National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Testing strategies for Lynch syndrome in people with endometrial cancer

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read with NICE's final scope for the assessment and the diagnostics assessment report. A glossary of terms is in appendix B. Academic-in-confidence information is marked [redacted].

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of testing strategies for Lynch syndrome in people with endometrial cancer.

Lynch syndrome is an inherited genetic condition associated with an increased risk of several cancers, particularly endometrial and colorectal cancer. It is caused by mutations in the DNA sequence of mismatch repair (MMR) genes. If a person has Lynch syndrome, these mutations are in every cell of their body and can be identified by genetic testing of non-tumour tissue This testing shows mutations inherited by a person in their 'germline' instead of those that are only in cancerous tissue.

Most endometrial cancers do not happen because of Lynch syndrome (sporadic cancer). Initial tests done on endometrial tumour tissue can help identify how likely it is that the cancer happened because a person has Lynch

syndrome and whether genetic testing of non-tumour tissue should be done to check for the condition.

Testing for microsatellite instability of endometrial tumour tissue or testing for loss of MMR protein using immunohistochemistry, or doing both, can show potential Lynch syndrome. But both tests can give false positives. Another test (*MLH1* promoter hypermethylation testing) can be done. A positive result on tumour tissue for this test shows that the cancer is likely to be sporadic, instead of caused by Lynch syndrome.

These tests can be used in different orders and combinations, called 'testing strategies'. Testing strategies included in this assessment are explained in table 1, and discussed in more detail in the final scope. All strategies include final genetic testing of non-tumour tissue to make a diagnosis of Lynch syndrome. Sometimes this testing can show changes in the sequences of the MMR genes for which it is not known if these changes cause Lynch syndrome or not, these are called variants of uncertain significance. Endometrial cancer can often be the first cancer to happen in people with Lynch syndrome and the best testing strategy may be different to the testing strategies used in colorectal cancer.

Identifying Lynch syndrome at the point of endometrial cancer diagnosis could:

- prevent other cancers in people with Lynch syndrome (such as colorectal cancer) through increased surveillance and strategies to reduce risk
- help to identify family members with Lynch syndrome, to reduce their risk of Lynch-syndrome associated cancers or increase early detection of cancer
- help family members diagnosed at an early age to consider family planning and, if they wish, have risk-reducing interventions, for example, a hysterectomy.

Provisional recommendations on the use of these technologies will be developed by the diagnostics advisory committee at the committee meeting on 27 February 2020.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does testing for Lynch syndrome in people with endometrial cancer represent a cost-effective use of NHS resources?
Populations	All people with endometrial cancer (with unknown Lynch syndrome diagnosis). Relatives of people with endometrial cancer diagnosed with Lynch syndrome who will have cascade testing. If data permits, subgroup analyses could be done for: • people with endometrial cancer under 70 years old • people with endometrial cancer who have previously had a Lynch syndrome related cancer (as defined in NHS England's National Genomic Test Directory Testing Criteria for Rare and Inherited Disease]) without germline testing for Lynch syndrome.
Interventions	Reflex testing strategies to identify Lynch syndrome after a diagnosis of endometrial cancer: • Strategy 1**:** MSI testing followed by germline testing for Lynch syndrome associated mutations. • Strategy 2**:** MSI testing followed by *MLH1* promoter hypermethylation testing, followed by germline testing for Lynch syndrome associated mutations. • Strategy 3: IHC MMR testing followed by germline testing for Lynch syndrome associated mutations. • Strategy 4: IHC MMR testing followed by *MLH1* promoter hypermethylation testing, followed by germline testing for Lynch syndrome associated mutations. • Strategy 5: MSI testing, followed by IHC testing if negative for potential Lynch syndrome (or strategy 1 if MSI detected), followed by germline testing for Lynch syndrome associated mutations. • Strategy 6: MSI testing, followed by IHC testing if negative for potential Lynch syndrome (or strategy 2 if MSI detected), followed by *MLH1* promoter

	hypermethylation testing, followed by germline testing for Lynch-syndrome associated mutations. • Strategy 7: IHC testing, followed by MSI testing if no abnormal MMR protein expression (or strategy 3 if abnormal expression seen), followed by germline testing for Lynch-syndrome associated mutations. • Strategy 8: IHC testing, followed by MSI testing if no abnormal MMR protein expression (or strategy 4 if abnormal expression seen), followed by *MLH1* promoter hypermethylation testing, followed by germline testing for Lynch-syndrome associated mutations. • Strategy 9: MSI and IHC testing, followed by germline testing for Lynch-syndrome associated mutations. • Strategy 10: MSI and IHC testing, followed by *MLH1* promoter hypermethylation testing, followed by germline testing for Lynch-syndrome associated mutations. • Strategy 11: germline testing for Lynch-syndrome associated mutations.
Comparator	No reflex testing.
Healthcare setting	Secondary and tertiary care.
Outcomes	Intermediate measures for consideration may include: • diagnostic accuracy • test failure rate • number of cascade tests on relatives • number of interventions related to surveillance for Lynch-syndrome related cancers (such as colonoscopies) • number of risk-reducing interventions for Lynch-syndrome related cancer (such as prophylactic surgery) • variants detected • concordance between MSI and IHC testing • Time to diagnosis
Clinical outcomes	Clinical outcomes for consideration may include: • number of Lynch syndrome diagnoses • morbidity and mortality of probands

	• morbidity and mortality of relatives • change in patient management (including for relatives of people diagnosed with endometrial cancer) • number of Lynch-syndrome related cancers
Patient-reported outcomes	Patient-reported outcomes for consideration may include: • health-related quality of life • anxiety and depression.
Costs	Costs will be considered from an NHS and personal social services perspective. Costs for consideration may include: • cost of testing (including sample preparation, consumables and staff time to do and interpret tests and obtain patient consent) • cost of cascade testing • cost of genetic counselling • cost of management of Lynch-syndrome related cancers • cost of surveillance for Lynch-syndrome related cancers • cost of risk-reducing interventions The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Abbreviations in table: IHC, immunohistochemistry; MSI, microsatellite instability; MMR, sequence of DNA mismatch repair.

Further details including descriptions of the interventions, comparator, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Test performance

The EAG did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of immunohistochemistry (IHC)- and microsatellite instability (MSI)-based testing strategies for detecting Lynch syndrome in people with endometrial cancer. Details of the systematic review start on page 62 of the diagnostics assessment report.

Test accuracy

The systematic review aimed to identify data on the test accuracy and test failure rates of IHC- and MSI-based strategies for detecting Lynch syndrome in people with endometrial cancer. Data on the time taken to make a diagnosis of Lynch syndrome were also included in the search. The EAG also found data on the concordance (agreement) of IHC and MSI-based testing strategies to detect potential Lynch syndrome. Details of full eligibility criteria start on page 33 of the diagnostics assessment report.

The EAG identified 41 studies (reported in 44 papers) with data on the test accuracy of MSI- and IHC-based strategies for detecting Lynch syndrome in people with endometrial cancer, prevalence of Lynch syndrome in this population, or concordance of MSI and IHC testing done on endometrial tumour samples. One unpublished study (PETALS) was also available as academic in confidence. Full characteristics of the studies are described in the diagnostics assessment report on page 65.

Two studies were done in the UK (Anagnostopoulos et al. 2017, and PETALS). Ten studies (Backes et al. 2009, Bruegl et al. 2017, Dillon et al. 2017, Dudley et al. 2015, Egoavil et al. 2013, Hampel et al. 2006, McConechy et al. 2015, Ring et al. 2016, PETALS, Svampane et al. 2014) were in unselected populations. That is, all patients diagnosed with endometrial cancer during the study's recruitment period were included, without any restrictions by age, cancer histology or family history. Age was used as an inclusion criterion in several other studies (for example, people had to be 50 years old or younger), as was the need to have a previous or other cancer at

the same time as endometrial cancer (including Lynch syndrome associated cancers).

The reference standard used was germline testing for Lynch syndrome causing mutations (that is, genetic testing of a person's non-tumour tissue to look for inherited mutations). This reference standard was included in all strategies being assessed as a final test to confirm suspected Lynch syndrome. So, the EAG's report focused on estimating the accuracy of the various combinations of index tests (MSI, IHC and *MLH1* promoter hypermethylation) in identifying people who could potentially have Lynch syndrome, to be confirmed through testing with the reference standard.

The EAG highlighted that in many studies not all people who had the index test also had the reference standard. For example, only people who tested positive for potential Lynch syndrome on index tests may have gone on to have the reference standard. The EAG highlighted that, while this may reflect how testing is done in clinical practice, it could lead to biased results in accuracy studies (partial verification bias).

The EAG split test accuracy studies into complete (7 studies) and partial (26 studies):

- **Complete test accuracy studies**: People who had index tests (IHC, MSI, *MLH1* promoter hypermethylation testing) went on to have reference standard testing whatever the results of the index tests were. The EAG only included studies in which at least 95% of people who had index tests also had a reference standard test. This was to minimise any possible sampling and spectrum bias that could have happened in studies in which fewer people who had the index test went on to have the reference standard. This 95% criterion excluded 2 studies: Goodfellow et al. (2003, 23% of people having index tests had reference standard) and Ferguson et al. (2014, 75% of people having index tests had reference standard). Further details on these studies can be found in an addendum to the EAG's report.

