Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – protocol

Title of project

Testing strategies for Lynch syndrome in people with endometrial cancer

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The views expressed in this protocol are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors. The authors have no conflicts of interest.

Glossary of terms

CEAC	Cost-effectiveness acceptability curves
CRD	Centre for Reviews and Disseminations
DAC	Diagnostic Advisory Committee
DARE	Database of Abstracts of Reviews of Effects
DNA	Deoxyribonucleic acid
EAG	External Assessment Group
HNPCC	Hereditary non-polyposis colorectal cancer
HTA	Health Technology Assessment
IHC	Immunohistochemistry
LY	Life-years
MLH1	MutL homologue 1
MLH2	MutS homologue 2
MLPA	Multiplex ligation-dependent probe amplification
MSH6	MutS homologue 6
MSI	Microsatellite instability
NGS	Next generation sequencing
NICE	The National Institute for Health and Care Excellence
QALY	Quality-adjusted life-years
PMS2	Postmeiotic segregation increased 2
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
WTP	Willingness-to-pay

1. 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. It runs in families and a person with Lynch syndrome has a 50:50 chance of passing it on to their children. 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. Testing for Lynch syndrome amongst people who have womb cancer is not usually carried out, or may only be done when they have a history of Lynch syndrome in their family, or if they have been diagnosed with womb cancer at a younger age (under 50). The main ways to identify if someone who has cancer is at higher risk of having Lynch syndrome are (1) immunohistochemistry and (2) microsatellite instability-based tests. Immunohistochemistry looks for missing proteins, and microsatellite instability testing looks for changes in the patterns of our DNA. The missing proteins and changes to DNA are associated with Lynch syndrome-related cancers. Other tests can help to rule out cancers that are not caused by Lynch syndrome. People found to be at higher risk of Lynch syndrome by either of the two tests can be given extra tests to diagnose the condition. The aim of the current project is to review the clinical and cost-effectiveness of testing for Lynch syndrome amongst people who have endometrial cancer, and their biological relatives.

2. Decision problem

2.1 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) will assess 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.

2.2 Population and target condition

2.2.1 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] Endometrial cancer starts to occur when the cells of the endometrium grow very rapidly. This causes the lining of the uterus to thicken in certain areas, which may form a mass of tissue known as tumour. 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]

2.2.2. 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 has 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.

2.3 Interventions

The two main approaches to identifying people who are at higher risk of Lynch syndrome are described below. Both tests are conducted on tumour tissue.

2.3.1 Immunohistochemistry

Immunohistochemistry (IHC) 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.

2.3.2 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 of 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.

Additional testing can be conducted to help rule out sporadic epigenetic silencing of MLH1 which might present as Lynch syndrome (see section 2.3.3 - MHL1 promoter hypermethylation testing).

2.3.3. MLH1 promoter hypermethylation testing

Hypermethylation is an epigenetic process that switches off the expression of proteins. MLH1 promoter hypermethylation testing is conducted on tumours. 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]

2.4 Diagnostic test

Currently, there is no single test that is used to identify all cases of Lynch syndrome. 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) 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 variant are identified.[19,20] This includes testing for other somatic or germline pathogenic variants (e.g. biallelic MuTYH, POLE, double somatic MMR variants).

2.5 Care pathway

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.

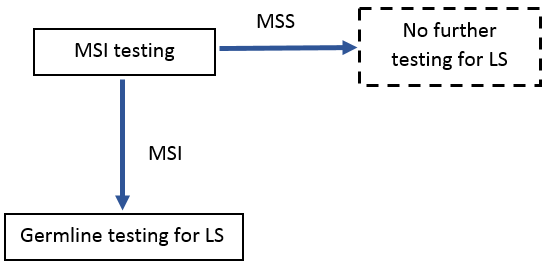

Figure 1: Strategy 1: MSI testing alone (MSS: microsatellite stable, MSI: microsatellite instability, LS: Lynch syndrome)

