NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Testing strategies for Lynch syndrome in people with endometrial cancer

Final scope

August 2019

1 Introduction

The medical technologies topic oversight group identified this topic (testing strategies for Lynch syndrome for people with endometrial cancer) as suitable for evaluation by the Diagnostics Assessment Programme on the basis of a topic briefing.

The final scope was informed by discussions at the scoping workshop on 4 July 2019 and assessment subgroup meeting on 17 July 2019. A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technology based on information provided to NICE by experts. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

Lynch syndrome is an inherited genetic condition that is associated with an increased risk of several cancers, including endometrial and colorectal cancer. NICE's guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer recommends using immunohistochemistry- or microsatellite instability-based strategies to test for Lynch syndrome in people diagnosed with colorectal cancer. Currently, testing for Lynch syndrome in people diagnosed with endometrial cancer is often not done, or may only occur for subgroups of people with an identified risk factor for the condition; for example, age at diagnosis or a family history of Lynch syndrome related cancers. Endometrial cancer can be the first cancer to occur in people with Lynch syndrome and the optimal testing strategy may be different to testing strategies used in colorectal cancer.

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

- prevent the occurrence of further cancers in people with Lynch syndrome (such as colorectal cancer) through increased surveillance and strategies aimed at reducing risk (such as a healthy lifestyle and the use of aspirin)
- help to identify family members with Lynch syndrome with the aim of subsequently reducing the incidence of primary cancers in affected relatives and increasing early detection if cancer occurs
- enable family members diagnosed at an early age to consider family planning and if they wish to have risk reducing interventions, for example, a hysterectomy.

A description of Lynch syndrome can be found in section 3.2.

2.2 Lynch syndrome testing

A cell's DNA mismatch repair (MMR) system identifies and corrects errors in DNA that occur when the cell replicates. If this system isn't working (MMR deficiency), mutations will accumulate in a cell's DNA at an increased rate; if these occur in cell growth control genes this leads to uncontrolled cell growth and tumour formation. Lynch syndrome is caused by inherited pathogenic versions of genes that encode the DNA MMR system (that is, an MMR gene with a mutation in its sequence that means the protein it encodes does not function). The pathogenic variant is inherited from a person's parent (a germline mutation) and is present in every cell in the body (a constitutional mutation). This increases the risk that the DNA MMR system will stop working in some of the cells in a person's body during their lifetime; increasing the risk of some cancers for people with the condition (in particular colorectal and endometrial cancer).

Microsatellite instability testing (MSI; section 2.2.1) and immunohistochemistry (IHC; section 2.2.2) are initial tests that can be done on tumour tissue to see if it has deficient MMR functionality, suggesting that it may have been caused by Lynch syndrome.

Clinical experts have highlighted that next generation sequencing of tumour DNA can be used to identify tumours with mutations in MMR genes (Hampel et al., 2018). Checking if the mutation is also present in the germline (that is, in non-tumour tissue) will then identify if a person has Lynch syndrome. This would be done instead of MSI and IHC testing. However, clinical experts commented that this is not currently used in the NHS.

2.2.1 Microsatellite instability testing

Microsatellites are short (1 to 6 bases) repeats of DNA sequence that occur at thousands of places, or loci, across the human genome. They are particularly prone to errors during DNA replication. This is usually corrected by a cell's DNA MMR system; therefore, if there is variation in microsatellite repeats (known as microsatellite instability [MSI]) in a tumour, this suggests it has deficient MMR.

MSI assays look at a panel of microsatellite markers and require DNA extraction from tumour tissue. Assays can differ in the panel of microsatellite marker sites they assess, both in terms of their number and identity. The Bethesda Panel is made up of 5 microsatellites sites: 2 mononucleotide loci (BAT-25 and BAT-26) and 3 dinucleotide loci (D2S123, D5S346, and D17S250). A change in size of these sites indicates microsatellite instability:

- MSI-High: 30% or more microsatellite markers show instability
- MSI-Low: Less than 30% microsatellite markers show instability
- Microsatellite stable (MSS): No markers show instability.

Modifications to this panel of markers have been proposed to improve sensitivity and specificity for detecting potential Lynch syndrome related cancers. These include using alternative microsatellite loci and increasing the number of loci included in a panel (reviewed in Baudrin et al. 2018). Other assays use entirely different microsatellite loci. The sensitivity and specificity of an MSI assay to detect microsatellite instability may be affected by the microsatellite loci it uses. The Association for Clinical Genomic Science's (ACGS's) best practice guidelines for genetic testing and diagnosis of Lynch syndrome recommends that analysis should include a minimum of 5 markers of which at least 3 should be mononucleotide repeats. This guideline also recommends a minimum of 30% neoplastic/hyperplastic/dysplastic cell content for DNA analysis. It recommends that tumours be macro-dissected where feasible, to enrich for neoplastic/hyperplastic/dysplastic cell content.

For endometrial tumours that are MSI-Low, there may be variation in practice concerning whether these are considered to indicate that a tumour has MMR deficiency (Stelloo et al. 2017). Clinical experts commented that practice may vary. The ACGS's best practice guidelines for genetic testing and diagnosis of Lynch syndrome states that tumours with 1 of 5 mononucleotide markers showing instability should be reported as insufficient to be classed as instability associated with Lynch syndrome. Further testing may be indicated depending on the context (family history, tumour type, sample status). NHS England's National Genomic Test Directory (Testing Criteria for Rare and Inherited Disease) specifies that tumour should show high/intermediate MSI for further Lynch syndrome related testing to occur.

MSI assays typically compare the size of microsatellite markers from tumour tissue with normal (non-tumour) tissue to identify MSI in a tumour (that is, microsatellite sequences that vary in length in tumours compared to normal tissue). However, the size of some microsatellite loci is stable in a population (monomorphic or quasimonomorphic). MSI assays that use these microsatellite loci can compare microsatellite sizes measured in tumour tissue to the known population values to identify MSI, and do not need a corresponding normal tissue sample to be analysed.

MSI testing typically uses polymerase chain reaction (PCR) amplification of microsatellite sequences and analysis of the size and/or sequence of the resulting fragments. Next generation sequencing (NGS) can also be used to detect MSI using a large number of microsatellite loci. However, clinical experts commented that at present in the NHS, PCR is used to assess for MSI.