- **Partial test accuracy studies**: Only people who had a positive result for potential Lynch syndrome after index testing went on to also have the reference standard. The EAG only included studies in which at least 95% of people with positive index tests went on to have reference standard testing. For these studies, only data on the numbers of true and false positive results from index tests were available (that is, no data on true or false negatives needed to calculate sensitivity and specificity).

Data on the prevalence of Lynch syndrome from 31 studies and concordance between IHC and MSI-based testing in 23 studies were also extracted.

Variants of uncertain clinical significance on germline testing were considered as negative for Lynch syndrome in the EAG's test accuracy analysis.

Quality assessment

The EAG used the QUADAS-2 tool to assess the risk of bias and applicability for test accuracy studies. QUADAS-2 measures this using 4 domains: patient selection, index test, reference standard, and flow and timing.

Complete test accuracy studies

The EAG commented that the methodological and reporting quality of the 7 studies was poor. There was a high risk of bias in 2 or more domains for 5 studies, 1 study was at high risk of bias in 1 domain (Tian et al. 2019) and the remaining study was unclear in most domains (Lu et al. 2007). Lu et al. (2007) was used by the EAG for test accuracy values in its base-case analysis. Risk of bias for this study was unclear for most domains (5 out of 7) and low for the rest. Chao et al. (2019) was used in a scenario analysis. This study was considered to have a high risk of bias for patient selection and in the flow and timing domain.

In 5 studies there was a high risk of bias for patient selection, because patients were excluded on the grounds of age, having synchronous cancers (two or more tumours found at the same time or up to 6 months after

diagnosis), or because they were considered to be at low risk of having Lynch syndrome (based on age and family history). In 1 study there was not enough information to determine if there was bias in how patients had been selected (Lu et al. 2007). There was only 1 study with low risk of bias in patient selection, which enrolled patients consecutively (Salvador et al. 2019).

Flow of patients was considered at high risk of bias in 4 studies. Three studies did not include all patients in their analysis (not everyone who had a germline test also had the index tests; Chao et al. 2019, Rubio et al. 2016, Tian et al. 2019) and 1 study did not give all patients the same reference standard (Berends et al. 2003).

The EAG had significant concerns about how applicable the studies were to UK practice for patient selection. None of the 7 studies were done in the UK.

Full details of the quality assessment of complete test accuracy studies are in the diagnostics assessment report from page 86.

Full details of the quality assessment of the partial test accuracy studies are in the diagnostics assessment report from page 91.

Concordance studies

Concordance studies assess how often tests produce the same result. The EAG used a quality appraisal tool for studies of diagnostic reliability (QAREL) to assess studies providing data on concordance between IHC and MSI-based testing (23 studies).

The EAG commented that in general the quality of studies was poor. Only the unpublished PETALS study met the criteria in more than half of the questions. In particular, 18 studies were not considered to be comparable with clinical practice in the UK, with populations selected based on age, type of endometrial cancer and presence of synchronous or metachronous (another diagnosis of cancer 6 months or more after the first one) cancers. Only 3 studies (Bruegl et al. 2017, Egoavil et al. 2013, PETALS) were considered

representative of UK clinical practice. The EAG also highlighted a lack of information on who was doing or interpreting tests, reporting of blinding to the results of other assessors and a patient's clinical status. There was also a lack of information for most studies on order of testing and if testing was done in laboratories participating in quality assurance programmes.

Full details of the quality assessment of these studies are in the diagnostics assessment report from page 97.

2.2 Clinical effectiveness

The EAG did a systematic review to identify evidence on the benefits and harms of testing for Lynch syndrome for people with endometrial cancer and their relatives, with a focus on the benefits and harms of colorectal and endometrial cancer surveillance. Details of the systematic review, including eligibility criteria, start on page 40 of the diagnostics assessment report.

No studies met the inclusion criteria.

Evidence on intermediate outcomes

Prevalence of Lynch syndrome in people with endometrial cancer

Prevalence of Lynch syndrome was lower in studies that recruited unselected samples of people (which matches the population for this assessment), with a median of 3.2% (range 0 to 5.3%). This median value came from the unpublished PETALS study ([redacted] out of [redacted] people tested, including [redacted] known to have Lynch syndrome). In the studies with unselected samples, variants in the *MSH6* MMR gene were the most common (39%), then *MSH2* (32%), *MLH1* (20%) and *PMS2* (9%).

Accuracy of index tests (complete test accuracy studies)

The EAG did not do a meta-analysis of test accuracy because only a few heterogeneous studies were identified. Individual patient data from Lu et al. (2007) were used to inform strategy accuracy estimates in the economic model base case.

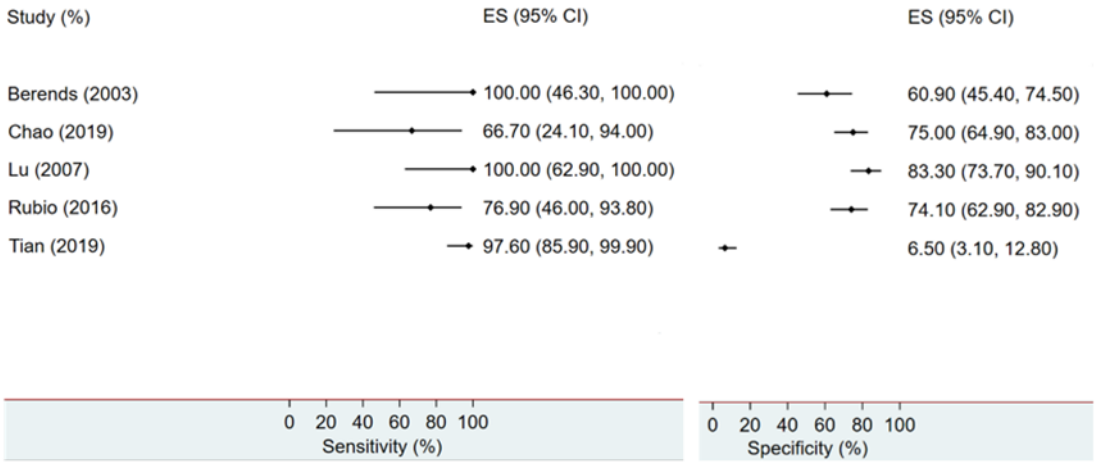
Accuracy of the index tests; that is, MSI- and IHC-based testing strategies used alone, in combination, and with or without subsequent *MLH1* promoter hypermethylation testing, were compared against a reference standard used to determine if a person did have Lynch syndrome. The reference standard used was germline testing (testing of non-tumour tissue) for Lynch syndrome associated mutations in MMR genes.

Four of the complete test accuracy studies assessed both IHC and MSI testing on a common group of people (Lu et al. 2007, Berends et al. 2003, Chao et al. 2019, Rubio et al. 2016). Point estimates for sensitivity ranged from 66.7 to 100% for IHC and from 41.7 to 100% for MSI. For specificity, point estimates for IHC ranged from 60.9 to 83.3%. For MSI the range was 69.2 to 89.9%. The EAG commented that there was no statistically significant difference between the tests.

IHC alone

Data on the accuracy of IHC alone (that is, without *MLH1* promoter hypermethylation testing) were available from 5 studies. Sensitivity and specificity values are shown in figure 1 (variants of uncertain significance were considered as negative for Lynch syndrome). One study (Lu et al. 2007) had data on accuracy by individual MMR proteins. The EAG commented that there were far more false positives for MLH1 (12) than for MSH2 and MSH6 combined (4). If variants of unknown significance were considered as positive for Lynch syndrome (data from 2 studies) estimates of test accuracy were similar.

Figure 1 Sensitivity and specificity of IHC testing alone



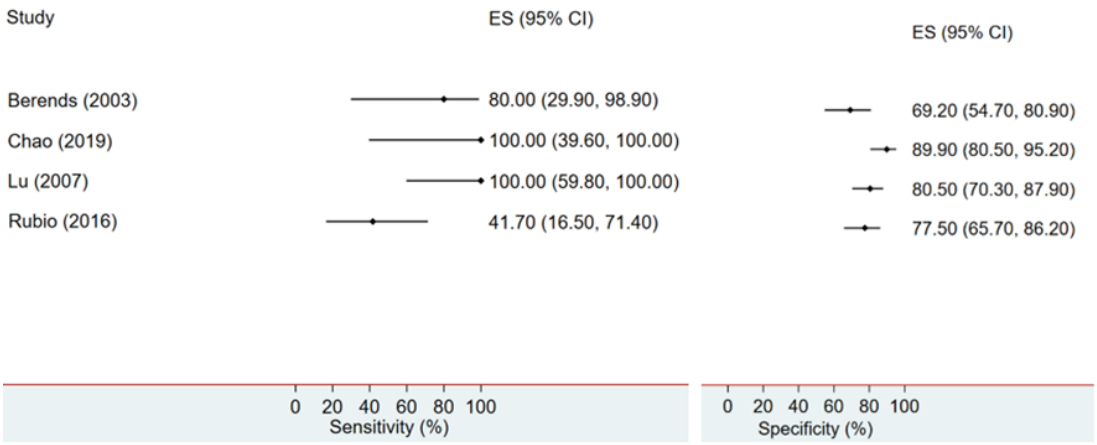
Tests failed in up to 1% of samples across studies (1 out of 522 tumours in total). Across the studies, IHC testing was not done in up to 16.2% of cases because there was insufficient tumour tissue or for other unspecified reasons.

