NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Testing strategies for Lynch syndrome in people with endometrial cancer

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 6 August 2020

THEME: Accuracy of microsatellite instability testing

Comment number	Name and organisation	Section number	Comment	NICE response
1	Newcastle University	Subsection: 1.1	Summary: The Newcastle University Cancer Genetics team is dedicated to improving the identification of people with Lynch syndrome in order to enhance their care, by rapid detection and removal of cancers and using aspirin and dietary modification to significantly reduce the tumour burden. We have also been focused over the last decade on developing improved functional assays for mismatch repair deficiency. We have developed a next generation sequencing based microsatellite instability (MSI) assay, which is highly sensitive and specific and suitable for large-scale deployment (Gallon et al. 2019; PMID: 31471937; DOI: 10.1002/humu.23906). We agree that MSI testing in endometrial cancer appears to be less sensitive than in other Lynch syndrome cancers. As we explain in detail below, however, all literature based on the Bethesda/NCI panel should be disregarded as the lack of sufficient mononucleotide repeats in the panel means that MSH6 cannot be reliably identified. More recent literature is largely based on the Promega fragment length analysis system, which does use mononucleotide repeats. The MSI assay we have developed over the last 10 years (Gallon et al 2019; PMID: 31471937; DOI: 10.1002/humu.23906) is now in clinical use in the North East for colorectal cancer testing and is being assessed in endometrial cancer. (Declaration of interest: this assay has been patented by Newcastle University and negotiations are underway to commercialise the assay for more widespread use.)	Thank you for your comment which the committee considered. The committee noted that work on this assay is underway to improve detection of MMR deficiency in endometrial cancers, and that further evidence may be generated in the future. Section 4.17 of the guidance reports the committee's considerations that future developments may affect the cost effectiveness of testing strategies. Additional text has been added to this section in the final guidance to note that there are emerging technological developments, such as the use of next generation sequencing to test for MSI as part of tumour characterisation. NICE reviews the evidence 3 years after publication of its guidance to ensure that any relevant new data is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available. If further data becomes available on this assay when used to assess endometrial cancer, please submit this to diagnsotics@nice.org.uk.

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			Initial use of this assay on available Lynch syndrome endometrial cancers identified 29 of 39 tumours (74%) as MSI-H, whereas the assay detected MSI-H in 45/48 (93.8%) Lynch syndrome colorectal cancers and 20/22 (90.9%) other Lynch syndrome cancers. In partnership with colleagues in Manchester, the endometrial cancer samples used to develop the current guideline are being analysed and used to train the Newcastle assay to be more sensitive to MMR deficiency in endometrial cancers. It remains possible that IHC will continue to be more sensitive to MSI, but making IHC an absolute requirement of endometrial cancer screening runs the risk of testing not being deployed at all. Despite NICE guidance in 2017, fewer than half of all trusts have testing in place for Lynch syndrome in colorectal cancers (NHSE Lynch syndrome advisory committee June 2020). A significant factor is the staffing crisis among histopathologists. According to the incoming President of the Royal College of Pathologists at the recent HSJ online debate, only 3% of departments are fully staffed. Where IHC for the MMR proteins is in place it should be continued for endometrial cancer testing, but it is highly likely that endometrial cancer testing will not be deployed in many centres if this technique is a prerequisite of providing the service. We contend that the guidance should require an effective functional assay for MMR deficiency. At present, IHC for the four MMR proteins followed by methylation analysis is the preferred approach, but a molecular approach based on MSI testing or direct	The committee also noted that the provided sensitivity figure for the assay when used to assess MSI in endometrial tumours (74%) is lower than studies identified in the EAG's report (see figure 24 in the diagnostics assessment report). The committee heard from clinical experts that there is a shortage of histopathologists, but they also highlighted that there is also a shortage of biomedical scientists needed to do MSI tests. A clinical expert also commented that adding MMR IHC to existing characterisation of an endometrial tumour adds little time, so if there is a histopathologist available to characterise the tumour, they will also be able to do the MMR IHC.

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			sequencing of the MMR genes would be acceptable if demonstrated to be of comparable efficiency and cost. Detail of MSI testing: The panel of microsatellite markers used for MSI analysis is critical to its performance. Many of the studies used to inform this guidance use out-dated marker panels that have poor sensitivity and specificity in multiple cancer types, not just endometrial cancers. Most significantly, the frequently used NCI panel contains only two mononucleotide repeats. MMR deficiency due to loss of MSH6 function, which is the most frequent cause of MMR deficiency in Lynch syndrome-related endometrial cancer (see Subsection 3.6), is detectable only through analysis of mononucleotide repeats. The three dinucleotide repeat markers used in the NCI panel are insensitive to MSH6 deficiency. The usual threshold for MSI-H classification (instability in ≥30% of markers) cannot be applied for the detection of MSH6 deficiency when the majority of markers in the panel are insensitive dinucleotide repeats. This is a critical oversight of the guidance that needs to be addressed when selecting studies to estimate the diagnostic performance of MSI analysis. We recommend that, as well as including MSI analysis in the testing guidance, it should be specified that MSI analysis of mononucleotide repeats exclusively must be used.	
2	Newcastle University	Subsection: 3.10	As stated in Subsection: 3.6, MSH6 is the most common MMR gene affected in Lynch syndrome endometrial cancer patients. It is well established in the literature that MSH6 deficiency leads to MSI in	Thank you for your comment which the committee considered.