2.2.2 Immunohistochemistry (IHC) for mismatch repair proteins

IHC uses antibodies to detect decreased or abnormal expression of MMR proteins in tumour tissue samples. Absent or reduced nuclear staining of 1 or more MMR proteins suggests that there may be a pathogenic mutation in a gene encoding these proteins. MMR proteins detected by IHC are MLH1, MSH2, MSH6 and PMS2. Laboratories may differ in the source of the antibodies used to carry out these tests.

Clinical experts commented that *MLH1* promoter hypermethylation testing would only be done after IHC testing if abnormal MLH1 expression is seen (see section 2.2.3.1 below). Germline testing for Lynch syndrome associated mutations (see section 2.2.3.2) after IHC testing should still be done on the full panel of MMR genes.

Some mutations in MMR genes may produce a protein which although present in the cell, and detected by IHC, is non-functional (Shia 2008).

Clinical experts commented that doing IHC testing on endometrial tissue obtained during hysterectomy can be difficult because of issues with tissue fixation. Biopsy tissue can be used, but this is not always available (for example, if the initial biopsy was done at a different hospital).

The British Association of Gynaecological Pathologists have produced guidance on the Recommended Terminology for Reporting Mismatch Repair Protein Immunohistochemistry with or without *MLH1* Promoter Methylation Results.

Clinical experts commented that at present IHC is typically done in the NHS with a panel of antibodies for all 4 mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2). The ACGS's best practice guidelines for genetic testing and diagnosis of Lynch syndrome recommends that testing is done for all 4 MMR proteins. Studies have suggested initially only doing IHC for MSH6 and PMS2, potentially followed by MSH2-IHC and MLH1-IHC if indicated, commenting that this may be the most cost-effective approach (Cho et al. 2019; Hall et al. 2010; Stello et al. 2017). However, further studies have suggested that this method may fail to detect some cases of Lynch syndrome (Pearlman et al. 2018). Clinical experts commented that initially testing with antibodies for MSH6 and PMS2, followed by further testing of all MMR proteins if abnormal staining is identified could be used in the NHS.

2.2.3 Further tests to confirm a Lynch syndrome diagnosis

Microsatellite instability and loss of MMR protein expression in tumours can occur because of Lynch syndrome but can also occur in sporadic tumours (that is, tumours not caused by an inherited gene mutation). Further testing can help to identify sporadic tumours.

When testing for Lynch syndrome in colorectal cancer, the presence of ***BRAF* mutations** has been used to identify sporadic tumours. However, clinical experts have stated that *BRAF* mutations are rare among sporadic endometrial tumours, so this test is not useful in testing strategies for Lynch syndrome in this cancer (Metcalf and Spurdle, 2014).

2.2.3.1 MLH1 promoter hypermethylation testing

Tumours with deficient MMR often occur because of sporadic epigenetic silencing of *MLH1* by promoter hypermethylation. That is, where the *MLH1* gene acquires methylation (a type of chemical modification of DNA) during a person's lifetime. This stops MLH1 protein being produced from the gene in cells in which this has occurred (loss of expression) and consequently, MMR no longer works. If a tumour is positive for MSI or has abnormal MLH1 protein expression on IHC testing, *MLH1* promoter hypermethylation testing can be done on tumour DNA. If this is positive, it suggests that the tumour is sporadic. The testing requires DNA to be extracted from a tumour (which may not have already been done if IHC testing, rather than MSI testing, is the initial tumour test).

Constitutional epimutation of *MLH1* has been described (that is, methylation of the *MLH1* promoter in the germline that can be inherited and is present in all tissue; Hitchens and Ward, 2009; Dámaso et al. 2018). Clinical experts commented that people with this epimutation would be considered to have Lynch syndrome (and would be offered surveillance and risk reducing

interventions) but it is likely to be rare. Testing normal (that is, non-tumour) tissue for *MLH1* promoter hypermethylation can be done alongside testing of tumour tissue to identify if the methylation is inherited or has occurred sporadically. The ACGS's best practice guidelines for genetic testing and diagnosis of Lynch syndrome recommends that a matched constitutive sample (blood or normal tissue) be analysed either in parallel or following identification of promoter methylation in the tumour. Clinical experts commented that testing for constitutional epimutation of *MLH1* is done in some parts of the NHS, but not all.

2.2.3.2 Germline testing for Lynch syndrome associated mutations

Comprehensive screening for constitutional mutations in the MMR genes (that is, mutations that are inherited and are present in every cell), and possibly the *EPCAM* gene, is the gold standard for diagnosing Lynch syndrome. This involves gene sequencing to detect point mutations and small insertions or deletions in these genes. Next generation DNA sequencing can also be used for copy number variation analysis. Multiplex ligation-dependent probe amplification (MLPA) can also be used to detect larger structural changes to genes, such as deletions, duplications or rearrangements. This testing is done on DNA from non-tumour tissue, normally extracted from a blood sample. The ACGS's best practice guidelines for genetic testing and diagnosis of Lynch syndrome provide guidance on germline testing for Lynch syndrome associated mutations.

Comprehensive screening for constitutional mutations in MMR genes can identify novel sequence variations in these genes that are of unknown significance, that is, it is unknown whether they are pathological or non-pathological. It can therefore be uncertain as to whether people with such sequence variants should be diagnosed as having Lynch syndrome or not. Clinical experts commented that information from the tumour about microsatellite instability or loss of expression in IHC can help inform decisions about whether a mutation is likely to cause Lynch syndrome. The ACGS's best practice guidelines for genetic testing and diagnosis of Lynch syndrome provides guidance on the interpretation of MMR mutations.

Many people with tumours that have deficient MMR (and no *MLH1* promoter hypermethylation) do not have any germline Lynch syndrome associated mutations detected. This may be because deficient MMR is entirely due to somatic mutations in MMR genes (that is, non-inherited mutations); somatic biallelic inactivation. Clinical experts commented that sequencing of MMR genes in the tumour sample can help to determine whether mutations causing defective MMR repair are entirely due to sporadic mutations (which will be present in the tumour but not germline DNA). This can provide reassurance

that a person does not have Lynch syndrome that has been missed in germline testing (for example, if caused by a complex DNA structural arrangement).