MSI testing alone

Data on the accuracy of MSI testing alone (that is, without *MLH1* promoter hypermethylation testing) were available from 4 studies. Sensitivity and specificity values are shown in figure 2 (variants of uncertain significance were considered as negative for Lynch syndrome). If variants of uncertain significance were considered as positive for Lynch syndrome (data from 2 studies) estimates of test accuracy were similar. Three different panels of MSI markers were used in the studies. Two studies used the same panel of MSI markers (Lu et al. 2007, Rubio et al. 2016)[1]. Samples that were MSI-Low (less than 30% microsatellite markers show instability) were considered as negative for Lynch syndrome in the studies. One study (Rubio et al. 2016) also had accuracy data on when MSI-Low was considered positive for Lynch syndrome. Results were very similar, with only 1 result being reclassified from true negative to false positive after changing the test threshold.

[1] Panels of MSI markers used in studies were: (1) BAT25, BAT26, D2S123, D5S346, and D17S250. (2) BAT25, BAT26, BAT40, D2S123, D5S346, and D173250. (3) BAT-25, BAT-26, NR-21, NR-24, NR-27, and MONO-27

Figure 2 Sensitivity and specificity of MSI testing alone



No test failures were reported in the studies. MSI testing was not done in 1.7 to 25.2% of cases because of insufficient tumour tissue or other unspecified reasons.

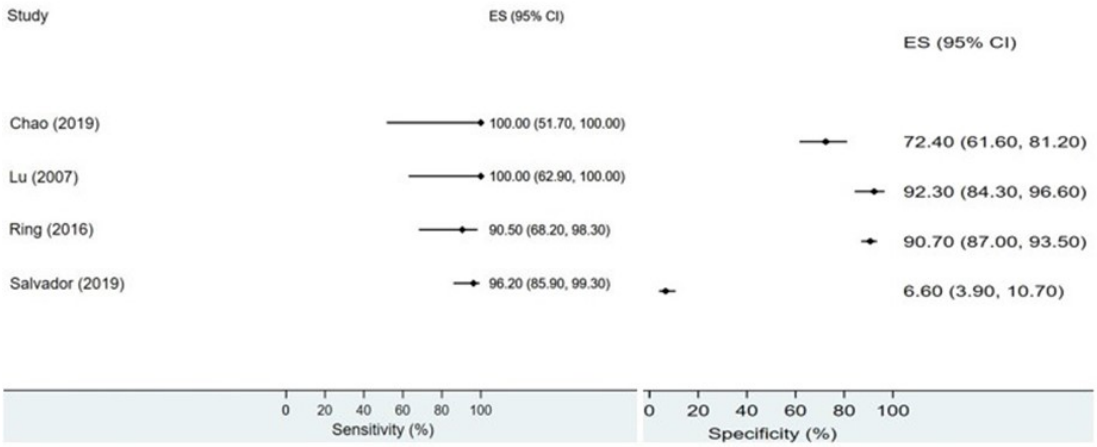
***MLH1* promoter hypermethylation testing after MSI or IHC testing**

There were data on the accuracy of IHC- or MSI-based testing strategies when these tests were done before *MLH1* promoter hypermethylation testing from 4 studies. The studies varied in if *MLH1* promoter hypermethylation testing was done:

- In 2 studies (Lu et al. 2007; Salvador et al. 2019) *MLH1* promoter hypermethylation testing was done for tumours that were categorised as MSI-H or had IHC loss (MLH1 or MLH1/PMS2). In Lu et al. (2007), 92.3% of tumours tested were hypermethylated.
- In Chao et al. (2019) *MLH1* promoter hypermethylation testing was done only if MLH1 loss was seen on IHC; 80% of tumours tested were hypermethylated.
- In Ring et al. (2016) the circumstances for *MLH1* promoter hypermethylation testing were not reported.

Sensitivity and specificity values from the studies are shown in figure 3. If variants of unknown significance were considered as positive for Lynch syndrome (data from 2 studies) estimates of test accuracy were similar.

Figure 3 Sensitivity and specificity when *MLH1* promoter hypermethylation testing was done after MSI or IHC testing (from erratum of EAG's report)



There were limited data on test failure because of *MLH1* promoter hypermethylation testing. No studies reported that *MLH1* promoter hypermethylation could not be done.

Concordance between IHC and MSI testing

Complete concordance between IHC and MSI testing was reported in 20 studies. That is, in these studies IHC and MSI testing were both done on samples whatever the results of 1 of the tests. Full details can be found in the diagnostics assessment report on page 118.

The EAG commented that there was a high level of agreement between IHC and MSI testing. That is, both tests had the same result for potential Lynch syndrome with a median agreement of 91.8% with a range of 68.2% to 100%.

A few studies provided analysis of discordant results (numbers of discordant cases were generally low in studies):

- In 4 studies *MLH1* promoter hypermethylation was common (50% to 83% discordant results).
- In Bruegl et al. (2017) and Lu et al. (2007) in most, or all, discordant results no Lynch-associated germline mutations were found.

- One (out of 7) discordant results in Bruegl et al. (2017) had a germline mutation in the *MSH6* gene, and the only discordant result in Hampel et al. (2006) also had a germline mutation in this gene. In both cases, IHC showed loss of MSH6 but MSI testing showed microsatellite stability.
- In 3 studies (Lu et al. 2007, Bruegl et al. 2017, McConechy et al. 2015) 20% to 57% of discordant results were because of *MLH1* promoter hypermethylation in germline samples.
- In Anagnostopoulos et al. (2017) there were only discordant results if MSI-Low was considered negative for potential Lynch syndrome.

Partial test accuracy studies

The EAG also calculated positive predictive values for the partial test accuracy studies (studies for which data on true or false negatives were not available so sensitivity and specificity values could not be calculated). Results are in the diagnostics assessment report from page 127.

Evidence on clinical outcomes

No studies with data on clinical outcomes met the EAG's inclusion criteria. The most common reason for exclusion was that studies were not randomised controlled trials. Several excluded studies were used to inform parameter estimates for the economic model.

Evidence on patient-reported outcomes

Across 7 studies, 30 out of 100 people declined genetic counselling (Anagnostopoulos et al. 2017, Egoavil et al. 2013, Ferguson et al. 2014, Leenen et al. 2012, Millar et al. 1999, Najdawi et al. 2017, PETALS). Across 15 studies, 76 out of 1,124 people offered germline testing declined it.

2.3 Costs and cost effectiveness

The EAG did a search to identify evidence on the cost effectiveness of testing for Lynch syndrome for people with endometrial cancer using IHC- and MSI-based testing strategies. The EAG also did a de novo economic model to assess the cost effectiveness of the different testing strategies.

Systematic review of cost-effectiveness evidence

The EAG did a systematic review to find studies assessing the cost effectiveness of testing for Lynch syndrome in people with endometrial cancer using IHC- and MSI-based strategies, compared with no testing for Lynch syndrome. Full details are in the diagnostics assessment report on page 180.

Five studies were identified (Resnick et al. 2009, Kwon et al. 2011, Bruegl et al. 2014, Goverde et al. 2016, Snowsill et al. 2019). Snowsill et al. (2019) was the only study which took a UK perspective. This study assessed 6 strategies:

- no testing
- MSI alone
- MSI then *MLH1* promoter hypermethylation testing
- IHC alone
- IHC then *MLH1* promoter hypermethylation testing
- direct to germline testing.

The base-case deterministic results in Snowsill et al. (2019) showed that IHC with *MLH1* promoter hypermethylation testing (strategy 4 in this assessment) was the most cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of about £14,200 per quality-adjusted life year (QALY) gained. The IHC alone strategy (strategy 3 in this assessment) produced the most QALYs and was the most expensive. But, the results were not considered cost effective compared with IHC with *MLH1* promoter hypermethylation, with an ICER of about £129,000 per QALY gained, which is above what NICE normally considers a cost-effective use of NHS resources. Probabilistic analysis showed that there was a 36% probability that IHC with *MLH1* promoter hypermethylation testing was the most cost-effective strategy at a maximum acceptable ICER of £20,000 per QALY gained.

The EAG thought that Snowsill et al. (2019) provided a comprehensive reference model and used this study and previous reviews of testing for Lynch

syndrome for people with colorectal cancer (Snowsill et al. 2014; Snowsill et al. 2017) to inform its modelling approach.

Economic analysis

The EAG developed a de novo economic model to estimate the costs and benefits of offering testing to identify Lynch syndrome (using different testing strategies) for people with a new diagnosis of endometrial cancer. This also included the benefits and costs of offering testing to relatives if Lynch syndrome was identified.