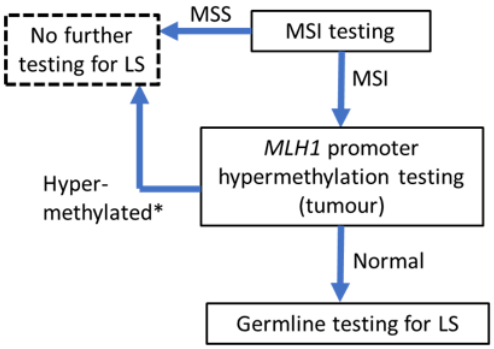

Figure 2: Strategy 2: MSI testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)

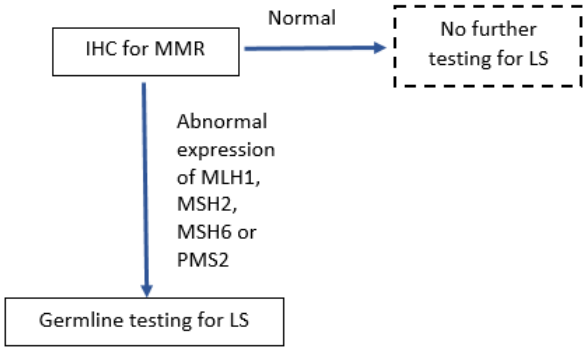

Figure 3: Strategy 3: IHC-based testing (LS: Lynch syndrome)

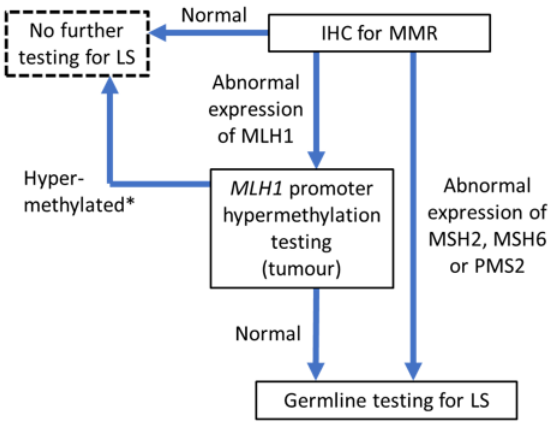

Figure 4: Strategy 4: IHC testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)

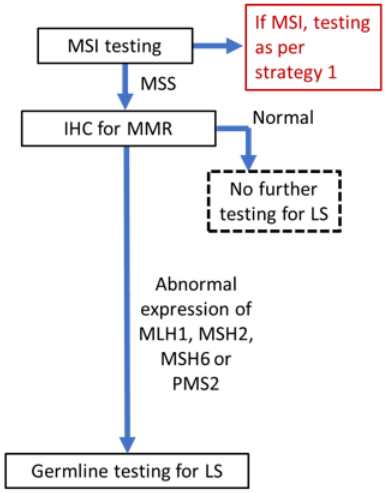

Figure 5: Strategy 5: MSI testing followed by IHC testing

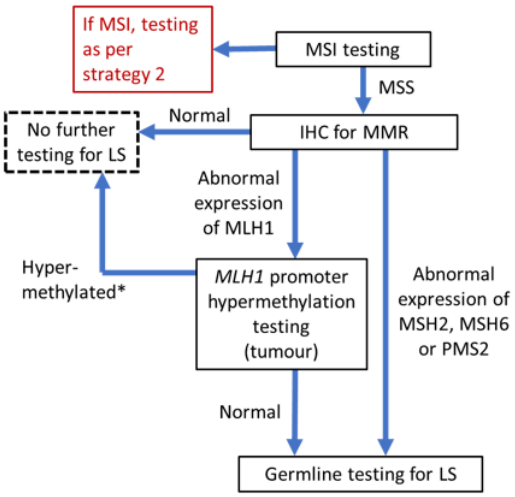

Figure 6: Strategy 6: MSI followed by IHC testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)

