidelines for the management of Lynch syndrome advise colonoscopic surveillance should be performed every 2 years[25]. This is the frequency of colonoscopy modelled in our base case commencing for all individuals at age 25. However, recent reports based on review of findings from the PLSD, [108, 109] suggest that intervals between colonoscopic surveillance are not correlated with decreased incidence of CRC or stage at diagnosis. Whilst the evidence is limited, suggestion that biennial colonscopy can be replaced by surveillance every 3 years with limited reduction in effectiveness was explored in scenario analysis 6. 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 BSG guidance on CRC surveillance.[25] In our model, colonoscopy starts at age 25 for all individuals. However, new guidelines state individuals with MLH1 or MSH2 mutations should commence 2 yearly colonoscopy at age 25, while those with MSH6 or PMS2 can start surveillance later at age 35. This is illustrated in figure X.

This would result in fewer overall colonoscopies being performed, as is the case in scenario analysis 6, although assumption that there would be no change in effectiveness is less secure

as targeted management due to known risk may be expected to improve effectiveness of surveillance.**EC incidence**

For EC, we source incidence data from the Prospective Lynch Syndrome Database, recently published in Genetics in Medicine.[42] This database reported gene-based risk of cancer based on 6350 individuals with Lynch syndrome. Risks are reported at age 25, 40, 50, 60,70 and 75. We fitted a piecewise linear model to these data to derive annual incidence from cumulative incidence.

Gynaecological surveillance

Benefits of gynaecological surveillance are uncertain and and clinical practice throughout the UK varies with respect to what surveillance involves and to whom it is offered. Most recent guidelines on surveillance practices have been published by the Manchester International Consensus [20]. Invasive gynaecological surveillance in females with LS is no longer recommended due to lack of evidence that outcomes are improved over symptom awareness and urgent investigation of red flag symptoms . Instead annual review from the age of 25 with an appropriate clinician to discuss red flag symptoms and where necessary contraceptive and fertility needs should be encouraged and gynaecological referral should be made upon is a specific need.

We follow these recommendations in our modelling by assuming all females from age 25 who have not undergone hysterectomy (for treatment of EC or as prophylactic surgery) access non-invasive surveillance which involves annual review with a GP. We assume 10% of those attending are referred onward for gynaecological review and invasive surveillance consisting gynaecological examination, pelvic ultrasound, CA-125 analysis and aspiration biopsy. This is assumed to reduce mortality by 10.2%, an assumption in line with previous evaluations of lynch screening.[10] 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 which may be accrued we perform scenario analysis removing gynaecological surveillance entirely from the model (see 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 randomised controlled trial[10] 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 EC and CRC. A draft report on the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch[10] syndrome finds 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 [20] strongly recommends that MMR pathogenic variant carriers take aspirin chemoprevention. Optimal dosage is currently unknown and the CaPP3 randomised control trial[10] is ongoing to determine this. Therefore, we assume individuals take daily aspirin over the life course and benefits continue over time.
In scenario analysis 7 we exclude aspirin to assess the bearing this measure has on cost-effectiveness.

VuS

Probands with positive index results on tumour tissue and negative germline results are considered LS negative, but in a proportion of these clinical suspicion of LS remains. Similarly, negative results for currently identified pathogenic mutations on germline testing may be found. These Variations of Uncertain Significance (VuS) may be latterly identified as pathogenic for LS or not in which case management can either be scaled up or down accordingly. In these cases 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 LS and management. Clinical experts suggest that whilst somatic analysis may not fully resolve the pathogenic status of VuS patients around 50-60% of them would derive some benefit from it (A. Wallace, Manchester Centre for Genomic Medicine, 27th December 2019) allowing upgrading or downgrading of VuS and influencing their associated long term management.

Work is ongoing to reduce the number of VuS. The InSiGHT MMR Variant Interpretation Committee which is recognised by ClinGen as the Expert Panel and are in the process of being recognised by the FDA as the MMR Variant Classification Expert Panel (VCEP) have achieved a reduction the number of Class 3 VuS by 35%.[110]

We used a VuS estimate of 1.2% in our model from clinical effectiveness review but clinical expert opinion suggests this figure may be higher at 2-5% (Demetra Georgiou, Principal genetic counsellor, London North West University Healthcare NHS Trust, 13th December 2019).

Somatic analysis may cost up to £800 (Demetra Georgiou, Principal genetic counsellor, London North West University Healthcare NHS Trust, 16th January 2020), which would introduce 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 VuS, which are then varied during sensitivity analysis, to assess the sensitivity of the ICER to this parameter. Given any additional costs involved may be recouped by the ability to downgrade potential VuS 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.

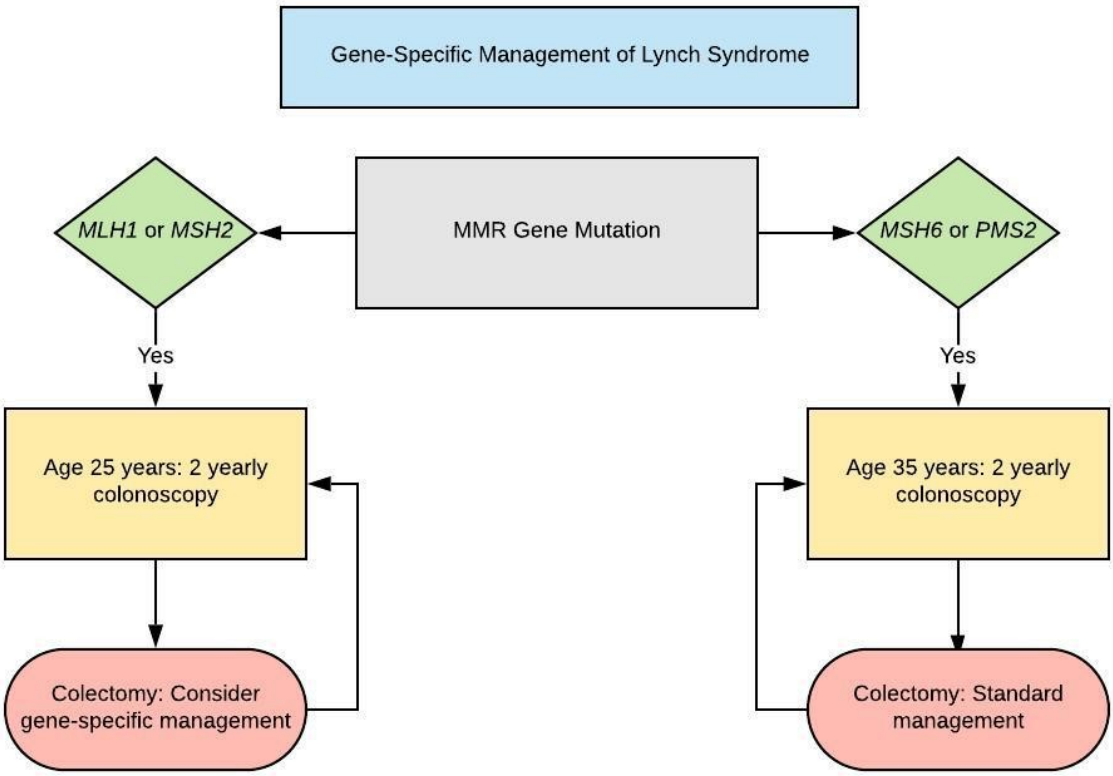


Figure 31: Gene-specific Lynch flowchart

Figure reproduced from Monahan et al. 2019[25]

Costs

The majority of costs were obtained directly from previous work presented to NICE[10] as sources were recent, relevant, local and clinical experts confirmed figures quoted through personal communications. Hospital related costs were obtained from the most current NHS reference tables.[45]

Costs are reported reported in 2017/18 £UK 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,[111]

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 an estimated £39 (cost of a general practitioner appointment). [5] Pre-test genetic counselling/MDT review was estimated to cost £642.19 for probands and £514.43 for relatives with post-test genetic counselling was estimated to cost £141.44 for both. [107] Diagnostic mutation testing for LS was estimated as £755 (with testing conducted on all four genes) and predictive mutation testing for relatives was estimated as £165 (testing on single MMR gene under suspiscion). [111]

A one-off cost of CRC is incurred at the time of CRC incidence (dependent on the patient age and stage at diagnosis), with no further cost being accrued due to time in CRC states or at time of death from CRC. These costs were sourced from Snowsill et al. [40] 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 the cost of colonoscopy is £325.00[45] averaging across outpatient diagnostic and therapeutic colonoscopies, with an increased cost of £2.89 per colonoscopy secondary to average costs occurred from complications associated with the procedure. [10]

For EC a one-off treatment cost of £6,510 is assumed, calculated in line with previous work.[10] A cost of £3,428 is assigned to prophylactic hysterectomy and bilateral salpingo-ophrectomy. Women who have not had surgical prophylaxis undergo annual surveillance to detect EC. 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..[10]

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.

Costs involved with diagnostic testing are taken as average of costs reported by genetic laboratories throughout the UK,[111] and as such reflect the average national cost. Cost of DNA sequencing are decreasing It is thought that costs of testing may be reduced in the future. A micro-costing study of testing strategies for Lynch syndrome by Ryan et al. [111] 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, true costs

associated with testing is likely to lie between sourced estimates from experts and costs calculated in their single-site specialist centre.[111] 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, except for those with stage 4 CRC and those in their first year of EC. Our assumption is line with previous work presented to NICE.[10, 103] While 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 3 cancer would experience some disutility compared with those who were disease-free. Also, one might expect that those who die from EC experience a period of impaired quality of life prior to death.

To reflect this, we carried out a scenario analysis (scenario analysis 4) where we assumed that those with stage 3 CRC experienced utility half-way between stage 4 cancer and good health. We further assumed that those who died of EC experienced one year in a health state equivalent to stage 4 CRC prior to death.

A paucity of information is available in the literature regarding health related quality of life (HRQoL) in either Lynch, EC or CRC patients and efforts to find suitable information to reflect these parameters were unsuccessful.

For this reason, impacts of testing on probands is also not well understood other than directly from patients, as insufficient evidence can be found to support the implementation of a QALY detriment from the literature. Unpublished survey data provided by University of Manchester via NICE ([redacted], 19th July 2019) 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 upon which no patterns of psychological outcomes could be identified. This illustrates the difficulty in obtaining such data, and particularly its transfer for use within health economic models.

6.2. Final Model Input Parameters

This section discusses the source of inputs for all model parameters, with Tables X1 and X2 providing a summary of these. .

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Table 12: Summary of test related model inputs

Parameter Name	**Base Case Value**	**Source**
Diagnostic Parameters		
Test Accuracy		
Strategy 1: Sensitivity	1	Lu et al. 2007[14]
Strategy 1: Specificity	0.805	Lu et al. 2007[14]
Strategy 2: Sensitivity	0.625	Lu et al. 2007[14]
Strategy 2: Specificity	0.966	Lu et al. 2007[14]
Strategy 3: Sensitivity	1	Lu et al. 2007[14]
Strategy 3: Specificity	0.833	Lu et al. 2007[14]
Strategy 4: Sensitivity	1	Lu et al. 2007[14]
Strategy 4: Specificity	0.967	Lu et al. 2007[14]
Strategy 5: Sensitivity	1	Lu et al. 2007[14]
Strategy 5: Specificity	0.782	Lu et al. 2007[14]
Strategy 6: Sensitivity	0.625	Lu et al. 2007[14]
Strategy 6: Specificity	0.954	Lu et al. 2007[14]
Strategy 7: Sensitivity	1	Lu et al. 2007[14]
Strategy 7: Specificity	0.791	Lu et al. 2007[14]
Strategy 8: Sensitivity	1	Lu et al. 2007[14]
Strategy 8: Specificity	0.942	Lu et al. 2007[14]
Strategy 9: Sensitivity	1	Lu et al. 2007[14]
Strategy 9: Specificity	0.791	Lu et al. 2007[14]

Strategy 10: Sensitivity	1	Lu et al. 2007[14]
Strategy 10: Specificity	0.942	Lu et al. 2007[14]
Strategy 11: Sensitivity	1	Lu et al. 2007[14]
Strategy 11: Specificity	1	Lu et al. 2007[14]
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	Snowsill et al. 2014[103] Menko et al. 2019[105] Bruwer et al. 2013[106]
Genetic testing direct	0.500	Assumption
Genetic testing proband (diagnostic)	0.950	Assumption
Genetic counselling relative	0.775	Barrow 2014 MD thesis[104] Menko et al. 2019[105]
Genetic testing relative (predictive)	0.767	Barrow 2014 MD thesis [104] Menko et al. 2019[105]
Declined diagnostic testing or no mutation found		
Clinical suspicion of LS	[redacted]	Based on PETALS (number tested)
VUS result obtained	0.12	Assumption, clinical opinion
Costs		
IHC	£210.00	Snowsill et al. 2017[10]

MSI	£217.00	UK Genetic Testing Network, 2018[111] (Average of 3 MSI test prices)
MLH1 promoter methylation	£156.00	UK Genetic Testing Network, 2018[111]
Offer of counselling	£28.25	Band 6 nurse time
Pre-test clinic related costs and genetic counselling appointment proband	£642.19	Slade et al. 2016[112] & personal communication Demetra Georgiou (Prinicipal genetic counsellor, St. Mark's Hosp)
Genetic testing on germline proband	£755.00	UK Genetic Testing Network, 2018[111]
Post-test clinic related costs and follow up proband	£141.44	D. Georgiou (expert clinical opinion) & Slade et al. 2016[112]
Pre-test clinic related costs and genetic counselling appointment relative	£514.43	D. Georgiou (expert clinical opinion) & Slade et al. 2016[112]
Genetic testing on germline relative	£165.00	UK Genetic Testing Network, 2018[111]
Post-test clinic related costs and follow up relative	£141.44	D. Georgiou (expert clinical opinion) & Slade et al. 2016[112]
GP appointment	£39.00	NHS Reference Costs 2017/18 [45]

Table 13: Summary of other model input parameters

Parameter	Base case value	Source
Population		
Number of relatives per proband	6	Snowsill et al. 2017[10]
Proportion of relatives who are first-degree relatives of proband	0.424	
Proportion of relatives receiving predictive testing found to have LS	0.440	
Proportion of relatives who are women	0.500	Assumption
Natural history		
Prevalence of LS among all EC	[redacted]	nine studies (reported in 11 papers) that assessed in prevalence of LS in unselected samples of women with endometrial cancer; (PETALS).[13, 48, 51, 52, 55-57, 66, 72, 84]
Gene distribution among all EC (*MLH1* / *MSH2* / *MSH6* / *PMS2*)	[redacted]	4 unselected studies from our CE review, including PETALS (unpublished)[13, 51, 57]
CRC incidence with LS (lognormal distribution)		[2, 12, 40]
…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 LS (table by age, per 100,000 person years)		[6]
…Under 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	
…Over 90	304.2	

CRC incidence for men without LS (table by age, per 100,000 person years)		[6]
…Under 25	2.3	
…25–30	2.3	
…30–35	5.6	
…35–40	9.1	
…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	
…Over 90	460.3	
CRC mortality rate (without LS)		
…Stage I	0.014	
…Stage II	0.052	
…Stage III	0.148	
…Stage IV	0.544	
CRC mortality hazard ratio with LS (Stages I–III)	0.660	
EC mortality rate with LS	0.004	[2]
EC mortality rate without LS (by age)		[6]
...15–45	0.026	
…45–55	0.028	
…55–65	0.031	
…65–75	0.048	
…Over 75	0.092	
Effectiveness of risk reduction		
Age range for gynaecological surveillance	25-75	
Interval of surveillance	1.000	
Mortality rate decrease from gynaecological surveillance	0.102	
Aspirin risk reduction	0.56	[10]
Effectiveness of risk reduction		
Age range for surveillance colonoscopy	25–75	
Interval between colonoscopies	2.000	
Uptake of colonoscopy if diagnosed LS	1.000	
Uptake of colonoscopy if diagnosed PLS	1.000	[113]
Hazard ratio for CRC incidence if undergoing colonoscopy	0.387	
CRC stage distribution in surveillance		[10]
…Stage I	0.686	

…Stage II	0.105	
…Stage III	0.128	
…Stage IV	0.081	
CRC stage distribution not in surveillance (sporadic)		
…Stage I	0.176	
…Stage II	0.270	
…Stage III	0.295	
…Stage IV	0.259	
CRC stage distribution not in surveillance (LS)		[114]
…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	Snowsill et al. 2014[103] Menko et al. 2019[105] Bruwer et al. 2013[106]
…Acceptance of counselling (direct testing)	0.5	Assumed
…Acceptance of diagnostic testing (given accepted counselling)	0.950	Expert Opinion D. Georgiou
…Sensitivity	1	Assumed
…Specificity	1	Assumed
Predictive MMR mutation testing		
…Acceptance of counselling	0.775	[113]
…Acceptance of predictive testing (given accepted counselling)	0.765	[113]
Costs	**£**	
Colonoscopy	583	
Stage I CRC (by age)		
…40–49	8754	
…50–59	5712	
…60–69	4623	
…70–79	3178	
…80–100	1380	
Stage II CRC (by age)		
…40–49	8741	
…50–59	7016	
…60–69	5352	
…70–79	3455	
…80–100	1546	
Stage III CRC (by age)		
…40–49	14490	
…50–59	9692	

…60–69	7259	
…70–79	4485	
…80–100	1561	
Stage IV CRC (by age)		
…40–49	11705	
…50–59	8444	
…60–69	6509	
…70–79	4365	
…80–100	807	
Utilities		
Baseline utility model		[44]
…Intercept	0.9509	
…Male	0.0212	
…Age	−0.0003	
…Age²	-3.32×10^{-5}	
…(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 LS	1	Assumed
…Diagnosed with putative LS	1	Assumed
Colorectal cancer (multipliers)		
…Stage I	1	Assumed
…Stage II	1	Assumed
…Stage III	1	Assumed
…Stage IV	0.789	[10]
Endometrial cancer (multiplier)	1	Assumed
Utility decrement on diagnosis of EC for one year	0.036	[10]

6.3. Cost effectiveness results

The simulated population of the model consists of individual probands, at a specified age, diagnosed with endometrial cancer in 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 EC diagnosis of the proband 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 GBP. The incremental cost per QALY when each strategy is compared to a no testing approach in the proband is presented followed by the pairwise comparative ICERs for all strategies.

6.4. Base case results

6.4.1. Cost-effectiveness results

Table 14. summarises the base case cost-effectiveness results (prior to rounding) ranked by lowest to highest cost per QALY when compared against the no testing strategy. IHC with MLH1 methylation is the most cost effective strategy with germline testing direct incurring highest costs per QALY vs no testing. All 11 strategies are considered cost effective at a willingness to pay threshold of £20K per QALY.

Table 14: Testing strategy ranked from lowest to highest ICER vs no testing

Strategy	QALYs	Cost	ICER vs no testing (Cost per QALY)
IHC with MLH1 methylation	0.0669	£632.78	£9,459.32
IHC	0.0681	£791.73	£11,628.23
MSI	0.0683	£838.20	£12,265.95
MSI with MLH1 methylation	0.0419	£515.65	£12,298.41
IHC followed by MSI with MLH1 methylation	0.0671	£867.53	£12,925.61
MSI and IHC simultaneously with MLH1 methylation	0.0671	£891.37	£13,280.76
IHC followed by MSI	0.0685	£1,025.67	£14,981.99
MSI followed by IHC	0.0685	£1,029.34	£15,018.13
MSI and IHC simultaneously	0.0685	£1,067.69	£15,595.83
MSI followed by IHC with MLH1 methylation	0.0420	£716.51	£17,045.57
Germline Testing only	0.0666	£1,164.07	£17,478.16

Full incremental analysis

IHC with MLH1 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.

Base-case results (shown in Table 15) show that MSI with MLH1 was the cheapest strategy with expected mean costs of approximately £520, and expected to yield 0.0419 QALYs. The comparison between no testing and IHC with MLH1 extendedly dominated the comparison between no testing and the MSI with MLH1 methylation strategy (i.e. was less costly and more effective than a combination of other comparators). This demonstrated that IHC with MLH1 strategy was the most cost-effective testing strategy with its ICER (£9420 per QALY). Whilst IHC, MSI and IHC followed by MSI strategies were also on the cost-effectiveness frontier, ICERs were well above accepted threshold levels in the UK and all strategies were dominated (i.e. more costly and less effective than one or more of the comparators).

Table 15: Base-case results

Strategy	**Expected mean costs (£)**	**Incremental costs (£)**	**Expected mean QALYs**	**Incremental QALYs**	**ICER (£)**
No testing	0	-	0	0	-
MSI with MLH1 methylation	£520	£520	0.0419	0.0419	Extendedly dominated
IHC with MLH1 methylation	£630	£630	0.0669	0.0669	£9420
MSI followed by IHC with MLH1 methylation	£720	£90	0.0420	-0.0249	Dominated

IHC	£790	£160	0.0681	0.0012	133,330
MSI	£840	£50	0.0683	0.0002	250,000
IHC followed by MSI with MLH1 methylation	£870	£30	0.0671	-0.0012	Dominated
MSI and IHC simultaneously with MLH1 methylation	£890	£20	0.0671	0.0000	Dominated
IHC followed by MSI	£1025	£185	0.0685	0.0002	£925,000
MSI followed by IHC	£1030	£5	0.0685	0.0000	Dominated
MSI and IHC simultaneously	£1070	£45	0.0685	0.0000	Dominated
Germline testing	£1160	£135	0.0666	-0.0019	Dominated

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years

6.4.2. Number of people identified with Lynch

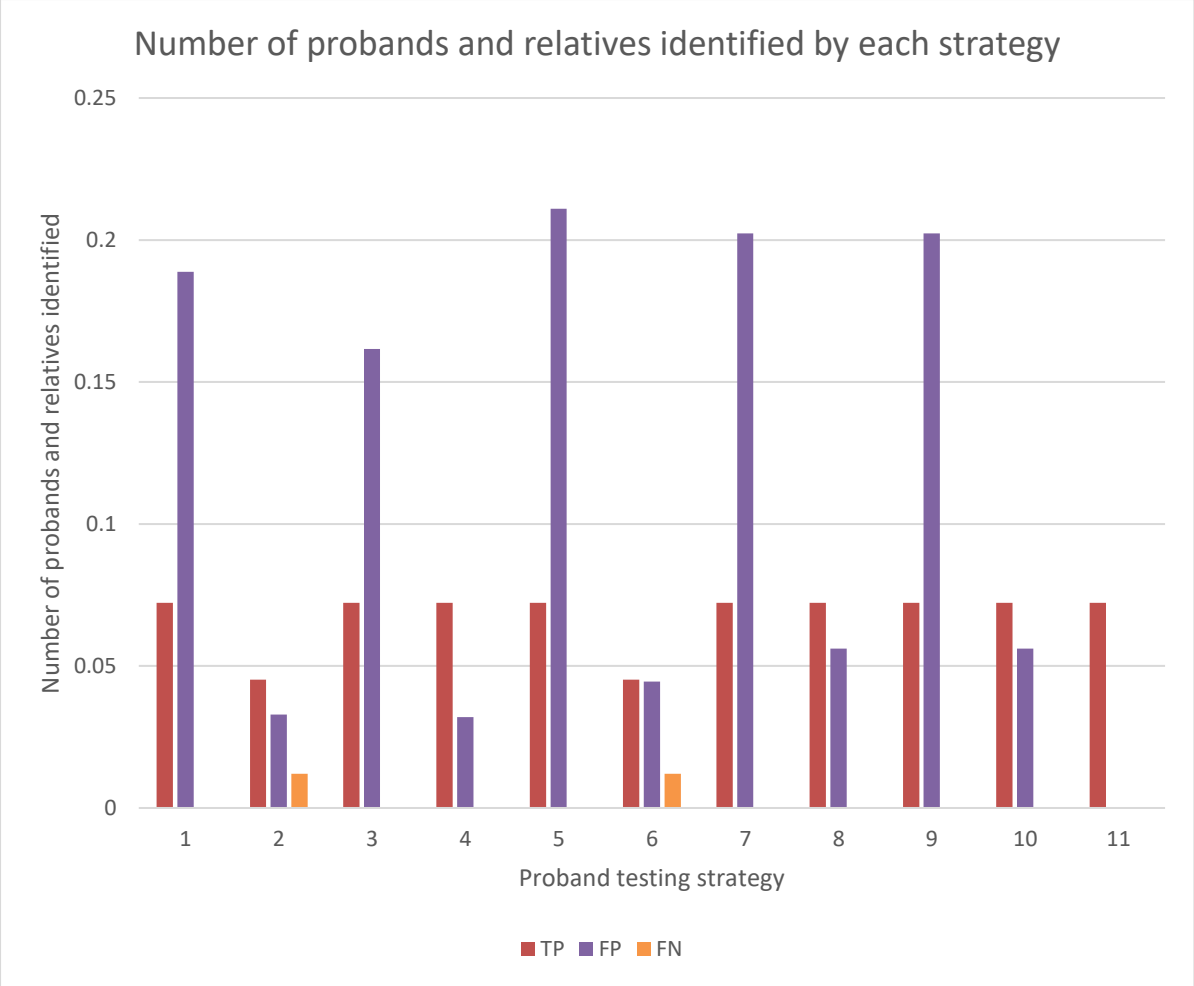

Figure 32: Number of probands and relatives with Lynch syndrome identified by each strategy

FN false negative, FP false positive, TP true positive

The number of probands and relatives with Lynch syndrome identified for the 11 strategies are illustrated in Figure 32. This shows very similar numbers of true positive LS individuals are identified across all testing strategies except for strategies 2 and 6 (MSI with MLH1 hypermethylation and MSI followed by IHC with MLH1 hypermethylation). This is expected as sensitivity of these testing strategies are the lowest of all other 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. Additionally, if probands receive a positive diagnosis

but no causative mutation is found (i.e. Lynch assumed diagnosis), their first degree relatives are treated as having LS but second degree relatives and beyond are treated as not having LS.

6.4.3. Long term clinical outcomes

6.4.3.1. Results from long term modelling of cancer outcomes

Cumulative incidence of identifying Lynch syndrome

These following graphs show model predictions of CRC and EC 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 with Lynch syndrome.