NHS England's National Genomic Test Directory (Testing Criteria for Rare and Inherited Disease; R210) states that a somatic Lynch syndrome panel test should be used for living affected individuals with Lynch related cancer if they have:

- Colorectal or endometrial cancer, AND
- Tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND
- Tumour is normal on testing of: *BRAF*1 V600E and/or *MLH1* hypermethylation analysis, AND
- Germline Lynch panel did not reveal a pathogenic mutation, AND
- Personal/family pattern of disease whereby demonstration of acquired MMR mutations (and therefore exclusion of constitutional MMR abnormality) enables downscaling of surveillance.

Test criteria for a somatic Lynch syndrome panel test in deceased affected individuals with Lynch-related cancer are also provided.

Clinical experts commented that if a person has deficient MMR (from tumour testing) but no germline mutation identified and no somatic cause identified, they can be considered to have Lynch-like syndrome (also known as putative or cryptic Lynch syndrome). Clinical experts commented that in this case, decisions about any treatment or surveillance to be offered will be made by a clinical geneticist based on an individual assessment.

The Manchester International Consensus Group (Crosbie et al., 2019) recommended that where tumour tests suggest Lynch syndrome but there is no Lynch syndrome associated pathogenic variant identified, clinicians should seek to establish the existence of other somatic or germline pathogenic variants, such as biallelic *MuTYH*, *POLE*, and/or double somatic MMR pathogenic variants, which may have prognostic implications. Cho et al. (2019; International Society of Gynecological Pathologists Endometrial Cancer Project) recommended that because of the occurrence of potential somatic mutations in MMR genes, somatic mutation analysis should be considered if germline testing in appropriately triaged patients is negative.

2.2.4 Reference standard

Clinical experts commented that an appropriate reference standard to assess the accuracy of tumour tests to detect Lynch syndrome is germline testing for constitutional mutations in MMR genes. This should include:

- DNA sequencing, and
- Techniques to detect larger structural abnormalities (such as MLPA or the use of NGS data to identify structural variants).

Clinical experts commented that further techniques can potentially be used to detect larger genetic abnormalities (such as Southern blotting and gene-targeted array-based comparative genomic hybridization) but that these are likely to be less accurate. Unless specifically testing for it, reference standards will miss constitutional methylation of the *MLH1* promoter.

3 Target conditions

3.1 Endometrial cancer

Endometrial cancer develops from the lining of the uterus (the endometrium) and accounts for most uterine cancers (about 95%). Cancer registration statistics (Office for National Statistics; accessed 5 June 2019) reported 7,862 cases of cancer of the uterus registered in England in 2017. The incidence rate increases with age; rates increase sharply from 45 to 49 years old and the highest incidence rates are for people 75 to 79 years old. Most people are diagnosed at stage I; 69% of cases where stage was known in England in 2014 (Uterine cancer incidence statistics, Cancer Research UK, accessed 29 April 2019).

Being overweight or obese increases the risk of developing endometrial cancer (Womb [uterus] cancer, NHS). Clinical experts commented that increasing levels of obesity in younger people is increasing the incidence of endometrial cancer in this group.

90% of people survive uterine cancer for at least 1 year, 79% survive at least 5 years and 77.5% survive at least 10 years. Stage of disease at diagnosis is a strong determinant of survival; 99% people at stage I survive at least 1 year compared to 45% of people at stage IV (Uterine cancer incidence statistics, Cancer Research UK, accessed 29 April 2019).

The lifetime risk of uterine cancer has been estimated as about 3% for females born after 1960 in the UK (Uterine cancer incidence statistics, Cancer Research UK, accessed 29 April 2019). Risk of uterine cancer is increased by several factors, including being overweight or obese or having Lynch syndrome.

About 85% of people diagnosed with uterine cancer in England in 2013 to 2014 had surgery to remove their primary tumour (alone, or with other treatment). Incidence varied by stage at diagnosis, from 95.6% at stage 1 to 44.0% at stage 4. In addition, 21% of people had curative or palliative

radiotherapy and 16% had curative or palliative chemotherapy, as part of their primary cancer treatment. Incidence varied by stage at diagnosis; with people diagnosed at stage 1 having the lowest incidence of radiotherapy and chemotherapy (Uterine cancer incidence statistics, Cancer Research UK, accessed 29 April 2019).

MMR function is lost in about 20 to 30% of endometrial cancers. The majority are not caused by Lynch syndrome, but about 25% are because of inherited mutations in the MMR genes.

3.2 Lynch syndrome

Lynch syndrome is an inherited genetic condition caused by a mutation in 1 of 4 DNA MMR genes: *MLH1*, *MSH2*, *MSH6* or *PMS2*. In addition, deletion of part of the *EPCAM* gene can also cause Lynch syndrome by epigenetic silencing of the adjacent *MSH2* gene. MMR genes encode proteins that are involved in recognising and repairing errors in DNA sequence, which occur when DNA is replicated during cell division. Mutations in MMR genes can lead to impaired functioning of the MMR system and a failure to repair DNA errors. Over time, this allows mutations in a cell's genome to accumulate, potentially leading to cancer.

People with Lynch syndrome are at increased risk of developing several types of cancer (discussed below), and typically develop cancer at an earlier age. The risk of cancer varies depending on which MMR gene is mutated, and by type of cancer; guidance on gene and cancer specific risks is provided in the Prospective Lynch Syndrome Database (http://www.lscarisk.org). Which MMR gene is mutated can also affect the age of onset of Lynch syndrome related cancer. People with Lynch syndrome are also at higher risk of developing multiple cancers; either synchronous (diagnosed within 6 months) or metachronous (diagnosed more than 6 months apart).

Tumours with defective MMR frequently occur in people without Lynch syndrome (sporadic tumours). Mutations in MMR genes can entirely arise during a person's lifetime (rather than being inherited; biallelic somatic mutation) or sporadic DNA methylation (a chemical modification of DNA) of the *MLH1* gene promoter can occur, inhibiting its expression (epigenetic silencing). Most endometrial cancers that show MSI are as a result of *MLH1* promoter hypermethylation (Constantinou and Tischkowitz, 2017). Testing for hypermethylation of the *MLH1* promoter in tumours that have MSI, or abnormal MLH1 protein expression, can help to identify sporadic cancers caused by this mechanism (see section 2.2.3.1).