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			mononucleotide repeat microsatellites only, and these markers must be used to detect MSH6 deficiency accurately. MSH6 is not involved in the repair of di-, tri-, tetra-, penta-, and hexa-nucleotide repeats, and therefore these microsatellites are insensitive to MSH6 deficiency. Furthermore, it has been shown that capillary electrophoresis traces from dinucleotide repeats – frequently used in out-dated MSI marker panels such as the NCI panel (Boland et al. 1998; PMID: 9823339) – are harder to interpret than those from mononucleotide repeats (Buhard et al. 2004; PMID: 15528790; DOI: 10.1155/2004/159347). MSI marker panels exclusively composed of mononucleotide repeats have been used to re-classify MSI-L tumours as MSS due to removal of ambiguous results from dinucleotide repeats (Murphy et al. 2006; PMID: 16825502; DOI: 10.2353/jmoldx.2006.050092). Panels of five mononucleotide repeats were previously shown to have 97-100% sensitivity for MSH6 deficiency in cancers of the colon, endometrium, and urothelium (You et al. 2010; PMID: 21081928; DOI: 10.1038/sj.bjc.6605988). Therefore, MSI analysis of mononucleotide repeats exclusively is recommended for tumour testing. The studies used to define the diagnostic performance of MSI analysis must be interpreted with knowledge of the MSI marker panel used. As the MSI marker panel used is so critical for the estimation of MSI analysis sensitivity, studies that do not use panels exclusively composed of mononucleotide repeats should, in our opinion, either be excluded, or two scenarios should be assessed: First, using estimations of MSI analysis using only those studies that exclusively used mononucleotide repeat	The EAG's systematic review did not exclude studies on the basis of the MSI panel used, and data from all these studies was provided for committee. The EAG explained that they had intended to conduct subgroup analysis for the different combinations of microsatellite markers, but because of the small number of studies identified this was not possible. The committee noted that the composition of an MSI panel may impact on the sensitivity of the test to detect MSI in an endometrial cancer sample. However, it was limited by the data available. Notably Chao et al. (which is described as a suitable panel in the consultation response) was included in the EAG's report and was used in a scenario analysis to provide an estimate of cost effectiveness of MSI and IHC testing. This was considered by the committee in its decision-making (see section 4.13 of the guidance). In addition, as described in greater detail in the response to consultation comment 5 below, the

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			markers for MSI analysis; Second, using estimations of MSI analysis using all of the relevant studies identified. Three of the four studies listed in Subsection 3.10 use out-dated panels. One of these does not specify MSI classification thresholds and so its results are difficult to interpret. In addition, all studies have low sample numbers. These limitations likely explain the observed study heterogeneity. Summaries for each study are given below. Berends et al. 2003 (PMID: 14645426; DOI: 10.1200/JCO.2003.04.094): • MSI analysis used the NCI panel (two mononucleotide repeats and three dinucleotide repeats). Samples with zero or one unstable markers were classified as MSI-L, and samples with two or more unstable markers were classified as MSI-H. • 8 patients had germline MMR gene variants, 5 known pathogenic, and 3 of uncertain significance. 5 of 8 ECs were MSI-H (62.5% sensitivity), and the other 3 ECs were MSI-L. • The 3 MSI-L ECs were from patients with MSH6 variants (2 cases) or an MLH1 VUS (539T>G, https://www.ncbi.nlm.nih.gov/clinvar/variation/90257/). The patient with an MLH1 VUS cannot be considered to have Lynch syndrome. • The MSI results of Berends et al. 2003 should be interpreted with care. The MSI-L results in MSH6 variant carriers should be considered positive if the single unstable marker was in either of the mononucleotide repeats (hence ≥30% of microsatellites	PETALS study which was provided to the committee in confidence as a pre-publication manuscript used an MSI assay that consisted of 5 mononucleotide repeats. Accuracy data from this study was also used in a scenario analysis in the economic model and was considered by the committee in its decision making (see section 4.13 of the guidance). The committee noted that the sensitivity estimate for MSI testing from this study (56.3%) was lower than for IHC testing (100%; see section 4.5 of the guidance). The committee therefore did consider analyses that used accuracy estimates generated from MSI tests with mononucleotide panels in its decision making.

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			capable of detecting MSH6 deficiency were unstable). The use of an out-dated marker panel may explain the two negative results from MSH6 deficient endometrial cancers. Lu et al. 2007 (PMID: 17925543; DOI: 10.1200/JCO.2007.10.8597): • MSI analysis used an adapted NCI panel (three mononucleotide repeats and three dinucleotide repeats). Samples with no unstable markers were classified as MSS, samples with one unstable marker were classified as MSI-L, and samples with two or more unstable markers were classified as MSI-H. • 9 patients had germline MMR gene variants. 8 of 8 ECs tested for MSI were MSI-H (100% sensitivity). 1 EC was not tested for MSI. • The MSI results of Lu et al. 2007 should be interpreted with care. Whilst MSI analysis was 100% sensitive it would be informative to know which markers were unstable in each sample, particularly the MSH6 deficient endometrial cancers, as an out-dated marker panel was used. Rubio et al. 2016 (PMID: 27398995; DOI: 10.1159/000447972): • MSI analysis used the same adapted NCI panel (three mononucleotide repeats and three dinucleotide repeats) as used by Lu et al. 2007. Thresholds for sample classification were not specified. MSI-L is given as an abbreviation in tables but is not used. It is possible MSS and MSI-L results are combined as in Berends et al. 2003 as both are considered negative results for the	

