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Title: *Testing strategies for Lynch syndrome in people with endometrial cancer*

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Declared competing interests of the authors

None of the authors have any competing interests.

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Rider on responsibility for report

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Contributions of authors

Rachel Court (Information specialist) developed the search strategy and undertook searches. Chris Stinton (Senior Research Fellow), Hannah Fraser (Research Associate), Lena Alkuhudairy (Senior Research Fellow), and James Keasley (Academic Foundation 2 doctor) conducted the clinical effectiveness systematic review, this included: screening and retrieving papers, assessing against the inclusion criteria, appraising the quality of papers and abstracting data from papers for synthesis. Chris Stinton (Senior Research Fellow) led the clinical effectiveness review. Mary Jordan (Research Fellow), Peter Auguste (Research Fellow) and Jason Madan (Professor in Health Economics) contributed to the cost-effectiveness review and undertook the health economic modelling. Dimitris Grammatopoulos (Professor of Molecular Medicine) provided clinical guidance and helped develop the model structures. Sian Taylor-Phillips (Associate Professor), led the project, and contributed to all stages for clinical and cost effectiveness. All authors were involved in writing draft and final versions of the report.

Academic and commercial in confidence information:

Please note that throughout the report academic in confidence (AIC) information is marked yellow and underlined and commercial in confidence (CIC) information is marked blue and underlined.

1. Clinical effectiveness additional information

1. Section 3.1.3 (Methods of analysis/synthesis) of the report did not provide an explanation of our 95% uptake rule as applied to complete test accuracy studies. The replacement sections is provided on pages 4 - 6, with new information in italics. On pages 7 – 8, we provide brief details and test accuracy estimates of the studies that were excluded from the complete test accuracy section because of the 95% rule.
2. We have provided additional information on the method by which test accuracy estimates were calculated for the PETALS study on page 9.

3.1.3. Methods of analysis/synthesis

In the gold standard study design for assessing test accuracy an entire sample of participants receives both the index test and the reference standard. This allows direct, unbiased, comparisons of the agreement between the two tests. For reasons such as cost and practicality, in many test accuracy studies only a subsample of participants receive both tests, i.e. individuals who are index test positive (at higher risk for the disease or condition) receive the reference standard, while individuals who are index test negative do not receive the reference standard. While this approach accurately reflects how tests are used in clinical practice it leads to partial verification bias (also called detection bias or work-up bias); data are missing and the true diagnostic status of participants who are negative on the index is not known. Partial verification can lead to overestimation of sensitivity and underestimation (or overestimation) of specificity.[33] Inaccurate test accuracy metrics can have an impact on clinical practice in relation to referral decisions and costs.

In this report, test accuracy results are divided into 'complete' test accuracy studies (in which all participants receive both the index test and the reference standard) and 'partial' test accuracy studies (in which only participants who are index test positive receive the reference standard). For 'complete' test accuracy studies we present results on all available test accuracy metrics, i.e. true positives, false positives, true negative, false negatives, sensitivity, specificity, positive predictive values, and negative predictive values. *Systematic variation is known to occur in the uptake of tests and other interventions; people who choose to undertake one health service or therapy are more likely to receive other health services/therapies (healthy user/screenee effect) and to engage in other healthy behaviours (healthy adhere effect) than those who do not. These can lead to sampling and spectrum biases, which effect test accuracy estimates. To minimise the risk of these biases influencing our results, we only included studies in which 95% of study participants who undertook index tests also received the reference standard.* For 'partial' test accuracy studies, we present results only for those test accuracy metrics that relate to participants who have received both the index test and reference standard, i.e. true positives, false positives, and positive predictive values. Further, as there is a risk that the likelihood that someone will receive the reference standard is associated with disease status (e.g. individuals who truly have a disease may be more likely to get the reference standard than those who do not have the disease), which biases positive predictive value upwards, we only included studies in which at least 95% of women who were eligible for germline testing (those who were index test positive)

received it. The sensitivity, specificity, positive predictive- and negative predictive estimates presented in this report were all calculated by the review authors and based on the true positive, false positive, false negative, and true negative values that were reported in individual papers. Confidence intervals were calculated using Wilson's continuity correction.[34]