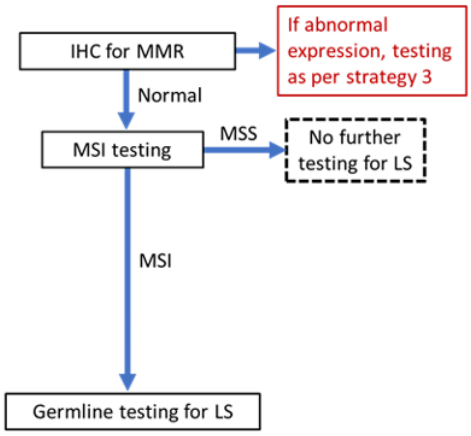

Figure 7: Strategy 7: IHC followed by MSI testing

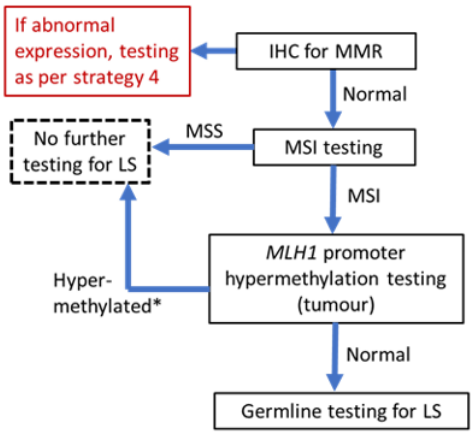

Figure 8: Strategy 8: IHC testing followed by MSI testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome)

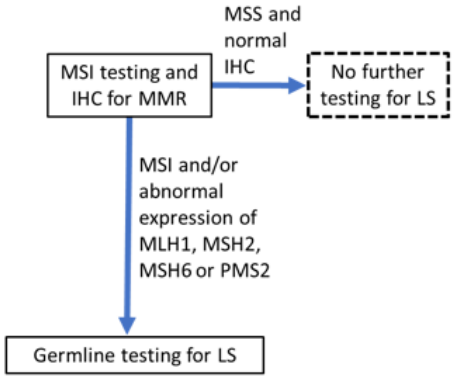

Figure 9: Strategy 9: MSI and IHC testing

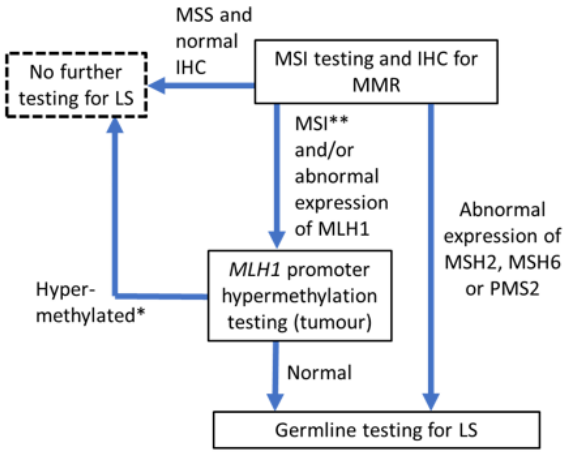

Figure 10: Strategy 10: MSI and IHC testing with MLH1 promoter hypermethylation testing (*if a germline sample is tested and is also hypermethylated diagnose Lynch syndrome, ** MLH1 promoter hypermethylation testing not conducted after MSI if MLH1 expression on IHC is normal and abnormal expression of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

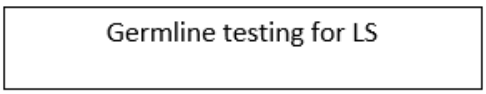

Figure 11: Strategy 11: Germline testing only

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] There is some evidence that daily aspirin,[25] and prophylactic hysterectomy and bilateral salpingo-oophorectomy reduce the risk of endometrial and ovarian cancers.[26] Colorectal cancer surveillance is associated with a decreased risk of colorectal cancer incidence and mortality.[27] It is unclear if gynaecological surveillance is beneficial.[28]

3 Decision questions and objectives

3.1 Decision questions

The overall objectives of this project are to examine the test accuracy of IHC and MSI-based strategies to detect Lynch syndrome in people who have endometrial cancer, and the clinical and cost effectiveness 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*?*

4. 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 will follow the principles outlined in the Cochrane Handbook of Diagnostic Test Accuracy[29] and the NICE Diagnostic Assessment Programme manual.[30]

