# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# DIAGNOSTICS ASSESSMENT PROGRAMME

## Diagnostics consultation document

# Testing strategies for Lynch syndrome in people with endometrial cancer

The National Institute for Health and Care Excellence (NICE) is producing guidance on testing strategies for Lynch syndrome in people with endometrial cancer in the NHS in England. The diagnostics advisory committee has considered the evidence and the views of clinical and patient experts.

**This document has been prepared for public consultation.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the diagnostics assessment report and the diagnostics assessment report addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound, and a suitable basis for guidance to the NHS?

**Equality issues**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology



Issue date: June 2020

- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

**Note that this document is not NICE's final guidance on testing strategies for Lynch syndrome in people with endometrial cancer. The recommendations in section 1 may change after consultation.**

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering the comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the diagnostics assessment programme manual.

**Key dates:**

Closing date for comments: 13 July 2020

Second diagnostics advisory committee meeting: 6 August 2020

# 1 Recommendations

1.1 Offer testing for Lynch syndrome to people who are diagnosed with endometrial cancer. Use these tests:

- Do immunohistochemistry (IHC) testing to identify tumours with mismatch repair (MMR) deficiency.
- If IHC is positive, do MLH1 promoter hypermethylation testing of tumour DNA.
- If the MLH1 promoter hypermethylation test is negative, confirm Lynch syndrome by genetic testing of germline DNA.

1.2 Healthcare professionals should inform people about the possible implications of test results for both themselves and their relatives, and give support and information. Discussion of genetic testing should be done by a healthcare professional with appropriate training.

1.3 Laboratories doing IHC for MMR proteins should take part in a recognised external quality assurance programme.

**Why the committee made these recommendations**

Lynch syndrome is an inherited condition that increases the risk of certain types of cancer, including endometrial and colorectal cancer. Testing for Lynch syndrome is recommended after a diagnosis of colorectal cancer. But endometrial cancer is often the first cancer that people with Lynch syndrome will have. So, Lynch syndrome could be identified earlier if tests were done after a diagnosis of endometrial cancer.

If Lynch syndrome is diagnosed, treatment and surveillance can be offered to reduce the risk of having another Lynch syndrome-associated cancer (in particular colorectal cancer) or identify it earlier. Genetic testing for Lynch syndrome can also be offered to relatives with the aim of preventing Lynch syndrome-associated cancer developing or detecting it at an early stage.

Several types of tests can be done in different orders and combinations to see if endometrial cancer is likely to have been caused by Lynch syndrome. Economic modelling has shown that IHC testing then MLH1 promoter testing is likely to be the most cost-effective approach. If it looks like a person may have Lynch syndrome after both tumour tests have been done, genetic testing of a person's non-tumour DNA should be done to confirm this.

It is important that support and information are available for people deciding to be tested for Lynch syndrome.

# 2 The diagnostic tests

## *Clinical need and practice*

2.1 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, or near, 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.

2.2 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 relatives with Lynch syndrome, to reduce their risk of Lynch syndrome-associated cancers or increase early detection of cancer
- help relatives diagnosed at an early age to consider family planning and, if they wish, have risk-reducing interventions, for example, a hysterectomy.

2.3 Currently, testing for Lynch syndrome in people diagnosed with endometrial cancer is often not done, or may only be done, for people with an identified risk factor for the condition. This could be age at diagnosis or a family history of Lynch syndrome-related cancers.

## *The interventions*

2.4 Most endometrial cancers do not develop because of Lynch syndrome (sporadic cancer). Tests done on endometrial tumour tissue can help identify how likely it is that the cancer happened because a person has Lynch syndrome and if genetic testing of non-tumour tissue should be done to check for the condition.

2.5 Testing for microsatellite instability (MSI) in endometrial tumour tissue or testing for loss of MMR proteins using immunohistochemistry (IHC), or doing both, can show potential Lynch syndrome. But both tests can give false positives. So, 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 being caused by Lynch syndrome.