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			detection of MMR deficiency. It is also possible that a threshold different to the standard (≥30%) was used, e.g. some studies use a more stringent threshold of ≥40%. • 14 patients had germline pathogenic MMR variants. 12 of 14 endometrial cancers were tested for MSI, 5 of 12 were MSI-H and 7 of 12 were MSS. 2 of 7 MSS ECs were from MSH2 gene carriers, and the other 5 were from MSH6 gene carriers. • The MSI results of Rubio et al. 2016 should be interpreted with care. The MSS results could be MSI-L according to standard definitions, as no clear classification thresholds are given. The use of an out-dated marker panel may explain the large number of negative results from MSH6 deficient endometrial cancers. Chao et al. 2019 (PMID: 31307542; DOI: 10.1186/s40880-019-0388-2): • MSI analysis used a commercial kit of five mononucleotide repeats. Samples with no unstable markers were classified as MSS, samples with one unstable marker were classified as MSI-L, and samples with two or more unstable markers were classified as MSI-H. • 6 patients had germline pathogenic MMR variants. 4 of 6 endometrial cancers were tested for MSI, all were MSI-H. • The MSI results of Chao et al. 2019 should be interpreted with care. Whilst this study used an appropriate panel of microsatellites for MSI analysis, the number of endometrial cancers (from Lynch syndrome gene carriers) tested for MSI was very low.	

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3	Newcastle University	Subsection: 3.12	As there is no statistically significant difference between MSI analysis and IHC for the detection of tumour MMR deficiency, it is not clear why MSI analysis is considered to have a worse outcome than IHC in the cost-effectiveness model (see Table 1).	Thank you for your comment which the committee considered. The EAG noted that MSI-based strategies tended to have lower specificity than IHC-based strategies, so had higher numbers of false positives for potential Lynch syndrome in the model. This increased costs markedly as those with positive test results incur genetic counselling and germline testing costs. It is also important to note that the cost effectiveness estimates in table 1 in the guidance (produced using accuracy estimates from Lu et al.) were not the only cost-effectiveness estimates used by the committee in their decision making. They also considered cost effectiveness estimates generated using accuracy data from Chao et al., the PETALS study and a meta-analysis (Snowsill et al. 2019), as described in section 4.13 of the guidance.

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4	Newcastle University	Subsection: 4.4	It is certainly possible that IHC of endometrial cancers can detect more people with Lynch syndrome than MSI analysis. However, this needs to be formally assessed using the appropriate methods for both IHC and for MSI analysis, most significantly the use of MSI marker panels composed exclusively of mononucleotide repeats – please see Comment on subsection: 3.10 for more details.	Thank you for your comment which the committee considered. The committee noted that the PETALS study (which was used in a scenario analysis in the economic modelling and was considered in committee decision making - see section 4.13 of the guidance) used an MSI panel, the Promega MSI analysis system v1.2, that includes 5 mononucleotide repeat markers.
5	Newcastle University	Subsection: 4.5	Whilst we agree PETALS will overall be very informative for assessing the impact of Lynch syndrome screening in endometrial cancer patients, the results of MSI analysis are difficult to interpret until it is specified what marker panel was used – please see Comment on subsection: 3.10 for details.	Thank you for your comment which the committee considered. The MSI panel used in the PETALS study was the Promega MSI analysis system v1.2. Section 4.5 of the guidance has been amended to include this information.

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6	Newcastle University	Subsection: 4.3	Clinical pathways are heterogeneous. The new Genomic Medicine service supporting the Genomic Laboratory Hubs will require large scale genomic analysis of solid tumours, initially with gene panels and then Whole Genome Sequencing. The target is to provide a turnaround of 7 to 10 days. This is unlikely to be achieved for some years, given the recent disruption, but MSI analysis can be easily achieved in this timescale. If samples from the tumour are collected on arrival in the Pathology department and referred to the GLH, molecular analysis can be provided in under 2 weeks. The Newcastle MSI assay (Gallon et al 2019; PMID: 31471937; DOI: 10.1002/humu.23906) uses the ubiquitous MiSeq NGS platform. The results clearly distinguish MSI-High from microsatellite stable, without an "MSI-Low" category, expediting reporting further. In the past, acquiring DNA from tumours has been a rate-limiting step. The challenge of establishing pipelines for routine extraction of tumour DNA were addressed by the 100,000 Genomes Project, with turnaround times <18 days from sample receipt to whole genome sequencing results (Turnbull et al. 2018; PMID: 29462260; DOI: 10.1093/annonc/mdy054). These advances will filter through to routine care. It is likely that, with a check of tumour cell content, MSI analysis could be used on pre-surgical tumour biopsies to provide results for clinical MDT meetings prior to treatment.	Thank you for your comment which the committee considered. The committee noted that increased genomic analysis of tumours and streamlining of the testing pipeline could mean that the results of MSI testing based on next generation sequencing technology will be available in a shorter time. However, the committee noted that this is a future development and that the process for MSI testing may still mean that test results are not available as quickly as IHC testing which can be done at the time of reporting the histopathology.