4.1 Identification and selection of studies

4.1.1 Search strategy

The search strategy will comprise 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 will be developed iteratively and undertaken in a range of relevant bibliographic databases. The search terms will relate to endometrial cancer and lynch syndrome. There will be no restrictions on date or language. Searches will be conducted in the following databases: MEDLINE All (Ovid); Embase (Ovid); Cochrane Database of Systematic Reviews (Wiley); CENTRAL (Wiley); Database of Abstracts of Reviews of Effects (DARE) (Centre for Reviews and Disseminations (CRD)); Health Technology Assessment (HTA) database (CRD/INAHTA); Science Citation Index and Conference Proceedings (Web of Science); PROSPERO International Prospective Register of Systematic Reviews (CRD). The search will be developed in MEDLINE (Ovid) and adapted as appropriate for other databases. A copy of the draft search strategy is provided in Appendix 1.

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

4.1.2 Study eligibility criteria

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

Population	<u>All questions</u> People with endometrial cancer with no known diagnosis of Lynch syndrome
Target condition	<u>All questions</u> Lynch syndrome
Intervention	<u>All 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 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 will include 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	<u>Key question</u> 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 <u>Sub question 1a</u> Concordance between IHC and MSI (fractions, kappa, % agreement) <u>Sub question 1b</u> Any available characteristics of the population or tumours, including family history, and results of germline testing <u>Sub question 2</u> 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 will be included, including cross-sectional test accuracy studies, randomised controlled trials, cohort studies and case-control studies. Head-to-head (direct comparison) studies will be 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 will be included, including randomised controlled trials, cross-sectional test accuracy studies, cohort studies and case-control studies
Publication type	All questions Peer reviewed papers Abstracts and manufacturer data will be 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 will be extracted and reported.
Language	All questions English

Papers that fulfil the following criteria will be 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 will be excluded.

4.1.4 Review strategy

Two reviewers (CS, LAK/HF) will independently screen the titles and abstracts of records identified by the searches. Any disagreements will be resolved through discussion, or retrieval of the full publication. Potentially relevant publications will be 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 will be resolved through consensus, with the inclusion of a third reviewer (HF/LAK, STP) if required. Records that are excluded at full text stage will be documented, including the reasons for their exclusion.

4.2 Extraction and study quality

4.2.1 Data extraction strategy

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

4.2.2 Assessment of study risk of bias

The risk of bias of test accuracy studies will be assessed using a modified QUADAS-2.[32] Two reviewers (CS, LAK/HF) will independently assess study risks of bias. Disagreements will be resolved through consensus, with the inclusion of a third reviewer (HF/LAK, STP) if required. As recommended by the QUADAS-2 group, an overall quality score will not be determined.[32] The results of each risk of bias item will be presented in table and graph form.

4.3 Methods of analysis/synthesis

Test accuracy results will be presented for testing strategies 1 – 10, comparing the index tests to the eligible reference standards. Test accuracy will not be assessed for strategy 11 as this approach does not include an index test. For studies that include an initial test followed by *MLH1* promoter hypermethylation testing, we will analyse 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 will report results together and separately for each protein. For MSI results, we will report the panel used as per the papers. If possible, a subgroup analysis will be undertaken for the different combinations of microsatellite markers. Subgroup analysis will also be undertaken on MSI-low and MSI-high patients. Our main analysis will assume MSI low are test negative. Furthermore, if data permit, we will conduct subgroup analyses of test accuracy by (1) age (under vs over 70 years) and (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"). If enough homogeneous

studies are available then a meta-analysis will be undertaken. Otherwise, a narrative summary of the evidence will be presented.

Variants of uncertain clinical significance on germline testing are not considered to have Lynch syndrome in our test accuracy analysis. The EAG will record 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 will descriptively record the characteristics of these cases such as family history, IHC results and discordant cases between the two index tests. This will provide 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 will be considered the primary reference standard. If there are insufficient studies using these reference standards, we will include 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 will make a record of the additional tests that are used. If sufficient data are available, we will 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.