Lynch syndrome related cancers

Endometrial cancer

The proportion of endometrial cancer attributed to Lynch syndrome has been reported as between 1 and 6% (for example, Bruegl et al. 2014; Crosbie et al. 2019). A recent systematic review and meta-analysis (Ryan et al. 2019) reported that about 3% endometrial cancers can be attributed to Lynch syndrome. Estimates of the lifetime risk of endometrial cancer for people with Lynch syndrome vary but are often reported as being between 40 and 60% (compared to about 3% in the general population). Endometrial cancer tends to occur at an earlier age for people with Lynch syndrome, and 40 to 60% of women with the condition develop endometrial cancer as their first Lynch syndrome associated malignancy (Lu et al. 2005; Tafe et al. 2013).

Colorectal cancer

Lynch syndrome accounts for about 3% of colorectal tumours. People with Lynch syndrome have a risk of 33 to 46% (to 70 years old) of colorectal cancer; compared to a general population risk of 5.5% for women and 7.3% for men (Snowsill et al. 2016).

Other Lynch syndrome related cancers

The highest risk of cancer for people with Lynch syndrome is for colorectal and endometrial cancer. However, people with the condition may also have an elevated risk of additional cancers. Potentially, Lynch-related cancers include ovarian cancer, pancreatic cancer, ureteric cancer, transitional cell cancer of renal pelvis, gastric cancer, hepatobiliary tract cancer, small bowel cancer, glioblastoma, prostate cancer, multiple sebaceous adenomata, multiple sebaceous epitheliomas, multiple keratoacanthomas, sebaceous carcinoma, endocervical cancer (from NHS England's National Genomic Test Directory [Testing Criteria for Rare and Inherited Disease]).

The Royal College of Obstetricians and Gynaecologists' Management of Women with a Genetic Predisposition to Gynaecological Cancers guideline reports that the lifetime risk of **ovarian cancer** for people with Lynch syndrome is 10 to 12% (compared to 1.4% in the general population). Higher risk levels have also been reported; for example, a cumulative risk to 75 years old of 17% for people with pathogenic *MSH2* variants (Møller et al. 2018). The risk of ovarian cancer varies depending on MMR gene; with higher risk for people with mutations in the *MLH1* and *MSH2* genes (Helder-Woolderink et al. 2016; Constantinou and Tischkowitz, 2017).

3.3 Diagnostic and care pathway

3.3.1. Diagnosing Lynch syndrome

NHS England's National Genomic Test Directory (Testing Criteria for Rare and Inherited Disease) specifies testing criteria for inherited MMR deficiency (Lynch syndrome). Living affected individuals with Lynch-related cancer should meet 1 of the following criteria:

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

Testing criteria for deceased affected individuals are also provided.

Clinical experts commented that there is variation in the amount of testing done in the NHS for Lynch syndrome for people diagnosed with endometrial cancer. This includes testing all tumours (MSI and IHC testing) and no routine testing. Testing may also only be done for people considered to be at higher risk of Lynch syndrome: if they have endometrial cancer below a certain age (for example, 50 or 60 years old), if they have had multiple Lynch syndrome related tumours or if they have a family history of Lynch syndrome related tumours. Several guidelines have recommended testing for Lynch syndrome for all people with endometrial cancer.

Clinical experts highlighted the importance of taking a full family history assessment at diagnosis of endometrial cancer. They also commented that getting a comprehensive family history can be difficult, and that relying on this to select people for Lynch syndrome testing will miss cases. In addition, only testing for Lynch syndrome up to a certain age will also miss people with the condition who could benefit from surveillance and risk reducing interventions (discussed below), for themselves and also any relatives identified with Lynch syndrome as a result of the initial diagnosis. Clinical experts also commented that selecting people for Lynch syndrome testing on the basis of pathological features of their tumour will also miss people with the condition.

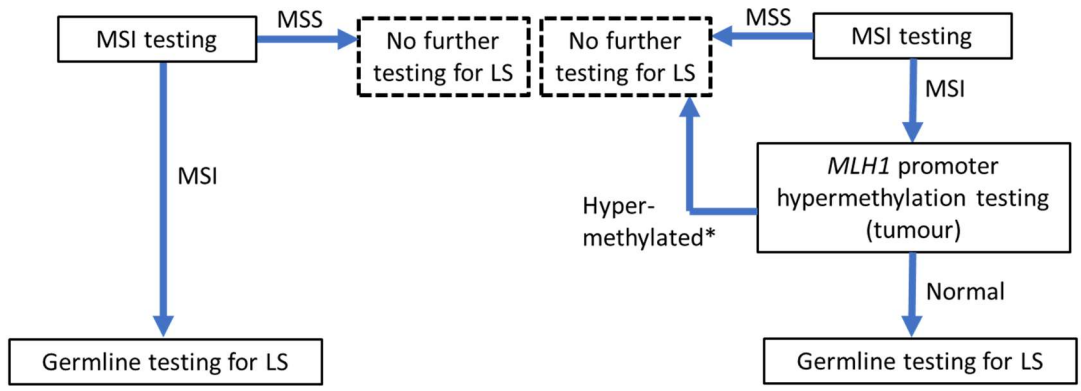
The Royal College of Pathologists' Dataset for histological reporting of endometrial cancer (2017) states that pathological features of endometrial carcinomas associated with Lynch syndrome include lower uterine segment location, undifferentiated areas and abundant tumour infiltrating lymphocytes.

Testing strategies

Several strategies can be used to test for Lynch syndrome for people with endometrial cancer; based on initial MSI and IHC testing. These strategies are similar to those assessed in NICE's guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer, although *BRAF* testing has been removed because clinical experts advised that this would not be useful in endometrial cancer (see section 2.2.3). An overview of the strategies to be included in this assessment is presented in figures 1 to 5.

Clinical experts commented that if family history is available, this can be discussed at a gynaecological oncology Multidisciplinary Team (MDT) meeting. A referral to clinical genetics services can be made if this indicates a potential inherited condition.