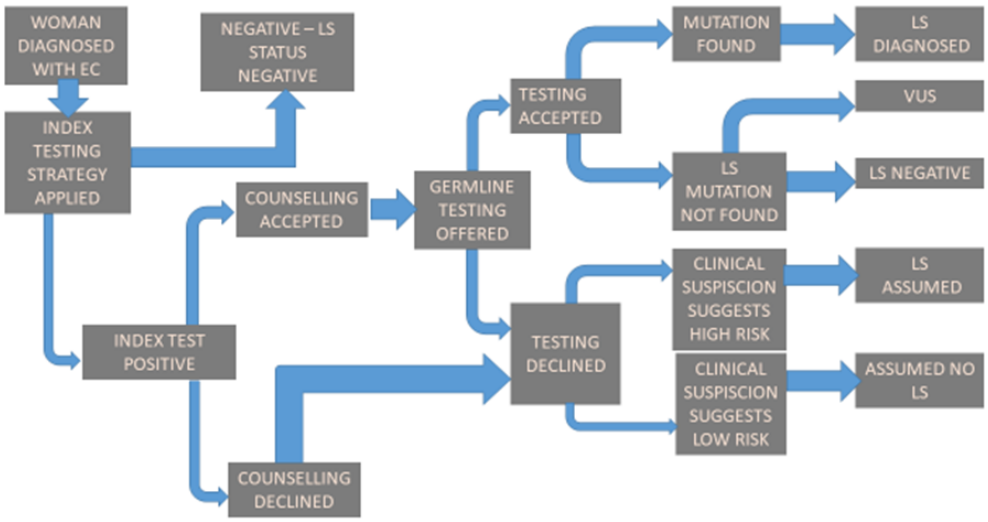
Model structure

The EAG's model had 2 parts. A decision tree (in Excel) modelled the accuracy and costs of the different testing strategies to identify people with Lynch syndrome after being diagnosed with endometrial cancer (known as probands; the first family member to have medical testing for a genetic condition). This also included testing for the relatives of people diagnosed with Lynch syndrome (cascade testing). A second model (in R) then modelled the long-term effects of this diagnosis (and adoption of surveillance and risk-reducing interventions) on colorectal and endometrial cancer incidence across the rest of people's lives.

Initial testing: decision tree

This part of the model estimated the number of people with endometrial cancer who were diagnosed with Lynch syndrome across each of the 11 different testing strategies (compared with no reflex testing for Lynch syndrome). It also estimated the number of relatives of these people who were diagnosed with Lynch syndrome, and the costs associated with testing. An overview of the decision tree is shown in figure 4.

Figure 4 Overview of decision tree for diagnostic testing for Lynch syndrome after diagnosis of endometrial cancer for probands



Initial index tests (IHC, MSI and *MLH1* promoter hypermethylation testing) are used to identify people diagnosed with endometrial cancer who may have Lynch syndrome. If index testing is negative, people are assumed to have sporadic endometrial cancer (and have no further testing). If the index testing is positive for potential Lynch syndrome, people are offered genetic counselling. If people then agree to germline testing, this will either confirm they have Lynch syndrome (LS diagnosed), identify a variant of unknown significance (VUS) or identify no Lynch-causing mutation (LS negative).

If people decline genetic counselling or germline testing and they are considered to have a low risk of Lynch syndrome, they are assumed Lynch syndrome negative (assumed no LS). But, for some people who decline germline testing, there is a clinical suspicion of a high risk of Lynch syndrome. These people are assumed to have Lynch syndrome (LS assumed). The proportion of people with a clinical suspicion of a high risk of Lynch syndrome was taken from the unpublished PETALS study ([redacted]%).

For strategy 11, no index testing happens and everyone with endometrial cancer is offered genetic counselling with subsequent germline testing (if accepted).

The accuracies of the index testing were taken from a study (Lu et al. 2007) in the clinical effectiveness review. This study was used to compare the different testing strategies. Index testing strategies that identified more people with Lynch syndrome for confirmatory germline testing allowed more people to benefit from risk reducing interventions and surveillance (discussed below) that can reduce the risk of other Lynch syndrome associated cancers. But false positive results from index testing (that is, people who turn out not to have Lynch syndrome on germline testing) mean there are costs of more genetic testing but no benefits.

There was no further modelling for people with negative index test results, who may or may not have Lynch syndrome. Index testing strategies that identify fewer people with Lynch syndrome (that is, more false negatives) are penalised in the model because fewer people with Lynch syndrome benefit from the risk-reducing interventions and surveillance that they would have had if Lynch syndrome had been identified.

Outcomes of the diagnostic model

People who are diagnosed with Lynch syndrome by germline testing after endometrial cancer (probands) are offered surveillance and risk-reducing interventions for colorectal cancer but not endometrial cancer. This is because they are assumed to have had a total abdominal hysterectomy and bilateral salpingo-oophorectomy, which is assumed to eliminate all future risk of endometrial cancer. Genetic testing for Lynch syndrome is also offered to their relatives (cascade testing).

People who are assumed not to have Lynch syndrome (that is, positive index testing but decline germline testing and low clinical suspicion of Lynch syndrome) are not offered risk-reducing interventions or surveillance, and no onward testing of their relatives is done. People who are assumed to have

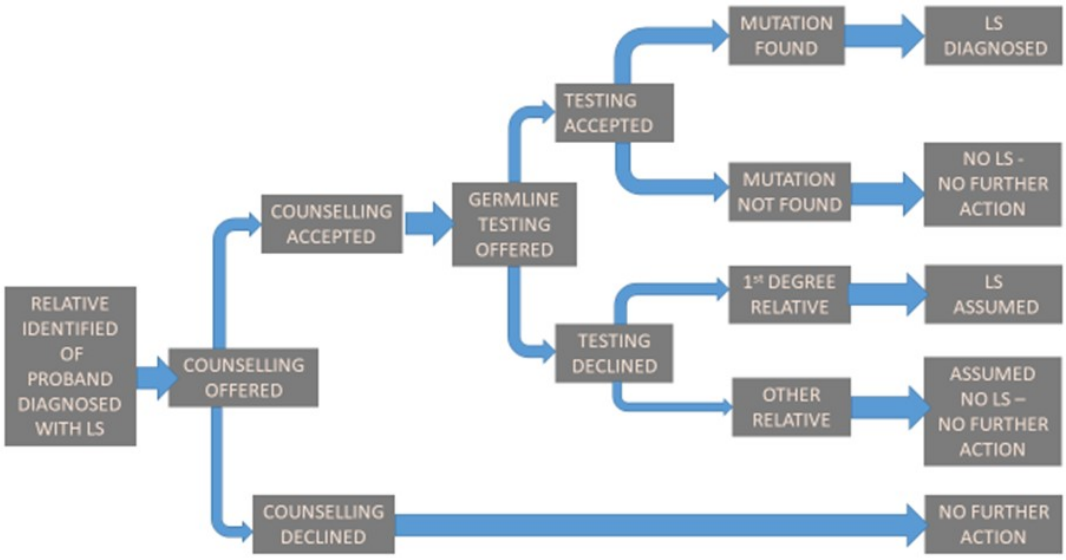
Lynch syndrome (that is, positive index testing but decline germline testing and high clinical suspicion of the condition) are offered surveillance and risk-reducing interventions. This is also offered to their first-degree relatives. Everyone who is assumed to have Lynch syndrome in the absence of germline testing is also assumed to benefit from surveillance and risk-reducing interventions to the same extent as people with Lynch syndrome, even though many of this group will not actually have Lynch syndrome. The EAG noted that it may have overestimated benefit for this group but highlighted that this is likely to have a small effect overall, because it is a small proportion of the total population.

People who test negative for Lynch syndrome causing mutations on germline testing are not offered risk-reducing interventions and no testing of relatives is done. But, a small proportion of this group is assumed to have a variant of uncertain significance identified by genetic testing (1.2%; based on clinical opinion). The EAG thought that this population would be assumed to have Lynch syndrome (LS assumed).

Cascade testing of relatives

Relatives of probands diagnosed with Lynch syndrome only have germline testing to see if they have the same Lynch-causing mutation present (that is, no index testing). Before any genetic testing of relatives, it was assumed that they would be offered genetic counselling (see figure 5).

Figure 5 Overview of decision tree for Lynch syndrome testing for relatives



Relatives diagnosed with Lynch syndrome are offered risk-reducing interventions and surveillance. No further interventions or surveillance are offered if no Lynch-causing mutation is found. First-degree relatives who decline germline testing are assumed to have Lynch syndrome and are offered surveillance and risk-reducing interventions.

First-degree relatives of probands who are assumed to have Lynch syndrome do not have germline testing because no mutation has been identified in the proband to test for. They are all offered risk-reducing interventions and surveillance.