Test accuracy results are presented for testing strategies 1 – 10, comparing the index tests to the eligible reference standards. Test accuracy was not assessed for strategy 11 as this approach does not include an index test. For studies that included an initial test followed by MLH1 promoter hypermethylation testing, we have analysed data at each stage of the process, i.e. (1a) IHC alone, then (1b) IHC plus MLH1 promoter hypermethylation testing, (2a) MSI-based testing alone, then (2b) MSI-based testing plus MLH1 promoter hypermethylation testing. For IHC results, we have reported results together and separately for each protein. For MSI results, we have reported the panel used as per the papers, and provided a narrative summary of results on MSI-L and MSI-H patients. Subgroup analysis was not conducted for the different combinations of microsatellite markers due to the small number of studies and the wide range of panels used. Our main analysis assumed MSI low are test negative. Due to insufficient data we did not conduct subgroup analyses of test accuracy by (1) age (under vs over 70 years) or (2) amongst people who have had a prior Lynch syndrome-related cancer (as defined in NHS England's National Genomic Test Directory, "Testing Criteria for Rare and Inherited Disease"). A narrative summary of the evidence is presented because meta-analysis was not possible due to heterogeneity. Variants of uncertain clinical significance on germline testing are not considered to have Lynch syndrome in our test accuracy analysis. The EAG has recorded how many of these there are for scenario analysis in the economic modelling, considering either all or none as having Lynch syndrome. In practice, patients with a negative germline test result (with no somatic cause of the tumour identified) but a positive index test may be considered to have Lynch-like syndrome (also known as putative or cryptic Lynch syndrome) and undergo further investigation or surveillance. In particular, further investigation is undertaken if there is family history of Lynch syndrome. Due to this, the EAG descriptively recorded the characteristics of these cases such as family history, IHC results and discordant cases between the two index tests. This provides contextual information about the possibility of Lynch-like syndrome, and variants of uncertain clinical significance. However, for the reporting of test accuracy data, germline testing using sequencing with or without MLPA was

considered the primary reference standard. We included studies using other diagnostic tests outlined in the Association for Clinical Genomic Science best practice guidelines for genetic testing and diagnosis of Lynch syndrome, i.e. array-based comparative genomic hybridization, and long-range PCR.[31] The uncertainty around the effectiveness of germline testing to diagnose all cases of Lynch syndrome (see above regarding Lynch-like syndrome) is a potential weakness of the reference standard and a limitation of this review. As a sub-analysis, for studies that report extra steps to the reference standard (e.g. sequencing of tumours, or incorporating family history data), we recorded the additional tests that are used. Due to the small number of studies using alternative tests, we did not compare the results of these multi-stage reference standards to the results of germline testing for MLH1, MSH2, MSH6, and PMS2 using sequencing with or without MLPA.

Studies excluded from the complete test accuracy section because of the 95% rule

Two studies were excluded from the complete test accuracy section [1,2]. These are briefly described below.

Goodfellow et al.[60]

Description of study

Goodfellow et al is prospective cohort study of 441women newly diagnosed with endometrial cancer. The index test was MSI-based testing, followed by MLH1 methylation testing where MSI was high or low (n = 137). The reference standard was single-strand conformational variant analysis (which was not an eligible reference standard in our review) and sequencing (MSH6 gene only). From the 441 participants, 441 (100%) received the index test, and 100 (22.7%) received the reference standard.

Results

Data were extractable for the 100 women who received both the index test and the reference standard. There were 7 true positives, 0 false negatives, 53 false positives, and 40 true negatives. Test accuracy estimates are as follows:

- Sensitivity 100.0% (95% confidence intervals, 56.1 - 100.0%)
- Specificity 43.0% (95% CI 32.9 - 53.7%)
- Positive predictive value 11.7% (95% CI 5.2 - 23.2%)
- Negative predictive value 100.0% (95% CI 89.1 - 100.0%)

Ferguson et al.[58]

Description of study

Ferguson et al is prospective cohort study of 118 women newly diagnosed with endometrial cancer. The index tests were IHC (MLH1, MSH2, MSH6, and PMS2 proteins) and MSI. The reference standard was sequencing plus MLPA (MLH1, MSH2, MSH6, and PMS2 genes). From the 118 participants, 117 (99.2%) tumours were tested with MSI, 118 (100%) tumours were tested with IHC, and 89 (75.4%) women had germline testing.