Figure 1 MSI testing based strategies (MSS: microsatellite stable, MSI: microsatellite instability, LS: Lynch syndrome)

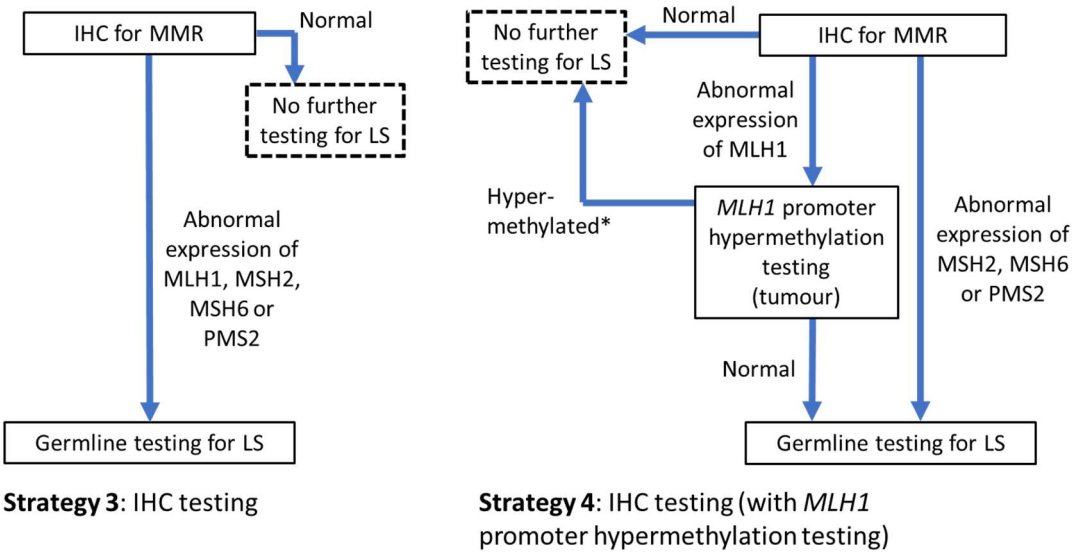


Strategy 1: MSI testing

Strategy 2: MSI testing (with *MLH1* promoter hypermethylation testing)

* If a germline sample is tested and is also hypermethylated - diagnose Lynch syndrome

Figure 2 IHC testing based strategies (LS: Lynch syndrome)



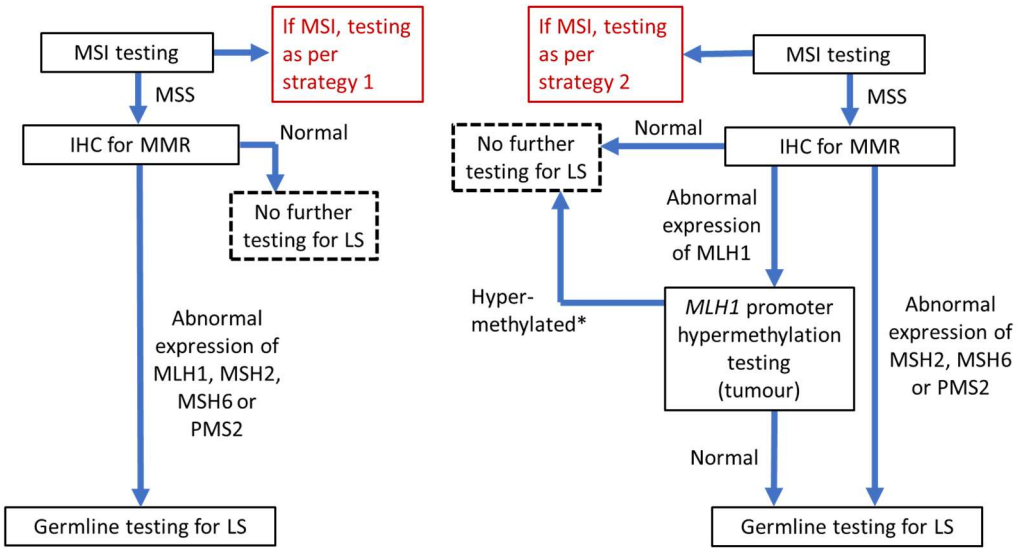
* If a germline sample is tested and is also hypermethylated - diagnose Lynch syndrome

Clinical experts highlighted that abnormal expression of MLH1 (with or without abnormal expression of PMS2) would be the criteria used to decide if *MLH1* promoter hypermethylation testing should be done (after IHC testing).

Clinical experts commented that both MSI and IHC testing could be done on an endometrial tumour sample in clinical practice, and that this should be included in this assessment. While it might be expected that there would be a lot of agreement between the tests, doing both may help to increase detection of people with Lynch syndrome. These 2 initial tests could be used in different ways. This could be sequential if the initial test (MSI or IHC testing) did not indicate potential Lynch syndrome, to help identify false negative results. Testing could either initially be for MSI (with IHC testing in the event of microsatellite stability; see figure 3), or an initial test with IHC (with MSI testing if no abnormal expression of MMR proteins was seen; see figure 4).

Alternatively, both tests could initially be done on a tumour sample, and further testing done if either test suggested potential Lynch syndrome (that is, microsatellite instability or abnormal expression of any of the MMR proteins, or both; see figure 5).

Figure 3 MSI testing followed by IHC testing based strategies (MSS: microsatellite stable, MSI: microsatellite instability, LS: Lynch syndrome)

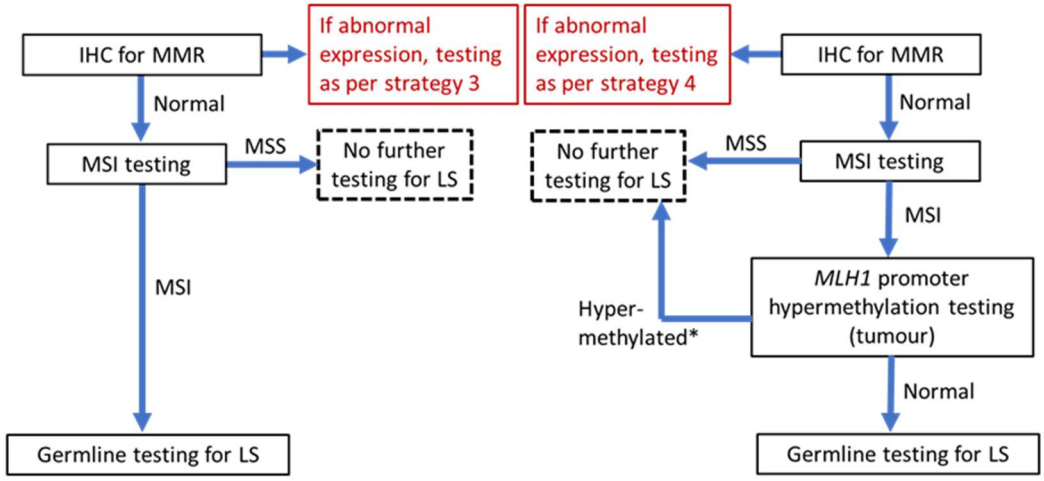


Strategy 5: MSI then IHC testing

Strategy 6: MSI then IHC testing (with *MLH1* promoter hypermethylation testing)