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THEME: Cost effectiveness analyses: Microsatellite instability-based strategies

Comment number	Name and organisation	Section number	Comment	NICE response
7	Newcastle University	Subsection: 3.18	Given the heterogeneity of the studies – please see Comment on subsection: 3.10 – the results may be heavily dependent on which is used. It is not clear why Lu et al. 2007 was selected.	Thank you for your comment which the committee considered. The External Assessment Group (EAG) explained that Lu et al. (2007) was used in their base case analysis as it was the only paper that provided individual level data and therefore allowed some direct comparison of cost effectiveness between strategies. The EAG provided further information on the rationale for this decision and limitations of using Lu et al. (2007) on pages 175 to 178 of the diagnostics assessment report. The committee noted that the cost effectiveness results varied depending on which study was used to provide accuracy estimates for the model. The EAG provided scenario analyses in which different studies were used for the accuracy of testing strategies in the model: a meta-analysis (Snowsill et al. 2019), Chao et al. (2019) and the PETALS study. The committee considered the cost effectiveness estimates from all these analyses, as well as the base case that used Lu et al., in its decision making, as described in section 4.13 of the guidance.
8	Newcastle University	Subsection: 3.25	If multiple strategies have ICERs <£17,500/QALY, should these strategies also be recommended in the final guidance	Thank you for your comment which the committee considered.

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			as being viable alternatives? Different laboratories have set ups better suited for one strategy or another, and therefore flexibility in guidance should be provided.	The ICER estimates under £17,500 per QALY gained referred to in the consultation comment relate to pairwise analysis of strategies; that is, where each testing strategy is compared independently to no testing. However, the committee preferred to use a fully incremental analysis to produce cost effectiveness estimates (ICERs) for decision-making; that is where all the strategies are compared to each other (as well as no testing) to see what the optimum strategy is. This was because when making a decision to adopt a testing strategy for Lynch syndrome, providers will not just be deciding whether to test at all (compared to not doing testing), but also which of the available testing strategies they should adopt.
9	Newcastle University	Section: Table 1 Fully incremental base-case cost-effectiveness results (deterministic)	It would be interesting to see the ICERs for all strategies. A strategy can be dominated or extendedly dominated but still have an ICER that is only marginally greater than the strategies that dominate it. For example, in Snowsill et al. 2019 the ICER of MSI analysis followed by MLH1 methylation testing is £15,800/QALY, which is dominated by IHC analysis followed by MLH1 methylation testing with an ICER of £14,200/QALY. The difference between these ICERs is	Thank you for your comment which the committee considered. In addition to the fully incremental ICERs reported in the guidance document (table 1), pairwise ICERs (that is, each strategy compared independently to no testing), were reported in the diagnostics assessment report (table 14 on page 226), which were made available during consultation.

			relatively small and may be offset by the specific set ups of different diagnostic services. The reasons for the poorer outcome of MSI analysis are not explained, given it had 100% sensitivity for LS detection in the study used to inform this model (Lu et al. 2007), and MSI analysis and IHC were considered to have equivalent diagnostic accuracy – please see Comment on subsection: 3.10 and Comment on subsection: 3.12 for details.	The EAG also calculated net monetary benefit for all strategies, which were presented at the first committee meeting, and are stated in an addendum to the diagnostics assessment report. The deterministic net benefit of IHC followed by MLH1 promoter hypermethylation testing was the highest (£705 per person tested). The EAG commented that this was substantially higher than MSI testing-based strategies. The EAG also noted that MSI-based strategies tended to have lower specificity than IHC-based strategies, so had higher numbers of false positives for potential Lynch syndrome in the model. This increased costs markedly as those with positive test results incur genetic counselling and germline testing costs. It is also important to note that the cost effectiveness estimates in table 1 in the guidance (produced using accuracy estimates from Lu et al.) were not the only cost-effectiveness estimates used by the committee in their decision making. They also considered cost effectiveness estimates generated using accuracy data from Chao et al., the PETALS study and from a recent meta-analysis (Snowsill et al. 2019), as described in section 4.13 of the guidance.

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10	Newcastle University	Comment on subsection: 3.30	We believe that this is a very important point. Whilst the data from Chao et al. 2019 must be interpreted with care, this scenario highlights that cost-effectiveness is highly dependent on the measures of diagnostic accuracy used in the model, and that using a single scenario to decide on guidance is problematic: All of the studies proposed for modelling have critical limitations for defining diagnostic accuracy – please see Comment on subsection: 3.10 for details. Studies that use out-dated microsatellite marker panels containing dinucleotide repeats should be separated from studies that use the appropriate microsatellite marker panels containing exclusively mononucleotide repeats. We believe that this has to be considered in these draft guidance and, as stated above, that recommendations concerning MMR testing should be broadened to reflect this.	Thank you for your comment which the committee considered. The committee did consider the cost effectiveness estimates produced using Chao et al. (2019) to provide accuracy estimates for IHC and MSI testing in its decision making (as described in section 4.13 of the guidance). At the first committee meeting, 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 further 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. In addition, the committee also considered cost effectiveness estimates produced using accuracy data