Results – IHC

Data were extractable for 85 women who were tested with both the index test (IHC) and the reference standard. There were 7 true positives, 0 false negatives, 9 false positives, and 69 true negatives. Test accuracy estimates are as follows:

- Sensitivity 100.0% (95% confidence intervals, 56.1 - 100.0%)
- Specificity 88.5.0% (95% CI 78.7 - 94.3%)
- Positive predictive value 43.8% (95% CI 20.8 - 69.4%)
- Negative predictive value 100.0% (95% CI 93.4 - 100.0%)

Different estimates were reported in Table 4 of the paper, based on 89 participants:

- Sensitivity 100% (95% confidence intervals, 59 – 100%)
- Specificity 78.1% (95% CI 67.5 – 86.4%)
- Positive predictive value 28% (95% CI 12.1 – 49.4%)
- Negative predictive value 100% (95% CI, 94.4 – 100%)

Results - MSI

It was not possible for us to extract data and calculate test accuracy estimates for MSI-based testing due to insufficient reporting of results. However, table 4 of the paper reported the following test accuracy estimates based on 89 women who received with both MSI-based testing and the reference standard:

Sensitivity 85.7% (95% CI, 42.1 – 99.6%)
Specificity 81.7% (95% CI 71.6 – 89.4%)
Positive predictive value 28.6% (95% CI 11.3 – 52.2%)
Negative predictive value 98.5% (95% CI 92.1 – 100%).

[redacted]

2. Cost-effectiveness

Table 1: Expanded base case results (per 1000 women with EC screened)

Strategy	**CRC cases detected**	**CRC deaths averted**	**EC cases Detected**	**EC deaths averted**	**Mean costs (£)**	**Incremental costs (£)**	**Mean QALYs**	**Incremental QALYs**	**ICER (£)**	**Net Benefit at £20K per QALY**	**P(CE) at £20K per QALY**
No testing	0	0	0	0	0	-	0	0	-	0	11.9%
MSI with MLH1 methylation (S2)	14.7	9.5	0.8	0.2	£520,000	£520,000	41.9	41.9	Extendedly dominated	£322,910	1.4%
IHC with MLH1 methylation (S4)	23.3	15.2	1.3	0.3	£630,000	£630,000	66.9	66.9	£9420	£705,120	79.6%
MSI followed by IHC with MLH1 methylation (S6)	14.7	9.5	0.8	0.2	£720,000	£90,000	42.0	24.9	Dominated	£124,190	<1%
IHC (S3)	23.9	15.5	1.3	0.3	£790,000	£160,000	68.1	1.2	133,330	£570,000	4.4%

MSI (S1)	24.0	15.6	1.3	0.3	£840,000	£50	0.0683	0.0002	250,000	£528,510	2.6%
IHC followed by MSI with MLH1 methylation (S8)	23.4	15.2	1.3	0.3	£870	£30	0.0671	-0.0012	Dominated	£474,810	<1%
MSI and IHC simultaneously with MLH1 methylation (S10)	23.4	15.2	1.3	0.3	£890	£20	0.0671	0.0000	Dominated	£450,980	<1%
IHC followed by MSI (S7)	24.1	15.6	1.3	0.3	£1025	£185	0.0685	0.0002	£925,000	£343,530	<1%
MSI followed by IHC (S5)	24.1	15.6	1.3	0.3	£1030	£5	0.0685	0.0000	Dominated	£341,460	<1%
MSI and IHC simultaneously (S9)	24.1	15.6	1.3	0.3	£1070	£45	0.0685	0.0000	Dominated	£301,510	<1%
Germline testing (S11)	23.2	15.1	1.3	0.3	£1160	£135	0.0666	-0.0019	Dominated	£167,960	<1%

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years

Figure 1 Cost-Effectiveness Acceptability Curves for strategies with >5% probability of cost-effectiveness