* If a germline sample is tested and is also hypermethylated - diagnose Lynch syndrome

Figure 4 IHC testing followed by MSI testing based strategies (MSS: microsatellite stable, MSI: microsatellite instability, LS: Lynch syndrome)

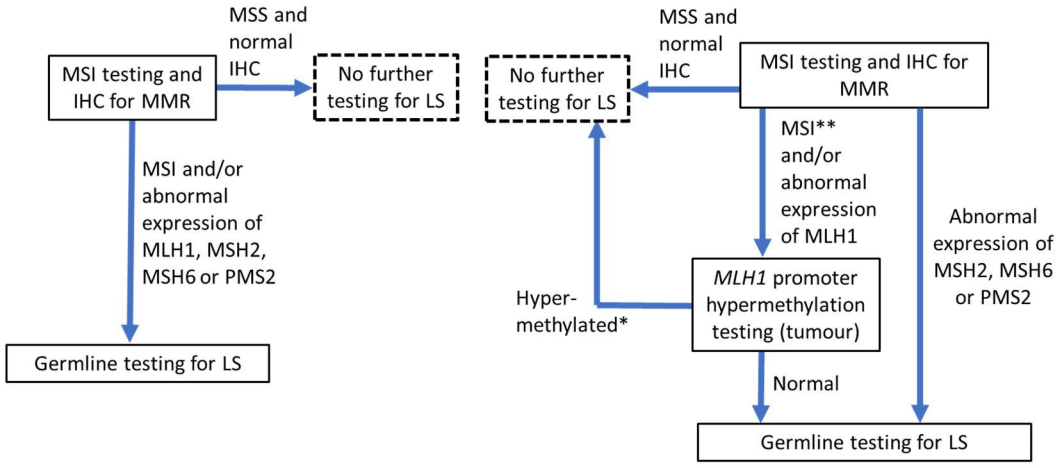


Strategy 7: IHC then MSI testing

Strategy 8: IHC then MSI testing (with *MLH1* promoter hypermethylation testing)

* If a germline sample is tested and is also hypermethylated - diagnose Lynch syndrome

Figure 5 Combined MSI and IHC testing based strategies (MSS: microsatellite stable, MSI: microsatellite instability, LS: Lynch syndrome)



Strategy 9: MSI and IHC testing

Strategy 10: MSI and IHC testing (with *MLH1* promoter hypermethylation testing)

***** If a germline sample is tested and is also hypermethylated - diagnose Lynch syndrome
** Clinical experts stated that *MLH1* promoter hypermethylation testing would not be done after MSI if MLH1 expression on IHC was normal and abnormal expression of other MMR proteins was present

A further strategy is to go directly to germline testing for Lynch syndrome (**strategy 11**) for people diagnosed with endometrial cancer; that is, with no initial tumour-based testing. A potential disadvantage of this approach is that if a sequence variant of unknown significance is identified in an MMR gene, there is no corresponding information from the tumour to help indicate if this leads to deficient DNA MMR. Any such variants identified take time to assess to decide if they should be considered pathogenic (with associated cost). Clinical experts also highlighted the impact on clinical genetics services of directly referring all people with endometrial cancer for germline testing. They commented that most of the people would be having definitive testing for a condition they do not have, and that consent for germline testing would need to be obtained for everyone with endometrial cancer (with associated costs). However, direct to germline testing would identify people with Lynch syndrome that tumour testing had incorrectly suggested did not have the condition (and who had not therefore gone on to have germline testing), so may identify more people with the condition.

Identification of Lynch syndrome in a person with endometrial cancer will initiate further testing for the identified MMR gene mutation in their family members (cascade testing; discussed below). People in whom a genetic condition is identified for the first time in a family are referred to as a proband.

Referral to clinical genetics service

Clinical experts highlighted the importance of a referral to a clinical genetics service to ensure that genetic counselling is offered to people who are at risk of having Lynch syndrome, before a diagnosis is made. This can help people understand whether genetic testing is appropriate or not, and what the implications are for them and their extended family. Some people may decide not to have germline testing for Lynch syndrome. Clinical experts commented that genetic counselling would always be offered before germline testing, but potentially not before tumour testing.

3.3.2. Management

Treatment of endometrial cancer in people with Lynch syndrome

The main treatment for endometrial cancer is removal of the womb (hysterectomy) together with the ovaries and fallopian tubes (bilateral salpingo-oophorectomy). Clinical experts highlighted that people with Lynch syndrome typically have endometrial cancer at an earlier age, potentially before they have completed their family, and may wish to opt for more conservative surgery if suitable. In addition, women who are identified as not having Lynch syndrome may opt to keep their ovaries. Pre-implantation genetic diagnosis may be an option if eggs or ovarian tissue are stored after removal.

Management and surveillance of people who have Lynch syndrome

People who are diagnosed with Lynch syndrome as a result of having endometrial cancer can be offered surveillance and risk reducing interventions for further cancer. Testing for Lynch syndrome can also be offered to their family members, who can then also be offered surveillance and risk reducing interventions for Lynch syndrome related cancers.

Clinical experts highlighted the importance of discussing with a person their MMR pathogenic variant-specific risk of cancer, and potentially likely age of onset, to inform decisions about whether to have risk reducing interventions or start surveillance, and at what age.

Risk reducing interventions

Surgery

The Royal College of Obstetricians and Gynaecologists' paper on the Management of Women with a Genetic Predisposition to Gynaecological Cancers states that most women with Lynch syndrome are offered total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, unless contraindicated, after completion of their families.