2.6 This assessment includes different combinations of IHC, MSI and MLH1 promoter hypermethylation testing done on endometrial tumour tissue to see if the cancer is likely to have been caused by Lynch syndrome.

2.7 All strategies include final genetic testing of non-tumour tissue to make a diagnosis of Lynch syndrome (germline testing). Sometimes this testing can show changes in the sequences of the MMR genes, but it is not known if these changes cause Lynch syndrome or not. These are called variants of uncertain significance.

### *The comparator*

2.8 No testing to identify Lynch syndrome for people with endometrial cancer.

## 3 Evidence

The diagnostics advisory committee (section 7) considered evidence on testing strategies using immunohistochemistry (IHC) and microsatellite instability (MSI) testing for Lynch syndrome from several sources. Full details of all the evidence are in the committee papers.

3.1 The external assessment group (EAG) did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of IHC- and MSI-based testing strategies for detecting Lynch syndrome in people with endometrial cancer.

### *Test performance*

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

3.3 Two studies were done in the UK (Anagnostopoulos et al. 2017 and PETALS). Nine studies (Backes et al. 2009, Bruegl et al. 2017, Buchanan et al. 2014, Dillon et al. 2017, Dudley et al. 2015, Egoavil et al. 2013, Hampel et al. 2006, 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.

3.4 Seven complete test accuracy studies were identified. These were studies in which people who had IHC or MSI testing, with or without 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.

3.5 Data on the prevalence of Lynch syndrome from 33 studies and concordance between IHC and MSI-based testing in 23 studies were also extracted.

### Prevalence of Lynch syndrome in people with endometrial cancer

3.6 Prevalence of Lynch syndrome was lower in studies that recruited unselected samples of people (which matches the population for this assessment). The median value was 3.2%. In the studies with unselected samples, variants in the MSH6 mismatch repair (MMR) gene were the most common, then MSH2.

### Accuracy of index tests

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

3.8 Accuracy of the index tests, that is, IHC- and MSI-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.

### *IHC testing alone*

3.9 Data on the accuracy of IHC alone (that is, without MLH1 promoter hypermethylation testing) were available from 5 studies (Berends et al. 2003, Chao et al. 2019, Lu et al. 2007, Rubio et al. 2016, Tian et al. 2019). Sensitivity values ranged from 66.7% to 100%. Specificity values ranged from 6.5% to 83.3%.

### *MSI testing alone*

3.10 Data on the accuracy of MSI testing alone (that is, without MLH1 promoter hypermethylation testing) were available from 4 studies (Berends et al. 2003, Chao et al. 2019, Lu et al. 2007, Rubio et al. 2016). Sensitivity values ranged from 41.7% to 100%. Specificity values ranged from 69.2% to 88.9%.

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

3.11 There were data from 4 studies on the accuracy of IHC- or MSI-based testing strategies when these tests were done before MLH1 promoter hypermethylation testing. The studies varied in when 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 values ranged from 90.5% to 100%. Specificity values ranged from 6.6% to 92.3%.

#### *IHC and MSI testing done on the same population*

3.12 Four of the complete test accuracy studies assessed both IHC and MSI testing on the same population (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.

#### Concordance between IHC and MSI testing

3.13 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. There was a median agreement of 91.8% with a range of 68.2% to 100%.

## *Clinical effectiveness*

3.14 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. No studies met the inclusion criteria.

## *Cost effectiveness*

#### Systematic review of cost-effectiveness evidence

3.15 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. 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 that took a UK perspective. The

EAG thought that Snowsill et al. (2019) provided a comprehensive reference model. It 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 model

3.16 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. 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 longer-term effects of this diagnosis (and adopting surveillance and risk-reducing interventions) on colorectal and endometrial cancer incidence across the rest of people's lives. This was for both the first family member to have Lynch syndrome identified after endometrial cancer and their relatives.