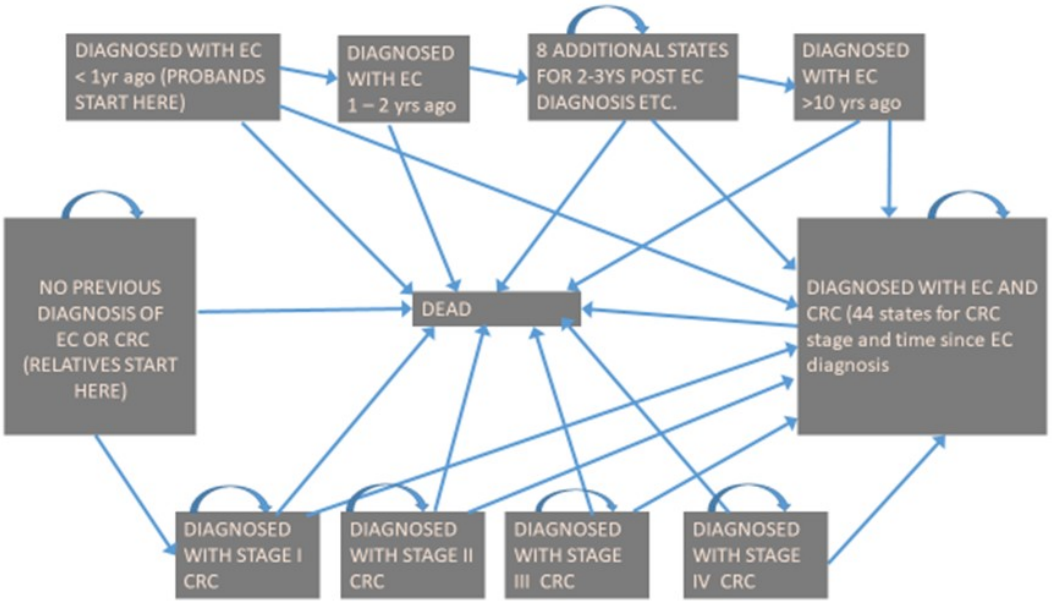
Long-term outcomes model

Risk-reducing interventions and surveillance are offered to probands and relatives with Lynch syndrome (or assumed to have the condition) for colorectal cancer. Unlike probands, who are assumed to have had a total abdominal hysterectomy and bilateral salpingo-oophorectomy and have no risk of having further endometrial cancer, any female relatives diagnosed with Lynch syndrome (who have not had endometrial cancer) are offered risk-reducing interventions and surveillance for endometrial cancer.

A longer-term model was developed to estimate the effect of a diagnosis of Lynch syndrome (and resulting risk-reducing interventions and surveillance) on the occurrence of 2 Lynch-syndrome associated cancers: endometrial and colorectal cancer (see figure 6). This was a Markov cohort state transition model coded in R, with a 1-year cycle length. This modelled people from the moment that they were diagnosed with Lynch syndrome until their death. The EAG used the model to calculate the costs and benefits for people with Lynch syndrome identified at a range of different ages (25 to 74 years old).

Not everyone with a diagnosis of Lynch syndrome was assumed to accept the risk-reducing interventions available in these models.

Figure 6 Overview of long-term model for diagnosis of Lynch-syndrome associated colorectal cancer and endometrial cancer



Probands and relatives diagnosed with Lynch syndrome enter the model without having had colorectal cancer. Probands enter the model having been diagnosed with endometrial cancer (and having had surgery, which means it cannot happen again). Their relatives enter without endometrial cancer, but female relatives can develop endometrial cancer over their lifetime. People can develop both endometrial and colorectal cancer in the model, but only 1 of

each cancer. People can also die from causes other than colorectal or endometrial cancer.

Full details of the model structure are in the diagnostics assessment report from page 53.

The model was used to calculate the benefits of being diagnosed with Lynch syndrome and then adopting risk-reducing measures and surveillance for colorectal and endometrial cancer. This was done by comparing the costs and health-related quality of life calculated by the model when it was run with and without the benefits of these interventions on the incidence and severity of colorectal and endometrial cancer. The risk-reducing and surveillance measures included in the model were:

- People have aspirin, which reduces their risk of developing endometrial and colorectal cancer.
- Colonoscopy occurs every 2 years from age 25 (or the age at which Lynch syndrome is diagnosed) until 74 years old. This both reduces risk of developing colorectal cancer and, if it does occur, increases the likelihood that the cancer will be detected at an earlier stage.
- Female relatives with Lynch syndrome can have a hysterectomy with bilateral salpingo-oophorectomy. This is assumed to eliminate all risk of endometrial cancer.
- Female relatives who have not had surgical prophylaxis have annual surveillance to detect endometrial cancer, with 10% needing a referral for invasive surveillance. This does not reduce incidence of endometrial cancer but reduces mortality by about 10%. In a scenario analysis this intervention is removed from the model.

Population

The cohort of people entering the model with recently diagnosed endometrial cancer were 48 years old. Relatives diagnosed with Lynch syndrome, or Lynch syndrome assumed, could be any age between 25 and 74 years old. The prevalence of Lynch syndrome in this population was taken from the

median prevalence of the condition from 9 studies of unselected people with endometrial cancer: 3.2% (median value was from the unpublished PETALS study).

The proportion of each MMR gene mutation in people with Lynch syndrome was pooled from 4 studies (Hampel et al. 2006, Bruegl et al. 2017, Egoavil et al. 2013, unpublished PETALS study): *MLH1* [redacted]%, *MSH2* [redacted]%, *MSH6* [redacted]% and *PMS2* [redacted]%.

Model inputs

Diagnostic accuracy

The EAG used data from 1 study (Lu et al. 2007) to inform estimates of sensitivity and specificity for the different test strategies for the model. One study was used for consistency (that is, accuracy estimates produced from the same population) and to avoid illogical results, which may have happened if different studies were used for difference strategies. The EAG did not consider that pooling results across studies was appropriate because there were only a few heterogeneous studies.

Lu et al. was not considered to be the most applicable or least biased study for any of the strategies. But it was the only study that provided individual patient level data that could be used to estimate test accuracy for most strategies. Nine out of 100 people with endometrial cancer had Lynch syndrome in this study. The study was done in the USA and enrolled people diagnosed with endometrial cancer before 50 years old. Both MSI and IHC testing was done on samples, then *MLH1* promoter hypermethylation testing (but this was not done for everyone, particularly if they were MSI-High). The IHC protein panel did not include PMS2.

The EAG was able to use individual patient data from this study to estimate sensitivity and specificity for strategies 1, 3, 4, 5, 7, 9 and 11. But it was more difficult to measure accuracy estimates for strategies that had MSI testing then *MLH1* promoter hypermethylation testing. This was because, of the

25 people who had MSI-High tumours, only 13 had *MLH1* promoter hypermethylation testing done as well. All of these were in people with no Lynch-associated germline mutation detected, so sensitivity could not be calculated from these data. The EAG assumed that, when done after an MSI-High result, *MLH1* promoter hypermethylation testing is 'correct' 66% of the time. That is, for people with Lynch syndrome with MSI-High results, *MLH1* promoter hypermethylation testing will correctly lead to germline testing for 66% of cases. For people without Lynch syndrome and MSI-High results, *MLH1* promoter hypermethylation testing will correctly rule out germline testing 66% of the time. The EAG cautioned that test strategies using accuracy estimates produced in this way should be viewed with extreme caution (that is, strategies that use *MLH1* promoter hypermethylation testing after MSI testing; strategies 2, 6, 8 and 10).

Full details on the sensitivity and specificity estimates for the model are in the diagnostics assessment report on page 175. Sensitivity and specificity estimates used in the base-case model are shown in table 2. For strategies 1 to 10 the accuracy estimates refer only to the index tests done. Germline testing will be done in the model for all people considered as having potential Lynch syndrome after the index tests in these strategies (in strategy 11 people go straight to germline testing). In the model germline testing is assumed to have 100% sensitivity and specificity.

The EAG also did a scenario analysis in which accuracy estimates from the unpublished PETALS study were used in the model, for strategies 1, 2, 3, 4, 9 and 10 (see table 2). The EAG commented that [redacted]

[redacted]

Table 2 Sensitivity and specificity estimates used across strategies in base case and scenario analysis

Strategy	Accuracy estimates derived from Lu et al. (2007) (Base case)		Accuracy estimates from PETALS study (scenario)	
	Sensitivity	Specificity	Sensitivity	Specificity
Strategy 1 MSI alone	1.000	0.805	0.563	0.837
Strategy 2 MSI then *MLH1* promoter hypermethylation testing	0.625	0.966	0.563	0.969
Strategy 3 IHC alone	1.000	0.833	1.000	0.810
Strategy 4 IHC then *MLH1* promoter hypermethylation testing	1.000	0.967	1.000	0.975
Strategy 5 MSI then IHC	1.000	0.782	Same as base case	Same as base case
Strategy 6 MSI then IHC then *MLH1* promoter hypermethylation testing	0.625	0.954	Same as base case	Same as base case
Strategy 7 IHC then MSI	1.000	0.791	Same as base case	Same as base case
Strategy 8 IHC then MSI then *MLH1* promoter hypermethylation testing	1.000	0.942	Same as base case	Same as base case
Strategy 9 MSI and IHC	1.000	0.791	1.000	0.795
Strategy 10 MSI and ICH then *MLH1* promoter hypermethylation testing	1.000	0.942	1.000	0.961
Strategy 11 No index tests (straight to	1.000	1.000	Same as base case	Same as base case

germline)				

Further model parameters

Acceptance of genetic counselling and germline testing

The following assumptions were made about the uptake of germline testing and genetic counselling:

- 92.5% of probands attend genetic counselling after a positive index test result (Snowsill et al. 2014).
- 95% of people attending genetic counselling go on to have germline testing (expert opinion).
- For strategy 11 (no index tests, direct to germline testing), 50% of people are assumed to accept germline testing (Snowsill et al. 2019).