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				from the PETALS study which used a panel of mononucleotide MSI markers. This analysis estimated that IHC followed by MLH1 promoter hypermethylation testing was the most cost-effective strategy.
11	Newcastle University	Subsection: 4.13	For the reasons discussed in Comments on section: Table 1 Fully incremental base-case cost-effectiveness results (deterministic), this interpretation is dependent on the scenario used for the model. Cost-effectiveness analysis in the additional scenario modelled using Chao et al. found MSI analysis dominated IHC – see Subsection: 3.30. Chao et al. 2019 is the only study discussed in Subsection: 3.10 that used an appropriate panel of markers for MSI analysis, and supports inclusion of MSI as a viable alternative to IHC. This should be considered in the guidance.	Thank you for your comment which the committee considered. The committee did consider the cost effectiveness estimates produced using Chao et al. (2019) to provide accuracy estimates for IHC and MSI testing in its decision making (as described in section 4.13 of the guidance). In addition, the committee also considered cost effectiveness estimates produced using accuracy data from the PETALS study which used a panel of mononucleotide MSI markers. This analysis estimated that IHC followed by MLH1 promoter hypermethylation testing was the most cost-effective strategy.

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THEME: Cost effectiveness analyses: General comments

Comment number	Name and organisation	Section number	Comment	NICE response
12	Institute of Biomedical Science	3.25	Table 1 Fully incremental base-case cost-effectiveness results (deterministic), please if we could add specificity/ sensitivity of each test strategy	Thank you for your comment which the committee considered. The sensitivity and specificity of each of the test strategies used in the base case analysis can be found on page 175 to 178 in the diagnostics assessment report.
13	University of Exeter	Evidence / cost effectiveness	Please see our recently published economic evaluation of testing for Lynch syndrome in endometrial cancer patients, directly based on the PETALS study: Snowsill TM, Ryan NAJ, Crosbie EJ. Cost-effectiveness of the Manchester approach to identifying Lynch syndrome in women with endometrial cancer. Journal of Clinical Medicine. 2020;9(6):1664. This study confirms the finding of the Committee that testing is likely to be cost-effective and that IHC with MLH1 methylation is likely to be the optimal strategy from an economic perspective.	Thank you for your comment which the committee considered.

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14	Royal College of Physicians (RCP)	General	NICE are recommending MMR IHC for endometrial cancer and not MSI testing as a first line test. This is fully justified from the evidence presented in terms of cost efficiency and test accuracy, and it is great to see that the feedback of patients and clinicians has been taken into consideration and the recognition that point of care MMR IHC is a more clinically valuable pathway than centralised MSI testing.	Thank you for your comment which the committee considered.
15	British Gynaecological Cancer Society		I agree with the recommendations. All women with EC should have LS by IHC first. Please ask for the information to be discussed by gynaecologist/specialist nurse at time of first surgery; also needs to go in the patient information testing and the need for a standard operating procedure in requesting the testing and reporting to patient and GP of the results.	Thank you for your comment which the committee considered. At the committee meeting, a patient expert commented that the Eve Appeal is producing educational material to help support discussions about testing for Lynch syndrome.
16	British Gynaecological Cancer Society		• The proposed strategy is appropriate and welcomed based on current evidence	Thank you for your comment which the committee considered.
17	British Gynaecological Cancer Society		• Has all of the relevant evidence been taken into account? *Yes* • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? *Yes* • Are the recommendations sound, and a suitable basis for guidance to the NHS? *Yes*	Thank you for your comment which the committee considered.

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18	British Gynaecological Cancer Society		I agree with the [above] comments. I have attached a few comments as well, as I think there can be some clarity around the testing process and when patients need to be counselled for this. **Has all the relevant evidence been taken into account?** Yes **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes. The evidence strongly supports testing for Lynch syndrome in all women diagnosed with endometrial cancer. **Are the recommendations sound, and a suitable basis for guidance to the NHS?** The recommendations address an important issue and are strongly supported. There should be clarification of the process of testing and the point at which discussion about implications of test results and consent is undertaken with the patient. 1.1	Thank you for your comment which the committee considered. Thank you for your comment which the committee considered. Recommendation 1.1 has been amended to clarify that testing for Lynch syndrome should be done for people who are diagnosed with endometrial cancer using these tests: Use immunohistochemistry (IHC) to identify tumours with mismatch repair (MMR) deficiency: • If IHC is abnormal with loss of MLH1, or loss of both MLH1 and PMS2 protein expression, do MLH1 promoter hypermethylation testing of tumour DNA. If MLH1 promoter hypermethylation is not detected, offer germline genetic testing to confirm Lynch syndrome. • If IHC is abnormal with loss of MSH2, MSH6 or isolated PMS2 protein expression, offer germline genetic testing to confirm Lynch syndrome. Recommendation 1.2 in the guidance states that healthcare professionals should inform people about the

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			The initial screening process with IHC and MLH1 promoter hypermethylation testing should be undertaken routinely as part of the diagnostic process for all patients with endometrial cancer and does not require individual consent. This is also an important factor for molecular characterisation of prognostic groups for endometrial cancer irrespective of Lynch syndrome. This is already the established practice for patients with colorectal cancer. **If IHC is positive, do MLH1 promoter hypermethylation testing of tumour DNA** This statement is confusing and it would be clearer if the phrases of "positive" or "negative" results are avoided: rather than stating IHC is "positive" it should be stated that if IHC shows abnormal/deficient/absent MMR protein expression, then further testing is required to exclude Lynch syndrome. MLH1 promoter hypermethylation testing of tumour DNA is undertaken only if MLH1 is absent on IHC, and not for all patients with abnormal MMR expression. Genetic testing for Lynch syndrome is then offered to patients when there is abnormal expression of mismatch repair proteins on IHC; for those tumours with	possible implications of test results for both themselves and their relatives and give support and information. Discussion of genetic testing and taking consent should be done by a healthcare professional with appropriate training.