### Population

3.17 The cohort of people entering the model with recently diagnosed endometrial cancer was 48 years old. Relatives diagnosed with Lynch syndrome could be any age between 25 and 74 years old. The prevalence of Lynch syndrome in this population (3.2%) was taken from the PETALS study. The proportion of each MMR gene mutation in people with Lynch syndrome diagnosed after endometrial cancer was pooled from 4 studies (Hampel et al. 2006, Bruegl et al. 2017, Egoavil et al. 2013, unpublished PETALS study).

## Model inputs

### *Diagnostic accuracy*

3.18 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 different strategies. The EAG did not consider that pooling results across studies was appropriate because the few studies identified were heterogeneous. Data from a recent meta-analysis (Snowsill et al. 2019), Chao et al. (2019) and the unpublished PETALS study were used in scenario analyses.

### *Colorectal cancer incidence and effect of surveillance*

3.19 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. 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. If a person was having colonoscopic surveillance because Lynch syndrome had been diagnosed, this was assumed to identify colorectal cancer at an earlier stage (as well as reducing incidence).

### *Endometrial cancer incidence, surgical prophylaxis and gynaecological surveillance*

3.20 Incidence data for endometrial cancer were taken from the Prospective Lynch Syndrome Database (Dominguez-Valentin et al. 2020). The incidence differed by which MMR 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.

3.21 Female relatives with Lynch syndrome could choose to have hysterectomy with removal of both ovaries and fallopian tubes (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 gynaecological 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).

### *Costs*

3.22 Most costs were taken 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.

### *Health-related quality of life*

3.23 Baseline health-related quality of life for people 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.

3.24 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 had 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.

### Base-case results

3.25 When compared independently with no testing, all strategies had an incremental cost-effectiveness ratio (ICER) of less than £17,500 per quality-adjusted life year (QALY) gained. The fully incremental analysis (that is, all testing strategies compared against each other as well as no testing) is shown in table 1.

**Table 1 Fully incremental base-case cost-effectiveness results (deterministic)**

| Strategy | Incremental costs | Incremental QALYs | ICER | Net monetary benefit (compared with no testing; using a maximum ICER of £20,000 per QALY gained) |
|---|---|---|---|---|
| No testing | – | – | – | £0 |
| Strategy 2: MSI then MLH1 promoter hypermethylation testing | £520 | 0.0419 | Extendedly dominated | £323 |
| Strategy 4: IHC then MLH1 promoter hypermethylation testing | £630 | 0.0669 | £9,460 | £705 |
| Strategy 6: MSI then IHC then MLH1 promoter hypermethylation testing | £90 | -0.0249 | Dominated | £124 |
| Strategy 3: IHC alone | £160 | 0.0012 | £133,330 | £570 |
| Strategy 1: MSI alone | £50 | 0.0002 | £250,000 | £529 |
| Strategy 8: IHC then MSI then MLH1 promoter hypermethylation | £30 | -0.0012 | Dominated | £475 |

| | | | | |
|---|---|---|---|---|
| testing | | | | |
| Strategy 10: MSI and IHC then MLH1 promoter hypermethylation testing | £20 | 0.0000 | Dominated | £451 |
| Strategy 7: IHC then MSI | £185 | 0.0002 | £925,000 | £344 |
| Strategy 5: MSI then IHC | £5 | 0.0000 | Dominated | £341 |
| Strategy 9: MSI and IHC | £45 | 0.0000 | Dominated | £302 |
| Strategy 11: No index testing (straight to germline testing) | £135 | -0.0019 | Dominated | £168 |

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 not extendedly dominated or dominated (that is, it is dominated by a 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.

3.26 The probabilistic ICER for strategy 4 was £11,600 per QALY gained compared with no testing (compared with a deterministic ICER of £9,420 per QALY gained). At a maximum ICER of £20,000 per QALY gained, which is what NICE normally considers a cost-effective use of NHS resources, this strategy had a 93% probability of being cost effective compared with no testing.