Testing for relatives

The following assumptions were made about offering testing for Lynch syndrome to the relatives of probands:

- There are 6 relatives per proband (2.5 of which are first-degree relatives; Snowsill et al. 2014).
- All 6 relatives contact a GP and 77.5% are referred to a genetic counsellor (Menko et al. 2019). Of these, 76.7% have germline testing for Lynch syndrome (Barrow et al, 2014).
- 44% of relatives who are tested have Lynch syndrome (Snowsill et al. 2014).

Colorectal cancer incidence and effect of surveillance

Age-related incidence of colorectal cancer for people with Lynch syndrome was taken from Snowsill et al. (2019). This was assumed to differ by which MMR gene was mutated and was estimated using gene specific data from the Prospective Lynch Syndrome Database. A log-normal distribution was fitted to the data to estimate the incidence of colorectal cancer over time (based on this model having the best fit to the data, according to Akaike Information Criterion). A hazard ratio of 0.387 (Jarvinnen et al. 2000) was applied to estimate the effect of colonoscopic surveillance on reducing the incidence of

colorectal cancer. The EAG highlighted that this was an observational study which could have considerable bias. But there was no more relevant recent data, and effectiveness may have increased since 2000 when the study was done. The EAG also did an extreme scenario analysis which assumed no benefit of surveillance on colorectal cancer incidence. A further scenario also assumed a colonoscopy every 3 years, rather than every 2 years.

Mortality risk increased by stage of cancer. The proportions presenting with colorectal cancer were 18.8% for stage 1, 48.8% for stage 2, 21.3% for stage 3 and 11.3% for stage 4 (Snowsill et al. 2019). If a person was having colonoscopic surveillance because their Lynch syndrome had been diagnosed, this was assumed to identify colorectal cancer at an earlier stage (as well as reducing incidence). The proportions with each stage of colorectal cancer for a person in this case were 68.6% for stage 1, 10.5% for stage 2, 12.8% for stage 3 and 8.1% for stage 4.

Endometrial cancer incidence, surgical prophylaxis and gynaecological surveillance

Incidence data for endometrial cancer were taken from the Prospective Lynch Syndrome Database (Dominguez-Valentin et al. 2020). The incidence differed by which MMR repair gene was mutated. A fitted piecewise linear model was used to estimate annual incidence at different ages.

Data from Cancer Research UK on uterine cancer survival statistics were used for the incidence of death from endometrial cancer, assuming no difference for people with and without Lynch syndrome.

Female relatives with Lynch syndrome could choose to have hysterectomy with bilateral salpingo-oophorectomy, which eliminated all future risk of endometrial cancer. The uptake of this surgery increased with age, from 20% at 35 years old to 80% at 75 years old.

The EAG highlighted considerable uncertainty about the benefit of gynaecological surveillance, and variation in practice across the UK. In its

base case, the EAG assumed all female relatives with Lynch syndrome who were 25 years or older (who had not had a hysterectomy) would have annual non-invasive surveillance done by a GP. Of these, 10% would be referred for invasive surveillance (gynaecological examination, pelvic ultrasound, cancer antigen-125 analysis and aspiration biopsy). Gynaecological surveillance was assumed to reduce mortality by 10.2% (Snowsill et al. 2017). The EAG also did a scenario analysis in which no gynaecological surveillance was done.

Aspirin

Everyone diagnosed with Lynch syndrome is assumed to take aspirin, which reduces the annual probability of developing colorectal and endometrial cancer by 44% (based on the CaPP2 trial results). This is assumed to occur for the rest of a person's lifetime. A scenario analysis removes aspirin use from the model.

Costs

Most costs were from work done for previous NICE guidance on testing for Lynch syndrome after colorectal cancer (Snowsill et al. 2017). Hospital-related costs were from the most current NHS reference tables.

The EAG used test costs from the UK Genetic Testing Network (confirmed by clinical experts) in the base case (table 3). It also used costs from a micro-costing study (Ryan et al. 2019) in a scenario analysis. The EAG cautioned that these costs were obtained from a major tertiary centre and it considered them to be extremely low.

Table 3 Test costs used in base-case and scenario analysis

Test	Base-case cost	Scenario analysis cost
IHC	£210	£21
MSI	£217	£28
MLH1 hypermethylation testing	£156	£28
Germline testing (probands for all 4 MMR genes)	£755	£176
Predictive mutation testing for relatives (single MMR gene)	£165	£165

The source for the base-case analysis was the UK Genetic Testing Network. The source for the scenario analysis was Ryan et al (2019). No breakdown of costs for predictive mutation testing per single MMR gene was in Ryan et al., so the EAG used the base-case value from the UK Genetic Testing Network.

Further testing-related costs are shown in table 4.

Table 4 Further testing related costs

Event	Cost	Source
Offering counselling to a proband (15 minutes of band 6 nurse time)	£28	NHS Reference Costs
Referral for a relative for genetic counselling (cost of a GP appointment)	£39	NHS Reference Costs
Pre-germline testing genetic counselling/MDT review for probands	£642	Slade et al. (2016) and expert opinion
Pre-germline testing genetic counselling/MDT review for relatives	£514	Slade et al. (2016) and expert opinion
Post-test genetic counselling (probands and relatives) done for everyone having germline testing regardless of result (largely clinic related administrative costs)	£141	Slade et al. (2016) and expert opinion

Colonoscopy was assumed to cost £325. An additional cost was added to this assuming that a small proportion of people having colonoscopies will need some subsequent hospital treatment (for perforations and bleeding events).

A one-off cost for colorectal cancer was used (depending on the patient age and stage at diagnosis). These costs were taken from Snowsill et al. (2019)

who used data from the Economic Evaluation of Health and Social Care Interventions Policy Research Unit, based on a whole-disease model of colorectal cancer (table 5).

Table 5 One-off costs for colorectal cancer applied in model

Age	Stage 1	Stage 2	Stage 3	Stage 4
0 to 49	£8,754	£8,741	£14,490	£11,705
50 to 59	£5,712	£7,016	£9,692	£8,444
60 to 69	£4,623	£5,352	£7,259	£6,509
70 to 79	£3,178	£3,455	£4,485	£4,365
80 and above	£1,380	£1,546	£1,561	£807

For endometrial cancer, a one-off cost of £6,510 was assumed (Snowsill et al. 2017). Prophylactic hysterectomy and bilateral salpingo-oophorectomy was assumed to cost £3,428. Annual gynaecological surveillance was assumed to cost £39, with an additional cost of £473 if referral for invasive surveillance was needed (10% of people).

No cost for aspirin was included.

Health-related quality of life and QALY decrements

Baseline health-related quality of life for relatives and probands in the model was calculated based on age and sex. Testing, the results of a diagnosis of Lynch syndrome, surveillance and risk-reducing interventions were assumed to have no effect on health-related quality of life.

In the base case, a decrease in health-related quality of life for people with colorectal cancer was only assumed to occur at stage 4 (a multiplier of 0.789; Snowsill et al. 2017). Because this may underestimate the effect of colorectal cancer on a person's quality of life, the EAG did a scenario analysis in which people with stage 3 colorectal cancer also experienced a decrease in health-related quality of life.

The health-related quality of life of people with endometrial cancer decreased by 0.036 (Snowsill et al. 2017) for 1 year.

Further key assumptions

The following assumptions, in addition to those discussed previously, were applied in the base-case analysis:

- Acceptance of MSI, IHC and *MLH1* promoter hypermethylation testing was 100%.
- MSI-Low results were treated as negative for Lynch syndrome.
- The sensitivity of MSI and IHC testing did not depend on which MMR gene was mutated.
- The cost of somatic analysis to determine if a variant of unknown significance is pathogenic was not included in the model.
- Test failure rate for MSI and IHC testing was 0% (median from systematic review).
- Germline testing is assumed not to give false positive results. That is, no one is falsely diagnosed with Lynch syndrome.
- Surveillance colonoscopies are immediately effective, and stop being effective as soon as they are stopped.
- Treatment for endometrial cancer was assumed to be total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without chemotherapy and radiotherapy.

Base-case results

For the purposes of decision making, the ICERs per QALY gained or lost will be considered. Full cost-effectiveness results are in the diagnostics assessment report from page 226.

When compared independently to no testing, all strategies had an ICER of less than £17,500 per QALY gained. The fully incremental analysis (that is, all testing strategies compared against each other as well as no testing) is shown in table 6.