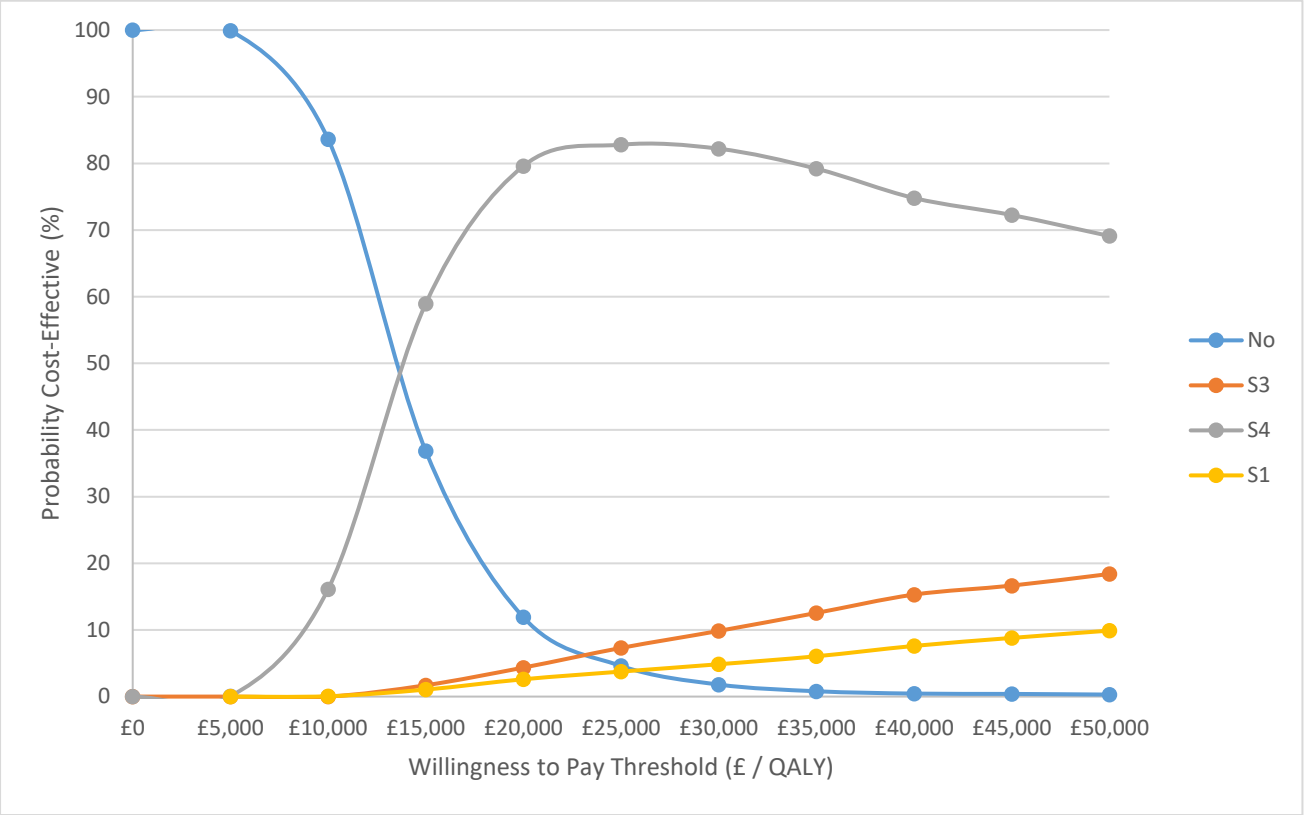
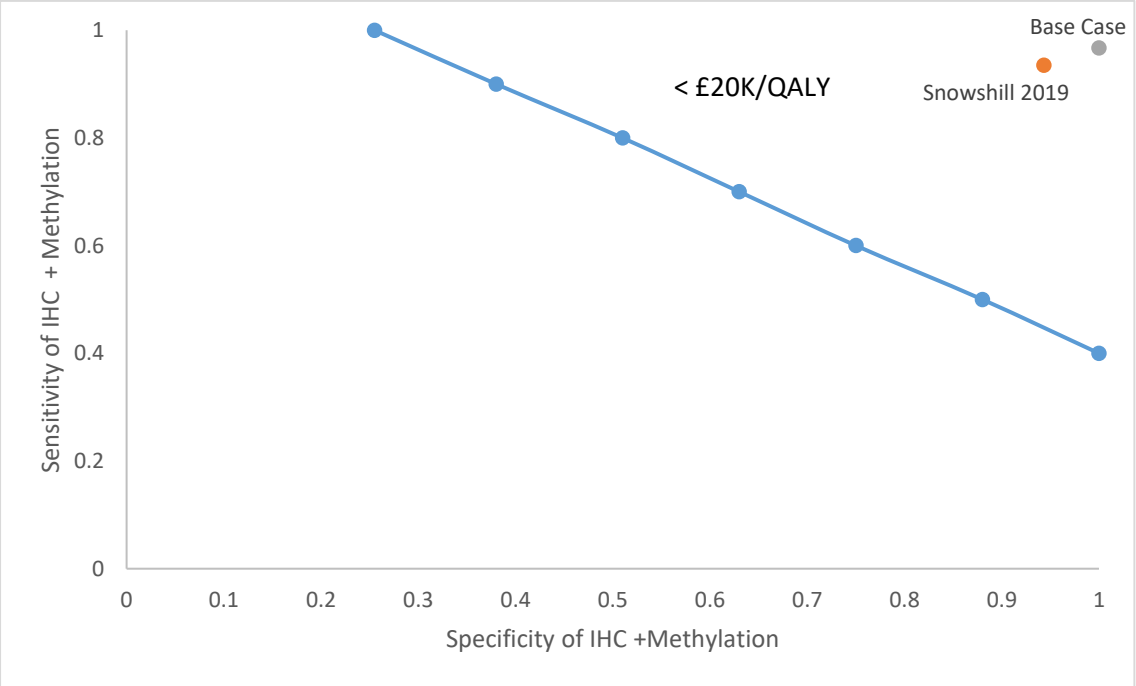


Fig 2: Test performance statistics at which S4 ceases to be cost-effective



Additional Scenario 1: Results when test performance statistics based on those reported by Snowshill et al (2019)

Strategy	**Expected mean costs (£)**	**Incremental costs (£)**	**Expected mean QALYs**	**Incremental QALYs**	**ICER (£ / QALY)**	**Net Benefit at £20K per QALY**
No testing	0	NA	0	NA	NA	0
MSI with MLH1 methylation	£653	£653	0.0567	0.0567	Extendedly dominated	£480
IHC with MLH1 methylation	£657	£657	0.0628	0.0628	£10,464	£598
MSI	£852	£195	0.0622	-0.0006	Dominated	£391
IHC	£897	£240	0.0652	0.0024	£100,000	£406
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years						

Additional Scenario 2: Results when test performance statistics based on those reported by Chao et al (2019)

Strategy	**Expected mean costs (£)**	**Incremental costs (£)**	**Expected mean QALYs**	**Incremental QALYs**	**ICER (£ / QALY)**	**Net Benefit at £20K per QALY**
No testing	0	NA	0	NA	NA	0
IHC	£612	£612	0.0508	0.0508	Extendedly Dominated	£405
MSI	£706	£706	0.0675	0.0675	£10,455	£644

ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years	

Additional Scenario 3: VUS and Lynch Assumed do not gain any benefits from treatment

Strategy	**Expected mean costs (£)**	**Incremental costs (£)**	**Expected mean QALYs**	**Incremental QALYs**	**ICER (£)**
No testing	0	-	0	0	-
MSI with MLH1 methylation	£520	£520	0.0416	0.0416	Extendedly dominated
IHC with MLH1 methylation	£630	£630	0.0665	0.0669	£9514
MSI followed by IHC with MLH1 methylation	£720	£90	0.0416	0	Dominated
IHC	£790	£160	0.0665	0	Dominated
MSI	£840	£50	0.0665	0	Dominated
IHC followed by MSI with MLH1 methylation	£870	£30	0.0665	0	Dominated
MSI and IHC simultaneously	£890	£20	0.0665	0	Dominated

with MLH1 methylation					
IHC followed by MSI	£1025	£185	0.0665	0	Dominated
MSI followed by IHC	£1030	£5	0.0665	0	Dominated
MSI and IHC simultaneously	£1070	£45	0.0665	0	Dominated
Germline testing	£1160	£135	0.0665	0	Dominated
ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MLH1, hypermethylation; MSI, microinstability; QALY, quality-adjusted life years					

Table 2: Net benefit per woman screened with EC, by strategy and scenario

Strategy	Base Case	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7	Scenario 8
MSI	£529	£137	£830	£416	£867	£521	£582	£284	-£204
MSI with MLH1 methylation	£323	£272	£567	£509	£528	£318	£355	£173	-£133
IHC	£570	£542	£857	£840	£906	£562	£623	£326	-£162
IHC with MLH1 methylation	£705	£711	£951	£956	£1,031	£697	£756	£466	-£23
MSI followed by IHC	£341	£341	£797	£797	£682	£334	£395	£96	-£392
MSI followed by IHC with MLH1 methylation	£124	£116	£538	£538	£330	£119	£156	-£26	-£332
IHC followed by MSI	£344	£348	£804	£805	£683	£336	£397	£98	-£390
IHC followed by MSI with MLH1 methylation	£475	£481	£906	£907	£802	£467	£526	£234	-£254
MSI and IHC simultaneously	£302	£306	£799	£802	£641	£294	£355	£56	-£432

MSI and IHC simultaneously with MLH1 methylation	£451	£475	£904	£918	£779	£443	£502	£211	-£278
Germline testing (S11)	£168	£168	£450	£450	£491	£160	£219	-£71	-£559