***Scenario analyses***

3.27 The EAG did several scenario analyses in its main report:

- Scenario 1: Using alternative test accuracy estimates (for strategies 1, 2, 3 and 4) 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) and people with endometrial cancer have the same utility as people with stage 4 colorectal cancer in their last year of life.
- 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.

3.28 In fully incremental analysis in the base case, MLH1 promoter hypermethylation testing (strategy number 4) was the most cost-effective strategy. In all scenarios except scenario 8, this strategy 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 (the ICER was higher than that of the next, more effective, alternative), fully dominated (had higher costs and worse outcomes than an alternative strategy) 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.

3.29 The EAG also did more scenario analyses in an addendum to its 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.

3.30 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 and no testing extendedly dominated IHC testing and MSI testing had an ICER of £10,455 per QALY gained compared with no testing. In Chao et al. higher estimates of both sensitivity and specificity were seen for MSI testing than IHC testing.

3.30.1 In additional scenario analysis 3, people with variants of uncertain significance and people who were assumed to have Lynch syndrome 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.

# 4 Committee discussion

**It is likely that people and their families will benefit substantially if Lynch syndrome is identified after endometrial cancer is diagnosed**

4.1 A patient expert highlighted that identifying Lynch syndrome after a diagnosis of endometrial cancer means interventions and surveillance can be adopted to reduce the risk of other Lynch syndrome-associated cancers or detect them earlier. Another benefit is that it allows testing for the condition to be offered to relatives, who can be identified as having Lynch syndrome before they have cancer. If a person knows they have Lynch syndrome they can make lifestyle changes to help reduce their cancer risk. As well as clinical surveillance that is offered to people with Lynch syndrome, such as colonoscopies, the symptoms of Lynch syndrome-associated cancers can also be highlighted to make sure people seek medical advice if they have symptoms. Knowing that a person is at higher risk of gynaecological cancer may also help to inform decisions about family planning. The committee noted that endometrial cancer is often the first Lynch syndrome-associated cancer that people

are diagnosed with, so provides an opportunity to identify the condition before other associated cancers, such as colorectal cancer, develop. The committee concluded that people and their families would likely benefit substantially if Lynch syndrome was identified after endometrial cancer is diagnosed.

**People should be informed of the possible implications of test results for both themselves and their families**

4.2 The committee heard that there can be considerable anxiety and uncertainty associated with genetic testing for hereditary cancer syndromes such as Lynch syndrome. A patient expert explained that waiting for test results can be a very anxious time. Test results can have a substantial effect on a person so it is very important that patients understand the full implications of a diagnosis of Lynch syndrome, for themselves and their families. This is especially important for people with a learning disability, who may need support from a carer to fully engage in discussions about testing and to provide informed consent. For people who have not had children yet, or who want more children, there may be anxiety and uncertainty about risk-reducing surgery, because after this it is not possible to give birth. Making this decision needs a good understanding of a person's risk of cancer (for example, based on their specific pathogenic variant of a mismatch repair [MMR] gene). People may also have concerns about the invasive nature of surveillance for cancer. The committee concluded that genetic counselling is very important for people with Lynch syndrome, or who are at risk of having Lynch syndrome, because it can help people understand if genetic testing is appropriate or not. It can also help people understand the importance of informing extended family about their risk of having Lynch syndrome and the benefits of being tested.