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			abnormal MLH1 expression only those without MLH1 promoter hypermethylation need further investigation. 1.2 This statement applies to those patients who are then referred for germline testing.	
19	British Society of Gastroenterology		I agree with the essence of this recommendation i.e. universal testing for Lynch in endometrial cancer. I agree that IHC should be the index test (i.e. not MSI) given the high frequency of patients with loss of MSH^ expression who have MSS cancers. However, there are some important clarifications which are required: 1. "If IHC is positive...." should read something like "If IHC demonstrates loss of expression of MMR proteins" as 'positive' has no meaning in this context, i.e. 'positive' is not an appropriate way to report an IHC result 2. Why do methylation of MMR proteins other than MLH1 are not expressed? i.e. if loss of MSH2, MSH6 or PMS2 without loss of MLH1 one should proceed with germline testing not methylation testing (as this is an unnecessary step)	Thank you for your comment which the committee considered. Recommendation 1.1 has been amended to clarify that testing for Lynch syndrome should be done for people who are diagnosed with endometrial cancer using these tests: Use immunohistochemistry (IHC) to identify tumours with mismatch repair (MMR) deficiency: • If IHC is abnormal with loss of MLH1, or loss of both MLH1 and PMS2 protein expression, do MLH1 promoter hypermethylation testing of tumour DNA. If MLH1 promoter hypermethylation is not detected, offer germline genetic testing to confirm Lynch syndrome. • If IHC is abnormal with loss of MSH2, MSH6 or isolated PMS2 protein expression, offer germline genetic testing to confirm Lynch syndrome.

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THEME: Recommendations

Comment number	Name and organisation	Section number	Comment	NICE response
20	University of Exeter	1) Recommendations	Please consider clarifying second bullet point: 'If IHC is positive (i.e., abnormal/absent expression of one or more MMR protein)...'	Thank you for your comment which the committee considered. Recommendation 1.1 has been amended to clarify that testing for Lynch syndrome should be done for people who are diagnosed with endometrial cancer using these tests: Use immunohistochemistry (IHC) to identify tumours with mismatch repair (MMR) deficiency: • If IHC is abnormal with loss of MLH1, or loss of both MLH1 and PMS2 protein expression, do MLH1 promoter hypermethylation testing of tumour DNA. If MLH1 promoter hypermethylation is not detected, offer germline genetic testing to confirm Lynch syndrome. • If IHC is abnormal with loss of MSH2, MSH6 or isolated PMS2 protein expression, offer germline genetic testing to confirm Lynch syndrome.
21	Patient expert, Genomics England National Participant Panel member	1.1	As the sensitivity of IHC and MLH1 promoter hypermethylation testing might be less than 100%, people with Lynch syndrome could still be missed. Accepting that no test is perfect, please consider adding a further recommendation to do germline testing of those people whose initial tumour tests do not indicate	Thank you for your comment which the committee considered. The recommendations in this guidance do not specify the only testing that should be done for potential Lynch syndrome in people with endometrial cancer. The

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			Lynch syndrome but who have an identified risk factor e.g. family history of Lynch syndrome-related cancer and or young age/pre-menopausal at diagnosis. This will inevitably incur additional cost, but I suspect the numbers of people would be few and the potential benefit to them and their families, if found to have Lynch syndrome, is huge.	committee noted that the recommendations do not specify a course of action that should be followed if initial tumour tests do not indicate the need for germline testing to confirm potential Lynch syndrome. Clinical experts commented that a referral to clinical genetics services may be made depending on an individual's characteristics. However, it was beyond the scope of this work to specify all circumstances in which such referrals should be considered. However, the recommendations do not prevent further testing for Lynch syndrome if clinically indicated. Text has been added to section 2.3 of the guidance document to note that clinical experts commented that even if tumour testing for potential Lynch syndrome is routinely done, a referral to clinical genetics services may still be needed if the tumour tests do not indicate possible Lynch syndrome but a person has an identified risk factor (such as a family history of Lynch syndrome-related cancer) that suggests the condition is likely.
22	Patient expert, Genomics England National Participant Panel member	1.1	What are the recommendations for someone whose IHC is positive, MLH1 test is negative, yet Lynch syndrome is not confirmed by germline testing? Is this out of scope?	Thank you for your comment which the committee considered. It was beyond the scope of this assessment to provide recommendations for testing for Lynch syndrome under

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Comment number	Name and organisation	Section number	Comment	NICE response
				all circumstances. Clinical experts highlighted that a decision to test for Lynch syndrome in the scenario described by the stakeholder would take into account a person's individual characteristics, including family history.
23	Patient expert, Genomics England National Participant Panel member	1.2	There's no mention of consenting here and I think this warrants inclusion, especially given future changes to consenting of genomic (somatic and germline) tests within the Genomics Medicine Service e.g. Discussion of genetic testing **and consenting** should be done by a healthcare professional with appropriate training	Thank you for your comment which the committee considered. Recommendation 1.2 has been amended in the final guidance to include reference to consenting as suggested.

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THEME: Future developments

Comment number	Name and organisation	Section number	Comment	NICE response
24	British Association of Gynaecological Pathologists	3.15 Cost-effectiveness	The cost effectiveness studies should consider including the more recent study. Whilst germline testing of all persons with endometrial cancer is presently the most expensive option and not adequate resources are available, looking at studies over the past few years (including colorectal cancer studies) show a decrease in costs of this option. NICE should keep this option on the horizon. Given that cost of consenting all persons with endometrial cancer, NICE could instigate an initiative to establishing universal consent with an 'opt out' rather than 'opt in' approach to consent. Ref: Ryan NAJ, Davison NJ, Payne K, Cole A, Evans DG, Crosbie EJ. A Micro-Costing Study of Screening for Lynch Syndrome-Associated Pathogenic Variants in an Unselected Endometrial Cancer Population: Cheap as NGS Chips?. *Front Oncol*. 2019;9:61 Da Cruz P A, DeLair D, Fix D, Soslow R, Park K, Chiang S, Reis-Filho J, Zehir A, Mandelker D, Murali R, Makker V, Cadoo K, Mueller K, Leitao M, Abu-Rustum N, Aghajanian C, Weigelt	Thank you for your comment which the committee considered. The EAG did use the cost estimates from Ryan et al. (2019) in a scenario analysis which was considered by the committee (see section 4.10 in the guidance). The committee noted that future developments, such as a lower cost of germline testing, may change the cost effectiveness results and potentially the committee's recommendation on the testing strategy to be used (see section 4.17 of the guidance). 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.

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Comment number	Name and organisation	Section number	Comment	NICE response
			B Concordance between Immunohistochemistry for DNA Mismatch Repair Proteins and Next Generation Sequencing for the Identification of Microsatellite Instability in Endometrial Cancer. Poster 242 USCAP 2020	
25	British Gynaecological Cancer Society		• The evidence and cost/benefit analysis of direct germline testing of all patients with EC should be reviewed in due course	Thank you for your comment which the committee considered. The committee noted that future developments, such as a lower cost of germline testing, may change the cost effectiveness results and potentially the committee's recommendation on the testing strategy to be used in the future (see section 4.17 of the guidance). 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.
26	British Association of Gynaecological Pathologists	4.8	The rapid development of genetic tests and variably pricing of NGS panels make a continuously contemporary assessment of costs impossible. Ryan and colleagues illustrate this point well in their paper. Ref:	Thank you for your comment which the committee considered. The committee noted that future developments, such as a lower cost of germline testing, may change the cost effectiveness results and potentially the committee's recommendation on the testing strategy to be used in the future (see section 4.17 of the

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THEME: Future developments

Comment number	Name and organisation	Section number	Comment	NICE response
			Ryan NAJ, Davison NJ, Payne K, Cole A, Evans DG, Crosbie EJ. A Micro-Costing Study of Screening for Lynch Syndrome-Associated Pathogenic Variants in an Unselected Endometrial Cancer Population: Cheap as NGS Chips?. *Front Oncol*. 2019;9:61	guidance). 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.

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THEME: Gynaecological surveillance

Comment number	Name and organisation	Section number	Comment	NICE response
27	British Association of Gynaecological Pathologists	3.21	What is a 'non-invasive' gynaecological surveillance that can be done in general practice. This needs to be elaborated on and not left to local implementation	Thank you for your comment which the committee considered. The EAG included gynaecological surveillance for people with endometrial cancer (who had not undergone hysterectomy) in their model in order to assess if this would have any impact on the cost effectiveness of strategies to identify people with Lynch syndrome. It also did a scenario in which no gynaecological surveillance was included in the model to investigate the impact of this. This work was not intended to provide recommendations on the most appropriate gynaecological surveillance to be done in general practice. At scoping on this topic, clinical experts commented that gynaecological surveillance does occur, although variably, across the NHS and it was therefore thought appropriate to investigate any impact on the costs of this on cost effectiveness estimates for Lynch syndrome testing. The EAG commented that assumptions in their model about any gynaecological surveillance offered were based on guidelines on surveillance practices that have been published by the Manchester International Consensus group: Crosbie EJ, Ryan NAJ, Arends MJ, Bosse T, Burn J, Cornes JM, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med 2019;**21**(10):2390–400.

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THEME: Gynaecological surveillance

Comment number	Name and organisation	Section number	Comment	NICE response
28	British Association of Gynaecological Pathologists	3.21	Cancer-125 analysis – this is known to be an extensively used and poorly predictive marker in general practice and non-specialist hospital practice. What is the evidence for use of CA125 in Lynch syndrome surveillance? What is the sensitivity and specificity? What pathway does a raised CA125 result force the patient into, given that it is used for ovarian cancer as well.	Thank you for your comment which the committee considered. As noted in the response to the above comment, inclusion of gynaecological surveillance in the EAG's model was purely to investigate the potential impact of this on cost effectiveness estimates for Lynch syndrome testing, given that clinical experts commented that this does occur in the NHS. This does not provide guidance on the most appropriate methods to do this surveillance. The EAG commented that CA125 testing was included in their modelling based on guidelines published by the Manchester International Consensus group (Crosbie et al. 2019). Clinical experts commented that there is considerable uncertainty about the utility of using CA125 as part of gynaecological surveillance.

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THEME: Implementation

Comment number	Name and organisation	Section number	Comment	NICE response
29	Royal College of Physicians (RCP)	General	The problem for the clinical service will be how this testing is funded to ensure capacity to report the cases in cellpath across the country - the same issues as discussed for CRC, where MSI alone won't suffice. It does need co-operation with local cancer services for a clinically led service to deliver the MMR IHC and request MSI where relevant. The IHC funding/capacity discussions need to be taken forwards at a local level in each Trust with engagement from gynae MDTs with the cancer alliances who would probably want to roll out the same process across the whole of their region, though possibly not all cancer alliances will do the same as we have seen on previous decisions and influences. Some cellpath won't be able to do it without funding upfront. The MLH1 promoter methylation testing and germline testing is something for the GLH to take forwards to discuss capacity and technology and the only real input for the GLH in this pathway therefore, given that we can forget MSI in this context. MLH1 promoter methylation testing and germline testing is already performed in Leeds who have been screening all endometrial cancers in West Yorkshire for Lynch since April 2019. We have developed a methylation testing and germline testing pipeline that essentially replicates this draft guidance, so can look at how we extend this out to the rest of the GLH region with full pathway into the NHS with end-to-end process funding, not just funding for the genetic tests. Based on the data we have to date, nearly 30% of endometrial cancers show MLH1 loss so the numbers requiring methylation testing are significant when compared to CRC.	Thank you for your comment which the committee considered.

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THEME: Implementation

Comment number	Name and organisation	Section number	Comment	NICE response
30	British Gynaecological Cancer Society		• The introduction of this recommendation alongside the existing testing for Lynch syndrome in colorectal cancers will increase the number of women referred to gynaecology services for screening and risk reduction surgery. Consideration should be given for the provision of a specialised familial gynaecology cancer clinics to support this patient group. • The RCOG and BGCS should work with patient representative groups to develop relevant patient information to support decision making with respect to screening and risk reduction surgery in women with Lynch syndrome.	Thank you for your comment which the committee considered.
31	British Gynaecological Cancer Society		I would like to add the 2 points: 1. Resources should be made available to laboratories expected to do the related work, and the due processes of getting approvals to take on the work followed. 2. Laboratories should report the findings (description of the results, e.g. absence of expression of MLH1 by IHC, presence of MLH1 hypermethylation), while the interpretation and recommendations about further steps in patient investigation and management left to the physician managing the case to consider in context of clinical history, information and all other investigations.	Thank you for your comment which the committee considered.

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THEME: Additional information and requests for clarification

Comment number	Name and organisation	Section number	Comment	NICE response
32	Newcastle University	Subsection: 2.5	IHC and MSI positives do not differentiate between sporadic cancers and those due to germline defects. Therefore, these are not “false positives”. Promoter hypermethylation testing helps to identify cases due to gene silencing, thereby enriching the cases referred for germline testing. Some Lynch syndrome cases will also be excluded due to gene silencing being the “second hit” (Moreira et al. 2015; PMID: 25557234; DOI: 10.1002/cncr.29190).	Thank you for your comment which the committee considered. ‘False positive’ in the context of section 2.5 refers to a false positive result from MSI or IHC for potential Lynch syndrome. Section 2.5 has been amended in the final guidance to make this clearer.
33	British Association of Gynaecological Pathologists	4.5	The PETALS study is quoted a lot in this document. Whilst undoubtedly a good trial studying the link between womb cancer and Lynch syndrome, it is not yet peer reviewed and published. Perhaps the limitations should also be documented.	Thank you for your comment which the committee considered. The committee noted that PETALS study has not yet been published (as stated in section 4.5 of the guidance) but heard from one of the authors at the second committee meeting that the manuscript had now been accepted for publication. The PETALs study is described as unpublished at several places in the guidance (for example sections 3.2, 3.17, 3.18 and 3.27).
34	British Association of Gynaecological Pathologists	4.13	The BAGP has published a guidance document on interpretation of MMR IHC freely available at https://www.thebagp.org/resources/?wpdmc=bagp-guidance-documents	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			This should be cited in the final document.	The guidance has been updated to state that the BAGP's guidance document can be used to help interpret MMR IHC (see section 4.13 in the final guidance).
35	Newcastle University	NA	Submitted by Prof. [redacted] along with Dr [redacted], Dr [redacted] and Dr [redacted](Cancer Prevention Research Group, Newcastle University)	Thank you for your comment which the committee considered.
36	Royal College of Physicians (RCP)	General	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our JSC on Palliative Medicine and would like to make the following comments.	Thank you for your comment which the committee considered.
37	Association of Surgical Oncology		No comments	Thank you for your comment which the committee considered.
38	University of Manchester		Ryan, N.A.J. et al. (2020) Feasibility of Gynaecologist Led Lynch Syndrome Testing in Women with Endometrial Cancer. J. Clin. Med. 9, 1842 Snowsill, T.M. et al. (2020) Cost-Effectiveness of the Manchester Approach to Identifying Lynch Syndrome in Women with Endometrial Cancer. J. Clin. Med. 9, 1664	Thank you for your comment which the committee considered.