5. 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 will conduct 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 will be used for the test accuracy question (see section 4) will be 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. These will be used in a linked-evidence approach if no end-to-end studies are found.

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[33] and the NICE Diagnostic Assessment Programme manual.[30]

5.1 Identification and selection of studies

5.1.1 Search strategy

The same search strategy as described in the methods for test accuracy will be used (see section 4.1 Identification and selection of studies).

5.1.2 Study eligibility criteria

Studies that satisfy the following criteria will be <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 <u>Sub question 2</u> Gynaecological cancers (endometrial, ovarian, cervical, vaginal and vulval)
Intervention	<u>Key question</u>

	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 <u>Sub question 1</u> Surveillance/testing for colorectal cancer <u>Sub question 2</u> Surveillance/testing for gynaecological cancers (endometrial, ovarian, cervical, vaginal and vulval)
Comparator	<u>Key question</u> No testing for Lynch syndrome <u>Sub questions 1 and 2</u> No surveillance/testing
Outcome	<u>Key question</u> 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 will be 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 will be extracted and reported.
Language	<u>All questions</u> English

Papers that fulfil the following criteria will be 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.

5.1.3 Review strategy

Two reviewers (CS, LAK/HF) will independently screen the titles and abstracts of records identified by the searches. Any disagreements will be resolved through discussion, or retrieval of the full publication. Potentially relevant publications will be 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 will be resolved through consensus, with the inclusion of a third reviewer (HF/LAK, STP) if required. Records that are excluded at full text stage will be documented, including the reasons for their exclusion.

5.2 Extraction and study quality

5.2.1 Data extraction strategy

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

5.2.2 Assessment of study risk of bias

The risk of bias of randomised control trials will be assessed using the Cochrane revised tool to assess risk of bias in randomized trials (RoB 2).[34] Risk of bias in controlled trials will be assessed using the Cochrane risk of bias in non-randomized studies of interventions (ROBINS-I) tool.[35] Two reviewers (CS, LAK/HF) will independently assess study risks of bias. Disagreements will be resolved through consensus, with the inclusion of a third reviewer (HF/LAK, STP) if required.

5.3 Methods of analysis/synthesis

We will use the following effect measures:

- Hazard ratio (HR) for time-to-event data (e.g. time to gynaecological cancer specific mortality)
- Risk ratio dichotomous outcomes (e.g. colorectal cancer incidence)

- Mean difference between arms for continuous outcomes (e.g. health-related quality of life).

We will not impute missing outcome data. We will perform the analysis based on the available data. If data permits and there is evidence of substantial heterogeneity (i.e. p value < 0.1 or $I^2 > 50\%$) we will investigate and report the possible reasons for heterogeneity. If data permits and studies are clinically similar, we will pool the results in meta-analyses. For dichotomous outcomes, we will calculate the risk ratio and the 95% confidence interval for each study and then pool the studies. For time-to-event data we will pool the hazard ratios. For continuous outcomes, we will pool the mean difference and the 95% confidence interval at the end of follow-up if studies measure the outcome on the same scale. If studies measure the outcome using different scales we will pool using the standardised mean difference and the 95% confidence interval. If data do not permit a pooled analysis then we will conduct a narrative synthesis.

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?

6.1 Identification and selection of studies

6.1.1 Search strategy

A comprehensive search of the literature for published economic evaluations, cost studies and health-related quality of life studies (HRQoL) will be performed. The database searches will be developed iteratively and combine terms for Lynch syndrome and economic/cost/HRQoL. The search will be informed by the strategy developed for the clinical effectiveness review and published economic and HRQoL search filters. This strategy may be further refined and other appropriate limits may be added. Databases will include:

MEDLINE All (Ovid);
Excerpta Medica database (Embase) (Ovid);
National Health Service Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) database (CRD);
Science Citation Index and Conference Proceedings Science (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 will be checked. The search will be developed in MEDLINE (Ovid) and adapted as appropriate for other databases.

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

Additional searches will be performed where necessary to identify other relevant inputs (e.g. incidence of Lynch cancers, resource use and costs, utility values, or survival analysis information) to support building the economic model.