## *Testing strategies*

### IHC testing may give quicker results than MSI testing, which can give patients more chances to join clinical trials

4.3 A patient expert explained that waiting for test results can be a very anxious time. The strategies assessed included IHC and MSI as the first tests used to identify tumours with MMR deficiency. The external assessment group (EAG) commented that it did not find data on the time taken to get test results when using IHC or MSI. However, clinical experts commented that based on their experience in the NHS the time taken to get IHC results (about 1 day) is much shorter than for MSI testing (about 6 weeks). They highlighted that when MSI testing is used, information may not be available for the first multidisciplinary team discussions on a person's cancer where decisions about treatment and further testing are made. They also noted that there is a risk that results arrive weeks later, separate to the histopathology report, may be missed and not acted on. Also, if a person's tumour is quickly identified as having MMR deficiency, they are able to be considered for clinical trials for new treatments such as immunotherapies. Clinical experts highlighted that it is important for all people with cancer to have the opportunity to enter relevant clinical trials, and that this is a way to access new treatments which could benefit them. Clinical experts also commented that an advantage of IHC testing is that it shows which MMR gene is likely to contain a pathogenic mutation. The committee concluded that there may be benefits for clinicians and for patients from using IHC compared with MSI as a first test for potential Lynch syndrome.

## *Clinical effectiveness*

### The relative accuracy of IHC and MSI testing is uncertain, but IHC may detect more people with Lynch syndrome

4.4 The EAG commented that in studies assessing both MSI and IHC testing on the same sample of patients (4 studies, see section 3.12) there was no

statistically significant difference between the accuracy of the tests. But the committee noted that the studies were unlikely to be powered to show any difference. The committee preferred to use comparative estimates of sensitivity and specificity for IHC and MSI from the individual studies, rather than ranges of midpoint estimates from all 4 studies. It noted that sensitivity estimates were generally higher for IHC than for MSI (that is, using IHC as the first test may detect more people with Lynch syndrome). Clinical experts commented that a concern about MSI testing is that it may miss tumours with mutations in MSH6 and highlighted the relatively high prevalence of mutations in this gene in Lynch syndrome-associated endometrial cancer (see section 3.6). The committee further noted that the level of concordance between IHC and MSI studies was in a range of 68% to 100% (see section 3.13). The committee concluded that there is uncertainty about the relative accuracy of IHC and MSI testing for potential Lynch syndrome done on endometrial tumour samples, but that there is some evidence that IHC may detect more people with Lynch syndrome.

**The PETALS study is highly relevant for this assessment**

4.5 An unpublished manuscript of the PETALS study was given to the committee as academic in confidence. The study authors commented that their results showed that IHC was more sensitive than MSI. The sensitivity of MSI testing was 56.3% compared with 100% for IHC testing. The committee noted that this was in general agreement with the results of the 4 studies directly comparing IHC and MSI in the EAG's systematic review (see section 4.4). The study authors also commented that they did not test everyone who had IHC or MSI testing with a reference standard; people with a negative result for both MSI and IHC testing for Lynch syndrome did not have the reference standard (germline testing) because of the cost. The committee noted that this may be a limitation of the study. The committee concluded that PETALS was likely to be highly relevant for this assessment because it was a recent UK-based study that assessed IHC,

MSI and MLH1 promoter hypermethylation testing in a population in the NHS newly diagnosed with endometrial cancer.

## *Cost effectiveness*

### There is uncertainty about the effect of colonoscopic surveillance on colorectal cancer incidence

4.6 For the effect of colonoscopic surveillance on colorectal cancer incidence in the model, the EAG used a hazard ratio of 0.387 from Jarvinnen et al. (2000). The committee noted that this was an observational study and that the true effect size is uncertain. The EAG did a scenario analysis in which no benefit of colonoscopy on colorectal cancer incidence was assumed. This was the only scenario in which the incremental cost-effectiveness ratios (ICERs) for all of the testing strategies compared with no testing were above £20,000 per quality-adjusted life year (QALY) gained, although the ICER for strategy 4 (IHC then MLH1 promoter methylation testing) was only just higher. Clinical experts commented that it would not be ethical to do a trial in which people with Lynch syndrome were randomised to have colonoscopic surveillance or not. They highlighted that the recent Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) recommend colonoscopic surveillance for people with Lynch syndrome. The committee concluded that although there is uncertainty about the effect of colonoscopic surveillance on colorectal cancer incidence, the EAG's scenario assuming no benefit was extreme and unlikely to be realistic.