The Institute of Cancer Research's Cancer Genetic Clinical Protocols (developed by the Cancer Genetics Clinical Academic Unit at The Royal Marsden and The Institute of Cancer Research; accessed 4 June 2019) have recommendations on offering risk reducing hysterectomy with bilateral salpingo-oophorectomy to MMR gene mutation carriers once they have completed their families. These protocols were being updated at the time of writing.

The Manchester International Consensus Group (Crosbie et al., 2019) strongly recommends that risk reducing total hysterectomy and bilateral salpingo-oophorectomy is offered no earlier than 35–40 years of age following completion of childbearing, for people with pathogenic variants of *MLH1*, *MSH2* and *MSH6*. Personal risk should be used to provide individualized counselling regarding optimal timing of the procedure. The group stated that the strength of evidence was insufficient to strongly recommend risk reducing surgery in *PMS2* pathogenic variant carriers. The group also provided additional recommendations on carrying out risk reducing surgery (see Crosbie et al., 2019).

Crosbie et al. (2019) also reviewed current guidance on prophylactic measures for gynaecological cancer for people with Lynch syndrome (eTable 1 in Supplementary material) which showed differing recommendations for offering prophylactic gynaecological surgery (with or without recommended age restrictions) after completion of family from several guideline groups.

Clinical experts commented that people with Lynch syndrome often choose to have risk reducing hysterectomy and bilateral salpingo-oophorectomy at an earlier age and would be offered hormone replacement therapy (HRT). The Manchester International Consensus Group (Crosbie et al., 2019) strongly recommended that women who undergo risk-reducing hysterectomy and removal of their ovaries are offered oestrogen-only HRT (preferably via the transdermal route) until the natural age of the menopause (age 51 years) or, in consultation with their specialist, until they wish to stop.

Chemoprevention

Aspirin can be offered to reduce the risk of Lynch syndrome related cancers. The Institute of Cancer Research's Cancer Genetic Clinical Protocols[1] recommend discussing the benefits and side-effects of aspirin chemoprevention with people over 25 years old. The Manchester International Consensus Group (Crosbie et al., 2019) strongly recommends that people with Lynch syndrome take aspirin chemoprevention to reduce their risk of

[1] These protocols are currently being updated.

colorectal and other cancers, within the context of a clinical trial, or through discussion with their doctor.

An update of NICE's guidance on colorectal cancer: diagnosis and management is currently underway. The scope of this update includes assessing the role of aspirin in the prevention of colorectal cancer in adults with clinical or genetic evidence of Lynch syndrome.

Clinical experts highlighted that the CaPP3 trial is currently investigating the optimal dose for cancer risk reduction. If people had not been enrolled in this trial, clinical experts commented that a lower dose of aspirin (from 75 to 300mg) is usually offered.

Cancer surveillance

Because people with Lynch syndrome are at a higher risk of developing some forms of cancer, increased surveillance can be offered to detect premalignant disease or cancer at an earlier stage.

i. Surveillance for colorectal cancer

The Institute of Cancer Research's Cancer Genetic Clinical Protocols[1] recommend offering colonoscopy every 18 months. This should start from 25 years old for people with pathogenic mutations in *MLH1, MSH2 or EPCAM*, or from 30 years old for people with pathogenic mutations in *MSH6* or *PMS2*. This should continue until 75 years old (when a review should occur).

The 2013 European Guidelines: Revised guidelines for the clinical management of Lynch syndrome (Vasen et al., 2013) recommends that people who have been identified as having a Lynch syndrome mutation have a colonoscopy every 1-2 years. The British Society of Gastroenterology's Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups recommends that people who have been identified as having a Lynch syndrome mutation are offered total colonic surveillance at least every 2 years from the age of 25.

ii. Surveillance for gynaecological cancers (endometrial and ovarian cancer)

For people with Lynch syndrome who do not want risk reducing surgery for gynaecological cancer, or who want to defer this to a later time (for example, while they complete their family), several tests can be used for gynaecological surveillance: pelvic ultrasound, endometrial biopsy, hysteroscopy and CA125 testing (Cornou et al., 2016).

[1] These protocols are currently being updated.

The Royal College of Obstetricians and Gynaecologists' paper on the Management of Women with a Genetic Predisposition to Gynaecological Cancers states that the efficacy of endometrial cancer surveillance in Lynch syndrome is still unproven. In addition: "Gynaecological surveillance of the endometrium by transvaginal ultrasound and aspiration biopsy starting from age 35–40 years may lead to the detection of early cancer, but should be performed as part of a clinical trial given the lack of proven benefit."

The paper also states that for people with a high risk of ovarian cancer who choose not to have risk-reducing bilateral salpingo-oophorectomy, the evidence for screening is yet to be established.

The Institute of Cancer Research's Cancer Genetic Clinical Protocols[1] state that ovarian and endometrial cancer surveillance is not recommended outside a research setting.

The Manchester International Consensus Group (Crosbie et al., 2019) recommends that people with Lynch syndrome who have not experienced gynaecological cancer should undergo optional annual review from the age of 25 with an appropriate clinician to discuss red flag symptoms for endometrial and ovarian cancer. The group did not recommend invasive gynaecological surveillance because they concluded that there was insufficient evidence that this improves outcomes over symptom awareness and urgent investigation of red flag symptoms.

Crosbie et al. (2019) also reviewed current guidance on the management of gynaecological cancer for people with Lynch syndrome (eTable 1 in Supplementary material). Recommendations on surveillance across the guidance vary, and included offering annual trans-vaginal ultrasound, endometrial biopsy and measurement of CA125. The ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up recommended that surveillance of the endometrium by gynaecological examination, transvaginal ultrasound and aspiration biopsy starting from the age of 35 years (annually until hysterectomy) should be offered to all Lynch syndrome mutation carriers (Colombo et al. 2016).

Clinical experts commented that there is considerable uncertainty about the benefits of surveillance for gynaecological cancers. In some parts of the NHS gynaecological surveillance may be offered for people diagnosed with Lynch syndrome, but not routinely. They highlighted that patients often find surveillance reassuring. When offered, clinical experts commented that surveillance would be likely to be annually, and would include transvaginal

[1] These protocols are currently being updated.

ultrasound, endometrial pipelle biopsy (the most commonly used test) and hysteroscopy.

iii. Surveillance for other Lynch syndrome related cancers

Clinical experts commented that testing for additional Lynch syndrome related cancers is not routinely done. The NICE guideline on pancreatic cancer in adults recommends to consider surveillance for pancreatic cancer for people with Lynch syndrome and first-degree relatives with pancreatic cancer. The full guideline includes a research recommendation that research should be undertaken to evaluate the most clinically effective and cost effective initial surveillance tests, additional tests and frequency of surveillance that produce the greatest diagnostic yield and overall surveillance efficiency.