Where direct evidence is unavailable for different testing strategies, or where such a comparison is not well supported with evidence, a linked approach to evidence will be considered in which evidence of clinical effectiveness is taken from studies using alternative test methodology and an assessment is made of the relative performance this methodology relative to the testing strategies for Lynch syndrome.

6.1.2. Review strategy

All records retrieved will be screened independently by two reviewers at title/abstract stage, of which potentially relevant records will be further examined at full-text. Any disagreements between the reviewers will be resolved by a discussion, or recourse to a third reviewer if an agreement cannot be reached.

6.2 Extraction and study quality

6.2.1 Data extraction strategy

Information will be extracted by two reviewers independently, using a pre-piloted data extraction form for the full economic evaluation studies. The data extraction form will be developed to summarise the main characteristics of the studies and to capture useful information for the economic model. From each paper included in the systematic review, we will extract 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 conclusion (author's and reviewer's). Each reviewer will cross-check each other's extractions, with any discrepancies resolved by discussion, or recourse to a third reviewer if an agreement cannot be reached.

6.2.2 Assessment of study methodological quality

The quality of any full economic evaluation studies will be assessed using the consolidated health economic evaluation reporting standards (CHEERS) checklist.[36] Any studies using an economic model will be further assessed against the framework for the quality assessment of decision analytic modelling developed by Philips and colleagues.[37]

6.3 Methods of analysis/synthesis

Due to the nature of economic analyses (different aims/objectives, study designs, populations, and methods) these findings from individual studies will be compared narratively, and recommendations for future economic analyses will be discussed.

Evaluation of costs, health-related quality of life and cost-effectiveness

Model structure

If appropriate model-based cost-effectiveness studies addressing the review question are not found, a de novo economic model will be constructed. In constructing the economic model, we will consult the previous Health Technology Assessment (HTA) report undertaken by Snowsill and colleagues.[10] These authors developed a decision analytical model which compared tumour-based strategies, direct mutation testing and no testing to identify Lynch syndrome in people with colorectal cancer. The model comprised two stages, a diagnostic and a management stage, which were used to simulate different pathways for a hypothetical cohort of people with colorectal cancer being screened for Lynch syndrome. The first stage used a decision tree structure to estimate the resource use and costs of diagnosis, and the number of probands and their first relatives who would be diagnosed with Lynch syndrome. The first stage of the model considered the different treatment (type of surgery, radiotherapy, hormone therapy and targeted therapy) options available to treat endometrial cancer. 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.

The development of the model will be an iterative process. First, we will develop a conceptual model, with consultation with clinical experts. The conceptual model will be used to identify the information required to parameterise the model. We anticipate that parameterisation will be driven by the findings from the clinical effectiveness systematic review and supported by clinical expert opinion. We anticipate that the model will comprise a decision tree linked to a Markov state decision analytical model (cohort or individual).

Strategies for inclusion within the diagnostic component of the model 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 will be compared against no testing for Lynch syndrome-related mutations.

With respect to strategies including MSI testing, the EAG will consider the variants of index tests identified from the literature and used as appropriate for evaluation.

Resource use and costs

As part of the framework to undertake the economic analysis, information will be required about the resource use and costs associated with the testing strategies used to identify Lynch syndrome in people with endometrial cancer. Additionally, resource use and costs will be required for the long-term management and surveillance of people with Lynch syndrome and their relatives and costs associated with the cancers they might have. Probands with Lynch syndrome will be offered surveillance for colorectal cancer (and if management of endometrial cancer is fertility sparing monitoring for endometrial and ovarian cancer) and risk-reducing interventions (e.g. aspirin as a chemopreventative treatment). Probands without Lynch syndrome will follow the UK Bowel cancer screening programme. Additionally, relatives who are diagnosed with Lynch syndrome through testing, will be offered surveillance for colorectal and gynaecological cancers (endometrial and ovarian) and risk-reducing interventions (aspirin as chemopreventative treatment and hysterectomy with or without bilateral salpingo-oophorectomy as a surgical strategy) for Lynch syndrome. Relatives without Lynch syndrome will follow the usual NHS bowel screening programme.