### There is uncertainty about the benefit of gynaecological surveillance, but raising awareness of symptoms is likely to improve earlier detection

4.7 Clinical experts commented that the extent of surveillance for gynaecological cancers offered to people with Lynch syndrome varies across the NHS. There was also considerable uncertainty about the

effectiveness of this surveillance to reduce the occurrence or severity of gynaecological cancer. The EAG included the cost and impact of gynaecological surveillance in its base-case model but highlighted that removing this from the model in a scenario analysis did not have a large effect on results. Clinical and patient experts (see section 4.1) commented that, even if gynaecological surveillance is not done, raising awareness of the early symptoms of gynaecological cancers to people with Lynch syndrome is likely to improve early diagnosis.

**The costs of straight-to-germline testing may have been underestimated**

4.8 Strategy 11 assessed the costs and benefits of going straight to germline testing for people diagnosed with endometrial cancer; that is, no first testing of tumour samples to identify people likely to have Lynch syndrome. Clinical experts commented that this would result in more variants of uncertain significance being detected (that is, mutations in MMR genes which may or may not cause Lynch syndrome) because initial tumour tests would not rule out non-pathogenic mutations (with no MMR deficiency in the tumour). This would mean staff time would be needed to analyse and assess if the person should be considered as having Lynch syndrome. Tests on endometrial tumour tissue may be needed in these people to determine if the tumour was MMR-deficient. Costs related to this were not included in the economic model. In addition, clinical experts commented that if everyone with endometrial cancer had germline testing this would drastically increase the workload of genetic services who would need to offer genetic counselling to ensure that informed consent for the tests was obtained. Clinical experts also highlighted that there have been fewer studies done on Lynch syndrome-causing mutations for some ethnic groups, so there were likely to be more variants of uncertain significance identified by a straight-to-germline testing strategy (without the benefit of information from the tumour tests). The committee concluded that the costs of strategy 11 were likely to have been underestimated in the model.

**The effect of cancer on health-related quality of life is likely to have been underestimated, which undervalues the benefit of diagnosing Lynch syndrome**

4.9 In the economic model, an effect on health-related quality of life for people with colorectal cancer was only assumed to happen at stage 4 of the disease. A relatively small effect on health-related quality of life for people with endometrial cancer was also assumed, which lasted for only 1 year in the model. A scenario analysis in which people with stage 3 colorectal cancer also had reduced health-related quality of life increased the incremental gain in quality-adjusted life years (QALYs) for all strategies compared with no testing (and cost effectiveness compared with no testing). The committee concluded that the effect of cancer on health-related quality of life was likely to have been underestimated in the model, so the cost effectiveness of testing for Lynch syndrome may also have been underestimated.

**There is uncertainty about the costs of testing for Lynch syndrome**

4.10 The EAG explained that the post-test clinic-related costs and follow-up costs it had used in its model related to time taken to give results of testing to patients. Clinical experts commented that the cost of about £141 used was likely to be an underestimate. The committee also discussed the costs used in the base-case model for the tests. The EAG commented that costs of testing were reducing over time. It had used cost estimates from a micro-costing study (Ryan et al. 2019) in a scenario analysis to investigate this, which were much lower than the base-case values. Using these lower costs improved the cost effectiveness of testing for Lynch syndrome. The committee concluded that there is some uncertainty about the true value of costs associated with testing for Lynch syndrome.

**It is appropriate to use a linked-evidence approach to estimate the cost effectiveness of testing for Lynch syndrome after endometrial cancer**

4.11 The EAG did not find any evidence on the effect on clinical outcomes of testing for Lynch syndrome when people were diagnosed with endometrial cancer. So, it used a linked-evidence approach to assess:

- how many people with Lynch syndrome each of the strategies would identify and
- the effect of changes to care for people with a diagnosis on the future incidence of endometrial and colorectal cancer (for them and their families).