Clinical experts further commented that *Helicobacter pylori* screening may be offered to people with mutations in MMR genes that increase risk of gastric cancer. This would be arranged by a person's GP.

People with Lynch syndrome should be given advice about symptoms of Lynch syndrome related cancers and what to do if they think they are experiencing any.

Cascade testing

If a person is identified as having Lynch syndrome, their first-degree relatives (parents, siblings and children) have a 50% risk of also having the condition. Where the familial mutation has been identified, cascade testing (with appropriate genetic counselling) should be offered to at risk relatives to see if they have the same Lynch syndrome causing mutation (before any cancer occurs). Clinical experts commented that cascade testing would typically be offered from 18 years old.

3.4 Patient issues and preferences

There is considerable anxiety and distress associated with genetic testing for hereditary cancer syndromes. Being diagnosed with Lynch syndrome, or being at risk of it, can be very difficult to cope with. The knowledge of being at an increased risk of cancer but not knowing if cancer will develop can cause considerable anxiety. Parents of children with Lynch syndrome can feel guilty about passing on Lynch syndrome to their children. Many people have concerns about genetic testing, screening or whether to have risk reducing surgery. 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 whether genetic testing is appropriate or not. Genetic counselling helps explain what a positive or negative result means and what the implications are for the person and their extended family. 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.

After having a salpingo-oophorectomy (removal of fallopian tubes and ovaries) sudden onset of menopause will occur (if it has not already) and there is an increased risk of developing osteoporosis (thinning of the bones). Complications can also occur during surgery; for example, bleeding, infection, and injuries to the urinary tract and bowel. After this risk reducing surgery it also will not be possible to give birth to any (further) children. Choosing whether, and when, to have risk reducing surgery after being diagnosed with Lynch syndrome (which can potentially be early in a person's life if diagnosed through cascade testing of family members) can be a difficult decision, and requires a good understanding of an individual's risk of cancer (for example, based on their specific pathogenic variant of an MMR gene). Knowledge that a person is at higher risk of gynaecological cancer may help to inform decisions about family planning. If a person is diagnosed with Lynch syndrome and is trying to have children, this can increase their anxiety if they are struggling to conceive and are considering having prophylactic surgery in the future.

4 Comparator

No reflex testing to identify Lynch syndrome for people with endometrial cancer. Clinical experts commented that some testing for Lynch syndrome may be done if family history is available that suggests the condition, but noted that a comprehensive family history is often not taken and, when taken, often does not include every Lynch syndrome related cancer.

5 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 (further description is in section 3.3): • **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 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 for consideration may include: • Health-related quality of life • Anxiety and depression
	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.

6 Other issues for consideration

The extent of any gynaecological cancer surveillance offered to people who have not had risk reducing surgery varies in the NHS. Economic modelling should investigate the impact of offering gynaecological surveillance on cost effectiveness estimates. The economic model produced for NICE's guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer included gynaecological surveillance in its base case. This comprised of annual gynaecological examination, transvaginal ultrasound, endometrial aspiration biopsy and CA125 testing. Women with Lynch syndrome were assumed to be offered gynaecological surveillance from 35 years old, or at the time of their diagnosis, up to 70 years. The EAG for this assessment acknowledged uncertainty around the benefit of gynaecological surveillance, and investigated this in scenario analyses in which surveillance was assumed to have no benefit (but its costs were still included), and by removing gynaecological surveillance from the model entirely, with no associated costs or benefits modelled (scenarios 3 and 4 reported in the diagnostics assessment report from page 238 onwards).

Clinical experts highlighted that tumours with *MSH6* mutations often do not show microsatellite instability or are MSI-Low (You et al. 2010; Liccardo et al. 2017). They highlighted that this is particularly an issue for endometrial cancer because people with an inherited mutation in this gene tend to be at higher risk of endometrial cancer.

Costs of DNA sequencing are decreasing and lower costs in the future may affect the cost effectiveness of the assessed strategies. Economic modelling could investigate the effects of any decreases in costs of germline testing for Lynch syndrome (for example, with threshold analysis).

If possible, the impact of assuming that MSI-Low is a positive or negative result (to indicate potential Lynch syndrome) on diagnostic accuracy estimates for MSI testing could be assessed. The impact of any change in

accuracy resulting from this on cost effectiveness estimates for MSI testing could also be investigated.

Clinical experts commented that testing strategies that use both MSI and IHC testing are used in clinical practice (and have therefore been included in the testing strategies included in this assessment). However, they did highlight potential issues with implementing the use of both tumour tests. This included the difference in time to get results (which would be available earlier from IHC testing than MSI testing) and the need to coordinate testing and results from different services.

7 Potential 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.

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 MSI and IHC to detect potential Lynch syndrome associated endometrial cancer may decrease in older cohorts because the occurrence of 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 with increased age).

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

Clinical experts further commented that the numbers of variants of unknown significance that are 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.

8 Potential implementation issues

Potential adoption **levers** identified by the NICE Adoption and Impact team include:

- 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.

Potential adoption **barriers** identified by the NICE Adoption and Impact team include:

- The need for multiple departments and specialities to work together to oversee the testing strategies and appropriate response 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 IHC tests can be challenging; appropriately 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.

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Appendix A Glossary of terms

Constitutional mutations
Mutations that are inherited and are present in every cell

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 occur during a person's lifetime.

Methylated
DNA which 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
A person serving as the starting point for the genetic study of a family

Somatic mutation
A change in the DNA in any cells of the body, except the germ cells (sperm and egg), which isn't 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

Appendix B Abbreviations

EPCAM
Epithelial cell adhesion molecule

IHC
Immunohistochemistry

MLH1
MutL homolog 1

MLPA
Multiplex ligation-dependent probe amplification

MMR
Mismatch repair

MSH2, MSH6
MutS homologs 2 and 6

MSI
Microsatellite instability

MSS
Microsatellite stable

PCR
Polymerase chain reaction

PMS2
Post meiotic segregation increased 2

Appendix C References

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