Table 6 Fully incremental base-case cost-effectiveness results (deterministic)

Strategy	Incremental costs	Incremental QALYs	ICER
No testing	–	–	–
Strategy 2 MSI then *MLH1* promoter hypermethylation testing	£520	0.0419	Extendedly dominated
Strategy 4 IHC then *MLH1* promoter hypermethylation testing	£630	0.0669	£9,420
Strategy 6 MSI then IHC then *MLH1* promoter hypermethylation testing	£90	-0.0249	Dominated
Strategy 3 IHC alone	£160	0.0012	£133,330
Strategy 1 MSI alone	£50	0.0002	£250,000
Strategy 8 IHC then MSI then then *MLH1* promoter hypermethylation testing	£30	-0.0012	Dominated
Strategy 10 MSI and IHC then then *MLH1* promoter hypermethylation testing	£20	0.0000	Dominated
Strategy 7 IHC then MSI	£185	0.0002	£925,000
Strategy 5 MSI then IHC	£5	0.0000	Dominated
Strategy 9 MSI and IHC	£45	0.0000	Dominated
Strategy 11 No index testing (straight to germline testing)	£135	-0.0019	Dominated

Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year. Extendedly dominated means the ICER for a given strategy is higher than that of the next, more effective, alternative (that is, it is dominated by the combination of 2 alternatives and should not be used to calculate appropriate ICERs). Dominated means if a strategy has higher costs and worse outcomes than an alternative strategy.

The number of people with Lynch syndrome detected by the different strategies and outputs from the long-term model for colorectal and endometrial cancer are in the diagnostics assessment report from page 229.

Analysis of alternative scenarios

The EAG did several scenario analyses:

- Scenario 1: Using alternative test accuracy estimates (for strategies 1, 2, 3, 4 and 11) from the unpublished PETALS study.
- Scenario 2: Using alternate test costs from a micro-costing study (Ryan et al. 2019).
- Scenario 3: Combining scenarios 1 and 2.
- Scenario 4: Including further disutility for colorectal cancer (for stage 3).
- Scenario 5: Excluding gynaecological surveillance (cost and benefits).
- Scenario 6: Colonoscopy assumed to be every 3 years (instead of 2).
- Scenario 7: Aspirin removed from model.
- Scenario 8: Surveillance for colorectal cancer assumed to have no benefit.

For each of these scenario analyses an ICER per QALY gained was calculated. If a strategy was extendedly dominated it means its ICER was higher than that of the next, more effective, alternative (that is, it is dominated by the combination of 2 alternatives and should not be used to calculate appropriate ICERs). Dominated means if a strategy has higher costs and worse outcomes than an alternative strategy.

In all scenarios except scenario 8, IHC then *MLH1* promoter hypermethylation testing (strategy number 4) had an ICER of less than £12,000 per QALY gained in fully incremental analyses. In scenario 8, the ICER was £20,740 per QALY gained. In all scenarios except scenario 4, all other strategies were either extendedly dominated, fully dominated or had ICERs of over £90,000 per QALY gained (fully incremental analysis). In scenario 4, the ICER for IHC testing alone was £41,180 per QALY gained in the fully incremental analysis.

The EAG also did further scenario analyses in an addendum to their main report. In additional scenario 1, diagnostic accuracy estimates from a meta-analysis done for recent modelling work (Snowsill et al. 2019) were used instead of estimates from Lu et al. (2007). Accuracy data were only available for strategies using MSI and IHC alone (with or without subsequent *MLH1* promoter hypermethylation; strategies 1 to 4 in this assessment). In fully incremental analysis IHC with *MLH1* promoter hypermethylation testing had an ICER of £10,464 per QALY gained and IHC alone had an ICER of about £100,000 per QALY gained. MSI and MSI done before *MLH1* promoter hypermethylation were either dominated or extendedly dominated.

In additional scenario 2, accuracy data from Chao et al. (2019) were used. Only accuracy estimates for IHC and MSI alone were available. Here, MSI extendedly dominated IHC testing and had an ICER of £10,455 per QALY gained compared to no testing. In Chao et al. higher estimates of both sensitivity and specificity were seen for MSI testing than IHC testing (see figures 1 and 2).

In additional scenario analysis 3, people with variations of uncertain significance and people who were Lynch assumed did not gain any benefit from surveillance and risk-reducing interventions (in the base case, they were assumed to get the same benefit as people with Lynch syndrome). IHC with *MLH1* promoter hypermethylation had an ICER of £9,514 per QALY gained and dominated or extendedly dominated all other strategies.

Sensitivity analyses

The EAG only did sensitivity analyses (deterministic and probabilistic) for strategy 4 (IHC then *MLH1* promoter hypermethylation testing), compared with no testing, because in the base-case analysis this strategy was the most cost effective.

In one-way sensitivity analysis, changing the number of relatives who accepted genetic counselling (who then go on to have testing for Lynch syndrome) had the largest effect on the ICER. Decreasing the number of

relatives who accept counselling by 50% caused the ICER to increase to about £14,000 per QALY gained. Decreasing the prevalence of Lynch syndrome had the second largest increase upwards effect on the ICER. A decrease to 1.7% of people with endometrial cancer having the condition led to an increase in the ICER to about £13,640 per QALY gained.

Full details can be found in the diagnostics assessment report on page 252.

The probabilistic ICER for strategy 4 (10,000 simulations) was £11,600 per QALY gained (compared with a deterministic ICER of £9,420 per QALY gained). The cost-effectiveness acceptability curve is shown in figure 7. At a maximum acceptable ICER of £20,000 per QALY gained, this strategy had 93% probability of being cost effective compared to no testing.

Figure 7 Cost-effectiveness acceptability curve for IHC testing then MLH1 promoter hypermethylation testing (compared to no testing)

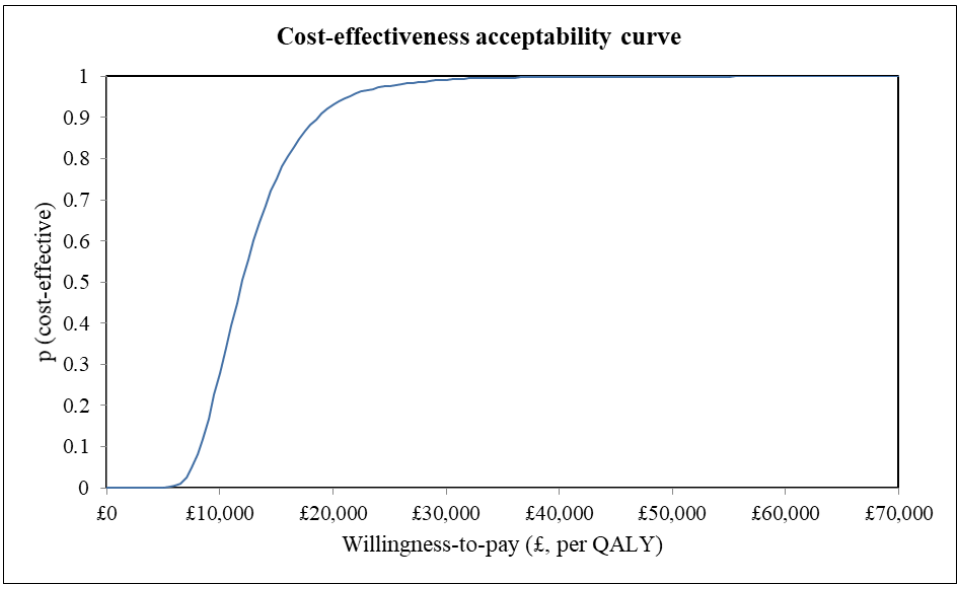
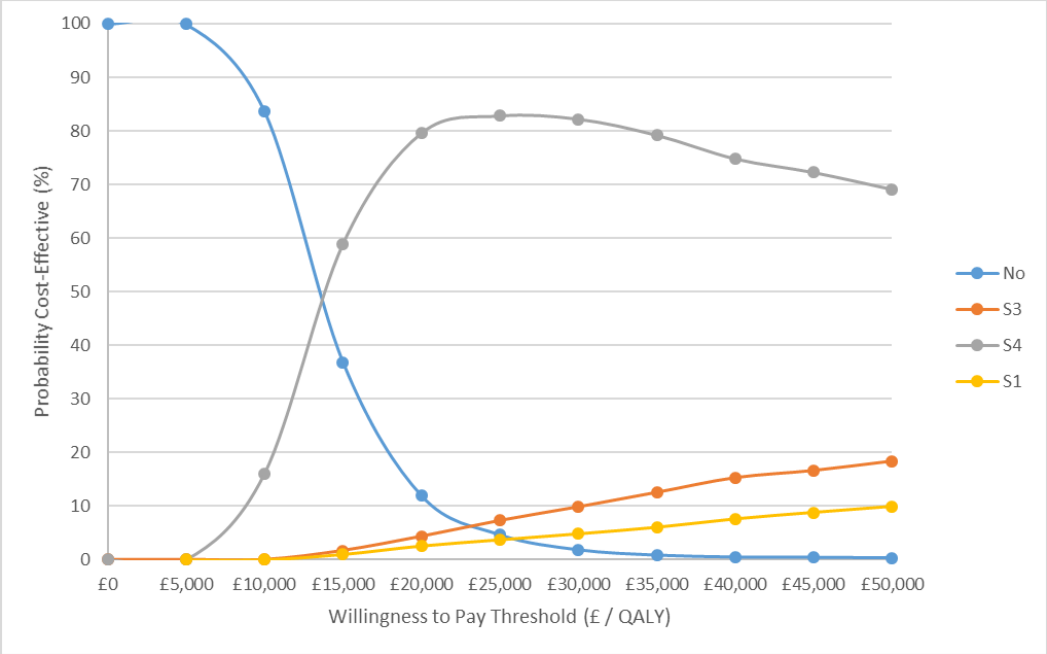


Figure 8 shows a cost-effectiveness acceptability curve when all strategies with a probability of cost effectiveness of 5% or higher were included.

Figure 8 Cost-effectiveness acceptability curve for all strategies with a probability of cost effectiveness of 5% or more (from the EAGs addendum to its report)



3 Summary

Clinical effectiveness

No clinical outcome data on the benefits of testing for potential Lynch syndrome using microsatellite instability (MSI)- or immunohistochemistry (IHC)-based strategies were found.

The EAG identified 4 studies that directly compared IHC and MSI testing. It commented that none of these studies showed a clear difference in accuracy. The EAG explained that there was high concordance in IHC and MSI testing in most studies.

Studies suggested that adding *MLH1* promoter hypermethylation testing after IHC increased the specificity of the testing strategy. There was little data showing the effect of *MLH1* promoter hypermethylation testing when used after an initial MSI test.

Cost effectiveness

When compared with no testing, all strategies had incremental cost-effectiveness ratios (ICERs) of less than £20,000 per quality-adjusted life year (QALY) gained in the base case. In fully incremental analysis, IHC then *MLH1* promoter hypermethylation testing (strategy 4) had an ICER of about £9,420 per QALY gained in the base case. All other strategies were either extendedly or fully dominated or had an ICER of over £130,000 per QALY gained. Cost-effectiveness results were robust to changes in the model (scenario and one-way sensitivity analysis). Only if no benefit from colonoscopic surveillance was assumed did the ICER for IHC then *MLH1* promoter hypermethylation increase to over £20,000 per QALY gained.

The conclusions from the EAG's economic model are similar to those of a recent publication (Snowsill et al. 2019) which also identified IHC then *MLH1* promoter hypermethylation as the most cost-effective strategy (although this study did not assess strategies that used both IHC and MSI testing).

Use of test accuracy data from an unpublished study (PETALS) showed that IHC then *MLH1* promoter hypermethylation testing was the most cost effective at a maximum acceptable ICER of £20,000 per QALY gained, which is the amount NICE usually considers a cost-effective use of NHS resources. Using test accuracy data from a meta-analysis from Snowsill et al. (2019) also produced similar results. Using test accuracy data from Chao et al. (2019) for MSI and IHC testing alone did produce different cost-effectiveness results, with MSI and no testing extendedly dominating IHC testing. This is because in this study MSI testing had better sensitivity and specificity than IHC testing.

4 Issues for consideration

Clinical effectiveness

There were limited data on the accuracy of the different testing strategies.

In its review of test accuracy studies, for complete test accuracy studies the external assessment group (EAG) only included studies in which 95% of people who had index testing had the reference standard. Studies that did not match this criterion were excluded from the review. This was because of concern about a possible systematic reason why people decline or are not offered the reference standard test. Excluded studies are in in the EAG's addendum to its report.

Studies showed high concordance of IHC and MSI testing. It is uncertain if either of these tests has an advantage when used as an initial test done on endometrial tumour samples for potential Lynch syndrome.

Cost effectiveness

There were limited data to inform the accuracy of the different test strategies. The EAG used one study (Lu et al. 2007, n=100) which allowed accuracy estimates for the strategies to be from the same population. In order to make accuracy estimates for *MLH1* promoter hypermethylation after an MSI-High result, the EAG had to assume the likely effect of the test. This assumption may have underestimated the accuracy of MSI followed by *MLH1* hypermethylation testing (strategy 2). The sensitivity estimates for strategies in which *MLH1* promoter hypermethylation testing was done after MSI are far lower than when this test was done after IHC (62.5% compared with 100%). So, cost effectiveness of strategy 2 may be better than the base-case results are suggesting.

Use of alternative data sources for test accuracy estimates did have some effect on cost-effectiveness results. Using data from Lu et al. (2007, base case), the PETALS study and a meta-analysis (Snowsill et al. 2019) showed IHC then *MLH1* promoter hypermethylation testing as the best strategy. But, data from Chao et al. (2019) suggested that MSI strategies may be more cost effective. But this study did not provide data on the effect of subsequent *MLH1* promoter hypermethylation.

There is uncertainty about the benefit of surveillance colonoscopies for people with Lynch syndrome.

There is also uncertainty about the benefit of gynaecological surveillance. No harms from this were included in the model. Removing gynaecological surveillance from the model had a small effect on results.

The effect on health-related quality of life of colorectal and endometrial cancer may have been underestimated. Because the benefit of the testing strategies is to reduce the incidence, and severity, of these cancers, this may have underestimated their cost effectiveness.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

All people with cancer are covered under the disability provision of the Equality Act (2010) from the point of diagnosis. Information from tests in this assessment may influence decisions on fertility and conception. Pregnancy is a protected characteristic under the Equality Act.

The specificity of microsatellite instability (MSI) or immunohistochemistry (IHC) to detect potential Lynch syndrome associated endometrial cancer may decrease in older cohorts because somatic MLH1 promoter hypermethylation increases with age (that is, a larger proportion of endometrial tumours with deficient MMR will be because of somatic, rather than inherited, causes).

Clinical experts highlighted that endometrial cancer is often the first Lynch syndrome related cancer that happens in women with the condition. Testing people at the point of endometrial cancer diagnosis will provide an opportunity to identify the condition earlier and prevent later Lynch-syndrome related cancer.

Clinical experts further commented that the numbers of variants of uncertain significance identified may vary by ethnicity. People from ethnic groups in which few studies identifying mutations in Lynch syndrome associated genes have been done are more likely to have a variant of unknown significance identified by testing.

6 Implementation

The NICE adoption and impact team noted the following, which should help with implementing testing strategies:

- Pathways and systems for testing for Lynch syndrome for people with colorectal cancer have already been implemented in the NHS.
- There is an understanding among clinicians about the importance of knowing if someone has Lynch syndrome.

The NICE adoption and impact team noted potential barriers to implementing testing strategies:

- The need for multiple departments and specialities to work together to oversee the testing strategies and respond to results.
- Funding streams for tests, cross-clinical commissioning groups and specialist NHS England commissioned services.
- Increased workload for laboratories and genetic services.
- The need for coordinated reporting of results, potentially from different laboratories.
- The need to ensure that appropriate counselling and consent for testing is done.
- New pathways may need to be established if different strategies to those used for colorectal cancer are recommended.
- Interpreting immunohistochemistry tests can be challenging. Trained staff and quality assurance mechanisms would need to be in place to ensure accuracy of results.

- Increase in workload for procedures needed for cancer surveillance (for example, colonoscopies) if more people are diagnosed with Lynch syndrome.
- Uncertainty about whether surveillance for gynaecological cancer, or other Lynch-syndrome related cancers, should be done if a person is diagnosed with Lynch syndrome.
- Access to testing may be more difficult for people who have been previously treated for a Lynch-syndrome related cancer abroad because the relevant medical records and tumour samples needed to make this decision might not be available.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Warwick Evidence:

Testing strategies for Lynch syndrome in people with endometrial cancer. Diagnostics commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Sponsor of technologies included in the final scope:

- The University of Manchester

Other commercial organisations:

- Biocartis NV
- Promega UK Ltd

Professional groups and patient and carer groups:

- Association of Surgical Oncology
- British Association of Gynaecological Pathologists
- British Gynaecological Cancer Society
- The EVE Appeal
- Institute of Biomedical Science
- Ovarian Cancer Action
- Oxford University Hospitals NHS Foundation Trust
- Portsmouth Hospitals NHS Trust
- Royal College of Physicians
- Royal College of Radiologists

- UK Cancer Genetics Group
- UK Clinical Genetics Society

Research groups:

- Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Review Group
- University of Exeter Medical School, Health Economics Group

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency
- NHS England

Appendix B: Glossary of terms

Epigenetic
Changes to DNA other than to its base sequence (A, C, G and T) that can affect how DNA is used to produce proteins. An example includes methylation of DNA (see below).

Germline mutation
A change in the DNA of a body's reproductive cells that is present in the DNA of every cell of their offspring.

Hypermethylation
An increase in the epigenetic methylation of DNA.

Lifetime risk
The risk that an event (for example, cancer) will happen during a person's lifetime.

Methylated
DNA that is altered by the addition of a methyl group. When this happens in a gene's promoter region it can supress gene expression.

Microsatellite instability
Expansion or reduction in the length of repetitive DNA sequences (microsatellites) in tumour DNA compared to normal DNA.

Proband
The first family member to have medical testing for a genetic condition.

Somatic mutation
A change in the DNA in any cells of the body, except the germ cells (sperm and egg), which is not passed to a person's children. These changes to the DNA a person inherited from their parents can accumulate over a person's lifetime as their cells divide. If somatic mutations occur in cell growth control genes this can lead to uncontrolled cell growth and tumour formation.

Reflex testing
Testing that is done automatically in response to patient characteristics or the results of other tests.