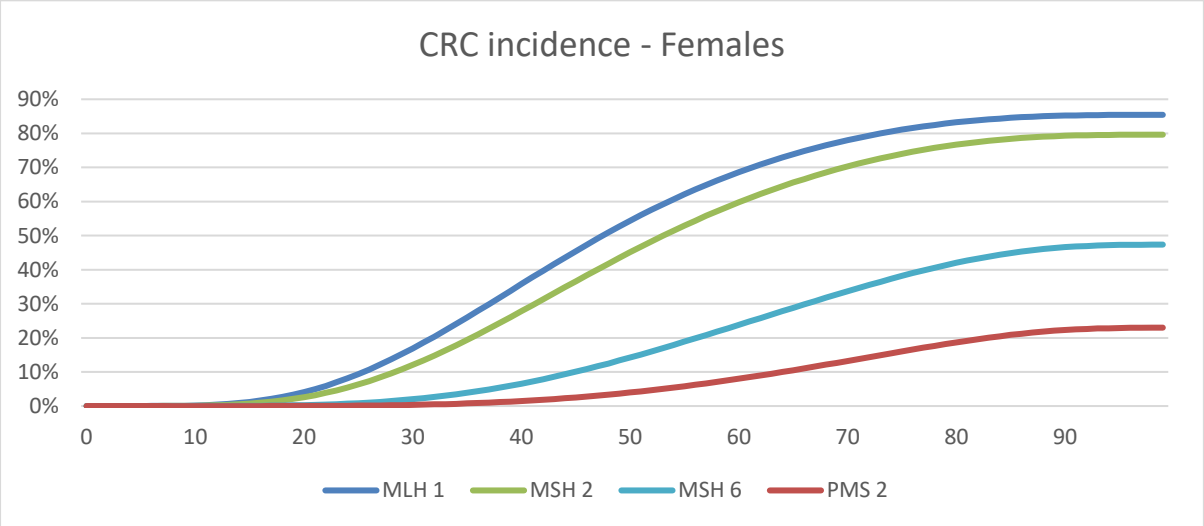

Figure 33: Cumulative incidence of CRC in females with Lynch syndrome

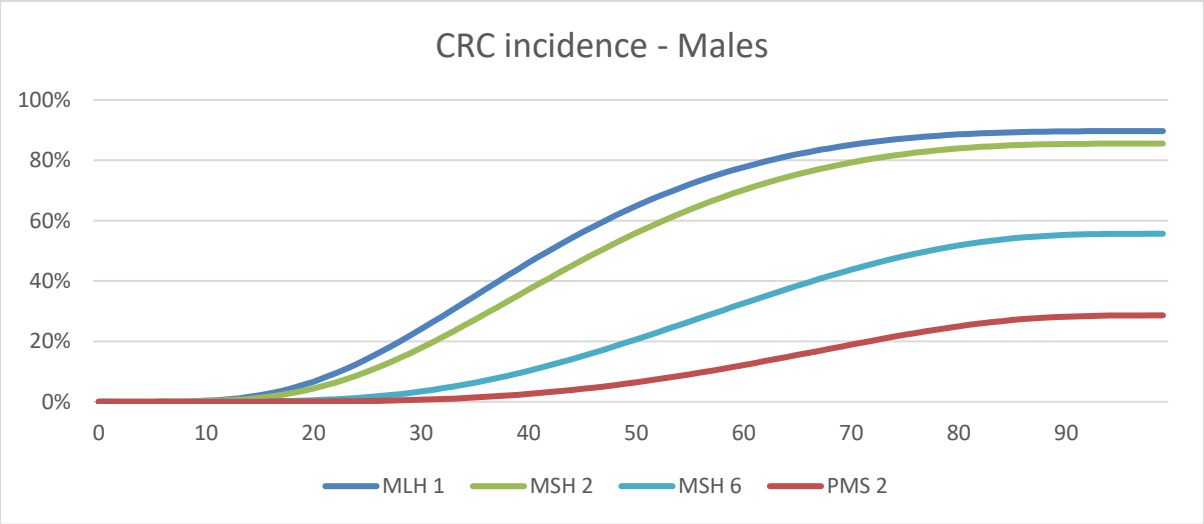

Figure 34:Cumulative incidence of CRC in males with Lynch syndrome

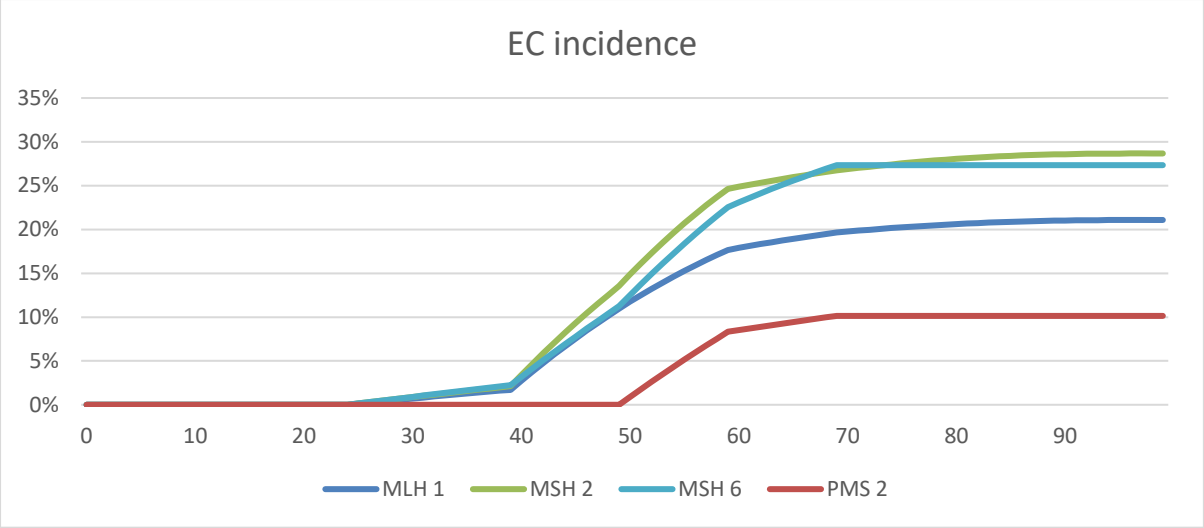

Figure 35:Cumulative incidence of EC in females with Lynch syndrome

Figure 36 below shows the predicted improvement in life expectancy when a person of a given age who has not previously had a Lynch cancer is identified with Lynch (through cascade testing) and measures initiated to reduce their risks. For women, being identified at age 30 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. 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 as modelled.

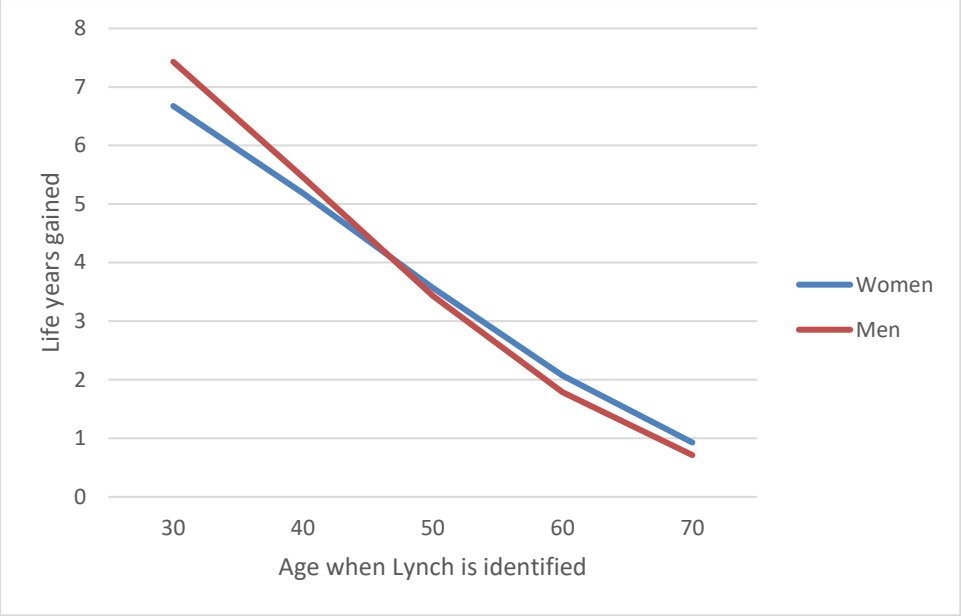

Figure 36: Predicted improvement in life expectancy with age at identification

This chart shows the benefits of identifying Lynch Syndrome in a cohort of women of the same age in terms of cases of CRC and EC avoided, and deaths from CRC or EC averted, when Lynch is identified. Results are presented per 100 women identified. A similar chart shows the CRC cases prevented and deaths averted per 100 men identified.

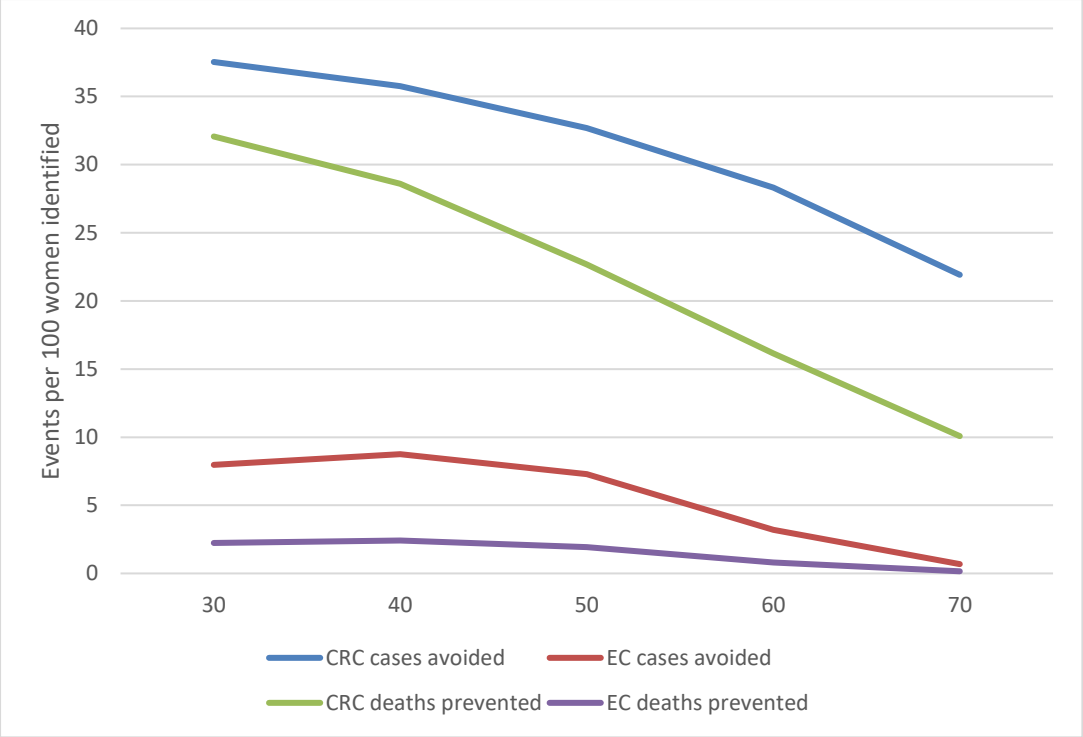

Figure 37: Benefits of identifying 100 women with lynch in a cohort of the same age

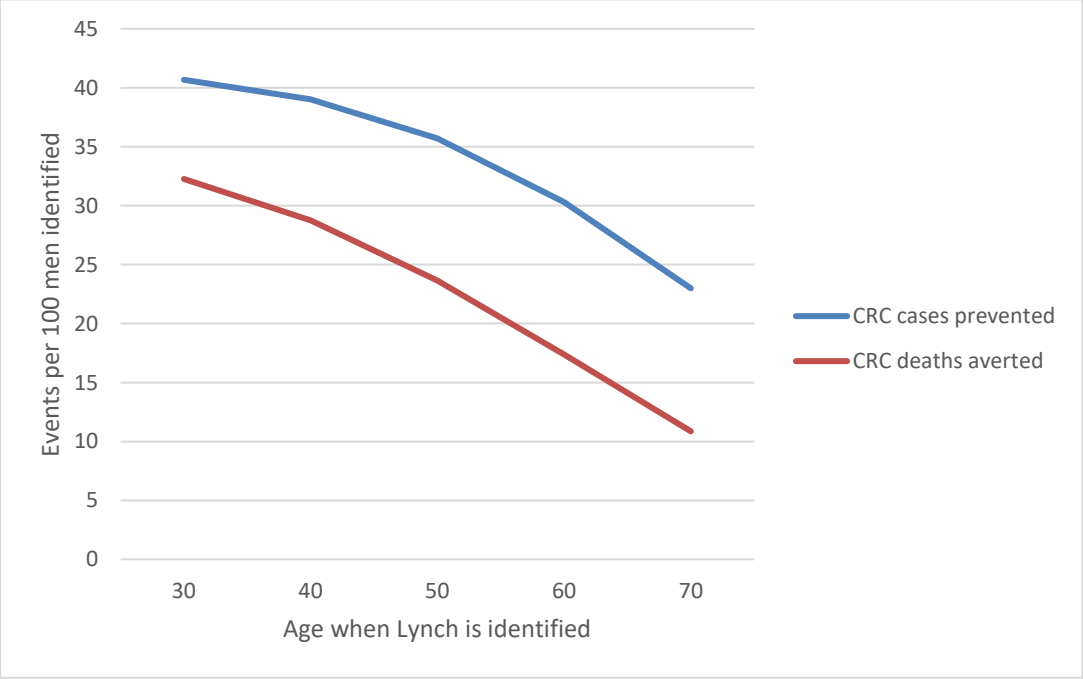

Figure 38: Benefits of identifying lynch 100 men in a cohort of the same age

The number of CRC cases and CRC deaths prevented when 100 women of a given age who have Lynch and have recently presented with EC benefit from CRC surveillance and risk reduction. This declines with age as the relative risk of dying from other causes increases.

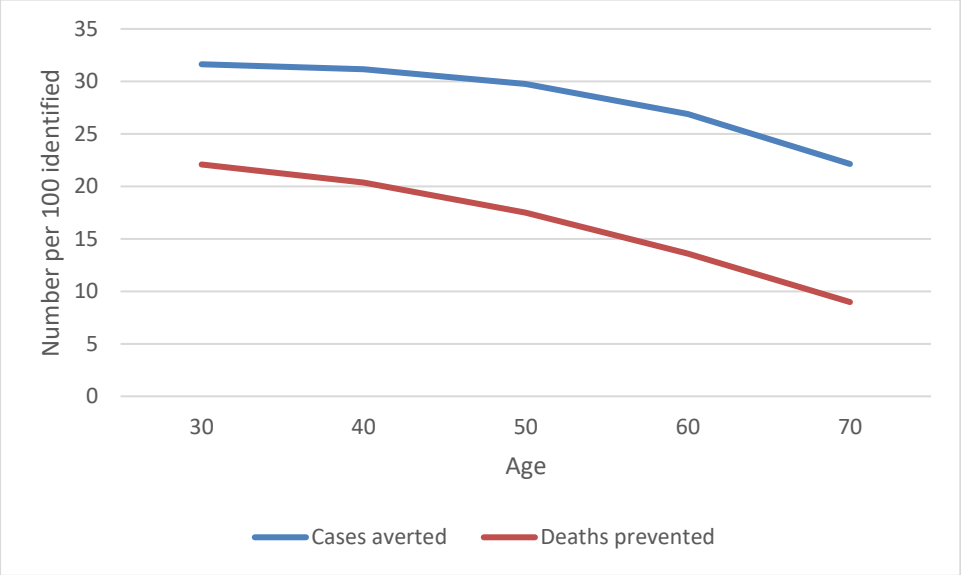

Figure 39: Number of CRC cases and CRC deaths prevented by identification of 100 EC probands

6.4.3.1.1. **Additional Outcomes**

Predicted lifetime QALY gains by age of Lynch identification

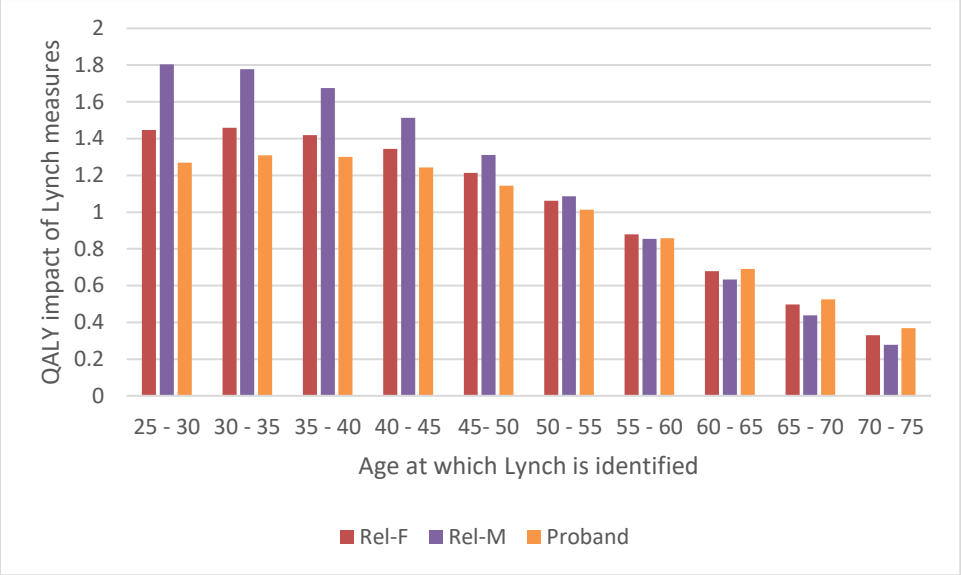

Figure 40: Number of CRC cases and CRC deaths prevented by identification of 100 EC probands

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

6.4.3.2. Disaggregated costs

If a person is identified with Lynch, they will incur additional costs due to protective measures such as surveillance and prophylactic surgery. At the same time, they may incur reduced Lynch cancer treatment costs if these measures are effective. This chart shows how the take up of such measures, from the age when a person is identified with Lynch, affects total costs. The costs for female relatives is significantly higher largely due to the costs of prophylactic surgery to prevent EC, which is not incurred by men, or women who have been diagnosed with EC.

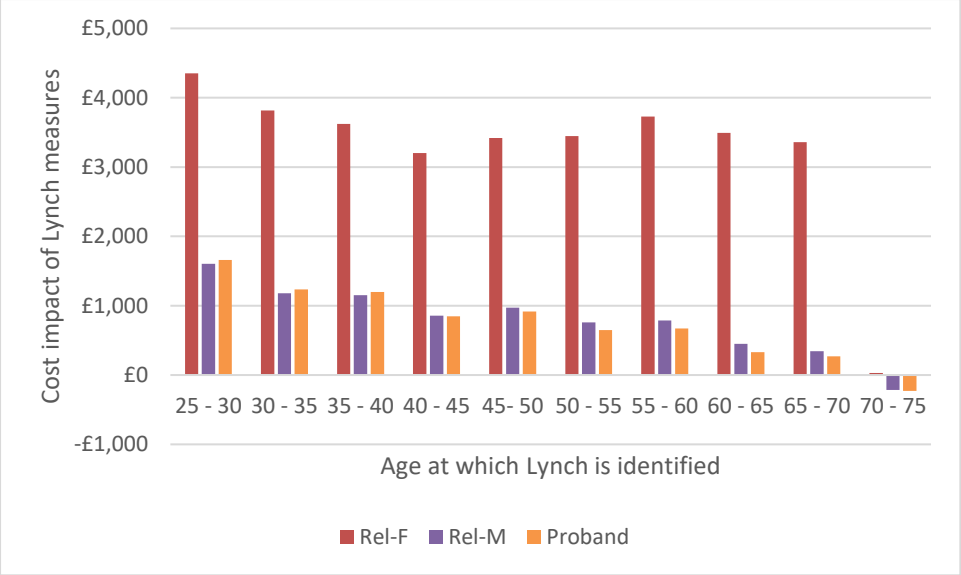

Figure 41: Cost impact of Lynch management across probands and male and female relatives

6.4.4. Subgroup analyses

Potential subgroup analysis of reflex testing in EC probands under 70 years old and probands who had previously had CRC but did not already have a LS status assigned was not feasible therefore no results are presented.

6.4.5. Scenario analyses

Scenario analysis results

We undertook several scenario analyses to estimate the impact to our base-case by changing key model input parameters, the full rationale for doing so detailed in previous sections 6.1 and 6.2. The following scenario analyses were undertaken: -

Scenario analysis 1: Strategy level test accuracy obtained from (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019)

Scenario analysis 2: Costs of testing obtained from (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019)

Scenario analysis 3: Strategy level test accuracy obtained from (PETALS study, personal communication, Ryan et al, University of Manchester, 11/12/2019) and costs of testing obtained from Ryan et al. (2019)[46]

Scenario analysis 4: Disutility inflated due to cancer

Scenario analysis 5: Gynaecological surveillance excluded

Scenario analysis 6: Three-year colonoscopy surveillance

Scenario analysis 7: Excluding benefit from Aspirin

Scenario analysis 8: Excluding HR reducing incidence of CRC due to surveillance

Scenario analysis 1 results

The results in Table 16 show that the most cost effective strategy remains IHC with MLH1 methylation testing, with an ICER of approximately £9280 per QALY in comparison to no testing. All other strategies were dominated or did not reach accepted cost-effectiveness threshold levels.

Table 16: Scenario analysis 1 results

Strategy	**Expected mean costs (£)**	**Incremental costs (£)**	**Expected mean QALYs**	**Incremental QALYs**	**ICER (£)**
No testing	£0	-	0.0000	-	-
MSI with MLH1	£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

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years

Using the test accuracy estimates from Ryan[95] resulted in a nominal decrease of £10 in average cost an almost identical QALY gain to decrease the ICER from our base case by £140 per QALY. 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. (2019)[46]

Using the testing costs obtained from Ryan et al. (2019),[46] the result show that IHC with MLH1 methylation testing strategy continues to be the most cost-effective, with an ICER of approximately £5830 when compared to the MSI with MLH1 methylation strategy. All other strategies continues to be dominated or did not reach acceptable cost-effectiveness threshold levels.

Table 17: 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	£436	£46	0.0671	0.0002	Extendedly dominated

MSI with MLH1					
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
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years					

Results of the microcosting study produced test cost estimates which were significantly reduced from those used in the base case and therefore an ICER almost half that of the base case was expected. As discussed previously, these costs are considered grossly underpresentative 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 Ryan et al. (2019)[95] and costs of testing obtained from Ryan et al. (2019)[46]

The results in Table 18 show that IHC with MLH1 methylation continue to be the most cost-effective strategy, with an ICER of £5690 per QALY.

Table 18: 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

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years

Scenario analysis 4

Table 19: Scenario analysis 4 results

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
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years					

Scenario analysis 5

Table 20: Scenario analysis 5 results

Strategy	**Expected mean costs (£)**	**Incremental costs (£)**	**Expected mean QALYs**	**Incremental QALYs**	**ICER (£)**
No testing	£0	-	0	-	-
MSI with MLH1	£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
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years					

Scenario analysis 6

Table 21: Scenario analysis 6 results

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	£680	£110	0.0416	-0.0246	Dominated

MLH1 methylation					
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

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years

Scenario analysis 7

Table 22: Scenario analysis 7 results

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
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years					

Scenario analysis 8

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Table 23: 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

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years

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 on CRC incidence in the presence/absence of surveillance. The ICER increases to £20,740, exceeding the cost effectiveness threshold of £20,000 per QALY. This is the greatest change in ICER found across all scenario analyses.

Summary

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

6.4.6. Deterministic/probabilistic sensitivity analyses

6.4.6.1. One-way sensitivity analysis results

Deterministic sensitivity analysis results were conducted by varying key model input parameters used in the base-case to assess the impact on the cost per QALY, and presented in the form of a tornado diagrams. Figure 42 shows the tornado diagram for the comparison between IHC with MLH1 methylation compared to a no testing strategy. We chose this comparison because in the base-case the incremental results showed that IHC with MLH1 methylation was the most cost-effective strategy. Additionally, IHC with MLH1 methylation had the most cost-effective ICER (approximately £9460 per QALY) when each testing strategy was compared to 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 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. Also, as expected, if there was a decrease in the prevalence of Lynch syndrome in 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 resulted in slight changes, but remained below current willingness-to-pay thresholds.

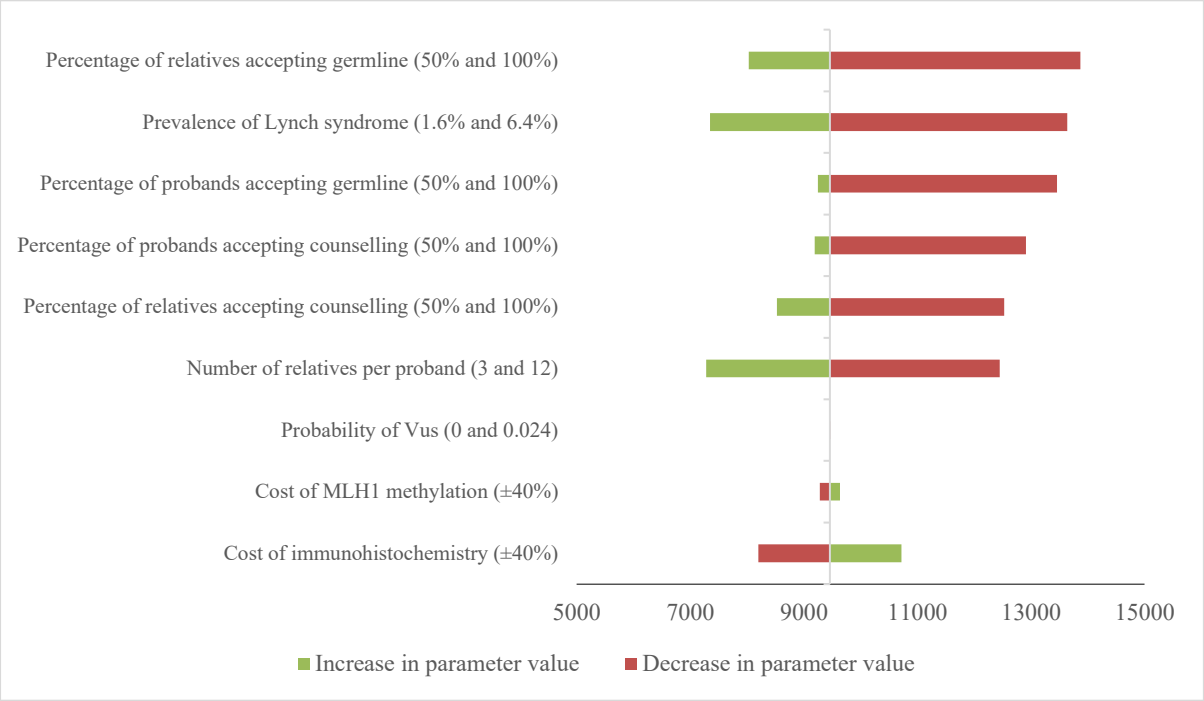

Figure 42: Tornado diagram for the impact of a ±50% change in individual parameters on the ICER per QALY gained

6.4.6.1. Probabilistic sensitivity analysis results

We report the probabilistic sensitivity (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. PSA results for the comparison between IHC with methylation versus no testing are summarised in Table X. We chose this comparison because this strategy was shown to be the most cost-effective in the base-case 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 are underestimated, which resulted in an ICER greater than that in the deterministic results.