Of note, probands diagnosed with Lynch-like syndrome (also termed putative lynch syndrome in previous DAR[10] will be modelled in our base case under the assumptions that 1) Somatic tumour testing is required to rule out sporadic cancer and achieve Lynch-like diagnosis, and 2) Cascade testing in relatives of Lynch-like diagnosed probands is not assumed to be the same as that of confirmed probands. Cascade testing is pursued among first degree relatives only. Risk of developing CRC in people with Lynch-like syndrome will be assumed the same as those with a definitive Lynch syndrome diagnosis.

Health outcomes

Three outcome measures will be used in the economic analysis, number of relatives identified with Lynch syndrome, life-years (LY) and quality-adjusted life-years (QALYs) gained. LY and QALYs gained will be calculated from survival information, including incidence and survival of endometrial cancer and colorectal cancer, and utility values obtained from the literature and other sources (e.g. elicited from experts). QALYs accrued will be derived based on the utility payoff assigned to the health states occupied along the management pathway. Under each testing strategy the expected mean benefits yielded are summed over the model time horizon and discounted at a 3.5% per annum rate.

Cost-effectiveness analysis

The cost-effectiveness analysis will consider the ratio between the costs incurred and benefits accrued for each testing strategy from the NHS and PSS perspective in a secondary/tertiary care setting. The results of the analysis will be presented in terms of an incremental cost-effectiveness analysis (ICER), where each testing strategy will be ranked, excluding options that were dominated or extendedly dominated, with results expressed as cost per QALY. We will also present secondary outcome results in the form of cost per asymptomatic person identified with Lynch syndrome. We will use univariate one-way sensitivity analysis to explore the impact of varying one parameter at a time, whilst keeping all other inputs constant to assess the robustness of the model, with results presented in the form of a tornado diagram. We anticipate undertaking scenario analyses around the number of relatives per proband, excluding benefits associated with relatives, including surveillance for colorectal cancer only, increasing/decreasing the incidence of colorectal cancer, increasing/decreasing the incidence of gynaecological cancers and treating MSI low results as positive and negative. Other scenario analyses will be undertaken as required through model development. Subgroup analysis for people with endometrial cancer under 70 years old and people with endometrial cancer who have previously had a Lynch syndrome related cancer, without germline testing, will be conducted if data permits. Probabilistic sensitivity analysis will be used to determine the impact of joint parameter uncertainty. In probabilistic sensitivity analysis, model parameters are assigned a distribution reflecting the amount and pattern of its variation, and cost-effectiveness results are calculated by simultaneously

selecting random values from each distribution. This process is repeated a number of times, with the 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 will be used to obtain cost-effectiveness acceptability curves (CEAC), which illustrate the effect of sampling uncertainty, and presents the probability that an intervention is optimal at a range of willingness-to-pay (WTP) threshold values.[38]

Areas anticipated to be beyond the scope of the assessment

The EAG's model will consider people with endometrial cancer, which is cancer of the lining of the womb (uterus). Explicitly, we will not consider precancerous conditions that can develop in the lining of the uterus (endometrium) within the model. For example, atypical endometrial hyperplasia is not yet cancer, but if left untreated, there is an increased risk that abnormal cells may become cancerous. To include this population into the model would require the following information:

- Amending the search for the clinical effectiveness review to include terms for atypical endometrial hyperplasia ('atypical hyperplasia' is too broad and would find results from other cancers)
- Incidence of Lynch syndrome in people with atypical endometrial hyperplasia
- How index tests perform in biopsy samples obtained from people with atypical endometrial hyperplasia
- Management/treatment (e.g. procedures) available/offered to people with atypical endometrial hyperplasia and the effectiveness of these strategies
- Effectiveness of prophylaxis and screening in people with atypical endometrial hyperplasia including those who decline prophylactic treatment
- Effectiveness of surveillance of other cancers (e.g. colorectal cancer and ovarian cancer) specifically in patients with atypical endometrial hyperplasia
- Health-related quality of life specifically in patients with atypical endometrial hyperplasia

7. Handling of information from manufacturers

All data submitted by the manufacturers/sponsors/stakeholders will only be considered if received by the External Assessment Group before 1st November 2019. Data that arrives after this date will not be considered. We will extract and quality appraise any data that meets the inclusion criteria, as stated in the methods section of this protocol.

Any 'commercial in confidence' data that is provided by manufacturers, academics, clinicians, or stakeholders, and specified as such, will be highlighted in blue and underlined in the assessment

report (followed by company name in parentheses). Any 'academic in confidence' data that is provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. All confidential data used in the cost-effectiveness models will also be highlighted. If confidential information is included in the model, we will provide a model with 'dummy variable values' for the confidential values (i.e. using non-confidential values).

8. Competing interests of authors and advisors

None of the authors have any competing interests.

9. Timetable/milestones

Draft assessment protocol	11.07.19
Final protocol	7.08.19
Progress report	31.10.19
Draft assessment report	2.01.20
Final assessment report	28.01.20

10. Team members' contributions

Warwick Evidence is an External Assessment Group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. The team planned for the work include:

Name: Chris Stinton
Title: Senior Research Fellow
Address: [redacted]
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Contribution: protocol development, lead clinical effectiveness reviewer, writing up

Name: Mary Jordan
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Name: Mr. Peter Auguste
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Contribution: Protocol development, systematic review of the health economic literature, health economic modelling, and report writing

Name: Hannah Fraser

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Contribution: Protocol development, second clinical effectiveness second reviewer

Name: Rachel Court

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Contribution: Develop the search strategies, undertake searches, write the search methods sections of the draft and final versions of the report and manage references.

Name: Lena Al-Khudairy

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Contribution: Supporting the clinical effectiveness team

Name: Jason Madan

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Address: [redacted]

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Contribution: Protocol development, coordinate health economic modelling, and report writing

Name: Dr Sian Taylor-Phillips

Title: Associate Professor of Screening and Test evaluation

Address: [redacted]

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Contribution: Project lead, design and planning of the review, implementation and write up.

9.1 Expert advisors

Name: Dimitris Grammatopoulos

Title: Professor of Molecular Medicine, Consultant in Clinical Biochemistry

Address: [redacted]

Tel: [redacted]

Email: [redacted]

Contribution: Clinical advisor on testing strategies

Appendix 1. Draft search strategy

Database: Ovid MEDLINE(R) ALL <1946 to July 08, 2019>

Search Strategy:

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1 uterine neoplasms/ (40206)

2 exp endometrial neoplasms/ (20524)

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. (66078)

4 1 or 2 or 3 (91903)

5 exp Colorectal Neoplasms, Hereditary Nonpolyposis/ (4398)

6 (lynch* adj3 syndrome*).ti,ab,kf. (2913)

7 ((lynch* adj3 famil*) and (cancer* or neoplasm*)).ti,ab,kf. (357)

8 (((familial or hereditary or inherit*) adj3 (colon* or colorectal*)) and (cancer or neoplasm*)).ti,ab,kf. (4574)

9 (((hereditary or familial) adj3 (nonpolyposis or non-polyposis)) and (colon* or colorectal*)).ti,ab,kf. (3193)

10 ((hereditary adj3 (cancer or neoplasm*)) and (colon* or colorectal*)).ti,ab,kf. (2874)

11 (familial adj3 (colon* or colorectal*)).ti,ab,kf. (1168)

12 HNPCC.ti,ab,kf. (2231)

13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (8071)

14 (EPCAM? or MLH1 or MSH2 or MSH6 or PMS2 or hMSH2 or hMLH1 or hPMS2 or hMSH6).ti,ab,kf. (9585)

15 (colon* or colorectal* or lynch* or HNPCC or hereditary).ti,ab,kf. (610298)

16 14 and 15 (4450)

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. (8243)

18 Amsterdam criteria.ti,ab,kf. (410)

19 13 or 16 or 17 or 18 (14127)

20 4 and 19 (1535)

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