A clinical expert commented that their hospital has been routinely testing for Lynch syndrome in all people with endometrial cancer for about 5 years. This has led to Lynch syndrome being identified in many families who otherwise would not have known, and for relatives to start cancer surveillance and risk-reducing measures. Clinical experts also highlighted that there is a strong link between Lynch syndrome and an increased risk of cancer. The committee also noted that the strategies all included the gold standard assessment (germline testing) to provide a diagnosis of Lynch syndrome after first testing. The committee concluded that it was appropriate to use a linked-evidence approach to estimate the cost effectiveness of testing for Lynch syndrome after a diagnosis of endometrial cancer.

**Testing for Lynch syndrome for people with endometrial cancer is likely to be a cost-effective use of NHS resources**

4.12 In the base case all testing strategies had ICERs of under £20,000 per QALY gained compared with no testing. Excluding the scenario in which no benefit was assumed for colonoscopic surveillance on colorectal cancer incidence (which the committee considered was unrealistic, see section 4.6), almost all of the testing strategies had ICERs under £20,000 per QALY gained compared with no testing in scenario analyses. In the scenario in which no benefit for aspirin was assumed, some strategies had ICERs of just over £20,000 per QALY gained. The committee also recalled that the effect of cancer on health-related quality of life was likely to have been underestimated in the model (see section 4.9). If a greater effect of cancer was used this would have improved the cost effectiveness of the testing strategies. The committee concluded that the most likely

ICER for testing for Lynch syndrome for people with endometrial cancer is likely to be less than £20,000 per QALY gained and that testing is likely to be a cost-effective use of NHS resources.

### IHC then MLH1 promoter hypermethylation testing is likely to be the most cost-effective strategy

4.13 In its base case, the EAG used data from Lu et al. (2007) for the testing strategies' accuracy. This was because this study had individual patient data that could be used to estimate sensitivity and specificity for most of the strategies. But, because of a lack of data, the EAG had to make assumptions to estimate values for MSI testing then MLH1 promoter hypermethylation testing. The EAG explained that its assumption that 66% of MLH1 promoter hypermethylation tests done after MSI testing were correct was based on an estimate used in Snowsill et al. (2019) of the probability of MLH1 promoter hypermethylation in sporadic tumours with MSI. The committee noted that when test accuracy estimates from Lu et al. (2007), the PETALS study and a recent meta-analysis (Snowsill et al. 2019) were used in the model, IHC then MLH1 promoter hypermethylation testing was consistently the most cost-effective strategy. Accuracy estimates from Chao et al. (2019) had also been used in a scenario analysis (only for IHC alone and MSI alone). Unlike the other studies, sensitivity was higher for MSI than IHC in this study, and MSI testing and no testing extendedly dominated IHC testing. Clinical experts highlighted that the sensitivity estimate from this study was based on 6 people with Lynch syndrome (4 people whose Lynch syndrome was identified by IHC testing and 2 people whose Lynch syndrome was not identified). A clinical expert highlighted that the 2 people whose Lynch syndrome was not identified by IHC had mutations in either the MSH2 or MSH6 gene. They explained that pathogenic mutations in these genes in particular often show some expression on IHC, which can make identifying MMR deficiency more difficult. They highlighted that the sensitivity of IHC to detect such mutations depends on the expertise of the pathologist and will be improved by following guidance on interpreting

MMR IHC. The committee concluded that, based on the base case and scenario analyses, IHC then MLH1 promoter hypermethylation testing (then germline testing to confirm a Lynch syndrome diagnosis) was likely to be the most cost-effective strategy.