Table 24: Probabilistic sensitivity analysis results for base cost per QALY

Strategy	**Expected mean costs (£)**	**Incremental costs (£)[a]**	**Expected mean QALYs**	**Incremental QALY**	**ICER (£) per QALY gained**
No screening	£0	-	0	-	-
IHC with methylation	£600	£600	0.0517	0.0517	£11,600
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; QALY, quality adjusted life years Exact results have been obtained from TreeAge, but were rounded by the authors and presented.					

The probabilistic results are presented in the form of an incremental scatterplot and its corresponding cost-effectiveness acceptability curves (CEAC). Figure 43 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 44 shows the probabilistic results presented in the form of a CEAC, which shows the probability that an intervention is cost-effective at different willingness-to-pay thresholds per QALY. At a willingness-to-pay threshold of £20,000 per QALY IHC has a 0.93 probability of being cost-effective when compared to no testing.

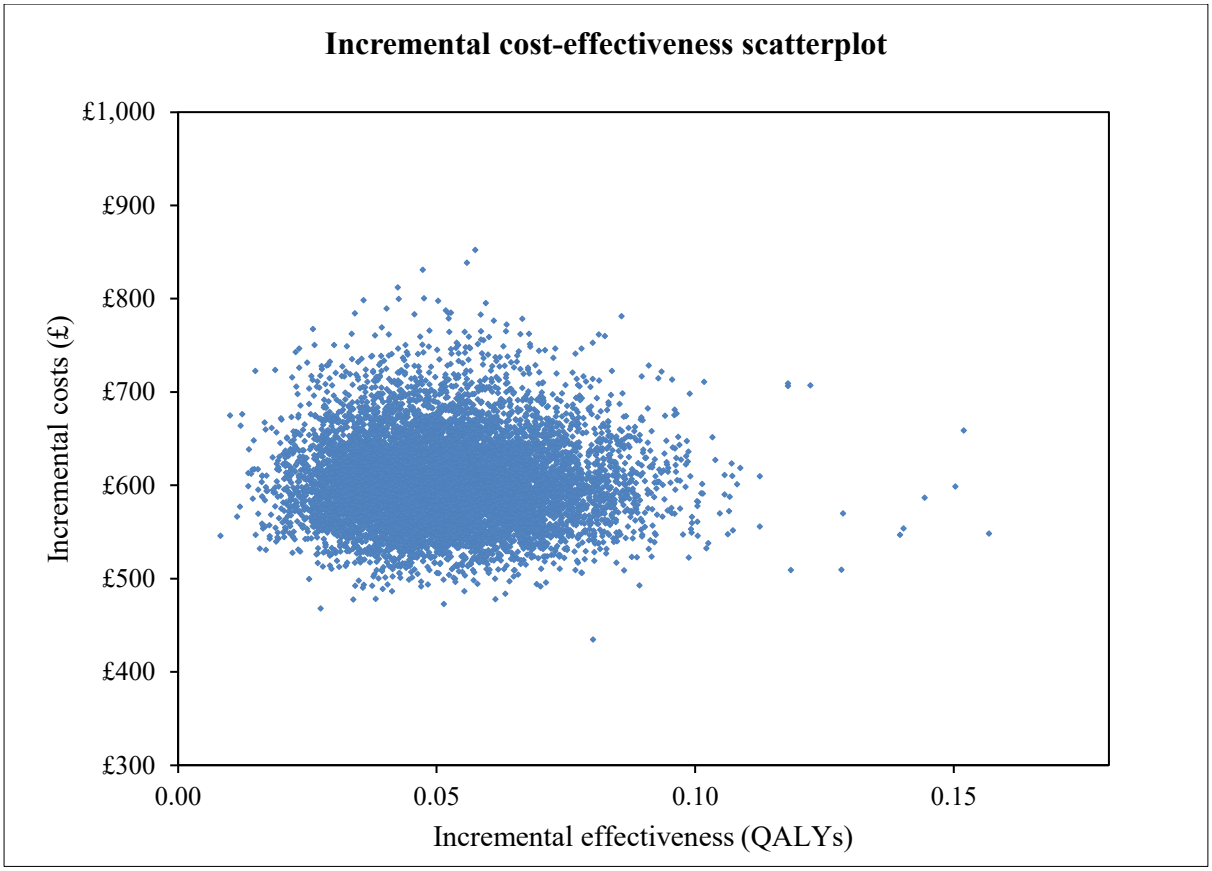

Figure 43: Incremental cost-effectiveness scatterplot for the comparison between IHC with MLH1 versus no screening

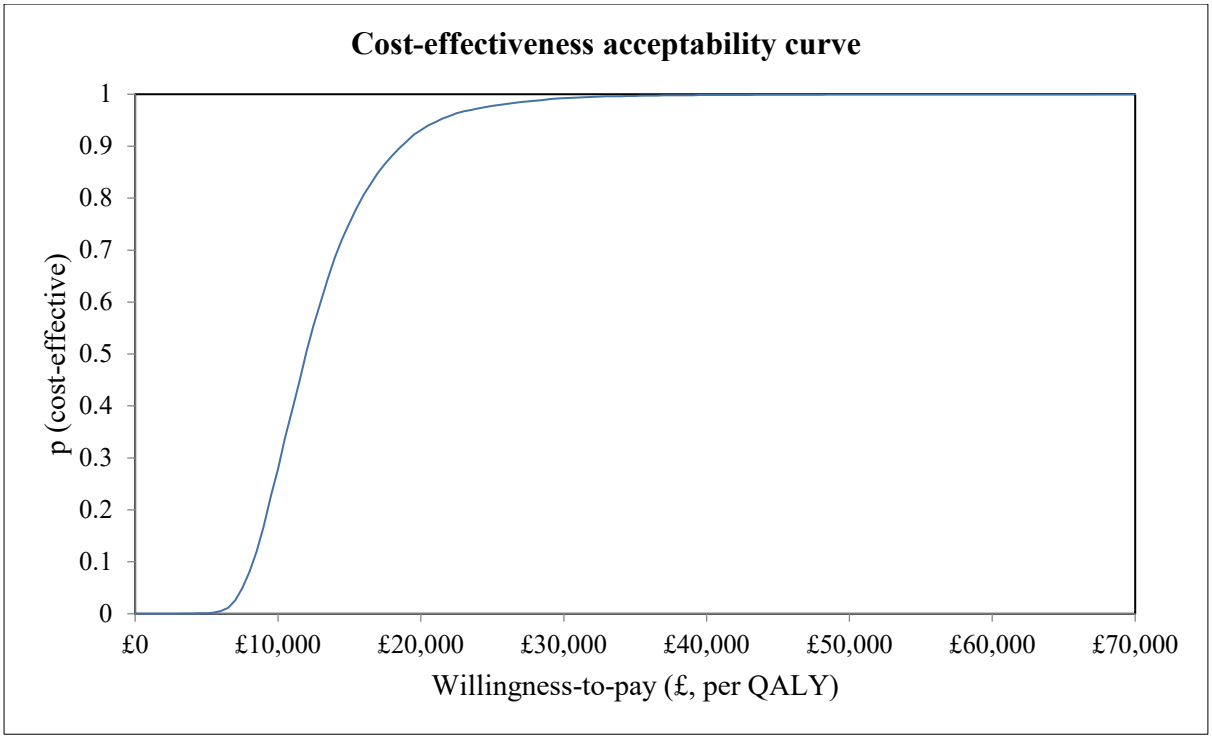

Figure 44: : Cost-effectiveness acceptability curve for the IHC with methylation strategy at different willingness-to-pay thresholds

7. Discussion

7.1. Statement of principal findings

The clinical effectiveness search identified 3308 studies of which 38 studies of test accuracy were included, of which 7 provided full 2x2 data. There were four head-to-head test accuracy studies comparing MSI and 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. 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 at high risk of bias. The economic model indicated that the IHC with MLH1 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 willingness to pay threshold of £20k per QALY.

7.2. 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, the benefits and harms of gynaecologic, and colorectal surveillance in 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 where 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 that 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 we specified that Lynch syndrome must have been diagnosed by genetic verifications of constitutional variants in the MMR genes (MHL1, MSH2, MSH6, and 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.[31] Variants in these four genes are thought to account for 97 – 99% of Lynch syndrome cases.[116] There is some evidence that variants in a fifth gene (EPCAM) may

be responsible for 1 – 3% of Lynch syndrome cases.[11] The exclusion of EPCAM may have led to us slightly underestimating the prevalence of Lynch syndrome. Further, 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, variants of uncertain significance may be reclassified. For example, Mersch et al reported that from a sample of 26,670 unique VUS 2,048 (7.7%) were reclassified.[117] In the majority of cases, these were downgraded to benign/likely benign (91.2%, 1867/2,048), with only a minority being upgraded to pathogenic/likely pathogenic (8.7%, 178/2,048).[117] Data in our review came from studies published from 1999 to 2019, with the earliest cases of VUS being reported in a study from 2003.[50] We considered VUS 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 English Language.

Conclusions from our economic model are similar to those of Snowsill et al.[40] 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 hypermethylation testing was found to be most cost effective with an ICER of £14,200. Whilst this is more expensive than our ICER of £9,420 per QALY some key differences between our base case assumptions provide a viable explanation. Firstly, we model surveillance and risk reduction interventions for both CRC and EC, including Aspirin prophylaxis, whereas the Snowsill et al. model only includes CRC surveillance measures. Whilst 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. Secondly, in their base case Snowsill et al. model EC probands entering the model at a specific age of 60 years whereas proband entry into our model occurs at 49 years old thereby limiting comparison as cost-effectiveness is sensitive to age of probands. However, PSA was conducted by Snowsill et al. on an alternative scenario where probands entered their model aged 50, allowing more direct evaluation, and showed the probability of IHC with methylation testing being cost effective in 90% of the 1000 iterations.

A similar model by PenTAG[10], examined optimal testing strategies for Lynch in CRC probands and their relatives. This model identified IHC plus Braf plus MLH1 hypermethlation testing as the most cost-effective with an ICER per QALY of £11,008 in their base case with CRC probands of mean age 58 years. Whilst 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 colorectal cancer 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 section 7.3 below. High-quality estimates of the effectiveness of surveillance colonoscopies are required as the benefits of long term effectiveness of screening for Lynch 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 benfits 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 due to somatic MMR mutations rather than from Lynch syndrome. This may also be used to identify VuS 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. Further, it was difficult to adequately reflect the full genetic counselling process in our model, and we modelled the whole diagnostic process as occurring within one year which may not represent the potentially more elongated process in practice.

7.3. Uncertainties

There was no randomised controlled trial 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 no consensus on which tests such surveillance entails. There was only observational evidence at high risk of bias for the benefit of colorectal cancer screening in individuals lynch syndrome, with no evidence indicating whether the test should be fecal immunochemical (FIT) or colonoscopy, and what the ages of eligibility or screening intervals should be in this cohort. There are ongoing trials of aspirin chemoprevention.

There was limited evidence on the sensitivity of the testing strategies, due to the low disease prevalence resulting in few cases per study, and lack of follow up of index test negatives to ascertain whether they were false negatives.

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 was 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 have a high risk of bias, and so model results should be interpreted with caution.

8.1. Implications for service provision

Whilst the concept of testing of endometrial cancer patients for Lynch syndrome is cost effective using the assumptions in the model, data were sparse and at 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 which indicated that IHC followed by methylation was underpinned by data from a study using only three out of the four target proteins. Further, whether to offer gynaecological surveillance and if so what tests at which intervals.

There was consistent data suggesting that testing women with endometrial cancer for Lynch syndrome will identify a significant number of women with variants of uncertain significance, and pathways are required to manage these women.

8.2. Suggested research priorities

We suggest two research priorities.

1. There was no randomised controlled trial evidence on the effect of earlier 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. Randomised controlled trials would provide evidence with 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. Whilst large full test accuracy studies may be prohibitively expensive due to the low prevalence of Lynch syndrome, follow up of negative cases through disease registers could be used to determine false negative cases. Further, there is very limited data on the test accuracy of MSI testing followed by hypermethylation testing in women with MSI-H.

9. References

1. National Institute for Health and Care Excellence. *Molecular testing strategies for Lynch syndrome in people with colorectal cancer: Diagnostics guidance [DG27]*. 2017. URL: https://nice.org.uk/guidance/dg27 (Accessed 2 August 2019).

2. Møller P, Seppälä T, Bernstein I, Holinski-Feder E, Sala P, Evans DG*, et al.* Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. *Gut* 2017;**66**(3):464-72. http://dx.doi.org/10.1136/gutjnl-2015-309675

3. Lu KH, Loose DS, Yates MS, Nogueras-Gonzalez GM, Munsell MF, Chen LM*, et al.* Prospective multicenter randomized intermediate biomarker study of oral contraceptive versus depo-provera for prevention of endometrial cancer in women with Lynch syndrome. *Cancer Prev Res (Phila)* 2013;**6**(8):774-81. http://dx.doi.org/10.1158/1940-6207.Capr-13-0020

4. Roett MA. Genital Cancers in Women: Uterine Cancer. *FP Essent* 2015;**438**:11-7.

5. Cancer Research UK. *Uterine cancer statistics*. 2016. URL: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Three (Accessed 2 August 2019).

6. Office for National Statistics. *Cancer survival in England: national estimates for patients followed up to 2017*. 2017. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsandd

iseases/bulletins/cancersurvivalinengland/nationalestimatesforpatientsfollowedupto2017 (Accessed 2 August 2019).

7. Ali AT. Reproductive factors and the risk of endometrial cancer. *Int J Gynecol Cancer* 2014;**24**(3):384-93. http://dx.doi.org/10.1097/igc.0000000000000075

8. Trabert B, Wentzensen N, Yang HP, Sherman ME, Hollenbeck AR, Park Y*, et al.* Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk? *Int J Cancer* 2013;**132**(2):417-26. http://dx.doi.org/10.1002/ijc.27623

9. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J*, et al.* Risk factors for endometrial cancer: An umbrella review of the literature. *Int J Cancer* 2018;**145**(7):1719-30. http://dx.doi.org/10.1002/ijc.31961

10. Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM*, et al.* Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation. *Health Technol Assess* 2017;**21**(51):1-238. http://dx.doi.org/10.3310/hta21510

11. Kuiper RP, Vissers LE, Venkatachalam R, Bodmer D, Hoenselaar E, Goossens M*, et al.* Recurrence and variability of germline EPCAM deletions in Lynch syndrome. *Hum Mutat* 2011;**32**(4):407-14. http://dx.doi.org/10.1002/humu.21446

12. Møller P, Seppala TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D*, et al.* Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 2018;**67**(7):1306-16. http://dx.doi.org/10.1136/gutjnl-2017-314057

13. Hampel H, Frankel W, Panescu J, Lockman J, Sotamaa K, Fix D*, et al.* Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. *Cancer Res* 2006;**66**(15):7810-7.

14. Lu KH, Schorge JO, Rodabaugh KJ, Daniels MS, Sun CC, Soliman PT*, et al.* Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer. *J Clin Oncol* 2007;**25**(33):5158-64.

15. Shia J. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part I. The utility of immunohistochemistry. *J Mol Diagn* 2008;**10**(4):293-300. http://dx.doi.org/10.2353/jmoldx.2008.080031

16. Hegde M, Ferber M, Mao R, Samowitz W, Ganguly A. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). *Genet Med* 2014;**16**(1):101-16. http://dx.doi.org/10.1038/gim.2013.166

17. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J*, et al.* Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004;**96**(4):261-8. http://dx.doi.org/10.1093/jnci/djh034

18. Castillejo A, Hernandez-Illan E, Rodriguez-Soler M, Perez-Carbonell L, Egoavil C, Barbera VM*, et al.* Prevalence of MLH1 constitutional epimutations as a cause of Lynch syndrome in unselected versus selected consecutive series of patients with colorectal cancer. *J Med Genet* 2015;**52**(7):498-502. http://dx.doi.org/10.1136/jmedgenet-2015-103076

19. Cho KR, Cooper K, Croce S, Djordevic B, Herrington S, Howitt B*, et al.* International Society of Gynecological Pathologists (ISGyP) Endometrial Cancer Project: Guidelines From the Special Techniques and Ancillary Studies Group. *Int J Gynecol Pathol* 2019;**38**(Suppl. 1):S114-22. http://dx.doi.org/10.1097/PGP.0000000000000496

20. Crosbie EJ, Ryan NAJ, Arends MJ, Bosse T, Burn J, Cornes JM*, et al.* The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. *Genet Med* 2019;**21**(10):2390–400. http://dx.doi.org/10.1038/s41436-019-0489-y

21. NHS England. *National Genomic Test Directory: Testing Criteria for Rare and Inherited Disease*. 2019. URL: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-march-19.pdf (Accessed 2 August 2019).

22. Sundar S, Balega J, Crosbie E, Drake A, Edmondson R, Fotopoulou C*, et al.* BGCS uterine cancer guidelines: Recommendations for practice. *Eur J Obstet Gynecol Reprod Biol* 2017;**213**:71-97. http://dx.doi.org/10.1016/j.ejogrb.2017.04.015

23. Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S*, et al.* Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 2013;**62**(6):812-23. http://dx.doi.org/10.1136/gutjnl-2012-304356

24. Kulkarni A, Brady AF. *Management of Women with a Genetic Predisposition to Gynaecological Cancers: Scientific Impact Paper No. 48*. Royal College of Obstetricians & Gynaecologists; 2015. URL: https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip48.pdf (Accessed 10 August 2019).
25. Monahan KJ, Bradshaw N, Dolwani S, Desouza B, Dunlop MG, East JE*, et al.* Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) [published online ahead of print 28 November 2019]. *Gut* 2019. http://dx.doi.org/10.1136/gutjnl-2019-319915
26. National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologist. *[A1] Effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome: Evidence review for Colorectal Cancer (update)*. London: National Institute for Health and Care Excellence; 2019. URL: https://www.nice.org.uk/guidance/GID-NG10060/documents/evidence-review (Accessed 10 January 2020).
27. ACOG Practice Bulletin No. 147: Lynch syndrome. *Obstet Gynecol* 2014;**124**(5):1042-54. http://dx.doi.org/10.1097/01.Aog.0000456325.50739.72
28. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F*, et al.* Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol* 2016;**27**(suppl 5):v103-10. http://dx.doi.org/10.1093/annonc/mdw327
29. *Handbook for Diagnostic Test Accuracy Reviews*. Cochrane Screening and Diagnostic Tests Methods Group. URL: https://methods.cochrane.org/sdt/handbook-dta-reviews (Accessed 2 August 2019).
30. National Institute for Health and Clinical Excellence. *Diagnostics Assessment Programme manual*. 2011. URL: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf (Accessed 2 August 2019).
31. Frayling I, Berry I, Wallace A, Payne S, Norbury G. *ACGS best practice guidelines for genetic testing and diagnosis of Lynch syndrome*. London: Association for Clinical

Genomic Science; 2016. URL: https://www.acgs.uk.com/media/10774/ls_bpg_approved.pdf (Accessed 6 August 2019).

32. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**(8):529-36. http://dx.doi.org/10.7326/0003-4819-155-8-201110180-00009

33. Whiting PF, Rutjes AW, Westwood ME, Mallett S. A systematic review classifies sources of bias and variation in diagnostic test accuracy studies. *J Clin Epidemiol* 2013;**66**(10):1093-104. http://dx.doi.org/10.1016/j.jclinepi.2013.05.014

34. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927;**22**(158):209-12.

35. *CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination; 2009. URL: https://www.york.ac.uk/crd/guidance/ (Accessed 19 October 2019).

36. Higgins J, Sterne J, Savović J, Page M, Hróbjartsson A, Boutron I, *et al.* A revised tool for assessing risk of bias in randomized trials In: Chandler. J, McKenzie. J, Boutron. I, Welch. V, editors. *Cochrane Methods*: Cochrane Database of Systematic Reviews; 2016.

37. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919. http://dx.doi.org/10.1136/bmj.i4919

38. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Eur J Health Econ* 2013;**14**(3):367-72. http://dx.doi.org/10.1007/s10198-013-0471-6

39. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36):iii-iv, ix-xi, 1-158.

40. Snowsill TM, Ryan NAJ, Crosbie EJ, Frayling IM, Evans DG, Hyde CJ. Cost-effectiveness analysis of reflex testing for Lynch syndrome in women with endometrial cancer in the UK setting. *PLoS One* 2019;**14**(8):e0221419. http://dx.doi.org/10.1371/journal.pone.0221419

41. Jarvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P, *et al.* Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 2000;**118**(5):829-34. http://dx.doi.org/10.1016/s0016-5085(00)70168-5

42. Dominguez-Valentin M, Sampson JR, Seppala TT, Ten Broeke SW, Plazzer JP, Nakken S, *et al.* Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med* 2020;**22**(1):15-25. http://dx.doi.org/10.1038/s41436-019-0596-9

43. Cancer Research UK. *Uterine cancer survival statistics*. URL: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/survival (Accessed 2 January 2020).

44. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**(5):509-18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x

45. NHS Improvement. *National Schedule of Reference Costs 2017/18*. 2018. URL: https://improvement.nhs.uk/resources/reference-costs/#rc1718 (Accessed 2 January 2020).

46. Ryan NAJ, Davison NJ, Payne K, Cole A, Evans DG, Crosbie EJ. A Micro-Costing Study of Screening for Lynch Syndrome-Associated Pathogenic Variants in an Unselected Endometrial Cancer Population: Cheap as NGS Chips? *Front Oncol* 2019;**9**:61. http://dx.doi.org/10.3389/fonc.2019.00061

47. Anagnostopoulos A, McKay VH, Cooper I, Campbell F, Greenhalgh L, Kirwan J. Identifying Lynch Syndrome in Women Presenting With Endometrial Carcinoma Under the Age of 50 Years. *Int J Gynecol Cancer* 2017;**27**(5):931-7. http://dx.doi.org/10.1097/IGC.0000000000000962

48. Backes FJ, Leon ME, Ivanov I, Suarez A, Frankel WL, Hampel H, *et al.* Prospective evaluation of DNA mismatch repair protein expression in primary endometrial cancer. *Gynecol Oncol* 2009;**114**(3):486-90. http://dx.doi.org/10.1016/j.ygyno.2009.05.026

49. Baldinu P, Cossu A, Manca A, Satta MP, Pisano M, Casula M, *et al.* Microsatellite instability and mutation analysis of candidate genes in unselected sardinian patients with endometrial carcinoma. *Cancer* 2002;**94**(12):3157-68.

50. Berends MJ, Wu Y, Sijmons RH, van der Sluis T, Ek WB, Ligtenberg MJ, *et al.* Toward new strategies to select young endometrial cancer patients for mismatch repair gene mutation analysis. *J Clin Oncol* 2003;**21**(23):4364-70.

51. 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 (Phila)* 2017;**10**(2):108-15. http://dx.doi.org/10.1158/1940-6207.CAPR-16-0219

52. Buchanan DD, Tan YY, Walsh MD, Clendenning M, Metcalf AM, Ferguson K, *et al.* Tumor mismatch repair immunohistochemistry and DNA MLH1 methylation testing of patients with endometrial cancer diagnosed at age younger than 60 years optimizes triage for population-level germline mismatch repair gene mutation testing. *J Clin Oncol* 2014;**32**(2):90-100. http://dx.doi.org/10.1200/JCO.2013.51.2129

53. Carnevali I, Libera L, Chiaravalli A, Sahnane N, Furlan D, Viel A, *et al.* Somatic Testing on Gynecological Cancers Improve the Identification of Lynch Syndrome. *Int J Gynecol Cancer* 2017;**27**(7):1543-9. http://dx.doi.org/10.1097/IGC.0000000000001010

54. Chao X, Li L, Wu M, Ma S, Tan X, Zhong S, *et al.* Comparison of screening strategies for Lynch syndrome in patients with newly diagnosed endometrial cancer: a prospective cohort study in China. *Cancer Commun* 2019;**39**(1):42. http://dx.doi.org/10.1186/s40880-019-0388-2

55. Dillon JL, Gonzalez JL, DeMars L, Bloch KJ, Tafe LJ. Universal screening for Lynch syndrome in endometrial cancers: frequency of germline mutations and identification of patients with Lynch-like syndrome. *Hum Pathol* 2017;**70**:121-8. http://dx.doi.org/10.1016/j.humpath.2017.10.022

56. Dudley B, Brand RE, Thull D, Bahary N, Nikiforova MN, Pai RK. Germline MLH1 Mutations Are Frequently Identified in Lynch Syndrome Patients With Colorectal and Endometrial Carcinoma Demonstrating Isolated Loss of PMS2 Immunohistochemical Expression. *Am J Surg Pathol* 2015;**39**(8):1114-20. http://dx.doi.org/10.1097/PAS.0000000000000425

57. Egoavil C, Alenda C, Castillejo A, Paya A, Peiro G, Sanchez-Heras AB, *et al.* Prevalence of Lynch syndrome among patients with newly diagnosed endometrial cancers. *PLoS One* 2013;**8**(11):e79737. http://dx.doi.org/10.1371/journal.pone.0079737

58. Ferguson SE, Aronson M, Pollett A, Eiriksson LR, Oza AM, Gallinger S, *et al.* Performance characteristics of screening strategies for Lynch syndrome in unselected women with newly diagnosed endometrial cancer who have undergone universal germline mutation testing. *Cancer* 2014;**120**(24):3932-9. http://dx.doi.org/10.1002/cncr.28933

59. Goodfellow PJ, Billingsley CC, Lankes HA, Ali S, Cohn DE, Broaddus RJ, *et al.* Combined Microsatellite Instability, MLH1 Methylation Analysis, and Immunohistochemistry for Lynch Syndrome Screening in Endometrial Cancers From GOG210: An NRG Oncology and Gynecologic Oncology Group Study. *J Clin Oncol* 2015;**33**(36):4301-8. http://dx.doi.org/10.1200/JCO.2015.63.9518

60. Goodfellow PJ, Buttin BM, Herzog TJ, Rader JS, Gibb RK, Swisher E, *et al.* Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers. *Proc Natl Acad Sci U S A* 2003;**100**(10):5908-13.

61. Kato A, Sato N, Sugawara T, Takahashi K, Kito M, Makino K, *et al.* Isolated Loss of PMS2 Immunohistochemical Expression is Frequently Caused by Heterogenous MLH1 Promoter Hypermethylation in Lynch Syndrome Screening for Endometrial Cancer Patients. *Am J Surg Pathol* 2016;**40**(6):770-6. http://dx.doi.org/10.1097/PAS.0000000000000606

62. Latham A, Srinivasan P, Kemel Y, Shia J, Bandlamudi C, Mandelker D, *et al.* Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J Clin Oncol* 2019;**37**(4):286-95. http://dx.doi.org/10.1200/JCO.18.00283

63. Leenen CH, van Lier MG, van Doorn HC, van Leerdam ME, Kooi SG, de Waard J, *et al.* Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer <= 70 years. *Gynecol Oncol* 2012;**125**(2):414-20. http://dx.doi.org/10.1016/j.ygyno.2012.01.049

64. Libera L, Sahnane N, Carnevali IW, Cimetti L, Cerutti R, Chiaravalli AM, *et al.* Microsatellite analysis of sporadic and hereditary gynaecological cancer in routine diagnostics. *J Clin Pathol* 2017;**70**(9):792-7. http://dx.doi.org/10.1136/jclinpath-2017-204348

65. Lin DI, Hecht JL. Targeted Screening With Combined Age- and Morphology-Based Criteria Enriches Detection of Lynch Syndrome in Endometrial Cancer. *Int J Surg Pathol* 2016;**24**(4):297-305. http://dx.doi.org/10.1177/1066896916629782

66. Mas-Moya J, Dudley B, Brand RE, Thull D, Bahary N, Nikiforova MN, *et al.* Clinicopathological comparison of colorectal and endometrial carcinomas in patients with

Lynch-like syndrome versus patients with Lynch syndrome. *Hum Pathol* 2015;**46**(11):1616-25. http://dx.doi.org/10.1016/j.humpath.2015.06.022

67. Masuda K, Banno K, Hirasawa A, Yanokura M, Tsuji K, Kobayashi Y*, et al.* Relationship of lower uterine segment cancer with Lynch syndrome: a novel case with an hMLH1 germline mutation. *Oncol Rep* 2012;**28**(5):1537-43. http://dx.doi.org/10.3892/or.2012.2008

68. McConechy MK, Talhouk A, Li-Chang HH, Leung S, Huntsman DG, Gilks CB*, et al.* Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. *Gynecol Oncol* 2015;**137**(2):306-10. http://dx.doi.org/10.1016/j.ygyno.2015.01.541

69. Mercado RC, Hampel H, Kastrinos F, Steyerberg E, Balmana J, Stoffel E*, et al.* Performance of PREMM(1,2,6), MMRpredict, and MMRpro in detecting Lynch syndrome among endometrial cancer cases. *Genet Med* 2012;**14**(7):670-80. http://dx.doi.org/10.1038/gim.2012.18

70. Millar AL, Pal T, Madlensky L, Sherman C, Temple L, Mitri A*, et al.* Mismatch repair gene defects contribute to the genetic basis of double primary cancers of the colorectum and endometrium. *Hum Mol Genet* 1999;**8**(5):823-9.

71. Modica I, Soslow RA, Black D, Tornos C, Kauff N, Shia J. Utility of immunohistochemistry in predicting microsatellite instability in endometrial carcinoma. *Am J Surg Pathol* 2007;**31**(5):744-51.

72. Nagle CM, O'Mara TA, Tan Y, Buchanan DD, Obermair A, Blomfield P*, et al.* Endometrial cancer risk and survival by tumor MMR status. *J Gynecol Oncol* 2018;**29**(3):e39. http://dx.doi.org/10.3802/jgo.2018.29.e39

73. Najdawi F, Crook A, Maidens J, McEvoy C, Fellowes A, Pickett J*, et al.* Lessons learnt from implementation of a Lynch syndrome screening program for patients with gynaecological malignancy. *Pathology* 2017;**49**(5):457-64. http://dx.doi.org/10.1016/j.pathol.2017.05.004

74. Ollikainen M, Abdel-Rahman WM, Moisio AL, Lindroos A, Kariola R, Jarvela I*, et al.* Molecular analysis of familial endometrial carcinoma: a manifestation of hereditary nonpolyposis colorectal cancer or a separate syndrome? *J Clin Oncol* 2005;**23**(21):4609-16.

75. Pecorino B, Rubino C, Guardala VF, Galia A, Scollo P. Genetic screening in young women diagnosed with endometrial cancer. *J Gynecol Oncol* 2017;**28**(1):e4. http://dx.doi.org/10.3802/jgo.2017.28.e4

76. Planck M, Rambech E, Moslein G, Muller W, Olsson H, Nilbert M. High frequency of microsatellite instability and loss of mismatch-repair protein expression in patients with double primary tumors of the endometrium and colorectum. *Cancer* 2002;**94**(9):2502-10.

77. Ring KL, Bruegl AS, Allen BA, Elkin EP, Singh N, Hartman AR*, et al.* Germline multi-gene hereditary cancer panel testing in an unselected endometrial cancer cohort. *Mod Pathol* 2016;**29**(11):1381-9. http://dx.doi.org/10.1038/modpathol.2016.135

78. Rubio I, Ibanez-Feijoo E, Andres L, Aguirre E, Balmana J, Blay P*, et al.* Analysis of Lynch Syndrome Mismatch Repair Genes in Women with Endometrial Cancer. *Oncology* 2016;**91**(3):171-6. http://dx.doi.org/10.1159/000447972

79. Salvador MU, Truelson MRF, Mason C, Souders B, LaDuca H, Dougall B*, et al.* Comprehensive Paired Tumor/Germline Testing for Lynch Syndrome: Bringing Resolution to the Diagnostic Process. *J Clin Oncol* 2019;**37**(8):647-57. http://dx.doi.org/10.1200/JCO.18.00696

80. Sarode VR, Robinson L. Screening for Lynch Syndrome by Immunohistochemistry of Mismatch Repair Proteins: Significance of Indeterminate Result and Correlation With Mutational Studies. *Arch Pathol Lab Med* 2019;**143**(10):1225-33. http://dx.doi.org/10.5858/arpa.2018-0201-OA

81. Shin SH, Yu EJ, Lee YK, Song YS, Seong MW, Park SS. Characteristics of hereditary nonpolyposis colorectal cancer patients with double primary cancers in endometrium and colorectum. *Obstet Gynecol Sci* 2015;**58**(2):112-6. http://dx.doi.org/10.5468/ogs.2015.58.2.112

82. Stelloo E, Jansen AML, Osse EM, Nout RA, Creutzberg CL, Ruano D*, et al.* Practical guidance for mismatch repair-deficiency testing in endometrial cancer. *Ann Oncol* 2017;**28**(1):96-102. http://dx.doi.org/10.1093/annonc/mdw542

83. Strazzullo M, Cossu A, Baldinu P, Colombino M, Satta MP, Tanda F*, et al.* High-resolution methylation analysis of the hMLH1 promoter in sporadic endometrial and colorectal carcinomas. *Cancer* 2003;**98**(7):1540-6.

84. Svampane L, Strumfa I, Berzina D, Svampans M, Miklasevics E, Gardovskis J. Epidemiological analysis of hereditary endometrial cancer in a large study population. *Arch Gynecol Obstet* 2014;**289**(5):1093-9. http://dx.doi.org/10.1007/s00404-013-3074-7

85. Takahashi K, Sato N, Sugawara T, Kato A, Sato T, Shimizu D*, et al.* Clinical characteristics of Lynch-like cases collaterally classified by Lynch syndrome identification strategy using universal screening in endometrial cancer. *Gynecol Oncol* 2017;**147**(2):388-95. http://dx.doi.org/10.1016/j.ygyno.2017.08.016

86. Tian W, Bi R, Ren Y, He H, Shi S, Shan B*, et al.* Screening for hereditary cancers in patients with endometrial cancer reveals a high frequency of germline mutations in cancer predisposition genes. *Int J Cancer* 2019;**145**(5):1290-8. http://dx.doi.org/10.1002/ijc.32389

87. Wang Y, Shi C, Eisenberg R, Vnencak-Jones CL. Differences in Microsatellite Instability Profiles between Endometrioid and Colorectal Cancers: A Potential Cause for False-Negative Results? *J Mol Diagn* 2017;**19**(1):57-64. http://dx.doi.org/10.1016/j.jmoldx.2016.07.008

88. Yoon SN, Ku JL, Shin YK, Kim KH, Choi JS, Jang EJ*, et al.* Hereditary nonpolyposis colorectal cancer in endometrial cancer patients. *Int J Cancer* 2008;**122**(5):1077-81.

89. de Jong AE, Hendriks YM, Kleibeuker JH, de Boer SY, Cats A, Griffioen G*, et al.* Decrease in mortality in Lynch syndrome families because of surveillance. *Gastroenterology* 2006;**130**(3):665-71. http://dx.doi.org/10.1053/j.gastro.2005.11.032

90. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, Peltomaki P, Aaltonen LA, Mecklin JP. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. *J Clin Oncol* 2009;**27**(28):4793-7. http://dx.doi.org/10.1200/jco.2009.23.7784

91. Ketabi Z, Gerdes AM, Mosgaard B, Ladelund S, Bernstein I. The results of gynecologic surveillance in families with hereditary nonpolyposis colorectal cancer. *Gynecol Oncol* 2014;**133**(3):526-30. http://dx.doi.org/10.1016/j.ygyno.2014.03.012

92. Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *Int J Cancer* 2007;**120**(4):821-4. http://dx.doi.org/10.1002/ijc.22446

93. Macrae F. *A randomised double blind dose non-inferiority trial of a daily dose of 600mg versus 300mg versus 100mg 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). Australian New Zealand Clinical Trials Registry; 2017. URL: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617000804381 (Accessed 2 January 2020).

94. Arber N. *A Randomised Double Blind Dose Non-inferiority Trial of a Daily Dose of 600mg Versus 300mg Versus 100mg of Enteric Coated Aspirin as a Cancer Preventive in Carriers of a Germline Pathological Mismatch Repair Gene Defect, Lynch Syndrome*. ClinicalTrials.gov; 2015. URL: https://clinicaltrials.gov/ct2/show/nct02497820 (Accessed 2 January 2020).

95. Ryan NAJ, Glaire MA, Blake D, Cabrera-Dandy M, Evans DG, Crosbie EJ. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. *Genet Med* 2019;**21**(10):2167–80. http://dx.doi.org/10.1038/s41436-019-0536-8

96. Resnick KE, Backes F, Hampel H, Matthews KS, Straughn JM, Cohn DE. A cost-effectiveness analysis of lynch syndrome screening among newly diagnosed endometrial cancer patients. *Gynecol Oncol* 2009;**112**(2 Suppl.):S4. http://dx.doi.org/10.1016/j.ygyno.2008.10.020

97. Kwon JS, Scott JL, Gilks CB, Daniels MS, Sun CC, Lu KH. Testing women with endometrial cancer to detect Lynch syndrome. *J Clin Oncol* 2011;**29**(16):2247-52. http://dx.doi.org/https://dx.doi.org/10.1200/JCO.2010.32.9979

98. Bruegl AS, Djordjevic B, Rajyalakshmi L, Lu KH, Sun CCL, Broaddus R. Cost analysis comparing universal tumor testing to clinically based criteria in the evaluation of endometrial adenocarcinomas for Lynch syndrome. *Gynecol Oncol* 2014;**133**(Suppl. 1):45. http://dx.doi.org/10.1016/j.ygyno.2014.03.128

99. Goverde A, Spaander MC, van Doorn HC, Dubbink HJ, van den Ouweland AM, Tops CM*, et al.* Cost-effectiveness of routine screening for Lynch syndrome in endometrial cancer patients up to 70years of age. *Gynecol Oncol* 2016;**143**(3):453-9. http://dx.doi.org/10.1016/j.ygyno.2016.10.008

100. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programme. Third edition*: Oxford: Oxford University Press; 2005.

101. Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S. Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review. *Health Technol Assess* 2004;**8**(12):iii, 1-121. http://dx.doi.org/10.3310/hta8120

102. Thorn J, Coast J, Andronis L. Interpretation of the Expected Value of Perfect Information and Research Recommendations: A Systematic Review and Empirical Investigation. *Med Decis Making* 2016;**36**(3):285-95. http://dx.doi.org/10.1177/0272989x15586552

103. Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C*, et al.* A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. *Health Technol Assess* 2014;**18**(58):1-406. http://dx.doi.org/10.3310/hta18580

104. Barrow P. *Hereditary Colorectal Cancer: Registration, Screening and Prognostic Biomarker Analysis* [Doctor of Medicine Thesis]. Manchester: The University of Manchester; 2014.

105. Menko FH, Ter Stege JA, van der Kolk LE, Jeanson KN, Schats W, Moha DA*, et al.* The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. *Fam Cancer* 2019;**18**(1):127-35. http://dx.doi.org/10.1007/s10689-018-0089-z

106. Bruwer Z, Futter M, Ramesar R. Communicating cancer risk within an African context: Experiences, disclosure patterns and uptake rates following genetic testing for Lynch syndrome. *Patient Educ Couns* 2013;**92**(1):53-60. http://dx.doi.org/10.1016/j.pec.2013.02.001

107. Moller P, Seppala T, Bernstein I, Holinski-Feder E, Sala P, Evans DG*, et al.* Incidence of and survival after subsequent cancers in carriers of pathogenic MMR variants with previous cancer: a report from the prospective Lynch syndrome database. *Gut* 2017;**66**(9):1657-64. http://dx.doi.org/10.1136/gutjnl-2016-311403

108. Seppala TT, Ahadova A, Dominguez-Valentin M, Macrae F, Evans DG, Therkildsen C*, et al.* Lack of association between screening interval and cancer stage in Lynch syndrome

may be accounted for by over-diagnosis; a prospective Lynch syndrome database report. *Hered Cancer Clin Pract* 2019;**17**:8. http://dx.doi.org/10.1186/s13053-019-0106-8

109. Seppala T, Pylvanainen K, Evans DG, Jarvinen H, Renkonen-Sinisalo L, Bernstein I*, et al.* Colorectal cancer incidence in path_MLH1 carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report. *Hered Cancer Clin Pract* 2017;**15**:18. http://dx.doi.org/10.1186/s13053-017-0078-5

110. Thompson BA, Spurdle AB, Plazzer JP, Greenblatt MS, Akagi K, Al-Mulla F*, et al.* Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locus-specific database. *Nat Genet* 2014;**46**(2):107-15. http://dx.doi.org/10.1038/ng.2854

111. UK Genetic Testing Network. *Colorectal Cancer, Hereditary Nonpolyposis and Lynch Syndrome*. 2018. URL: https://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/colorectal-cancer-hereditary-nonpolyposis-and-lynch-syndrome-534/ (Accessed 14 December 2019).

112. Slade I, Hanson H, George A, Kohut K, Strydom A, Wordsworth S*, et al.* A cost analysis of a cancer genetic service model in the UK. *J Community Genet* 2016;**7**(3):185-94. http://dx.doi.org/10.1007/s12687-016-0266-4

113. Barrow P, Green K, Clancy T, Lalloo F, Hill J, Evans DG. Improving the uptake of predictive testing and colorectal screening in Lynch syndrome: a regional primary care survey. *Clin Genet* 2015;**87**(6):517-24. http://dx.doi.org/10.1111/cge.12559

114. Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME*, et al.* Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med* 2006;**354**(26):2751-63. http://dx.doi.org/10.1056/NEJMoa053493

115. Heald B, Plesec T, Liu X, Pai R, Patil D, Moline J*, et al.* Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. *J Clin Oncol* 2013;**31**(10):1336-40. http://dx.doi.org/10.1200/jco.2012.45.1674

116. Tutlewska K, Lubinski J, Kurzawski G. Germline deletions in the EPCAM gene as a cause of Lynch syndrome - literature review. *Hered Cancer Clin Pract* 2013;**11**(1):9. http://dx.doi.org/10.1186/1897-4287-11-9

117. Mersch J, Brown N, Pirzadeh-Miller S, Mundt E, Cox HC, Brown K*, et al.* Prevalence of Variant Reclassification Following Hereditary Cancer Genetic Testing. *JAMA* 2018;**320**(12):1266-74. http://dx.doi.org/10.1001/jama.2018.13152

10. Appendices

10.1. Appendix 1: Literature search strategies

10.1.1. Clinical effectiveness

Summary of bibliographic database searches

Database	Date of search	Number of records
MEDLINE (Ovid)	07/08/2019	1,557
Embase (Ovid)	07/08/2019	2,775
Cochrane Library	08/08/2019	36
DARE and HTA	08/08/2019	7
Science Citation Index and Conference Proceedings Science (Web of Science)	08/08/2019	1,874
PROSPERO	28/08/2019	10

Total from database searches: 6259

Search strategies

Medline (via Ovid)

Search date: 07/08/2019

Actual database: Ovid MEDLINE(R) ALL <1946 to August 06, 2019>

Search Strategy:

---

1 uterine neoplasms/ (40281)

2 exp endometrial neoplasms/ (20609)

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. (66373)

4 1 or 2 or 3 (92254)

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. (613827)

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 (14227)

20 4 and 19 (1557)

Embase (via Ovid)

Search date: 07/08/2019

Actual database: Embase Classic+Embase <1947 to 2019 August 06>

Search Strategy:

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1 uterus cancer/ or exp endometrium cancer/ or uterus carcinoma/ or uterus sarcoma/ (70395)

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. (93982)

3 1 or 2 (117308)

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 (12444)

13 (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6).ti,ab,kw. (16365)

14 (colon* or colorectal* or lynch* or HNPCC or hereditary).ti,ab,kw. (852547)

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. (12188)

17 Amsterdam criteria.ti,ab,kw. (627)

18 12 or 15 or 16 or 17 (21665)

19 3 and 18 (2775)

Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) (both via Wiley)

Search date: 08/08/2019

ID Search Hits

#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,ab63

#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 36712

#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 (CDSR): 0

Cochrane Protocols (CDSR): 0

Trials (CENTRAL): 36

Database of Abstracts of Reviews of Effects (DARE) (via Centre for Reviews and Disseminations (CRD))

Health Technology Assessment (HTA) database (via CRD)

Search date: 08/08/2019

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

DARE: 1

HTA Database: 6

NHSEED: 7

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

Search date: 08/08/2019

# 16	1,874	#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	5,532	#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*

# 10	8,611	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	9,323	#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 8	2,875	TS=HNPCC *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 7	1,394	TS=(familial near/3 (colon* or colorectal*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 6	4,493	TS=(((hereditary) near/3 (cancer or neoplasm*)) and (colon* or colorectal*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 5	3,198	TS=(((hereditary or familial) near/3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 4	4,967	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	4,474	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*

Search date: 28/08/2019

#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

10.1.2. Cost-effectiveness

Summary of bibliographic database searches

Database	Date of search	Number of records
MEDLINE (Ovid)	28/08/2019	1105
Embase (Ovid)	29/08/2019	2209
NHSEED and HTA	30/08/2019	49
Science Citation Index and Conference Proceedings Science (Web of Science)	30/08/2019	1267
CEA Registry	30/08/2019	30
EconPapers (RePEc)	30/08/2019	13
ScHARRHUD	30/08/2019	8

Total from database searches: 4681

Search strategies

Medline (via Ovid)

Search date: 28/08/2019

Actual database: Ovid MEDLINE(R) ALL <1946 to August 27, 2019>

Search Strategy:

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1 uterine neoplasms/ (40333)

2 exp endometrial neoplasms/ (20699)

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. (66492)

4 1 or 2 or 3 (92409)

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. (615131)

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 (14276)

20 exp Immunohistochemistry/ (588192)

21 (immunohistochemistry or (IHC adj3 test*)).ti,ab,kf. (178647)

22 Microsatellite Instability/ (2896)

23 ((microsatellite adj3 instabilit*) or (msi adj3 test*)).ti,ab,kf. (7390)

24 20 or 21 or 22 or 23 (692837)

25 exp Economics/ (582592)

26 exp "Costs and Cost Analysis"/ (227344)

27 Health Status/ (77617)

28 exp "Quality of Life"/ (180175)

29 exp Quality-Adjusted Life Years/ (11281)

30 (pharmacoeconomic* or pharmaco-economic* or economic* or cost* or price or prices or pricing).ti,ab,kf. (790706)

31 (expenditure$ not energy).ti,ab,kf. (28328)

32 (value adj1 money).ti,ab,kf. (33)

33 budget*.ti,ab,kf. (27980)

34 (health state* or health status).ti,ab,kf. (60417)

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. (235497)

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. (226798)

37 (quality adj2 life).ti,ab,kf. (262642)

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. (58078)

40 resource*.ti,ab,kf. (312093)

41 (well-being or wellbeing).ti,ab,kf. (82618)

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 (2166732)

43 19 and 42 (880)

44 4 and 24 and 42 (277)

45 43 or 44 (1105)

Embase (via Ovid)

Search date: 29/08/2019

Actual database: Embase Classic+Embase <1947 to 2019 Week 34>

Search Strategy:

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1 uterus cancer/ (20062)

2 exp endometrium cancer/ (48235)

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. (94282)

4 1 or 2 or 3 (116223)

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 (12545)

14 (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6).ti,ab,kw. (16510)

15 (colon* or colorectal* or lynch* or HNPCC or hereditary).ti,ab,kw. (855173)

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. (12290)

18 Amsterdam criteria.ti,ab,kw. (630)

19 13 or 16 or 17 or 18 (21837)

20 exp immunohistochemistry/ (591817)

21 (immunohistochemistry or (IHC adj3 test*)).ti,ab,kw. (285471)

22 microsatellite instability/ (12199)

23 ((microsatellite adj3 instabilit*) or (msi adj3 test*)).ti,ab,kw. (10785)

24 20 or 21 or 22 or 23 (644776)

25 exp health economics/ (829976)

26 exp health status/ (230300)

27 exp "quality of life"/ (475637)

28 exp quality adjusted life year/ (24485)

29 (pharmacoeconomic* or pharmaco-economic* or economic* or cost* or price or prices or pricing).ti,ab,kw. (1044110)

30 (expenditure* not energy).ti,ab,kw. (39410)

31 (value adj2 money).ti,ab,kw. (2333)

32 budget*.ti,ab,kw. (37547)

33 (health state* or health status).tw. (79129)

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. (342112)

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. (331686)

36 (quality adj2 life).tw. (411142)

37 (decision adj2 model).tw. (9764)

38 (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw. (83448)

39 resource*.ti,ab,kw. (401756)

40 (well-being or wellbeing).tw. (107606)

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 (3041975)

42 19 and 41 (1824)

43 4 and 24 and 41 (541)

44 42 or 43 (2209)

NHS Economic Evaluation Database (NHS EED) (via Centre for Reviews and Disseminations (CRD))

Health Technology Assessment (HTA) database (via CRD)

Search date: 30/08/2019

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 - Science (via Web of Science)

Search date: 30/08/2019

# 22	1,267	#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	4,936	#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	5,549	#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	8,655	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	9,375	#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 8	2,876	TS=HNPCC *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 7	1,399	TS=(familial near/3 (colon* or colorectal*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*

# 6	4,501	TS=(((hereditary) near/3 (cancer or neoplasm*)) and (colon* or colorectal*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 5	3,203	TS=(((hereditary or familial) near/3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 4	4,977	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	4,520	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*

CEA Registry

Search date: 30/08/2019

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 (RePEc)

Search date: 30/08/2019

"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

ScHARRHUD

Search date: 30/08/2019

(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

10.1. Appendix 2: Quality assessment tools

QUADAS-2

First author surname and year of publication:

Name of first reviewer: Chris Stinton *Name of second reviewer:*

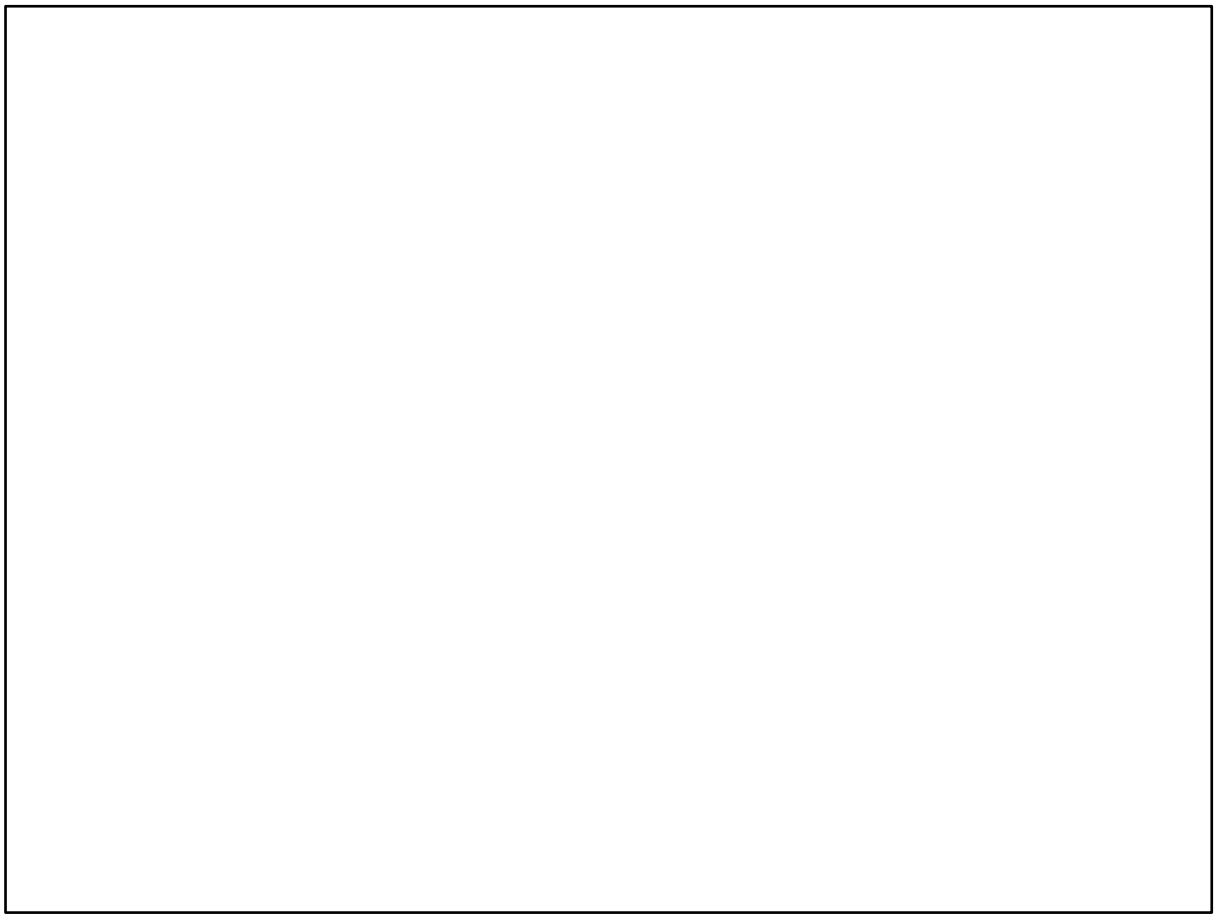
Date completed: *Date completed:*

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

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.

QAREL Tool

Item	Notes and comments to aid decision	Yes	No	Unclear	N/A
1. Was the test evaluated in a sample of subjects who were representative of those to whom the authors intended the results to be applied?					
2. Was the test performed by raters who were representative of those to whom the authors intended the results to be applied?					
3. Were raters blinded to the findings of other raters during the study?					
4. Were raters blinded to their own prior findings of the test under evaluation?					
5. Were raters blinded to the results of the reference standard for the target disorder (or variable) being evaluated?					
6. Were raters blinded to clinical information that was not intended to be provided as part of the testing procedure or study design?					

7. Were raters blinded to additional cues that were not part of the test?					
8. Was the order of examination varied?					
9. Was the time interval between repeated measurements compatible with the stability (or theoretical stability) of the variable being measured?*					X
10. Was the test applied correctly and interpreted appropriately?					
11. Were appropriate statistical measures of agreement used?**					
Total					

** Acceptable: Bland-Altman, ICC (for continuous data), kappa (for categorical/ordinal data – should be weighted, with an explanation of what weights were applied). Unacceptable: correlation coefficients on their own, significance testing of differences between coefficients.

10.2. Appendix 3: Data extraction form

Data extraction form for primary studies

Name of first reviewer: Chris Stinton *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

10.3. Appendix 4: Table of excluded studies with rationale

Reference	Reason for exclusion
Question 1	
1. Abbaszadegan, M. R., et al. (2009). "Microsatellite Instability in Young Women with Endometrioid type Endometrial Cancer." Iranian Journal of Public Health 38(3): 24-30.	No reference standard
2. Adams, R., et al. (2015). "Unusual immunohistochemistry staining patterns encountered in cancers screened for lynch syndrome." Laboratory Investigation 1): 144A.	Not enough information to quality appraise - abstract
3. Adan-Merino, L., et al. (2018). "Diagnosis and clinical behavior in patients with Lynch-like syndrome." Revista de Gastroenterologia de Mexico 83(4): 470-474.	Wrong population
4. Adar, T., et al. (2017). "Enhancing the identification of lynch syndrome through universal screening of both endometrial and colon cancers." Gastroenterology 152 (5 Supplement 1): S178.	Not enough information to quality appraise - abstract
5. Affolter, K., et al. (2013). "Base pair changes in assessing microsatellite instability and correlation to mismatch repair status by immunohistochemistry." Laboratory Investigation 1): 141A.	Not enough information to quality appraise - abstract
6. Aguirre, E., et al. (2016). "Screening for Lynch syndrome among endometrial cancer patients less than 60 years." Annals of Oncology. Conference: 41st European Society	Not enough information to quality appraise - abstract

for Medical Oncology Congress, ESMO 27(Supplement 6).	
7. Alenda, C., et al. (2012). "Prevalence of lynch syndrome among unselected endometrial cancer patients." Laboratory Investigation 1): 258A.	Not enough information to quality appraise - abstract
8. AlHilli, M. M., et al. (2017). "Predictors of Lynch syndrome and clinical outcomes among universally screened endometrial cancer patients." Gynecologic Oncology 145 (Supplement 1): 92.	Not enough information to quality appraise - abstract
9. Al-Nourhji, O., et al. (2017). "PD-L1 frequently expressed in endometrial carcinoma associated with mismatch-repair deficiency." Laboratory Investigation 97 (Supplement 1): 273A.	Not enough information to quality appraise - abstract
10. Andrade, C., et al. (2013). "Screening endometrial cancer for Lynch syndrome in a Brazilian public health care system cancer center." Gynecologic Oncology 130 (1): e100.	Not enough information to quality appraise - abstract
11. Anonymous (2006). "Uterine cancer could be harbinger of other cancers. An inherited mutation--Lynch syndrome--may lead to higher risk." Duke Medicine Health News 12(11): 9-10.	Editorial
12. Anonymous (2009). "Abstracts Presented for the 40th Annual Meeting of the Society of Gynecologic Oncologists." Gynecologic Oncology. Conference: 40th Annual Meeting of the Society of Gynecologic Oncologists. San Antonio, TX United States. Conference Publication: 112(2 SUPPL. 1).	Not enough information to quality appraise – abstract.
13. Anonymous (2010). "StatBite: Lynch syndrome increases the risk of various cancers." Journal of the National Cancer Institute 102(18): 1383.	Not enough information to

	quality appraise - abstract
14. Avila, M., et al. (2019). "Universal immunohistochemistry testing in endometrial cancer tumors maximizes Lynch Syndrome identification among affected individuals." Gynecologic Oncology 154 (1): e13.	Not enough information to quality appraise - abstract
15. Ayme, A., et al. (2017). "Systematic screening for lynch syndrome in a cohort of colorectal and endometrial cancer patients in switzerland: The SYSSYL study." Familial Cancer 16 (1 Supplement 1): S116.	Not enough information to quality appraise - abstract
16. Backes, F. J., et al. (2009). "Are prediction models for Lynch syndrome valid for probands with endometrial cancer?" Familial Cancer 8(4): 483-487.	Not test accuracy
17. Backman, A. S., et al. (2016). "A large proportion of lynch syndrom patients still undergo genetic screening first in connection with their diagnosis of cancer." Gastroenterology 1): S364.	Not enough information to quality appraise - abstract
18. Baker, T., et al. (2017). "Variable DNA mismatch repair-associated gene proRles in colorectal versus uterine cancers." Journal of Clinical Oncology. Conference 35(15 Supplement 1).	Not enough information to quality appraise - abstract
19. Ballester Victoria, R., et al. (2016). "Universal screening for Lynch Syndrome detection." Virchows Archiv 469 (Supplement 1): S202.	Not enough information to quality appraise - abstract
20. Banno, K., et al. (2003). "Identification of germline MSH2 gene mutations in endometrial cancer not fulfilling the new clinical criteria for hereditary nonpolyposis colorectal cancer." Cancer Genetics & Cytogenetics 146(1): 58-65.	Ineligible reference standard

21. Banno, K., et al. (2004). "Association of HNPCC and endometrial cancers." International Journal of Clinical Oncology 9(4): 262-269.	Review
22. Barinoff, J., et al. (2016). "HNPCC related endometrial carcinoma: Management in the clinical routine." International Journal of Gynecological Cancer 26 (Supplement 3): 125.	Not enough information to quality appraise - abstract
23. Bartley, A. N., et al. (2011). "Discordance between molecular and immunohistochemical analyses for lynch syndrome assessment." Laboratory Investigation 1): 144A.	Not enough information to quality appraise - abstract
24. Bartosch, C., et al. (2013). "Evaluation of MisMatch Repair (MMR) protein immunohistochemical expression in endometrial carcinomas." Virchows Archiv 463 (2): 311-312.	Not enough information to quality appraise - abstract
25. Bats, A., et al. (2013). "Clinico-pathological characteristics of endometrial cancer in lynch syndrome." International Journal of Gynecological Cancer 1): 73.	Not enough information to quality appraise - abstract
26. Batte, B. A., et al. (2014). "Consequences of universal MSI/IHC in screening ENDOMETRIAL cancer patients for Lynch syndrome." Gynecologic Oncology 134(2): 319-325.	Authors contacted due to unclear reporting. Authors could not confirm information around testing
27. Beneder, C., et al. (2008). "Is a screening according to the Lynch syndrome meaningful for young patients with endometrium carcinoma." Geburtshilfe und Frauenheilkunde 68(4): 431-431.	Foreign paper
28. Bennett, J., et al. (2017). "Mismatch repair protein expression in endometrioid carcinoma of the ovary:	Not enough information to

Incidence and clinicopathologic associations in 77 cases." Laboratory Investigation 97 (Supplement 1): 276A.	quality appraise - abstract
29. Benshushan, A., et al. (2017). "Genetics of endometrial cancer is greater than previously estimated in the our local population." International Journal of Gynecological Cancer 27 (Supplement 4): 100.	Not enough information to quality appraise - abstract
30. Billingsley, C. C., et al. (2015). "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." Gynecologic Oncology 1): 4-5.	Not enough information to quality appraise - abstract
31. Bohiltea, R. E., et al. (2016). "National genetic screening for endometrial cancer." Gineco.eu 12(1): 15-18.	No primary data. Not enough information to quality appraise
32. Boyd, J., et al. (1993). "MICROSATELLITE INSTABILITY IN SPORADIC ENDOMETRIAL CARCINOMAS AND THOSE ASSOCIATED WITH HNPCC." American Journal of Human Genetics 53(3): 22-22.	Not enough information to appraise - abstract
33. Brodsky, A. L., et al. (2019). "Genetic counselor involvement with abnormal immunohistochemistry results improves genetic testing in patients with endometrial cancer." Gynecologic Oncology 154 (Supplement 1): 282-283.	Not enough information to quality appraise - abstract
34. Bruegl, A., et al. (2012). "Lynch syndrome screening criteria: A new approach to identifying patients at risk via clinical history and pathology (CHiP) criteria." Gynecologic Oncology 1): S85-S86.	Not enough information to quality appraise - abstract
35. Bruegl, A., et al. (2013). "Screening by young age and family history of colon cancer misses the majority of	Not enough information to

endometrial cancer patients with lynch syndrome." Laboratory Investigation 1): 267A.	quality appraise - abstract
36. Bruegl, A., et al. (2013). "A population-based study to evaluate SGO criteria for the identification of Lynch syndrome among endometrial cancer patients." Gynecologic Oncology 130 (1): e28.	Not enough information to quality appraise - abstract
37. Bruegl, A., et al. (2017). "Does universal tissue testing provide universal answers? Clinical challenges associated with tumor screening for lynch syndrome associated endometrial cancer." Laboratory Investigation 97 (Supplement 1): 277A.	Not enough information to quality appraise - abstract
38. Bruegl, A., et al. (2013). "Utility of MLH1 methylation analysis in the clinical evaluation of lynch syndrome in women with endometrial cancer." Laboratory Investigation 1): 491A.	Not enough information to quality appraise - abstract
39. Bruegl, A. S., et al. (2014). "Evaluation of clinical criteria for the identification of Lynch syndrome among unselected patients with endometrial cancer." Cancer Prevention Research 7(7): 686-697.	No reference standard
40. Bruegl, A. S., et al. (2014). "Utility of MLH1 methylation analysis in the clinical evaluation of Lynch Syndrome in women with endometrial cancer." Current Pharmaceutical Design 20(11): 1655-1663.	No reference standard
41. Bruegl, A. S., et al. (2012). "An alternative approach to identify women at risk for colorectal cancer." Journal of Clinical Oncology. Conference 30(15 SUPPL. 1).	Not enough information to quality appraise - abstract
42. Bruegl, A., et al. (2012). "Common screening criteria for lynch syndrome: Who are we missing?" Gynecologic Oncology 125 (2): S195.	Not enough information to quality appraise - abstract

43. Bruegl, A. S., et al. (2013). "Poor performance of published clinical screening criteria for the population-based identification of endometrial cancer patients with Lynch Syndrome." Cancer Research. Conference: 104th Annual Meeting of the American Association for Cancer Research, AACR 73(8 SUPPL. 1).	Not enough information to quality appraise - abstract
44. Bruegl, A. S., et al. (2014). "Cost analysis comparing universal tumor testing to clinically based criteria in the evaluation of endometrial adenocarcinomas for Lynch syndrome." Gynecologic Oncology 1): 45.	No reference standard
45. Bruegl, A. S., et al. (2012). "Can clinical criteria reliably distinguish between sporadic and Lynch Syndrome-associated endometrial carcinomas with immunohistochemical loss of MLH1?" Cancer Prevention Research. Conference: 11th Annual AACR International Conference on Frontiers in Cancer Prevention Research. Anaheim, CA United States. Conference Publication: 5(11 SUPPL. 1).	Not enough information to quality appraise - abstract
46. Bruegl, A. S., et al. (2017). "Clinical challenges associated with universal screening for Lynch syndrome associated endometrial cancer." Gynecologic Oncology 145 (Supplement 1): 80-81.	Abstract only. Associated full paper included
47. Buchanan, D. D., et al. (2017). "Double somatic mutations as a cause of tumor mismatch repairdeficiency in population-based colorectal and endometrial cancer with Lynch-like syndrome." Cancer Research. Conference: American Association for Cancer Research Annual Meeting 77(13 Supplement 1).	Not enough information to quality appraise - abstract
48. Burks, R. T., et al. (1994). "Microsatellite instability in endometrial carcinoma." Oncogene 9(4): 1163-1166.	No reference standard. Not lynch testing

49. Busmanis, I. and I. Chew (2011). "MSI and mucinous differentiation in uterine endometrioid carcinoma." Virchows Archiv 1): S230.	Not enough information to quality appraise - abstract
50. Busmanis, I., et al. (2013). "MSI in an Asian series of primary uterine endometrioid carcinoma." Virchows Archiv 463 (2): 307-308.	Not enough information to quality appraise - abstract
51. Cadoo, K. A., et al. (2016). "Clinical characterization of DNA mismatch repair deficiency (MMR-D) in endometrial cancer (EC)." Journal of Clinical Oncology. Conference 34(Supplement 15).	Not lynch. No reference standard. Not enough information to quality appraise - abstract
52. Calkins, S. M., et al. (2012). "Lynch syndrome screening tests in uterine cancer patients >50 years depends on clinical and tumor morphology criteria: Evidence against universal testing." Laboratory Investigation 1): 262A.	Not enough information to quality appraise - abstract
53. Carvalho, S. D. and J. Pardal (2018). "Universal Lynch syndrome screening in endometrial cancer: Two years of experience." Virchows Archiv 473 (Supplement 1): s70.	Not enough information to quality appraise - abstract
54. Catasus, L., et al. (1998). "Microsatellite instability in endometrial carcinomas: clinicopathologic correlations in a series of 42 cases." Human Pathology 29(10): 1160-1164.	No reference standard
55. Cederquist, K., et al. (2004). "Mutation analysis of the MLH1, MSH2 and MSH6 genes in patients with double primary cancers of the colorectum and the endometrium: a	More than 10% wrong population

population-based study in northern Sweden." International Journal of Cancer 109(3): 370-376.	
56. Cesca, C., et al. (2001). "Absence of mismatch repair gene protein in subset of endometrioid carcinomas by immunohistochemistry." Laboratory Investigation 81(1): 134A-134A.	Not enough information to quality appraise - abstract
57. Cetinkaya, K. and E. Yuce (2017). "Lynch syndrome in patients treated for endometrial cancer." European Journal of Gynaecological Oncology 38(4): 607-613.	Unclear methods and wrong study design
58. Chao, X. P., et al. (2019). "A prospective cohort study about the screening tests of mismatch repair protein and clinical criteria for Lynch syndrome associated endometrial carcinoma. [Chinese]." Zhonghua yi xue za zhi 99(15): 1178-1183.	Foreign language
59. Chao, X. P., et al. (2019). "[A prospective cohort study about the screening tests of mismatch repair protein and clinical criteria for Lynch syndrome associated endometrial carcinoma]." Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal] 99(15): 1178-1183.	Foreign language
60. Chapel, D. B., et al. (2018). "Immunohistochemistry for mismatch repair protein deficiency in endometrioid endometrial carcinoma yields equivalent results when performed on endometrial biopsy/curettage or hysterectomy specimens." Gynecologic Oncology 149(3): 570-574.	Not lynch testing
61. Chavez, J. A., et al. (2018). "Tumor infiltrating lymphocytes and PD-L1 expression in 162 endometrial carcinomas with deficient mmr: Comparison between mlh1 methylation and lynch syndrome." Laboratory Investigation 98 (Supplement 1): 411.	Not enough information to quality appraise - abstract

62. Chen, L., et al. (2011). "Identifying Lynch syndrome in women with endometrial cancer." Gynecologic Oncology 1): S34.	Not enough information to quality appraise - abstract
63. Chen, L. M., et al. (2011). "Identifying Lynch syndrome in women with endometrial cancer." Familial Cancer 1): S39-S40.	Not enough information to quality appraise - abstract
64. Chern, J. Y., et al. (2017). "Utility of multi-gene panel testing with next generation sequencing in women with endometrial cancer." Journal of Clinical Oncology. Conference 35(15 Supplement 1).	Not enough information to quality appraise - abstract
65. Chew, I., et al. (2010). "Clinicopathologic features, DNA mismatch repair status and expression of ER and pr in endometrial adenocarcinomas in young women <=40 years old." Proceedings of Singapore Healthcare 2): S242.	Not enough information to quality appraise - abstract
66. Chiaravalli, A. M., et al. (2001). "Immunohistochemical pattern of hMSH2/hMLH1 in familial and sporadic colorectal, gastric, endometrial and ovarian carcinomas with instability in microsatellite sequences." Virchows Archiv 438(1): 39-48.	No reference standard. Wrong population
67. Chirasophon, S., et al. (2017). "High-risk epithelial ovarian cancer patients for hereditary ovarian cancer." Journal of Obstetrics & Gynaecology Research 43(5): 929-934.	No intervention
68. Cimetti, L., et al. (2014). "Gynaecological cancer as sentinel cancer in Lynch Syndrome: Clinico-pathological and molecular features." Virchows Archiv 1): S41.	Not enough information to quality appraise - abstract
69. Cohen, S. A. and D. E. McIlvried (2013). "Genetic counselor review of gynecologic pathology reports	Not enough information to

improves quality of screening program for Lynch syndrome." Familial Cancer 12 (4): 791-792.	quality appraise - abstract
70. Cohn, D. E., et al. (2000). "Atypical clustering of gynecologic malignancies: A family study including molecular analysis of candidate genes." Gynecologic Oncology 77(1): 18-25.	Case study
71. Conlon, N., et al. (2014). "Young patients with uterine serous carcinoma: A study of selected epidemiological and immunohistochemical features including expression of dna mmr proteins." Laboratory Investigation 1): 279A.	Not enough information to quality appraise - abstract
72. Cosgrove, C. M., et al. (2017). "A single institution pilot study for universal Lynch syndrome screening: A key step towards statewide screening and care." Gynecologic Oncology 145 (Supplement 1): 136.	Not enough information to quality appraise - abstract
73. Cossio, S. L., et al. (2010). "Clinical and histomolecular endometrial tumor characterization of patients at-risk for Lynch syndrome in South of Brazil." Familial Cancer 9(2): 131-139.	No reference standard
74. Costa Trachsel, I., et al. (2017). "Methylation study in the universal screening of Lynch Syndrome in endometrial and colorectal carcinoma." Virchows Archiv 471 (1 Supplement 1): S91.	Not enough information to quality appraise - abstract
75. Crim, A., et al. (2016). "Prevalence of lynch syndrome-associated tumors in minority patients with endometrial cancer." Gynecologic Oncology 143 (1): 212.	Not enough information to quality appraise - abstract
76. Crim, A. K., et al. (2017). "Feasibility of two-antibody vs four-antibody mismatch repair protein immunohistochemistry as initial screening for Lynch syndrome in patients with endometrial adenocarcinoma." Gynecologic Oncology 145 (Supplement 1): 44.	Not enough information to quality appraise - abstract

77. da Silva, F. C., et al. (2015). "Clinical and Molecular Characterization of Brazilian Patients Suspected to Have Lynch Syndrome." PLoS ONE [Electronic Resource] 10(10): 17.	Wrong population
78. Daniels, M. S., et al. (2013). "Outcomes of screening endometrial cancer patients for Lynch syndrome by patient-administered checklist." Gynecologic Oncology 131(3): 619-623.	No index tests
79. de la Chapelle, A. (2005). "The incidence of Lynch syndrome." Familial Cancer 4(3): 233-237.	Review
80. De Leon, E. D., et al. (2014). "Evaluation of lynch syndrome by immunohistochemistry and quantitative scoring by digital image analysis as a screening tool for the diagnosis of hereditary colon cancer and correlation with genetic analysis." Gastroenterology 1): S-346.	Not enough information to quality appraise - abstract
81. Dekker, N., et al. (2011). "Genetic counseling and testing for lynch syndrome in unselected patients with endometrial cancer." International Journal of Gynecological Cancer 3): S498.	Not enough information to quality appraise - abstract
82. Dempsey, K. M., et al. (2015). "Is it all Lynch syndrome?: An assessment of family history in individuals with mismatch repair-deficient tumors." Genetics in Medicine 17(6): 476-484.	Author contacted. Could not provide information to enable inclusion
83. Devlin, L. A., et al. (2008). "Germline MSH6 mutations are more prevalent in endometrial cancer patient cohorts than hereditary non polyposis colorectal cancer cohorts." Ulster Medical Journal 77(1): 25-30.	No intervention
84. Di Nanni, D. D., et al. (2018). "Association of tumour morphology with mismatch-repair protein status in endometrial cancers: A single unit experience." Virchows Archiv 473 (Supplement 1): s34.	Not enough information to quality appraise - abstract

85. Dillon, J. L., et al. (2016). "Universal screening for lynch syndrome in endometrial cancer: The dartmouth-hitchcock medical center experience." Journal of Molecular Diagnostics 18 (6): 1026.	Not enough information to quality appraise - abstract
86. DiMaio, M. A., et al. (2013). "Analysis of epcam expression in lynch syndrome associated neoplasia." Laboratory Investigation 1): 271A.	Not enough information to quality appraise - abstract
87. Doghri, R., et al. (2017). "Utility of immunohistochemistry in evaluation of microsatellite instability in endometrial carcinoma." Virchows Archiv 471 (1 Supplement 1): S83-S84.	Not enough information to quality appraise - abstract
88. Dong, F., et al. (2019). "Targeted next-generation sequencing in the detection of mismatch repair deficiency in endometrial cancers." Modern Pathology 32(2): 252-257.	Not lynch testing. No reference standard. No concordance information
89. Dottino, J. A. and K. H. Lu (2016). "Towards value-based universal Lynch syndrome identification in endometrial cancer patients." Gynecologic Oncology 143(3): 451-452.	Editorial
90. Dusek, M., et al. (2018). "Results of morphological screening for Lynch syndrome during the period 2013-2016." Ceskoslovenska Patologie 54(2): 86-92.	Foreign paper
91. Eiriksson, L., et al. (2015). "Performance characteristics of a brief Family History Questionnaire to screen for Lynch syndrome in women with newly diagnosed endometrial cancer." Gynecologic Oncology 136(2): 311-316.	Duplicate information and unclear reference standard. Included main paper by Ferguson 2014
92. Elvin, J. A., et al. (2016). "Evaluation of microsatellite instability (MSI) status in endometrial adenocarcinoma by	Not enough information to

comprehensive genomic profiling (CGP) identifies subset that may benefit from immunotherapy." Laboratory Investigation 1): 282A.	quality appraise - abstract
93. Erbarut Seven, I., et al. (2017). "Evaluation of Mismatch Repair (MMR) protein expression for Lynch syndrome screening in endometrial cancers in Turkish women: A preliminary study." Virchows Archiv 471 (1 Supplement 1): S93.	Not enough information to quality appraise - abstract
94. Erbarut Seven, I., et al. (2018). "Evaluation of mismatch repair (MMR) protein expression with cor-relation of germline mutation analysis for Lynch syndrome screening in endometrial cancers in Turkish women; Preliminary results." Virchows Archiv 473 (Supplement 1): s36.	Not enough information to quality appraise - abstract
95. Faquin, W. C., et al. (2000). "Sporadic microsatellite instability is specific to neoplastic and preneoplastic endometrial tissues." American Journal of Clinical Pathology 113(4): 576-582.	Wrong disease
96. Fein, L. A., et al. (2019). "Mismatch repair (MMR) screening among minority women with endometrial cancer." Gynecologic Oncology 154 (Supplement 1): 108.	Not enough information to quality appraise - abstract
97. Ferguson, S. E., et al. (2013). "Screening for Lynch syndrome in unselected women with endometrial cancer." Journal of Clinical Oncology. Conference 31(15 SUPPL. 1).	Not enough information to quality appraise - abstract
98. Fix, D., et al. (2017). "Simplified immunohistochemical and targeted sequencing approach reproduces classification of endometrial carcinoma into TCGA molecular subgroups." Laboratory Investigation 97 (Supplement 1): 285A.	Not enough information to quality appraise - abstract

99. Fountzila, E., et al. (2018). "Prognostic implications of mismatch repair deficiency in patients with early-stage colorectal and endometrial cancer." Annals of Oncology 29 (Supplement 8): viii654.	Not enough information to quality appraise - abstract
100. Frankel, W. L., et al. (2005). "Immunohistochemical staining for MLH1, MSH2 and MSH6 identifies germline mutations in mismatch repair genes in colorectal and endometrial cancers initially found to be microsatellite stable." Laboratory Investigation 85: 103A-103A.	Not enough information to quality appraise - abstract
101. Frimer, M., et al. (2016). "Germline mutations of the DNA repair pathways in uterine serous carcinoma." Gynecologic Oncology 141(1): 101-107.	No index tests or outcomes of interest
102. Frolova, A., et al. (2015). "Universal screening for Lynch syndrome in endometrial cancer results in increased acceptance of genetic counseling and testing." Gynecologic Oncology 1): 37.	Not enough information to quality appraise - abstract
103. Frolova, A. I., et al. (2015). "Impact of an immunohistochemistry-based universal screening protocol for Lynch syndrome in endometrial cancer on genetic counseling and testing." Gynecologic Oncology 137(1): 7-13.	Author contacted due to unclear information. Author could not provide information to warrant inclusion
104. Garg, K., et al. (2011). "Endometrial carcinomas with DNA mismatch repair abnormalities: Genotypic phenotypic correlations." Laboratory Investigation 1): 247A.	Not enough information to quality appraise - abstract
105. Garg, K., et al. (2009). "Selection of endometrial carcinomas for DNA mismatch repair protein immunohistochemistry using patient age and tumor morphology enhances detection of mismatch repair	No outcomes of interest

abnormalities." American Journal of Surgical Pathology 33(6): 925-933.	
106. Geurts-Giele, W. R., et al. (2014). "Somatic aberrations of mismatch repair genes as a cause of microsatellite-unstable cancers." Journal of Pathology 234(4): 548-559.	Wrong population – participants are known germline LS negative
107. Gleeson, J. and D. Gallagher (2016). "Diagnosing lynch syndrome." Irish Medical Journal 109(10): P487.	Not enough information to quality appraise - abstract
108. Gonzalez, L., et al. (2012). "Case-case study of factors associated to hMLH1, hMSH2, and hMSH6 protein expression among endometrial cancer patients of the University District Hospital of San Juan, Puerto Rico." International Journal of Gynecological Cancer 22(5): 826-829.	No reference standard
109. Halvarsson, B., et al. (2004). "Microsatellite instability analysis and/or immunostaining for the diagnosis of hereditary nonpolyposis colorectal cancer?" Virchows Archiv 444(2): 135-141.	Wrong population
110. Hampel, H. and A. De La Chapelle (2013). "How do we approach the goal of identifying everybody with Lynch Syndrome?" Familial Cancer 12(2): 313-317.	Review
111. Haraga, J., et al. (2017). "Significance of MSH2 promoter methylation in endometrial cancer with MSH2 deficiency." Annals of Oncology 28 (Supplement 5): v348.	Not enough information to quality appraise - abstract
112. Haraldsdottir, S., et al. (2014). "Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations." Gastroenterology 147(6): 1308-1316.e1301.	Not testing for lynch, no outcomes, wrong population

113. Haraldsdottir, S., et al. (2014). "Bi-allelic somatic tumor mutations explain the majority of colorectal and endometrial cancer cases with defective mismatch repair without an identifiable germline mutation or MLH1 epigenetic silencing." Journal of Molecular Diagnostics 16 (6): 771.	Subgroup analysis of lynch patients without germline mutation. Main paper Hampel 2005 is included
114. Hardisson, D., et al. (2003). "Tissue microarray immunohistochemical expression analysis of mismatch repair (hMLH1 and hMSH2 genes) in endometrial carcinoma and atypical endometrial hyperplasia: relationship with microsatellite instability." Modern Pathology 16(11): 1148-1158.	No reference standard. Wrong population
115. Hartnett, E., et al. (2015). "Evaluation of universal immunohistochemistry screening for diagnosing lynch syndrome in endometrial cancer patients at a tertiary care center." Gynecologic Oncology 139 (3): 599.	Not enough information to quality appraise - abstract
116. Joehlin-Price, A., et al. (2018). "Genomic profiling of undifferentiated endometrial carcinomas reveals frequent aberrations in SWI/ SNF chromatin remodeling genes, extensive microsatellite instability, and novel recurrent mutations in epigenetic regulatory genes." Laboratory Investigation 98 (Supplement 1): 428.	Not enough information to quality appraise - abstract
117. Jprn, U. (2012). "Evaluation of the usefulness and validity of the expanded criteria for primary screening of Lynch syndrome." Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000008192.	Trial registry. Author contacted but no relevant information provided to warrant inclusion
118. Kanaya, T., et al. (2005). "Association of mismatch repair deficiency with PTEN frameshift mutations in endometrial cancers and the precursors in a Japanese	More than 10% wrong population

population." American Journal of Clinical Pathology 124(1): 89-96.	
119. Kanbour-Shakir, A., et al. (2014). "Universal mismatch repair protein testing in endometrial cancer: A single institutional experience." Laboratory Investigation 1): 289A.	Not enough information to quality appraise - abstract
120. Kast, K., et al. (2016). "Prevalence of Lynch syndrome in unselected patients with endometrial or ovarian cancer." Archives of Gynecology & Obstetrics 294(6): 1299-1303.	No relevant information
121. Kawaguchi, M., et al. (2009). "Analysis of candidate target genes for mononucleotide repeat mutation in microsatellite instability-high (MSI-H) endometrial cancer." International Journal of Oncology 35(5): 977-982.	No reference standard
122. Kawaguchi, M., et al. (2009). "Analysis of a correlation between the BRAF V600E mutation and abnormal DNA mismatch repair in patients with sporadic endometrial cancer." International Journal of Oncology 34(6): 1541-1547.	No reference standard
123. Kim, M. K. (2016). "Rapid genetic screening experience among endometrial cancer about Lynch syndrome by surgeon." Annals of Oncology 27 (Supplement 9): ix100.	Not enough information to quality appraise - abstract
124. Kim, M. K. and E. J. Heo (2017). "Surgeon's role about genetic screening among endometrial cancer with regard to Lynch syndrome." Journal of Obstetrics and Gynaecology Research 43 (12): 1908.	Not enough information to quality appraise - abstract
125. Kim, M. K., et al. (2011). "Synchronous gynecologic malignancy and preliminary results of Lynch syndrome." Journal of Gynecologic Oncology 22(4): 233-238.	No reference standard
126. Kip, N. S., et al. (2015). "Evaluation to include endometrial carcinoma in universal lynch syndrome	Not enough information to

screening at geisinger health system." American Journal of Clinical Pathology 2): A234.	quality appraise - abstract
127. Kiyozumi, Y., et al. (2019). "Germline mismatch repair gene variants analyzed by universal sequencing in Japanese cancer patients." Cancer Medicine 06: 06.	Not lynch testing. No outcome information for the population of interest
128. Kobayashi, K., et al. (1996). "Mutational analysis of mismatch repair genes, hMLH1 and hMSH2, in sporadic endometrial carcinomas with microsatellite instability." Japanese Journal of Cancer Research 87(2): 141-145.	No reference standard. Not testing for lynch
129. Koptiuch, C., et al. (2019). "Incorporating paired germline/tumor analyses into a universal lynch syndrome screening program: Decreasing unexplained mismatch repair deficiency incidence." Familial Cancer 18 (Supplement 1): S68-S69.	Not enough information to quality appraise - abstract
130. Kost, E. R., et al. (2016). "Clinical and Pathologic Features of Hispanic Endometrial Cancer Patients With Loss of Mismatch Repair Expression." International Journal of Gynecological Cancer 26(6): 1129-1136.	No reference standard
131. Kowalski, L. D., et al. (1997). "Mutational analysis of MLH1 and MSH2 in 25 prospectively-acquired RER+ endometrial cancers." Genes, Chromosomes & Cancer 18(3): 219-227.	No reference standard. Not testing for lynch
132. Kurnit, K. C., et al. (2019). "Microsatellite instability in endometrial cancer: New purpose for an old test." Cancer 26: 26.	Commentary
133. Lautrup, C. K., et al. (2017). "Universal screening for lynch syndrome in patients with endometrial cancer." Familial Cancer 16 (1 Supplement 1): S126-S127.	Not enough information to quality appraise - abstract

134. Lee, H. I., et al. (2008). "Microsatellite instability in endometrial adenocarcinomas of young women." Korean Journal of Pathology 42(4): 202-207.	Foreign paper
135. Lee, H. J., et al. (2018). "Clinicopathologic characteristics of double primary endometrial and colorectal cancers in a single institution." Journal of Obstetrics & Gynaecology Research 44(5): 944-950.	Authors contacted due to unclear reporting. Authors could not confirm information around testing
136. Lee, J., et al. (2018). "Importance of genetic counseling referrals for high-risk women with endometrial cancer despite intact mismatch repair immunohistochemistry." Journal of Clinical Oncology. Conference 36(15 Supplement 1).	Not enough information to quality appraise - abstract
137. Lee, J., et al. (2018). "Missed opportunities: Genetic counseling and testing among an ethnically diverse cohort of women with endometrial cancer." Gynecologic Oncology 151(1): 153-158.	Authors contacted due to unclear reporting. Authors could not confirm information around testing
138. Lee, P. J., et al. (2018). "Clinical Targeted Next-Generation Sequencing Shows Increased Mutational Load in Endometrioid-type Endometrial Adenocarcinoma With Deficient DNA Mismatch Repair." International Journal of Gynecological Pathology 37(6): 581-589.	Ineligible reference standard. Wrong population
139. Leenen, C. H., et al. (2011). "Challenges and pitfalls in screening for lynch syndrome by molecular tumor tissue analysis." Gastroenterology 1): S352-S353.	Not enough information to quality appraise - abstract
140. Leenen, C. H., et al. (2010). "Routine MSI-analysis in endometrial cancer <= 70 years increases identification of	Not enough information to

patients at risk for lynch syndrome." Gastroenterology 1): S613.	quality appraise - abstract
141. Leenen, C. H. M., et al. (2011). "Routine MSI-analysis in endometrial cancer >=70 years increases identification of patients at risk for Lynch syndrome." Familial Cancer 1): S48.	Not enough information to quality appraise - abstract
142. Lim, M. C., et al. (2010). "Hereditary non-polyposis colorectal cancer/Lynch syndrome in Korean patients with endometrial cancer." Japanese Journal of Clinical Oncology 40(12): 1121-1127.	No index test
143. Lim, P. C., et al. (1996). "Absence of mutations in DNA mismatch repair genes in sporadic endometrial tumors with microsatellite instability." Clinical Cancer Research 2(11): 1907-1911.	No reference standard
144. Lin, D. and J. Hecht (2015). "Targeted screening with combined age and morphology based criteria enriches detection of lynch syndrome in endometrial cancer." Laboratory Investigation 1): 295A.	Not enough information to quality appraise - abstract
145. Livi, A., et al. (2017). "Routine mismatch repair immunohistochemistry analysis as a valuable method to improve lynch syndrome's diagnosis among women with endometrial cancer." Familial Cancer 16 (1 Supplement 1): S100-S101.	Not enough information to quality appraise - abstract
146. Long, B., et al. (2019). "Cancer susceptibility gene mutations in type I and II endometrial cancer." Gynecologic Oncology 152(1): 20-25.	No intervention. Wrong population
147. Long, Q., et al. (2014). "Role of endometrial cancer abnormal MMR protein in screening Lynch-syndrome families." International Journal of Clinical & Experimental Pathology 7(10): 7297-7303.	No reference standard

148. Lu, K., et al. (2003). "Prevalence of MLH1 or MSH2 germline mutations in young women with endometrial cancer." Cancer Epidemiology Biomarkers & Prevention 12(11): 1352S-1353S.	Not enough information to quality appraise - abstract
149. Lu, K. H., et al. (2005). "Defining criteria for Lynch Syndrome/HNPCC in women under 50 with endometrial cancer: Final results of a prospective, multi-center study." Journal of Clinical Oncology 23(16): 848S-848S.	Not enough information to quality appraise - abstract
150. Lucas, E., et al. (2018). "Mismatch Repair Protein Expression in Endometrioid Intraepithelial Neoplasia/Atypical Hyperplasia: Should We Screen for Lynch Syndrome in Precancerous Lesions?" International Journal of Gynecological Pathology 31: 31.	Wrong population
151. MacQueen, I., et al. (2016). "Targeted screening for lynch syndrome: Is the veteran population different?" Diseases of the Colon and Rectum 59 (5): e271.	Not enough information to quality appraise - abstract
152. Mafnas, C., et al. (2015). "Lynch syndrome screening: Discordance in MMR and germline test results." Laboratory Investigation 1): 177A.	Not enough information to quality appraise - abstract
153. Manchana, T. (2019). "Lynch syndrome screening in thai endometrial cancer patients." Gynecologic Oncology 154 (Supplement 1): 41.	Not enough information to quality appraise - abstract
154. Martin, B., et al. (2015). "Universal screening for gynecologic and colorectal cancer: A single institution experience." Laboratory Investigation 1): 297A.	Not enough information to quality appraise - abstract

155. Matthews, K. S., et al. (2008). "Lynch syndrome in women less than 50 years of age with endometrial cancer." Obstetrics & Gynecology 111(5): 1161-1166.	No reference standard
156. Mete, L. S., et al. (2019). "EARLY-ONSET ENDOMETRIAL CANCER PATIENTS ARE AT HIGH RISK FOR LYNCH SYNDROME REGARDLESS OF FAMILY HISTORY." Digestive and Liver Disease 51: E156-E157.	Not enough information to quality appraise - abstract
157. Miesfeldt, S., et al. (2018). "Association of patient navigation with care coordination in an Lynch syndrome screening program." Translational Behavioral Medicine 8(3): 450-455.	No relevant outcomes
158. Mills, A. M., et al. (2014). "Lynch syndrome screening should be considered for all patients with newly diagnosed endometrial cancer." American Journal of Surgical Pathology 38(11): 1501-1509.	Authors contacted due to unclear reporting. Authors could not confirm information around testing
159. Mills, A. M., et al. (2016). "Clinicopathologic Comparison of Lynch Syndrome-associated and "Lynch-like" Endometrial Carcinomas Identified on Universal Screening Using Mismatch Repair Protein Immunohistochemistry." American Journal of Surgical Pathology 40(2): 155-165.	Ineligible reference standard
160. Minamiguchi, K., et al. (2018). "Uterine endometrial carcinoma with DNA mismatch repair deficiency: magnetic resonance imaging findings and clinical features." Japanese Journal of Radiology 36(7): 429-436	Not lynch testing
161. Moir-Meyer, G. L., et al. (2015). "Rare germline copy number deletions of likely functional importance are	No index tests. Not testing for lynch

implicated in endometrial cancer predisposition." Human Genetics 134(3): 269-278.	
162. Moline, J., et al. (2013). "Implementation of tumor testing for lynch syndrome in endometrial cancers at a large academic medical center." Gynecologic Oncology 130(1): 121-126.	Authors contacted due to unclear reporting. Authors could not confirm information around testing
163. Murali, K., et al. (2019). "Prevalence and clinical implications of mismatch repair (MMR) deficiency in unselected non-serous epithelial ovarian cancer (EOC) patients." Familial Cancer 18 (Supplement 1): S59.	Not enough information to quality appraise - abstract
164. Musulen, E., et al. (2011). "Absence of V600E B-RAF mutation in MLH1-negative endometrial carcinoma." Laboratory Investigation 1): 261A.	Not enough information to quality appraise - abstract
165. Mutch, D. G., et al. (2004). "RAS/RAF mutation and defective DNA mismatch repair in endometrial cancers." American Journal of Obstetrics & Gynecology 190(4): 935-942.	No reference standard
166. Nakagawa, H., et al. (2003). "Identification and characterization of genomic rearrangements of MSH2 and MLH1 in Lynch syndrome (HNPCC) by novel techniques." Human Mutation 22(3): 258.	Wrong population
167. Nakagawa, H., et al. (2003). "Concordance of immunohistochemistry among HNPCC heterodimers MLH1 and PMS2, and MSH2 and MSH6 in microsatellite unstable colorectal and endometrial carcinomas." Laboratory Investigation **83**(1): 128A-129A.	Not enough information to quality appraise - abstract
168. Nguyen, T. D., et al. (2011). "When brachytherapy met genetic oncology. Can radiation oncologists improve the	Wrong study design

detection of hereditary non-polyposis colorectal cancer?" European Journal of Medical Genetics 54(1): 60-62.	
169. Nieminen, T. T., et al. (2009). "Molecular analysis of endometrial tumorigenesis: importance of complex hyperplasia regardless of atypia." Clinical Cancer Research 15(18): 5772-5783.	Not testing for lynch. More than 10% wrong population
170. Niessen, R. C., et al. (2009). "Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome." Genes Chromosomes and Cancer 48(8): 737-744.	Not testing for lynch
171. Niessen, R. C., et al. (2009). "PMS2 involvement in patients suspected of Lynch syndrome." Genes, Chromosomes & Cancer 48(4): 322-329	Not testing for lynch
172. Nofech-Mozes, S., et al. (2007). "Immunohistochenical analysis of mismatch repair (MMR) genes in premenopausal women with endometrial endometrioid adenocarcinoma (EEA)." Laboratory Investigation 87: 208A-208A.	Not enough information to quality appraise - abstract
173. Nugent, W., et al. (2011). "Retrospective review of endometrial cancer (EC) specimens in individuals younger than age 50 for microsatellite instability (MSI) testing and DNA mismatch repair enzyme (MMR) expression." Journal of Clinical Oncology. Conference: ASCO Annual Meeting 29(15 SUPPL. 1).	Not enough information to quality appraise - abstract
174. Offman, S. L., et al. (2012). "A clinicopathologic analysis of 419 consecutive endometrial carcinomas with emphasis on lower uterine segment tumors." Laboratory Investigation 1): 290A-291A.	Not enough information to quality appraise - abstract
175. Orbegoso Aguilar, C. M. A., et al. (2018). "MMR deficiency(d) in an unselected cohort of endometrial cancer (EC) patients, the Royal Marsden experience."	Not enough information to

Annals of Oncology. Conference: European Society for Medical Oncology Asia Congress, ESMO 29(Supplement 9).	quality appraise - abstract
176. Orbegoso Aguilar, C. M. A., et al. (2018). "Prevalence and clinical implications of mismatch repair (MMR) deficiency in unselected endometrial cancer (EC) patients." Annals of Oncology 29 (Supplement 8): viii342.	Not enough information to quality appraise - abstract
177. Orbegoso, C., et al. (2019). "Prevalence and clinical implications of Mismatch Repair (MMR) deficiency in unselected endometrial cancer (EC) patients." Familial Cancer 18 (Supplement 1): S61-S62.	Not enough information to quality appraise - abstract
178. Orfanelli, T., et al. (2019). "What happens in the real world? Assessment of two screening tools for Lynch syndrome in patients with endometrial cancer: Universal tumor testing versus clinical screening." Gynecologic Oncology 154 (Supplement 1): 220-221.	Not enough information to quality appraise - abstract
179. Ozdemir, T. R., et al. (2019). "Targeted Next-Generation Sequencing of MLH1, MSH2, and MSH6 Genes in Patients with Endometrial Carcinoma under 50 Years of Age." Balkan Medical Journal 36(1): 37-42.	No intervention
180. Padron, M. M. M., et al. (2019). "Use of a Targeted Lynch Syndrome Next Generation Sequencing Panel in Women at Risk for or With Endometrial Cancer." Obstetrics and Gynecology 133: 149S-150S.	Not enough information to quality appraise - abstract
181. Pai, R. K., et al. (2015). "Abrupt loss of MLH1 and PMS2 expression in endometrial carcinoma: molecular and morphologic analysis of 6 cases." American Journal of Surgical Pathology 39(7): 993-999.	Ineligible reference standard
182. Palmieri, G., et al. (2000). "Microsatellite analysis at 10q25-q26 in Sardinian patients with sporadic endometrial	No reference standard

carcinoma: identification of specification patterns of genetic alteration." Cancer 89(8): 1773-1782.	
183. Parc, Y. R., et al. (2000). "Microsatellite instability and hMLH1/hMSH2 expression in young endometrial carcinoma patients: associations with family history and histopathology." International Journal of Cancer 86(1): 60-66.	No reference standard
184. Peiro, G., et al. (2002). "Microsatellite instability, loss of heterozygosity, and loss of hMLH1 and hMSH2 protein expression in endometrial carcinoma." Human Pathology 33(3): 347-354.	No reference standard. Wrong population
185. Peiro-Marques, F. M., et al. (2017). "PD-L1 expression and overall survival in high grade endometrial carcinomas." Virchows Archiv 471 (1 Supplement 1): S92.	Not enough information to quality appraise - abstract
186. Peterson, L. M., et al. (2007). "Molecular genetic characterization of endometrial adenocarcinoma by microsatellite instability, KRAS, BRAF, and MLH1 promoter hypermethylation analysis, and DNA MMR protein immunohistochemistry." Journal of Molecular Diagnostics 9(5): 688-688.	Not enough information to quality appraise - abstract
187. Pyatt, R., et al. (2000). "The occurrence of microsatellite instability and DNA mismatch repair gene mutations in endometrial carcinomas." Faseb Journal 14(4): A789-A789.	Not enough information to quality appraise - abstract
188. Rabban, J. T., et al. (2014). "Association of tumor morphology with mismatch-repair protein status in older endometrial cancer patients: implications for universal versus selective screening strategies for Lynch syndrome." American Journal of Surgical Pathology 38(6): 793-800.	Authors contacted due to unclear reporting. Authors could not confirm information around testing

189. Ramsoekh, D., et al. (2008). "A high incidence of MSH6 mutations in Amsterdam criteria II-negative families tested in a diagnostic setting." Gut 57(11): 1539-1544.	Wrong population
190. Ranola, J. M. O., et al. (2019). "Modified capture-recapture estimates of the number of families with Lynch syndrome in Central Ohio." Familial Cancer 18(1): 67-73.	Wrong population
191. Resnick, K. E., et al. (2010). "Mismatch repair status and outcomes after adjuvant therapy in patients with surgically staged endometrial cancer." Gynecologic Oncology 117(2): 234-238.	No reference standard
192. Ring, K., et al. (2016). "The utility of a next-generation sequencing (NGS) panel to identify germline mutations associated with endometrial cancer." Laboratory Investigation 1): 306A.	Not enough information to quality appraise - abstract
193. Ring, K. L., et al. (2015). "Multi-gene panel testing in an unselected endometrial cancer cohort." Journal of Clinical Oncology. Conference 33(15 SUPPL. 1).	Not enough information to quality appraise - abstract
194. Ring, K. L., et al. (2014). "A prospective evaluation of universal tumor testing strategies for Lynch syndrome in endometrial cancer." Journal of Clinical Oncology. Conference 32(15 SUPPL. 1).	Not enough information to quality appraise - abstract
195. Ring, K. L., et al. (2014). "A new Lynch syndrome: What is the role for polymerase D1 mutations in hereditary endometrial cancer?" Gynecologic Oncology 1): 77.	Not enough information to quality appraise - abstract
196. Ring, K. L., et al. (2013). "Women 50 years or younger with endometrial cancer: the argument for universal mismatch repair screening and potential for	No reference standard

targeted therapeutics." International Journal of Gynecological Cancer 23(5): 853-860.	
197. Ritterhouse, L., et al. (2016). "Molecular signatures of hypermutated endometrial carcinomas." Journal of Molecular Diagnostics 18 (6): 1007.	Not lynch. No reference standard. Not enough information to quality appraise - abstract
198. Romero, A., et al. (2013). "Frequency and variability of genomic rearrangements on MSH2 in Spanish Lynch Syndrome families." PLoS ONE [Electronic Resource] 8(9): e72195.	Not enough information to quality appraise - abstract
199. Romero, I., et al. (2016). "Prospective comparison of different methods of identifying Lynch Syndrome (LS) associated endometrial cancer (EC) and prognostic factor (PF) impact." Journal of Clinical Oncology. Conference 34(Supplement 15).	Not enough information to quality appraise - abstract
200. Romero, I., et al. (2013). "Prospective correlation between clinical and pathologic criteria identification of Lynch syndrome (LS) in endometrial carcinoma (EC) patients and relapse." Journal of Clinical Oncology. Conference 31(15 SUPPL. 1).	Not enough information to quality appraise - abstract
201. Roth, R. M., et al. (2016). "Discordant Mismatch Repair Protein Immunoreactivity in Lynch Syndrome-Associated Neoplasms: A Recommendation for Screening Synchronous/Metachronous Neoplasms." American Journal of Clinical Pathology 146(1): 50-56.	
202. Rumilla, K. M., et al. (2009). "Clinical testing for defective DNA mismatch repair in 335 gynecologic neoplasms." Laboratory Investigation 1): 235A.	Not enough information to

	quality appraise - abstract
203. Ruszkiewicz, A., et al. (2002). "Correlation of mismatch repair genes immunohistochemistry and microsatellite instability status in HNPCC-associated tumours." Pathology 34(6): 541-547.	Wrong disease
204. Ryan, N., et al. (2019). "The case for screening all endometrial cancer patients for Lynch syndrome." BJOG: An International Journal of Obstetrics and Gynaecology 126 (6): e130.	Not enough information to quality appraise - abstract
205. Salyer, C., et al. (2019). "Comparison of effectiveness of two strategies to identify Lynch Syndrome in women with endometrial cancer." Gynecologic Oncology 154 (1): e12-e13.	Not enough information to quality appraise - abstract
206. Salyer, C. V., et al. (2019). "Lynch syndrome in women with endometrial cancer: Comparison of universal and age-based strategies in a California healthcare system." Gynecologic Oncology 154 (Supplement 1): 206-207.	Wrong population, wrong test, not lynch testing, not enough information to quality appraise - abstract
207. Sanchez Garcia, A., et al. (2016). "Evaluation of a 25-gene panel in patients with suspected lynch syndrome: Famosa study." United European Gastroenterology Journal 4 (5 Supplement 1): A656.	Not enough information to quality appraise - abstract
208. Sanchez Mete, L., et al. (2018). "Early-onset endometrial cancer patients with or without family history are at high risk for lynch syndrome." United European Gastroenterology Journal 6 (8 Supplement): A680-A681.	Not enough information to quality appraise - abstract
209. Saraiya, D. S., et al. (2014). "Women with dual gynecologic primary cancers can have mutations in Lynch	Not enough information to

syndrome genes or BRCA1/BRCA2, reflecting the overlap in clinical histories between these syndromes." Gynecologic Oncology 1): 47.	quality appraise - abstract
210. Sareen, P., et al. (2012). "Lynch syndrome: Should endometrial cancer patients in the 50-60 age group be screened?" Gynecologic Oncology 125 (2): S193.	Not enough information to quality appraise - abstract
211. Sari, A., et al. (2019). "Interobserver Agreement for Mismatch Repair Protein Immunohistochemistry in Endometrial and Nonserous, Nonmucinous Ovarian Carcinomas." American Journal of Surgical Pathology 43(5): 591-600.	No reference standard and only one index test
212. Shannon, C., et al. (2003). "Incidence of microsatellite instability in synchronous tumors of the ovary and endometrium." Clinical Cancer Research 9(4): 1387-1392.	No reference standard. No outcome data.
213. Schiavone, M. B., et al. (2016). "Mismatch repair abnormalities are associated with aggressive tumor pathology in young women with endometrial cancer." Gynecologic Oncology 1): 125.	Wrong population, wrong test, not lynch testing, not enough information to quality appraise - abstract
214. Schofield, L., et al. (2009). "Is routine screening for Lynch Syndrome in endometrial cancer using microsatellite instability and immunohistochemical tests worthwhile?" Twin Research and Human Genetics 12 (2): 231.	Not enough information to quality appraise - abstract
215. Semba, S., et al. (2000). "Analysis of the candidate target genes for mutation in microsatellite instability-positive cancers of the colorectum, stomach, and	Wrong population. No test accuracy data

endometrium." International Journal of Oncology 16(4): 731-737.	
216. Seven, I. E., et al. (2018). "Evaluation of mismatch repair (MMR) protein expression with correlation of germline mutation analysis for Lynch syndrome screening in endometrial cancers in Turkish women; preliminary results." Virchows Archiv 473: S36-S36.	Not enough information to quality appraise - abstract
217. Shamsani, J., et al. (2017). "Identification of genetic variants associated with risk of endometrial cancer." Twin Research and Human Genetics 20 (5): 447.	Not enough information to quality appraise - abstract
218. Shannon, C., et al. (2003). "Incidence of microsatellite instability in synchronous tumors of the ovary and endometrium." Clinical Cancer Research 9(4): 1387-1392.	No reference standard
219. Shirts, B., et al. (2016). "Using somatic mutations to classify pathogenic lynch syndrome variants." Journal of Molecular Diagnostics 18 (6): 946-947.	Wrong population, wrong test, not lynch testing, not enough information to quality appraise - abstract
220. Sobczuk, A., et al. (2008). "Microsatellite instability in women with endometrial cancer from the Lodz region of Poland." Menopause Review-Przeglad Menopauzalny 7(1): 42-45.	Foreign paper
221. Soliman, P. T., et al. (2005). "Women with synchronous primary cancers of the endometrium and ovary: do they have Lynch syndrome?" Journal of Clinical Oncology 23(36): 9344-9350.	No reference standard

222. Son, J., et al. (2019). "Molecular and pathologic features of endometrial cancer in young patients." Gynecologic Oncology 154 (1): e22.	Not enough information to quality appraise - abstract
223. Song, T., et al. (2016). "Women with double primary cancers of the colorectum and endometrium: do they have Lynch syndrome?" European Journal of Obstetrics, Gynecology, & Reproductive Biology 199: 208-212.	No reference standard and no concordance information for EC
224. Staebler, A., et al. (2000). "Altered expression of hMLH1 and hMSH2 protein in endometrial carcinomas with microsatellite instability." Human Pathology 31(3): 354-358.	No reference standard. Not testing for lynch
225. Stasenko, M., et al. (2019). "Clinical outcomes of patients with POLE-mutated endometrioid endometrial cancer." Gynecologic Oncology 154 (Supplement 1): 33.	Not enough information to quality appraise - abstract
226. Stelloo, E., et al. (2016). "Comprehensive analysis of microsatellite instability and mismatch repair protein expression in nearly 700 endometrial cancers." Virchows Archiv 469 (Supplement 1): S19.	Not enough information to quality appraise - abstract
227. Stewart, A. P. (2013). "Genetic testing strategies in newly diagnosed endometrial cancer patients aimed at reducing morbidity or mortality from lynch syndrome in the index case or her relatives." PLoS currents 5: 16.	Review
228. Straubhar, A., et al. (2016). "Cost analysis of universal screening for lynch syndrome in patients with endometrial cancer." Gynecologic Oncology 143 (1): 214.	Not enough information to quality appraise - abstract
229. Strickland, S. V., et al. (2017). "Evaluation of a universal mismatch repair protein immunohistochemistry	Not enough information to

screening strategy in women with endometrial carcinoma 60 years of age or younger." Laboratory Investigation 97 (Supplement 1): 311A.	quality appraise - abstract
230. Suerink, M., et al. (2018). "Findings Linking Mismatch Repair Mutation With Age at Endometrial and Ovarian Cancer Onset in Lynch Syndrome." JAMA Oncology 4(6): 889-890.	Response to editor, not a study
231. Sugawara, T., et al. (2015). "Efficient screening strategy for Lynch syndrome in Japanese endometrial cancer." Tohoku Journal of Experimental Medicine 235(2): 117-125.	Ineligible reference standard
232. Sugihara, T. (2016). "Analysis of correlation between Mmr (Mismatch Repair Genes) expression and clinicopathological factors in endometrial cancer. [Japanese]." Teikyo Medical Journal 39(2): 61-68.	Foreign paper
233. Swisher, E. M., et al. (1998). "Analysis of MSH3 in endometrial cancers with defective DNA mismatch repair." Journal of the Society for Gynecologic Investigation 5(4): 210-216.	No lynch testing. No test accuracy data
234. Takeda, T., et al. (2016). "Methylation Analysis of DNA Mismatch Repair Genes Using DNA Derived from the Peripheral Blood of Patients with Endometrial Cancer: Epimutation in Endometrial Carcinogenesis." Genes 7(10): 14.	No reference standard and no concordance information
235. Tanaka, T., et al. (2018). "The usefulness of evaluation of dna mismatch repair protein expression as a screening for lynch syndrome in endometrial cancer." International Journal of Gynecological Cancer 28 (Supplement 2): 1193.	Not enough information to quality appraise - abstract
236. Tangjitgamol, S., et al. (2017). "Prevalence and prognostic role of mismatch repair gene defect in	No reference standard

endometrial cancer patients." Tumour Biology 39(9): 1010428317725834.	
237. Tunnage, I. U., et al. (2019). "Clinical outcomes of patients with pole mutated endometrioid endometrial cancer." Gynecologic Oncology 153 (3): e9.	Not enough information to quality appraise - abstract
238. Vargas, R., et al. (2015). "Lynch syndrome screening in endometrial cancer patients with immunohistochemistry: A single center experience." Gynecologic Oncology 136(2): 407-407.	Not enough information to quality appraise - abstract
239. Vasen, H. F., et al. (2004). "Identification of HNPCC by molecular analysis of colorectal and endometrial tumors." Disease Markers 20(4-5): 207-213.	Review
240. Vassileva, V., et al. (2004). "Apoptotic and growth regulatory genes as mutational targets in mismatch repair deficient endometrioid adenocarcinomas of young patients." Oncology Reports 11(4): 931-937.	Ineligible reference standard
241. Vierkoetter, K. R., et al. (2014). "Lynch Syndrome in patients with clear cell and endometrioid cancers of the ovary." Gynecologic Oncology 135(1): 81-84.	Wrong disease
242. Walsh, C. S., et al. (2010). "Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening." Gynecologic Oncology 116(3): 516-521.	Authors contacted due to unclear reporting. Authors could not confirm information around testing
243. Wang, H., et al. (2018). "Screening for inherited cancer syndromes in Chinese patients with endometrial cancer." Annals of Oncology 29 (Supplement 8): viii345.	Not enough information to quality appraise - abstract

244. Wang, M., et al. (2016). "Genetic Testing for Lynch Syndrome in the Province of Ontario." Cancer 122(11): 1672-1679.	Not enough information to quality appraise. Population unclear
245. Watkins, J., et al. (2015). "Universal lynch screening in endometrial cancers: An examination of immunohistochemical subgroups and associated clinical and histologic features." Laboratory Investigation 1): 314A.	Not enough information to quality appraise - abstract
246. Watkins, J. C., et al. (2016). "Unusual Mismatch Repair Immunohistochemical Patterns in Endometrial Carcinoma." American Journal of Surgical Pathology 40(7): 909-916.	Same sample as Watkins 2017. Author contacted due to lack of information.
247. Watkins, J. C., et al. (2017). "Universal Screening for Mismatch-Repair Deficiency in Endometrial Cancers to Identify Patients With Lynch Syndrome and Lynch-like Syndrome." International Journal of Gynecological Pathology 36(2): 115-127.	Same sample as Watkins 2017. Author contacted due to lack of information
248. Westin, S. N., et al. (2008). "Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome." Journal of Clinical Oncology 26(36): 5965-5971.	Not testing for lynch
249. Wolf, B., et al. (2005). "Spectrum of germ-line MLH1 and MSH2 mutations in Austrian patients with hereditary nonpolyposis colorectal cancer." Wiener Klinische Wochenschrift 117(7-8): 269-277.	Wrong population
250. Wong, A., et al. (2019). "Universal endometrial carcinoma lynch syndrome screening in Singapore." Familial Cancer 18 (Supplement 1): S70-S71.	Not enough information to quality appraise - abstract

251. Wu, X., et al. (2017). "Implementation of a universal endometrial cancer lynch syndrome screening program: Lessons learned." Laboratory Investigation 97 (Supplement 1): 316A-317A.	Not enough information to quality appraise - abstract
252. Zannoni, G. F., et al. (2019). "Clear cell carcinoma of the endometrium: an IMMUNOHISTOCHEMICAL and molecular analysis of 45 cases." Human Pathology 30: 30.	Wrong population. Ineligible reference standard
253. Zauber, P., et al. (2015). "Strong correlation between molecular changes in endometrial carcinomas and concomitant hyperplasia." International Journal of Gynecological Cancer 25(5): 863-868.	Ineligible reference standard. Wrong population. No relevant outcome data
Question two	
1. Helder-Woolderink, J., de Bock, G., Hollema, H., van Oven, M. and Mourits, M., 2017. Pain evaluation during gynaecological surveillance in women with Lynch syndrome. *Familial cancer*, *16*(2), pp.205-210.	Participant, comparator and study design not relevant
2. Tzortzatos, G., Andersson, E., Soller, M., Askmalm, M.S., Zagoras, T., Georgii-Hemming, P., Lindblom, A., Tham, E. and Mints, M., 2015. The gynecological surveillance of women with Lynch syndrome in Sweden. *Gynecologic oncology*, *138*(3), pp.717-722.	Particpants,comparator and study design not relevant
3. Moldovan, R., Keating, S. and Clancy, T., 2015. The impact of risk-reducing gynaecological surgery in premenopausal women at high risk of endometrial and ovarian cancer due to Lynch syndrome. *Familial cancer*, *14*(1), pp.51-60.	Comparator and study design not relevant
4. Frolova, A.I., Babb, S.A., Zantow, E., Hagemann, A.R., Powell, M.A., Thaker, P.H., Gao, F. and Mutch, D.G., 2015. Impact of an immunohistochemistry-based universal screening protocol for Lynch syndrome in endometrial cancer on genetic counseling and testing. *Gynecologic oncology*, *137*(1), pp.7-13.	Comparator, outcomes and study design not relevant
5. Nebgen, D.R., Lu, K.H., Rimes, S., Keeler, E., Broaddus, R., Munsell, M.F. and Lynch, P.M., 2014. Combined colonoscopy and	Intervention, comparator and

endometrial biopsy cancer screening results in women with Lynch syndrome. *Gynecologic oncology*, *135*(1), pp.85-89.	study design not relevant
6. Ketabi, Z., Gerdes, A.M., Mosgaard, B., Ladelund, S. and Bernstein, I., 2014. The results of gynecologic surveillance in families with hereditary nonpolyposis colorectal cancer. *Gynecologic oncology*, *133*(3), pp.526-530.	Participant, comparator and study design not relevant
7. Helder-Woolderink, J.M., De Bock, G.H., Sijmons, R.H., Hollema, H. and Mourits, M.J.E., 2013. The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome. *Gynecologic oncology*, *131*(2), pp.304-308.	Comparator and study design not relevant
8. Huang, M., Sun, C., Boyd-Rogers, S., Burzawa, J., Milbourne, A., Keeler, E., Yzquierdo, R., Lynch, P., Peterson, S.K. and Lu, K., 2011. Prospective study of combined colon and endometrial cancer screening in women with lynch syndrome: a patient-centered approach. *Journal of oncology practice*, *7*(1), pp.43-47	Comparator, outcomes and study design not relevant
9. Jarvinen, H.J., Renkonen-Sinisalo, L., Aktán-Collán, K., Peltomaki, P., Aaltonen, L.A. and Mecklin, J.P., 2009. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. *J Clin Oncol*, *27*(28), pp.4793-4797.	Participant and study design not relevant
10. Wang, Y., Xue, F., Broaddus, R.R., Tao, X., Xie, S.S. and Zhu, Y., 2009. Clinicopathological features in endometrial carcinoma associated with Lynch syndrome in China. *International Journal of Gynecologic Cancer*, *19*(4), pp.651-656.	Intervention, comparator and study design not relevant
11. Renkonen-Sinisalo, L., Bützow, R., Leminen, A., Lehtovirta, P., Mecklin, J.P. and Järvinen, H.J., 2007. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *International journal of cancer*, *120*(4), pp.821-824.	Participant and study design not relevant
12. de Jong, A.E., Hendriks, Y.M., Kleibeuker, J.H., de Boer, S.Y., Cats, A., Griffioen, G., Nagengast, F.M., Nelis, F.G., Rookus, M.A. and Vasen, H.F., 2006. Decrease in mortality in Lynch syndrome families because of surveillance. *Gastroenterology*, *130*(3), pp.665-671	Comparator and study design not relevant

13. Collins, V., Meiser, B., Gaff, C., St. John, D.J.B. and Halliday, J., 2005. Screening and preventive behaviors one year after predictive genetic testing for hereditary nonpolyposis colorectal carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *104*(2), pp.273-281.	Participant, comparator and study design not relevant
14. Rijcken, F.E., Mourits, M.J., Kleibeuker, J.H., Hollema, H. and van der Zee, A.G., 2003. Gynecologic screening in hereditary nonpolyposis colorectal cancer. *Gynecologic oncology*, *91*(1), pp.74-80.	Participant, comparator and study design not relevant
15. Dove-Edwin, I., Boks, D., Goff, S., Kenter, G.G., Carpenter, R., Vasen, H.F. and Thomas, H.J., 2002. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer*, *94*(6), pp.1708-1712.	Participant, comparator and study design not relevant
16. Adar, T., Rodgers, L.H., Shannon, K.M., Yoshida, M., Ma, T., Mattia, A., Lauwers, G.Y., Iafrate, A.J., Hartford, N.M., Oliva, E. and Chung, D.C., 2018. Universal screening of both endometrial and colon cancers increases the detection of Lynch syndrome. *Cancer*, *124*(15), pp.3145-3153.	Comparator, outcome and study design not relevant
17. Salyer, C., Lentz, S., Dontsi, M., Armstrong, M.A., Butt, A., Hoodfar, E., Alvarado, M., Landers, E., Avila, M., Nguyen, N. and Powell, C.B., 2019. Comparison of effectiveness of two strategies to identify Lynch Syndrome in women with endometrial cancer. *Gynecologic Oncology*, *154*(1), pp.e12-e13.	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. Familial Cancer (2019) 18:S1–S88	Participant, comparator and study design not relevant
19. Crawford, R., Newcombe, B., Bolton, H., Ngu, S.F., Freeman, S., Addley, H., Jimenez-Linan, M., Armstrong, R. and Tischkowitz, M., 2017. The Ten Year Experience of A Regional Specialist Gynaecology Cancer Genetics Clinic with Lynch Syndrome. In *The European Society of Gynaecological Oncology International Meeting, ESGO 2017*. The European Society of Gynaecological Oncology..	Not enough information to quality appraise - abstract

20. Adar, T., Rodgers, L.H., Shannon, K.M., Yoshida, M., Ma, T., Mattia, A., Lauwers, G.Y., Iafrate, A.J. and Chung, D.C., 2017. A tailored approach to BRAF and MLH1 methylation testing in a universal screening program for Lynch syndrome. *Modern Pathology*, *30*(3), pp.440-447.	Participant not relevant
21. Hartnett, E., Stuckey, A., Danilack, V. and McCourt, C., 2015. Evaluation of universal immunohistochemistry screening for diagnosing Lynch syndrome in endometrial cancer patients at a tertiary care center. *Gynecologic Oncology*, *139*(3), p.599.	Comparator, outcomes and study design not relevant
22. Mutch, D.G., Powell, M.A., Schmidt, A., Broaddus, R., Ramirez, N., Tritchler, D., Ali, S., Lankes, H., O'Malley, D.M. and Goodfellow, P.J., 2015. Clinicopathologic features associated with defective DNA mismatch repair (MMR): A GOG 0210 cohort study of 1041 endometrioid endometrial cancer cases. *Gynecologic Oncology*, *137*, pp.20-21.	Intervention, comparator, study design not relevant
23. Fu, L., Sheng, J.Q., Li, X.O., Jin, P., Mu, H., Han, M., Huang, J.S., Sun, Z.Q., Li, A.Q., Wu, Z.T. and Li, S.R., 2013. Mismatch repair gene mutation analysis and colonoscopy surveillance in Chinese Lynch syndrome families. *Cellular oncology*, *36*(3), pp.225-231.	Participant and study design not relevant
24. Abstracts of the 13th International Meeting on Psychosocial Aspects of Hereditary Cancer (IMPAHC). March 7-8, 2013. Sydney, Australia. Fam Cancer. 2013 Feb;12 Suppl 1:S12-22. doi: 10.1007/s10689-013-9605-3.	Conference preceedings. no relevant data
25. Lu, K., L. Chen, H. Lynch, M. Munsell, T. Cornelison, S. Boyd-Rogers, M. Rubin, M. Daniels, D. Loose, and R. Broaddus. "A prospective, multicenter randomized study of oral contraceptive versus Depo-Provera for the prevention of endometrial cancer in women with Lynch syndrome." In *GYNECOLOGIC ONCOLOGY*, vol. 116, no. 3, pp. S4-S5. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA: ACADEMIC PRESS INC ELSEVIER SCIENCE, 2010.	Participant, intervention, outcome and study design not relevant
26. Wang Y, Xue F, Broaddus RR, Tao X, Xie S, Zhu Y. Clinicopathological features of endometrial carcinoma associated with lynch syndrome in China. *Zhongguo Fei Ai Za Zhi* 2009;**12**(6):700-5.	Intervention, comparator and study design not relevant

27. Järvinen, H.J., 2006. Endoscopic surveillance in hereditary nonpolyposis colorectal cancer. *Techniques in Gastrointestinal Endoscopy*, *8*(3), pp.110-113.	Participant and study design not relevant
28. Macrae F. *A randomised double blind dose non-inferiority trial of a daily dose of 600mg versus 300mg versus 100mg 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)*. Australian New Zealand Clinical Trials Registry; 2017. URL: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617000804381 (Accessed 2 January 2020).	Participants, and comparator not relevant
29. Arber N. *A Randomised Double Blind Dose Non-inferiority Trial of a Daily Dose of 600mg Versus 300mg Versus 100mg of Enteric Coated Aspirin as a Cancer Preventive in Carriers of a Germline Pathological Mismatch Repair Gene Defect, Lynch Syndrome*. ClinicalTrials.gov; 2015. URL: https://clinicaltrials.gov/ct2/show/nct02497820 (Accessed 2 January 2020)	Participant s and comparator not relevant

10.4. Appendix 5: Data extraction for economic evaluation studies

Date: 11 December 2019

Name of first reviewer: Peter Auguste

Study details	
Study title	Lynch Syndrome screening strategies among newly diagnosed endometrial cancer patients
First author	Kimberly Resnick
Co-authors	Michael Straughn, Floor Backes, Heather Hampel, Kellie Matthews and David Cohn
Source of publication Journal yy;vol(issue):pp	Obstetrics and Gynecology 2009; 114 (3): 530-536
Language	English Language
Publication type	Research article
Inclusion criteria/study eligibility/PICOS	
Population	Hypothetical cohort of 40,000 patients with newly diagnosed endometrial cancer
Intervention(s)	Sequence all, sequence women < 60 years of age, immunohistochemistry and sequencing
Comparator(s)	Amsterdam II criteria and sequencing
Outcome(s)	Cost per additional case of Lynch syndrome detected
Study design	Model-based cost-effectiveness analysis
Methods	
Target population and subgroups	Hypothetical cohort of 40,000 patients with newly diagnosed endometrial cancer

Setting and location	USA
Study perspective	Third-party payer perspective
Comparators	Amsterdam II criteria and sequencing
Time horizon	Not stated
Discount rate	Not reported
Outcomes	Cost per additional case of Lynch syndrome detected
Measurement of effectiveness	Number of Lynch syndrome cases identified
Measurement and valuation of preference based outcomes	Not applicable as results were not reported in terms of QALYs
Resource use and costs	Cost estimates included genetic consultation, full genetic sequencing, immunohistochemistry, MLH1 sequencing, MSH2 sequencing and MSH6 sequencing.
Currency, price date and conversion	US$, with costs reported in 2008 prices
Model type	Decision tree structure
Assumptions	Assumed that the starting population included 40,000 people expected to be diagnosed with endometrial cancer
Results	
Study parameters	Cost estimates included genetic consultation, full genetic sequencing, immunohistochemistry, MLH1 sequencing, MSH2 sequencing and MSH6 sequencing. Clinical parameters included the probability of women fulfilling the Amsterdam criteria, people who fulfil Amsterdam and have Lynch syndrome, all patients with Lynch Syndrome, people <

	60 years, people < 60 years with Lynch Syndrome, people with normal IHC, etc.
Incremental costs and outcomes	Base-case results reported per 40,000 patients (hypothetical cohort). IHC/single gene when compared to the Amsterdam testing strategy had an ICER of approximately US$13,800 per Lynch syndrome case detected
Characterising uncertainty	Authors undertook sensitivity analysis around the cost of full gene sequencing. These results showed that the ICER was sensitive to this input parameter.
Discussion	
Study findings	IHC/single gene when compared to the Amsterdam criteria testing strategy was more effective and more costly, with an ICER of approximately US$13,800 per lynch syndrome case detected.
Limitations	The authors acknowledged and discussed the following limitations of their analyses. First, they did not include costs (screening colonoscopies and potential surgical procedures) incurred following the detection of Lynch syndrome. Second, the analysis did not include/evaluate genotyping for the screening of mismatch repair deficiency.
Generalisability	The most cost-effective screening strategy was IHC/single gene, but the authors acknowledged that this strategy may not be universally available, thus questioning the generalizability of this testing strategy
Other	
Source of funding	Not reported
Conflicts of interest	One author (HH) received honoraria from Myriad Genetic Laboratories, Inc. for serving on an advisory group on Lynch

	syndrome. Other authors reported no other potential conflicts of interest.
Comments	The authors used a simple decision tree structure to estimate the cost-effectiveness of different strategies used to detect Lynch syndrome. Though the model structure used might have been appropriate to address the decision question, the analysis is limited as other downstream costs and benefits associated with procedures were not considered. Thus, the impact of identifying these additional cases remains unanswered. Analysis could have benefited from sensitivity analyses and reporting the results in the form of a tornado diagram. Additionally, authors could have undertaken a probabilistic sensitivity analysis.
Authors conclusion	
The model-based economic analysis reported here appears to be simplistic, but addressed the research question. Future model-based analyses could build on this simplistic model to include the costs incurred and benefits accrued from identifying Lynch syndrome.	
Reviewer's conclusion	
The immunohistochemistry strategy and sequencing was the most cost-effective strategy for identifying women with Lynch syndrome.	

Date: 11th December 2019

Name of first reviewer: Peter Auguste

Study details	
Study title	Testing women with endometrial cancer to detect lynch syndrome
First author	Janice Kwon
Co-authors	Jenna L. Scott, C. Blake Gilks, Molly S. Daniels, Charlotte C. Sun, Karen H. Lu
Source of publication Journal yy;vol(issue):pp	Journal of Clinical Oncology 2011; volume 29 (16): 2247-2252
Language	English Language
Publication type	Research article
Inclusion criteria/study eligibility/PICOS	
Population	Women with endometrial cancer in the general population
Intervention(s)	Endometrial cancer younger than 50 years with at least 1 first-degree relative Endometrial cancer younger than 50 years Endometrial cancer younger than 60 years Endometrial cancer at any age with at least 1 first-degree relative All endometrial cancers, any age
Comparator(s)	Amsterdam II criteria
Outcome(s)	Number of cases subject to immunohistochemistry triage, number of women identified with Lynch Syndrome, number of women with subsequent colorectal cancer, and cost per life-years gained

Study design	Model-based cost-effectiveness analysis
Methods	
Target population and subgroups	Women with endometrial cancer in the general population
Setting and location	USA
Study perspective	Societal perspective
Comparators	Amsterdam II criteria
Time horizon	Lifetime horizon (until all women reached the dead state)
Discount rate	Costs and benefits discounted at an annual rate of 3%
Outcomes	Cost per life-year gained
Measurement of effectiveness	Life-years
Measurement and valuation of preference based outcomes	Not applicable as results were not reported in terms of quality-adjusted life years
Resource use and costs	Costs were obtained from a number of sources: published literature on genetic counselling, immunohistochemistry for mismatch repair proteins, gene sequencing, colonoscopy, and colorectal cancer treatment costs
Currency, price date and conversion	US dollars; 2010 prices
Model type	Markov Monte Carlo simulation model
Assumptions	• Women with endometrial cancer were still at risk of colorectal cancer • Women confirmed as mutation carriers, it was assumed that they undergo annual colonoscopy • Regardless of the testing strategy included in the analysis, women were assumed to be comparable by having the same

	risk factors for colorectal cancer, including BMI, smoking, diet, diabetes and alcohol consumption. • Though not explicitly stated as an assumption, the authors assumed that that there is a 100% compliance with colonoscopy surveillance in confirmed mutation carriers.
Results	
Study parameters	Cost parameters included immunohistochemistry triage for four mismatch repair genes, genetic counselling, initial consult, genetic counselling, follow-up, physician counselling for gene test and screening, DNA sequencing, colonoscopy and average total lifetime cost of colorectal cancer treatment. Clinical parameters included prevalence, sensitivity and specificity of each testing strategy, lifetime risk of colorectal cancer, 5-year mortality from colorectal cancer
Incremental costs and outcomes	IHC triage of women any age, with at least one first-degree relative when compared to age < 50, at least one first-degree relative (least expensive strategy) had 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.
Characterising uncertainty	Analysts undertook one-way and two-way scenario analyses. Sensitivity analysis results showed that the ICER was robust to changes made to model input parameters.
Discussion	
Study findings	The testing strategy using IHC triage of women any age, with at least one first-degree relative was the most cost-effective testing strategy at the $50,000 willingness-to-pay threshold.
Limitations	Microsatellite instability (MSI) testing was not included in the analysis. However, the authors stated/justified excluding MSI. First, MSI is likely to have similar sensitivity for detecting

	Lynch Syndrome in women with endometrial cancer. Second, immunohistochemistry can be undertaken in any pathology lab, whilst MSI requires a more sophisticated analysis, which may not be readily available at all centres. Other limitations discussed by the authors included the uncertainty around key input parameters (prevalence of Lynch Syndrome within specific age subgroups, their colorectal cancer risks and mortality rates, and total lifetime costs for colorectal cancer treatment.
Generalisability	Not discussed by the authors
Other	
Source of funding	Janice Kwon
Conflicts of interest	No potential conflicts of interests
Comments	Authors have used an appropriate model to address the research question. The manuscript confirms to reporting standards set out to appraise model-based economic analyses. However, it was noted that tornado diagrams were not reported and the authors had not undertaken a probabilistic sensitivity analysis. Additionally, the viewpoint of the analysis was from a societal perspective. However, it was unclear what resource use and costs relating to this perspective were included in the analysis.
Authors conclusion	
If current practice continues to use Amsterdam II criteria to guide genetic testing for Lynch Syndrome, women with Lynch Syndrome will be missed. Testing with IHC triage of women any age, with at least one first degree relative was the most cost-effective testing strategy.	

Reviewer's conclusion

Date: 16 December 2019

Name of first reviewer: Peter Auguste

Study details	
Study title	Evaluation of clinical criteria for the identification of Lynch syndrome among unselected endometrial cancer patients
First author	Amanda Bruegl
Co-authors	Bojana Djordjevic, Brittany Batte, Molly Daniels, Bryan Fellman, Diana Urbauer
Source of publication Journal yy;vol(issue):pp	Cancer prevention research 2014; 7(7): 686-697
Language	English Language
Publication type	Research article
Inclusion criteria/study eligibility/PICOS	
Population	Women ≥ 18 years diagnosed with endometrial cancer and sufficient tissue from the surgery to conduct molecular analysis
Intervention(s)	Universal tissue testing (immunohistochemistry for all and MLH1 methylation analysis) (First analysis)
Comparator(s)	Society of Gynaecologic Oncology 5-10% clinical criteria
Outcome(s)	Cost per probable Lynch syndrome
Study design	Economic analysis
Methods	
Target population and subgroups	Women ≥ 18 years diagnosed with endometrial cancer and sufficient tissue from the surgery to conduct molecular analysis
Setting and location	?? Hospital setting and USA

Study perspective	Third-party payer perspective
Comparators	Society of Gynaecologic Oncology 5-10% clinical criteria
Time horizon	Not applicable
Discount rate	Not applicable
Outcomes	Cost per probable Lynch syndrome case detected
Measurement of effectiveness	Sensitivity and specificity were derived for the Society of Gynaecologic Oncology 5-10% clinical criteria to predict probable Lynch syndrome
Measurement and valuation of preference based outcomes	Not applicable as results not reported in terms of cost per QALY
Resource use and costs	Initial genetic counselling and follow-up visits, immunohistochemistry for MLH1, MSH2, MSH6 and PMS2, MLH1 promoter methylation assay for tumours with loss of MLH1, and single germline mutation testing.
Currency, price date and conversion	US $ dollars, 2012 prices
Model type	Not applicable
Assumptions	• 25-75% of women with endometrial cancer with immunohistochemistry loss of expression of a mismatch pair protein would have germline mutation detected • All women diagnosed as probable Lynch syndrome identified by tissue testing would receive genetic counselling and germline mutation testing • All first degree relatives would receive genetic counselling and germline mutation testing • 50% of immunohistochemically loss of DNA MMR protein would have identifiable germline mutation
Results	

Study parameters	Sensitivity and specificity for SGO 5-10% screening criteria were 36%; 95% CI (19.2%, 48.5%) and 77.3%; 95% CI (72.7%, 81.8%), respectively.
Incremental costs and outcomes	SGO 5-10% clinical criteria would identify 97 women who would undergo further evaluation (tissue testing and genetic counselling), of which 15 were diagnosed as probable Lynch syndrome by tissue testing. Based on germline detection rates of between 25% and 75%, the estimated cost for screening probable Lynch syndrome and their relative was US$3,000 to US$6300 per probable Lynch syndrome case identified. Under the universal tumour testing strategy identified 43 women with probable Lynch syndrome, which costed approximately US$252,700, with a cost of US$5,900 per Lynch syndrome case identified.
Characterising uncertainty	From the literature a range of estimates about the proportion of positive tissue tests associated with germline mutation. Authors also provided results based on a range of estimates about the number of potentially affected first degree relatives who met the SGO 5-10% clinical criteria
Discussion	
Study findings	The universal tumour testing strategy with immunohistochemistry and MLH1 methylation was more costly but was effective in identifying a greater number of women with probable Lynch syndrome when compared to using the SGO 5-15% clinical criteria screening strategy.
Limitations	Authors have acknowledged limitations to the economic analysis. First, the microsatellite instability analysis was excluded from the economic analysis. Authors have justified

	(MSI can potentially miss some MSI-high tumours that have intact positive immunohistochemistry expression of mismatch repair proteins) the exclusion from the analysis. Second, it was assumed that there is a 100% genetic counselling referral rate for endometrial cancer patients meeting the SGO 5-10% criteria, but referral rates are likely to be between 17 and 48%. Third, 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%.
Generalisability	Authors have not discussed the generalizability of the results
Other	
Source of funding	NIH Research training Grant (AB); NIH SPORE in Uterine Cancer (RB, KL)
Conflicts of interest	Not reported
Comments	Authors undertook a cost-effectiveness analysis comparing the SGO 5-10% clinical criteria compared to universal screening with immunohistochemistry for all and MLH1 methylation analysis. Authors have used some simplifying assumptions to conduct their analyses, which may have be strong in some instances. Results do not appear to be reported incrementally but can be derived. Also, authors have not undertaken any sensitivity analyses. Given the nature of the economic analysis, the authors have not considered including any 'downstream' cancers e.g. colorectal cancer and the benefits
Authors conclusion	
Using the existing SGO 5-10% clinical criteria to identify Lynch syndrome in women diagnosed with endometrial cancer is likely to miss some cases when compared to a	

strategy of using immunohistochemistry for DNA mismatch repair proteins and PCR-based MLH1 methylation analysis for tumours with loss of MLH1.
Reviewer's conclusion
Study adds to the current cost-effectiveness evidence about testing for Lynch syndrome in women with endometrial cancer. However, there are some concerns/queries in the economic analysis, and these results should be interpreted with caution.

Date: 11 December 2019

Name of first reviewer: Peter Auguste

Study details	
Study title	Cost-effectiveness of routine screening for Lynch syndrome in endometrial cancer patients up to 70 years if age
First author	Anne Goverde
Co-authors	Anon spaander, Helena va Doorn, Hendrikus Dubbink et al.,
Source of publication Journal yy;vol(issue):pp	Gynecologic Oncology 2016 (143): 453-459
Language	English Language
Publication type	Research article
Inclusion criteria/study eligibility/PICOS	
Population	Consecutive endometriosis cancer patients ≤70 years of age from eight Dutch hospitals
Intervention(s)	Routine screening for Lynch syndrome by analysis of Microsatellite instability, IHC for MLH1, MSH2, MSH6 and PMS2 protein expression in endometrial cancer patients up to the age of 70 years
Comparator(s)	Screening for Lynch syndrome in endometrial cancer patients using an age cut-off
Outcome(s)	Life-years gained based on the number of Lynch syndrome cases identified among probands and their relatives
Study design	Cost-effectiveness analysis
Methods	
Target population and subgroups	Population-based cohort of endometrial patients ≤ 70 years of age undergoing routine screening for Lynch syndrome

Setting and location	Not reported
Study perspective	Not reported
Comparators	Screening for Lynch syndrome in endometrial cancer patients using an age cut-off
Time horizon	Not clearly reported but assume that it is lifetime
Discount rate	Costs and benefits (LYG) were discounted at 3% per annum
Outcomes	Life-years gained based on the number of Lynch syndrome cases identified among probands and their relatives
Measurement of effectiveness	Life-years
Measurement and valuation of preference based outcomes	Not applicable
Resource use and costs	Direct medical costs (microsatellite instability analysis, immunohistochemistry, MLH1 hypermethylation analysis, genetic counselling and germline mutation analysis) were derived using micro-costing methodology
Currency, price date and conversion	Euros, 2013 prices and using a purchasing power parity to convert costs to Euros
Model type	Not applicable
Assumptions	• 80% adherence for index patients and LS carriers among their relatives • Endometriosis cancer patients without a pathogenic mutation would undergo Lynch syndrome surveillance • No health benefit or surveillance costs were calculated for the deceased • Female Lynch syndrome carriers among relatives were assumed to undergo surveillance of annual transvaginal ultrasonography and endometrial biopsy from 35 years of age until prophylactic surgery at 40 years of age. It was assumed that 18% of relatives accepted prophylactic surgery

	• Lynch syndrome carriers who did not accept prophylactic surgery were assumed to continue annual gynaecological surveillance up to the age of 75 years of age
Results	
Study parameters	Resource use and costs associated with the testing strategies, costs for surveillance and surgery. Clinical parameters included acceptance of prophylactic gynaecological surgery, complication rate following colonoscopy, lifetime risk of developing colorectal cancer for Lynch syndrome carriers and reduction in colorectal cancer risks by Lynch syndrome surveillance
Incremental costs and outcomes	Incremental costs and outcomes were reported for Lynch syndrome screening among endometrial cancer patients up to the age of 70 years compared to an age of up to 50 years. The total costs (minus savings by prevention of colorectal cancer) for Lynch syndrome was approximately €150,800 for endometrial cancer patients ≤ 50 years of age and total life-years of 45.4 years. For endometrial cancer patients ≤ 70 years the total costs was approximately €304,400, with 74.7 life years. Screening endometrial cancer patients ≤ 50 years compared to screening endometrial cancer patients up to 70 years resulted in an ICER of approximately €5,300 per life-year gained.
Characterising uncertainty	Authors undertook sensitivity analysis to assess the impact on the ICER. Results showed that the health benefits (life-years gained) per female relative had the greatest impact to the ICER.
Discussion	
Study findings	Routine screening of endometrial cancer patients up to the age of 70 years for Lynch syndrome by analysis of MSI, IHC and

	MLH1 hypermethylation was cost-effective when compared to screening up to the age of 50 years.
Limitations	The authors acknowledge limitations to the information available and of their economic analysis. With respect to the evidence, there were no studies with exact information about the benefit of aspirin treatment to prevent development. Additionally, other strategies about informing people about signs and symptoms of cancer were not included. Furthermore, health-related quality associated with the reduction in morbidity was not included due to the lack of evidence. Limitations about the economic analysis include the small number of people diagnosed with Lynch syndrome for the Dutch population, excluding Lynch syndrome surveillance for extra colonic cancers other that gynaecological cancers and authors undertook one-way sensitivity analysis only and not a probabilistic sensitivity analysis.
Generalisability	Generalizability may be compromised given the population-based dataset that underpinned the analysis was small with seven women diagnosed with Lynch syndrome from the Dutch population, which might have not been representative for other populations.
Other	
Source of funding	Erasmus MC Translational Medicine
Conflicts of interest	Authors declared no potential conflicts of interest
Comments	The economic analysis builds on the existing cost-effectiveness analyses of different screening strategies to detect Lynch syndrome in endometrial cancer patients. In

	comparison to previous analyses, this analysis included costs and benefits for relatives of probands.
Authors conclusion	
Routine screening by analysis of microsatellite, immunohistochemistry and MLH1 hypermethylation for Lynch syndrome in people diagnosed with endometrial cancer up to the age of 70 years was the most cost-effective strategy compared to an age cut-off.	
Reviewer's conclusion	
The economic analyses builds on the existing economic analyses previously undertaken.	

Date: 12 December 2019

Name of first reviewer: Peter Auguste

Study details	
Study title	Cost-effectiveness analysis of reflex testing for Lynch syndrome in women with endometrial cancer in the UK setting
First author	Tristan Snowsill
Co-authors	Neil Ryan, Emma Crosbie, Ian Frayling, Gareth Evans, Chris Hyde
Source of publication Journal yy;vol(issue):pp	PLOS ONE 2019; 14(8):
Language	English Language
Publication type	Research article
Inclusion criteria/study eligibility/PICOS	
Population	Women newly diagnosed with endometrial cancer, and their relatives
Intervention(s)	Reflex testing with MMR IHC (with or without MLH1 methylation testing if MLH1 stain abnormal) followed by referral for Lynch syndrome diagnostic mutation testing
Comparator(s)	Reflex testing with MSI (with or without MLH1 methylation testing if MSI identified) followed by referral to genetic counselling for LS diagnostic mutation testing, direct referral to genetic counselling for LS diagnostic mutation testing, and no testing for Lynch syndrome
Outcome(s)	Costs and quality adjusted life-years
Study design	Model-based cost-effectiveness analysis
Methods	

Target population and subgroups	Women newly diagnosed with endometrial cancer, and their relatives
Setting and location	UK NHS
Study perspective	National Health Service and Personal Social Service perspective
Comparators	Reflex testing with MSI (with or without MLH1 methylation testing if MSI identified) followed by referral to genetic counselling for LS diagnostic mutation testing, direct referral to genetic counselling for LS diagnostic mutation testing, and no testing for Lynch syndrome
Time horizon	Lifetime (until death or age 100 years)
Discount rate	Costs and benefits discounted at 3.5% per annum
Outcomes	Quality adjusted life-years
Measurement of effectiveness	Overall sensitivity and specificity for tumour-based tests were derived from meta-analyses using a bivariate methodology without covariates. Where information permitted, similar methods were used to derive sensitivity and specificity for other testing strategies. In the base-case the effectiveness of colorectal cancer was derived from information obtained from Järvinen et al. study, and in sensitivity analysis from the Arrigoni et al study.
Measurement and valuation of preference based outcomes	Details not provided. However, the authors stated that health-related quality of life was estimated from the literature through pragmatic literature review
Resource use and costs	Cost information were obtained from published sources, NHS reference costs and NHS price for tests offered to other NHS providers. Costs were included for the interventions,

Currency, price date and conversion	UK£ sterling and 2016/17 prices
Model type	Decision tree with Markov nodes
Assumptions	• Female relatives with Lynch syndrome are at risk of endometrial cancer, but the incidence was not included in the analysis • Diagnostic mutation testing identifies mutations causing Lynch syndrome as pathogenic. It was assumed that the sensitivity of diagnostic mutation was 0.90. In addition, the authors assumed that predictive mutation testing is 100% accurate. Furthermore, the authors assumed that 55% of endometrial cancer patients with tumour-based test results suggestive of Lynch syndrome attended genetic counselling, of which 10% would decline diagnostic mutation testing. • People undergoing colorectal cancer screening were assumed to be detected in the earlier stages
Results	
Study parameters	Both clinical (natural history, epidemiological information, health-related quality of life, diagnostic accuracy, preventative effectiveness and utility values) parameters and cost (costs associated with interventions, events and outcomes) parameters were clearly outlined.
Incremental costs and outcomes	Incremental analyses of the different testing strategies showed that immunohistochemistry with methylation was the most cost-effective strategy with an ICER of approximately £14,200 per QALY. The immunohistochemistry alone strategy was the most effective and the most costly, but the results did not reach cost-effectiveness when compared to immunohistochemistry with methylation, with an ICER of approximately £129,000 per QALY.
Characterising uncertainty	Authors undertook one-way sensitivity analyses, including probabilistic sensitivity analysis and scenario analyses. Also,

	authors undertook analyses by running the results for different sub-groups, by age.
Discussion	
Study findings	Immunohistochemistry with methylation was considered to be cost-effective when compared to all other strategies. Authors stated that the PSA results were in line with the deterministic results. From the 1000 iterations, there was a 0.36 probability that immunohistochemistry with methylation was cost-effective at a willingness-to-pay threshold of £20,000 per QALY. Results from the one-way sensitivity analysis showed that the ICER was sensitive to the age of the proband and the effectiveness of colonoscopy in reducing colorectal cancer incidence. Scenario analysis results showed that using the effectiveness of colonoscopic surveillance to reduce the colorectal cancer incidence derived from information obtained from Arrigoni et al., 2005, none of the testing strategies were cost-effective.
Limitations	Authors have clearly outlined the limitations of the analysis: • Colorectal cancer was the only 'downstream' cancer included in the analysis. Other gynaecologic cancers were not included • Colonoscopy was the only risk-reducing measure used in the analysis. Other potential risk-reducing measures (e.g. aspirin and gynaecological surveillance) were not included • Authors have not undertaken a systematic review to identify key model input parameters, but have alluded to using a pragmatic literature review • Authors assumed that the proportion of women with endometrial cancer with abnormal immunohistochemistry which show MLH1 abnormalities, was independent of age, but evidence suggests that there may be an association. • The exclusion of genetic testing for somatic MMR mutations, which can be used to *'confirm that a MMR deficient tumour with no constitutional pathogenic variant identified has arisen*

	due to somatic MMR mutations rather than from Lynch syndrome.'
Generalisability	This was not discussed per se. However, the authors mentioned that IHC is conducted to a high standard in the UK and, it is likely that published studies based in research centres will have a similar high standards, but routine clinical settings outside of the UK may have lower standards
Other	
Source of funding	*NAJR is an MRC Doctoral Research Fellow (MR/M018431/1) and DGE is an NIHR Senior Investigator (NF-SI-0513-10076). EJC and DGE are supported by the NIHR Biomedical research centre Manchester (IS-BRC-1215-20007). CJH is supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula (NIHR CLAHRC South West Peninsula). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The views expressed are those of the author(s) and not necessarily those of the MRC, NHS, the NIHR or the Department of Health and Social Care.*
Conflicts of interest	*IMF is an Honorary Medical Advisor to Lynch Syndrome UK and reports support from St Vincent's University Hospital (Dublin), Impact Genetics (Bowmanville, Ontario, Canada), and Ambry Genetics (Aliso Viejo, CA, USA), for travel, outside the submitted work. Other authors declare no potential conflicts of interest.*
Comments	Economic analysis was thoroughly thought through and well-conducted and it addresses the research question. The analysis builds on the existing research in this area. Economic analysis conforms to the good practice guidelines for undertaking an

	economic evaluation. One potential limitation of the analysis is the reporting of the results. In addition to the cost per QALY, the results could have been presented in terms of its natural units.
Authors conclusion	
Immunohistochemistry with MLH1 methylation testing for Lynch syndrome in young women may be cost-effective.	
Reviewer's conclusion	
Well-conducted economic analysis. However, this analysis could have been improved by undertaking systematic reviews to identify information for key model input parameters.	

10.5. Appendix 6: Quality assessment of economic evaluation studies

Table 25: CHEERS quality assessment checklist for economic evaluation studies

Assessment	Studies				
	Resnick et al., 2009	**Kwon et al., 2011**	**Bruegl et al., 2014**	**Goverde et al., 2016**	**Snowsill et al., 2019**
Title	Y	Y	Y	Y	Y
Abstract	Y	Y	Y	Y	Y
Introduction					
Background and objectives	Y	Y	Y	Y	Y
Methods					
Target population and subgroups	Y	Y	Y	Y	Y
Setting and location	?Y	?Y	?Y	Y	Y
Study perspective	Y	Y	Y	Y	Y
Comparators	Y	Y	Y	Y	Y
Time horizon	Y	Y	NA	?Y	Y
Discount rate	Y	Y	NA	Y	Y
Choice of health outcomes	Y	Y	Y	Y	Y
Measurement of effectiveness	Y	Y	Y	Y	Y

Assessment	Studies				
	Resnick et al., 2009	**Kwon et al., 2011**	**Bruegl et al., 2014**	**Goverde et al., 2016**	**Snowsill et al., 2019**
Measurement and valuation of preference-based outcomes	Y	NA	NA	NA	UNC
Estimating resources and costs	Y	Y	Y	Y	
Currency, price date, and conversion	Y	Y	Y	Y	Y
Choice of model	Y	Y	NA	NA	Y
Assumptions	Y	Y	Y	Y	Y
Analytical methods	Y	Y	Y	Y	Y
Results					
Study parameters	Y	Y	Y	Y	Y
Incremental costs and outcomes		Y	Y	Y	Y
Characterising uncertainty	Y	Y	Y	Y	Y
Discussion					
Study findings	Y	Y	Y	Y	Y
Limitations	Y	Y	Y	Y	Y
Generalizability	Y	NR	NR	Y	N
Other					

Assessment	Studies				
	Resnick et al., 2009	**Kwon et al., 2011**	**Bruegl et al., 2014**	**Goverde et al., 2016**	**Snowsill et al., 2019**
Source of funding	Y	Y	Y	Y	Y
Conflicts of interest	Y	Y	Y	Y	Y
N, no; NA, not applicable; NR, not reported; UNC, unclear ;Y, Yes					

Table 26: Philips' quality assessment checklist for studies that included an economic model

Philips' criteria		Studies		
		Resnick et al., 2009	**Kwon et al., 2011**	**Snowsill et al., 2019**
Structure				
1.	Is there a clear statement of the decision problem?	Y	Y	Y
2.	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	Y
3.	Is the primary decision maker specified?	Y	Y	Y
4.	Is the perspective of the model stated clearly?	Y	Y	Y
5.	Are the model inputs consistent with the stated perspective?	Y	N	Y
6.	Has the scope of the model been stated and justified?	Y	N	Y
7.	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y
8.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y
9.	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y
10.	Are the causal relationships described by the model structure justified appropriately?	Y	Y	Y
11.	Are the structural assumptions transparent and justified?	Y	Y	Y
12.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	Y
13.	Is there a clear definition of the options under evaluation?	Y	Y	Y
14.	Have all feasible and practical options been evaluated?	N	N	N
15.	Is there justification for the exclusion of feasible options?	N	Y	Y

Philips' criteria		Studies		
		Resnick et al., 2009	**Kwon et al., 2011**	**Snowsill et al., 2019**
16.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y
17.	Is the time horizon of the model sufficient to reflect all important differences between the options?	N	Y	Y
18.	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	N	Y	Y
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?	Y	Y	Y
20.	Is the cycle length defined and justified in terms of the natural history of disease?	NA	Y	Y
Data				
21.	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y	Y
22.	Where choices have been made between data sources are these justified appropriately?	N	N	N
23.	Has particular attention been paid to identifying data for the important parameters of the model?	UNC	UNC	N
24.	Has the quality of the data been assessed appropriately?	UNC	UNC	UNC
25.	Where expert opinion has been used are the methods described and justified?	N	NA	Y
26.	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	Y	Y
27.	Is the choice of baseline data described and justified?	Y	Y	Y
28.	Are transition probabilities calculated appropriately?	NA	UNC	Y
29.	Has a half-cycle correction been applied to both costs and outcomes?	NA	N	Y

Philips' criteria		Studies		
		Resnick et al., 2009	**Kwon et al., 2011**	**Snowsill et al., 2019**
30.	If not, has the omission been justified?	N	N	NA
31.	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	NA	NA	Y
32.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	NA	NA	Y
33.	Have alternative extrapolation assumptions been explored through sensitivity analysis?	NA	NA	Y
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?	Y	Y	Y
37.	Has the source for all costs been described?	Y	Y	Y
38.	Have discount rates been described and justified given the target decision maker?	Y	Y	Y
39.	Are the utilities incorporated into the model appropriate?	NA	NA	Y
40.	Is the source of utility weights referenced?	NA	NA	Y
41.	Are the methods of derivation for the utility weights justified?	NA	NA	Y
42.	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	N	Y
43.	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	Y	Y	Y
44.	Is the process of data incorporation transparent?	N	N	Y
45.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	NA	NA	Y

Philips' criteria		Studies		
		Resnick et al., 2009	**Kwon et al., 2011**	**Snowsill et al., 2019**
46.	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	NA	Y
47.	Have the four principal types of uncertainty been addressed?	N	N	Y
48.	If not, has the omission of particular forms of uncertainty been justified?	N	N	NA
49.	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	N	N	Y
50.	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	Y
51.	Has heterogeneity been dealt with by running the model separately for different sub-groups?	N	Y	Y
52.	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y
53.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	Y
54.	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	N	Y
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?	Y	NA	Y
57.	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	Y
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear				

10.6. Appendix 7: PSA distributions and approach

The tables below 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.

Table 27: Model inputs varied in the probabilistic sensitivity analysis

Variable	**Base-case value**	**Distribution**	**Parameters**
Test accuracy			
Sensitivity IHC with MLH1		Fixed	
Specificity IHC with MLH1	-	Beta	($\alpha = 56.10, \beta = 1.93$)
Costs (£, 2018/19 prices)			
GP visit	39.00	Lognormal	($\mu = 3.66, \sigma = 0.10$)
IHC test	210.00	Lognormal	($\mu = 5.35, \sigma = 0.10$)
MMR proband	755.00	Lognormal	($\mu = 6.63, \sigma = 0.10$)
MMR relative	165.00	Lognormal	($\mu = 5.11, \sigma = 0.10$)
Offer counselling	28.25	Lognormal	($\mu = 3.34, \sigma = 0.10$)
Pre-test proband	642.19	Lognormal	($\mu = 6.46, \sigma = 0.10$)
Post-test proband	141.44	Lognormal	($\mu = 4.95, \sigma = 0.10$)
Pre-test relative	514.13	Lognormal	($\mu = 4.95, \sigma = 0.10$)
Post-test relative	141.44	Lognormal	($\mu = 6.24, \sigma = 0.10$)
CRC incidence lognormal 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		Covariance matrix given in Table X.

Variable	Base-case value	Distribution	Parameters
Coefficient for:			
MSH	0.100		
MSH6	0.531		
PMS2	0.863		
Male	-0.118		
Previous cancer	-0.230		
CRC mortality			
Stage I	0.0090	Lognormal	(μ = -4.26, σ = 0.054)
Stage II	0.0345	Lognormal	(μ = -2.95, σ = 0.014)
Stage III	0.0977	Lognormal	(μ = -1.91, σ = 0.009)
Stage IV	0.5440	Lognormal	(μ = -0.42, σ = 0.357)
Aspirin incidence rate ratio	0.5800	Lognormal	(μ = -0.55, σ = 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 X in main report	Gamma	Param1 = 25, Param2 = see Table X
Endometrial cancer incidence [a]			
Gene			
MLH1 by age			
25	0	Fixed	Not applicable
40	0.019	Beta	α = 3.4, β = 173.6
50	0.147	Beta	α = 39.1, β = 226.6
60	0.273	Beta	α = 62.7, β = 166.9
70	0.352	Beta	α = 57.5, β = 105.9

Variable	Base-case value	Distribution	Parameters
75	0.370	Beta	α = 48.9, β = 83.3
MSH2			
25	0	Fixed	Not applicable
40	0.023	Beta	α = 2.8, β = 119.1
50	0.175	Beta	α = 32.5, β = 153.2
60	0.380	Beta	α = 58.4, β = 95.3
70	0.465	Beta	α = 54.4, β = 62.6
75	0.489	Beta	α = 44.2, β = 46.17
MSH6			
25	0	Fixed	Not applicable
40	0.023	Beta	α = 0.1, β = 4.8
50	0.126	Beta	α = 2.8, β = 19.7
60	0.283	Beta	α = 10.7, β = 27.2
70	0.411	Beta	α = 17.4, β = 24.9
75	0.411	Beta	α = 13.7, β = 19.7
PMS2			
25	0	Fixed	Not applicable
40	0	Fixed	Not applicable
50	0	Fixed	Not applicable
60	0.093	Beta	α = 0.5, β = 5.2
70	0.128	Beta	α = 1.0, β = 6.7
75	0.128	Beta	α = 1.0, β = 6.8

CRC, colorectal cancer; IHC, immunohistochemistry; MSI, microsatellite instability, MMR, mismatch repair; PSA, probabilistic sensitivity analysis

[a] Since cumulative incidence cannot decrease, 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 annual incidence rates sampled at each run could never be negative.

Table 28: Variance covariance matrix for multivariate normal distribution used for CRC incidence in PSA

0.0048610	0.0024265	0.00306302	-2.84316E-05,	-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,	-2.36405E-05,	0.009192278,
-2.84316E-05,	-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,	-2.36405E-05,	-0.003063665,	-0.003612567,	0.003639508,	0.001641483,
0.001470131,	0.005271669,	0.009192278,	-0.001316882,	-0.006267887,	0.001641483,	0.010196606

Table 29: Param 2 values for Gamma distribution giving uncertainty around CRC treatment cost

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