**Laboratories doing IHC testing for MMR proteins should take part in a recognised external quality assurance programme**

4.14 Clinical experts emphasised the importance of quality assurance to ensure that IHC testing for MMR proteins is done correctly. They also highlighted the British Association of Gynaecological Pathologists' recommended terminology for reporting mismatch repair protein immunohistochemistry with or without MLH1 promoter methylation results, which will be incorporated in future guidance from the Royal College of Pathologists. The committee concluded that laboratories doing IHC testing for MMR proteins should take part in a recognised external quality assurance programme.

## *Research considerations*

**Future developments in testing, interventions and increased testing for Lynch syndrome may affect cost effectiveness**

4.15 The committee noted that costs and other parameter estimates used in the economic model can change over time, which may affect the cost effectiveness of testing. For example, if more testing for Lynch syndrome increases the number of people with known Lynch syndrome in the general population, fewer people with the condition will need testing after endometrial cancer, and the prevalence of the condition for those tested will decrease. This could reduce the cost effectiveness of testing. However the committee noted that, in sensitivity analysis, decreasing prevalence of Lynch syndrome to 1.6% only increased the ICER for strategy 4 to about £13,500 per QALY gained. Clinical experts also highlighted ongoing research on further interventions that could be used for people with Lynch syndrome. The committee also noted that the costs

of sequencing DNA are decreasing. It concluded that future developments may affect the cost effectiveness of testing strategies, or their relative cost effectiveness compared with each other. The committee concluded that it is important to monitor future developments to identify if any changes to the recommendations are needed.

**It is important to monitor the effect of more widespread testing for Lynch syndrome to make sure that the expected benefits are seen in the NHS**

4.16 The committee considered it important to monitor the effect of adopting testing for Lynch syndrome for people with endometrial cancer. For example:

- the number of people tested (including relatives of people with Lynch syndrome identified after endometrial cancer who have cascade testing)
- the number diagnosed with Lynch syndrome (after endometrial cancer and their relatives) and
- the uptake of surveillance and risk-reducing interventions.

Clinical experts commented that there are plans to set up a national registry for Lynch syndrome, but that no funding for this work has yet been identified. The committee concluded that it is important to monitor the outcomes related to implementing more widespread testing for Lynch syndrome after endometrial cancer, to make sure that the expected benefits, as estimated by the model, are seen in the NHS.

# 5 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

# 6 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Mark Kroese

Chair, diagnostics advisory committee

March 2020

# 7 Diagnostics advisory committee members and NICE project team

## *Committee members*

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be assessed. If it is considered there is a conflict of interest, the member is excluded from participating further in that assessment.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

### Specialist committee members

**Mrs Kate Daniels**

Lay specialist committee member

**Dr Angela George**

Consultant Medical Oncologist and Consultant in Oncogenetics, Royal Marsden NHS Foundation Trust

**Miss Demetra Georgiou**

Principal Genetic Counsellor in Cancer, Guy's Regional Genetics Service, Guy's & St Thomas' NHS Foundation Trust

**Dr Fiona Lalloo**

Consultant in Clinical Genetics, Manchester Centre for Genomic Medicine, Manchester University Hospitals Foundation Trust

**Prof Pierre Martin-Hirsch**

Consultant Gynaecological Oncologist, Lancashire Teaching Hospitals NHS Trust

**Dr Tracie Miles**

Clinical Nurse Specialist and Information Nurse Specialist, The Eve Appeal

**Mrs Gail Norbury**

Consultant Clinical Scientist in Genetics, Guy's and St Thomas' NHS Foundation Trust

**Dr Anca Oniscu**

Consultant Pathologist, Royal Infirmary of Edinburgh

**Prof Naveena Singh**

Consultant Pathologist, Barts Health NHS Trust

**Dr Katie Snape**

Consultant Cancer Geneticist, South West Thames Regional Genetics Service, St George's Hospital

## *NICE project team*

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

**Thomas Walker**

Topic lead

**Rebecca Albrow**

Technical adviser

**Donna Barnes**

Project manager

ISBN: