National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Molecular testing for Lynch syndrome in people with colorectal cancer

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read in conjunction with the final scope issued by NICE for the assessment and the diagnostics assessment report. A glossary of terms can be found in Appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost-effectiveness of using molecular testing strategies, which include microsatellite instability (MSI) testing and immunohistochemistry (IHC) of mismatch repair proteins, to assess the likelihood of a person with colorectal cancer having Lynch syndrome.

Lynch syndrome is an inherited genetic condition that is associated with an increased risk of colorectal and other cancers and which can be diagnosed using genetic sequencing. It is caused by mutations in DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2*. Mutations in a further, non-MMR, gene *EPCAM* which is adjacent to the *MSH2* gene can also cause Lynch syndrome. These mismatch repair genes encode proteins which are involved in recognizing and repairing errors in DNA sequence that occur when DNA is copied and replicated during cell division. Where mutations in MMR genes are present, they can lead to impaired functioning of the MMR system

which can prevent the proper repair of DNA errors. Over time, this allows mutations to accumulate as cells divide, potentially leading to uncontrolled cell growth and cancer.

MSI testing and IHC of MMR proteins are intended to assess whether the DNA mismatch repair system is working effectively in tumour samples taken from people who have been diagnosed with colorectal cancer. Where deficiencies in DNA mismatch repair are detected by the tests, it is an indication that a person's cancer may have developed because they have Lynch syndrome. Microsatellites are short repetitive sequences of DNA that are prone to errors during replication. In tumours of people without a functioning DNA mismatch repair system, errors in copying microsatellite sequences cause them to vary in length, when compared to microsatellite sequences in tissue samples which do not contain cancer cells. This is known as microsatellite instability. A further test indicative of mutations in MMR genes is decreased (or abnormal) expression of proteins encoded by these genes in tumour tissue, which can be detected by IHC. IHC testing involves using antibodies to detect the presence of mismatch repair proteins.

While microsatellite instability and abnormal MMR protein expression in tumour tissue are indications of Lynch syndrome, sometimes these features can also be seen in sporadic colorectal cancers, that is cancers which are not caused by Lynch syndrome. Sporadic colorectal cancers can show loss of MLH1 protein expression caused by changes in the *MLH1* gene promoter, which can be identified by testing for tumour marker *BRAF* V600E or by testing for *MLH1* promoter hypermethylation. Testing for *BRAF* V600E and *MLH1* promoter methylation can therefore be used to help identify sporadic cancers which also have microsatellite instability or abnormal MLH1 protein expression on IHC testing. This helps to identify people who are false positives for Lynch syndrome on the initial MSI or IHC test to prevent them having unnecessary further genetic testing.

Currently, where molecular testing for Lynch syndrome is offered it is typically

only done for people considered to be at high risk of having Lynch syndrome. These include people with a family history of cancer and people who are younger than 50 years old at the onset of colorectal cancer. Expanding testing to all people with colorectal cancer may increase the detection of Lynch syndrome and identify families who could benefit from cascade genetic testing to determine if other family members have Lynch syndrome. This could lead to increased surveillance and consequently improved patient outcomes through earlier diagnosis and treatment, if cancer is present. Lynch syndrome is also associated with an increased risk of other cancers such as endometrial cancer, stomach cancer and brain cancer, so the clinical benefits of testing may extend beyond the colorectal cancer setting.

In this document the term 'proband' is used to describe individuals who are diagnosed with colorectal cancer, for whom different strategies can be employed to detect Lynch syndrome.

Provisional recommendations on the use of these technologies will be formulated by the diagnostics advisory committee at the committee meeting on 20 September 2016.

1.2 Scope of the evaluation

Table 1 Scope of the evaluation

Decision question	Does molecular testing for Lynch syndrome in all colorectal cancer patients represent a cost-effective use of NHS resources?
Populations	All colorectal cancer patients. If evidence permits, the following sub-populations will be included: • Colorectal cancer patients > 70 years old • Colorectal cancer patients < 70 years old • Colorectal cancer patients < 60 years old • Colorectal cancer patients < 50 years old
Interventions	• MSI testing, followed by ○ Comprehensive genetic testing (sequencing and MLPA) if microsatellite instability is

	detected
	• MSI testing, followed by
	  ○ *BRAF* V600E **or** *MLH1* promoter hypermethylation testing if microsatellite instability is detected, followed by
	  ○ Comprehensive genetic testing (sequencing and MLPA) in the event of a wild type *BRAF* V600E or unmethylated *MLH1* promoter test result.
	• MSI testing, followed by
	  ○ *BRAF* V600E **and** *MLH1* promoter hypermethylation testing if microsatellite instability is detected, followed by
	  ○ Comprehensive genetic testing (sequencing and MLPA) in the event of a wild type *BRAF* V600E or unmethylated *MLH1* promoter test result.
	• IHC MMR protein testing, followed by
	  ○ Comprehensive genetic testing (sequencing and MLPA) if MMR protein expression is abnormal.
	• IHC MMR protein testing, followed by
	  ○ *BRAF* V600E **or** *MLH1* promoter hypermethylation testing if MLH1 expression is abnormal.
	  ○ Comprehensive genetic testing (sequencing and MLPA) if any abnormal non-MLH1 expression or in the event of a wild type *BRAF* V600E or unmethylated *MLH1* promoter test result.
	• IHC MMR protein testing, followed by
	  ○ *BRAF* V600E **and** *MLH1* promoter hypermethylation testing if MLH1 expression is abnormal.
	  ○ Comprehensive genetic testing (sequencing and MLPA) if any abnormal non-MLH1 expression, or in the event of a wild type *BRAF* V600E or unmethylated *MLH1* promoter test result.
	• Comprehensive genetic testing (sequencing and MLPA).

Comparator	No 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 colonoscopies • Mutations detected
	Clinical outcomes for consideration may include: • Number of Lynch Syndrome diagnoses • Morbidity and mortality • Life expectancy of proband • Life expectancy of relative • Change in patient management (proband and relative) • Colorectal cancers prevented • Number of non-colorectal cancers
	Patient-reported outcomes for consideration may include: • Health-related quality of life and anxiety
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of testing proband (including cutting blocks) • Cost of cascade testing • Cost of genetic counselling • Cost of colonoscopic screening • Cost of management of colorectal cancer • Cost of gynaecological surveillance • Cost of prophylactic surgery
	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.

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

2 The evidence

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

2.1 Clinical Effectiveness

The EAG conducted a systematic review of the evidence on the diagnostic accuracy of microsatellite instability (MSI) and mismatch repair (MMR) protein immunohistochemistry (IHC) testing for Lynch syndrome and also any relevant end-to-end studies. Details of the systematic review can be found starting on page 71 of the diagnostics assessment report.

Diagnostic Accuracy

The EAG identified 10 diagnostic accuracy studies that met the inclusion criteria for the systematic review, 1 of which was based in the UK (Barnetson et al. 2006). One of these studies (Poynter et al. 2008) had two distinct samples which were treated separately in the review, so although there were 10 included studies, there were 11 included populations/data sets.

Four of the included studies were single-gate studies recruiting population-based samples, that is they recruited people with colorectal cancer regardless of their risk factors for Lynch syndrome. One study (Poynter et al. 2008) reported data from two separate populations, one of which appeared to be an unselected colorectal cancer population and one of which was at a high-risk of Lynch syndrome. The other 3 studies with population-based samples (Barnetson et al. 2006, Limburg et al. 2011, Southey et al. 2005) included colorectal cancer populations but specified age limits in their inclusion criteria. These were younger than 55, younger than 50 and younger than 45 years, respectively. The age of participants in Poynter et al. (2008) was not reported.

A further 4 studies (Caldes et al. 2004, Mueller et al. 2009, Overbeek et al. 2007, and Shia et al. 2005), plus the second population in Poynter et al. (2008), included people with colorectal cancer who were at high-risk of Lynch syndrome. These studies were all classified as single-gate studies that

recruited high-risk populations. The remaining 2 studies recruited patients with colorectal cancer who were known to have Lynch syndrome (Hendriks et al. 2003, Okkels et al. 2012) and are referred to as reference standard positive studies by the EAG. Studies based on high-risk populations and people known to have Lynch Syndrome were only used to inform sensitivity estimates for the index tests.

Quality appraisal of the included studies was done using the QUADAS-2 tool. The EAG commented that there was no evidence found to indicate that the included studies were at high risk of bias. A full summary of the quality appraisal of the included studies is presented in table 9 in the diagnostics assessment report (page 90).

The EAG noted that the index tests included in the assessment are highly susceptible to spectrum bias. In particular, the increased presence of MMR mutation carriers in a study population, for example because of the age of the study population, could change the apparent sensitivity and specificity of the index tests. Significant methodological and clinical heterogeneity across studies was also noted; in particular, the reference standard differed between studies and there was also variation between studies in the panel of markers used to detect MSI. Full detail of the reference standards used in individual studies is presented in table 8 in the diagnostics assessment report (page 84). Because of the methodological and clinical heterogeneity observed, the EAG did not consider meta-analyses to be appropriate, and results were presented as a narrative summary. Most of the included studies assessed MSI and IHC testing; however, as none of the studies made a direct comparison of MSI testing and IHC testing, results were reported separately for each of the index tests.

Accuracy of microsatellite instability testing

All of the included studies except Limburg et al. (2011) and Okkels et al. (2012) assessed MSI testing. Full details of the MSI tests used in included studies are shown in table 10 on page 95 of the diagnostics assessment

report. The EAG noted several differences in the MSI testing procedures used in the included studies:

- Three studies did not report the microdissection techniques used to prepare the samples.
- Variation in the panels of MSI markers used, in terms of the number and types of markers used.
- Differences in the way in which test results were categorised. Studies differ in whether they classify tumours using 2 categories (MSI positive or negative) or using 3 categories (MSI-High [MSI-H], MSI-Low [MSI-L] or microsatellite stable [MSS]).
- Differences in the thresholds used to categorise MSI.

Because of the differences in the populations included in the studies (single-gate population-based, single-gate high-risk, reference standard positive; see above), the EAG presented the results grouped by study type.

The EAG conducted 2 analyses of MSI testing based on how the reference standard of sequencing MMR genes is applied to identify positive cases of Lynch syndrome. In the primary analysis unclassified variants, that is where variation in the sequence of MMR genes is identified through DNA sequencing but it is not known whether this variation causes Lynch syndrome or not, were categorised as negative reference standard results. In the secondary analyses unclassified variants were categorised as positive reference standard results.

Sensitivity and specificity were calculated based on a positive MSI test result for Lynch syndrome being:

- MSI-H only, and
- MSI-H or MSI-L.

The results of the primary analysis are shown in table 2.

Table 2 Primary analysis: sensitivity and specificity of MSI testing

Study	Test positive: MSI-H Test negative: MSI-L or MSS		Test positive: MSI-H or MSI-L Test negative: MSS	
	Sensitivity [%] (95% CI)	**Specificity [%] (95% CI)**	**Sensitivity [%] (95% CI)**	**Specificity [%] (95% CI)**
Single-gate, population-based samples				
Poynter, 2008[a]	100.0 (93.9, 100.0)	61.1 (57.0, 65.1)	100.0 (93.9, 100.0)	29.5 (25.8, 33.4)
Barnetson, 2006	66.7 (47.2, 82.7)	92.5 (89.1, 95.2)	93.3 (77.9, 99.2)	84.5 (80.0, 88.2)
Southey, 2005	72.2 (46.5, 90.3)	87.8 (73.8, 95.9)	94.4 (72.7, 99.9)	58.5 (42.1, 73.7)
Single-gate, high-risk samples				
Caldes, 2004[b]	79.4 (62.1, 91.3)	-	79.4 (62.1, 91.3)	-
Mueller, 2009	91.3 (72.0, 98.9)	-	93.1 (77.2, 99.2)	-
Overbeek, 2007[b]	90.0 (59.6, 98.2)	-	90.0 (59.6, 98.2)	-
Poynter, 2008	86.8 (71.9, 95.6)	-	94.7 (82.3, 99.4)	-
Shia, 2005[b]	100.0 (85.8, 100.0)	-	100.0 (85.8, 100.0)	-
Reference standard positive study				
Hendriks, 2003	88.0 (68.8, 97.5)	-	92.0 (74.0, 99.0)	-
[a]Population based sample; [b]MSI-L not defined				
MSI-H: microsatellite instability high; MSI-L: microsatellite instability low; MSS: microsatellite stable				

Sensitivity increased and specificity decreased when MSI-L was considered to be a positive index test result, compared with when MSI-L was considered to be negative result. The EAG noted that including MSI-L as a positive result lowers the threshold for a positive index test result for Lynch syndrome.

Likelihood ratios and positive and negative predictive values were also calculated for the three population-based studies reporting MSI data, shown in table 3.

Table 3 Primary analysis: likelihood ratios and predictive values for MSI testing

Study	Test positive: MSI-H Test negative: MSI-L or MSS				Test positive: MSI-H or MSI-L Test negative: MSS			
	LR+ (95% CI)	LR- (95% CI)	PPV [%] (95% CI)	NPV [%] (95% CI)	LR+ (95% CI)	LR- (95% CI)	PPV [%] (95% CI)	NPV [%] (95% CI)
Single-gate, population-based samples								
Poynter, 2008[a]	2.57 (2.32, 2.85)	0.00 (NE)[b]	20.8 (16.2, 26.0)	100.0 (99.0, 100.0)	1.42 (1.35, 1.50)	0.00 (NE)[b]	12.6 (9.8, 16.0)	100.0 (97.9, 100.0)
Barnetson, 2006	8.94 (5.54, 14.20)	0.36 (0.21, 0.60)	45.5 (30.4, 61.2)	96.8 (94.1, 98.4)	6.01 (4.58, 7.89)	0.08 (0.02, 0.30)	35.9 (25.3, 47.6)	99.3 (97.4, 99.9)
Southey, 2005	5.92 (2.48, 14.10)	0.32 (0.15, 0.67)	72.2 (46.5, 90.3)	87.8 (73.8, 95.9)	2.28 (1.56, 3.33)	0.09 (0.01, 0.65)	50.0 (32.4, 67.6)	96.0 (79.6, 99.9)
[a] Population based sample; [b] Not estimable								
MSI-H: microsatellite instability high; MSI-L: microsatellite instability low; MSS: microsatellite stable, LR+: positive likelihood ratio, LR-: negative likelihood ratio, PPV: positive predictive value, NPV: negative predictive value.								

Secondary analyses were conducted, where data permitted, with unclassified variants considered to be positive reference standard results (for Lynch syndrome). The EAG noted that results were similar to those obtained when unclassified variants were considered to be negative. The results of the secondary analyses can be found on page 100 and page 104 of the diagnostics assessment report.

Accuracy of mismatch repair protein immunohistochemistry testing

IHC analysis was conducted in all of the 10 included studies; however, not all studies provided sufficient data to be included in analyses. In two study samples (the high-risk sample in Poynter et al. 2008 and Mueller et al. 2009) despite IHC testing being done, insufficient data were provided for these studies to be included in any of the IHC analyses.

The proteins targeted by the tests used and the way results were reported differed between the studies. In 7 studies (Barnetson et al. 2006, Limburg et

al. 2011, Southey et al. 2005, Caldes et al. 2004, Overbeek et al. 2007, Shia et al. 2005 and Hendriks et al. 2003) an overall result is given, that is where abnormal staining of any of the MMR proteins assessed is classed as a positive IHC test result. All of these 7 studies assessed MLH1, MSH2 and MSH6 proteins. In addition, Southey et al. (2005) and Overbeek et al. (2007) also assess PMS2. So for these two studies an abnormal PMS2 result would also be included as a positive index test result

As with the results for MSI testing, in the primary analyses unclassified variants are considered to be reference standard negatives and in secondary analysis unclassified variants were considered to be reference standard positives. Table 4 presents IHC test accuracy results from individual studies for the overall test performance of IHC.

Table 4 Primary analyses: accuracy of overall IHC testing

Study	Sensitivity [%] (95% CI)	Specificity [%] (95% CI)	LR+ (95% CI)	LR- (95% CI)	PPV [%] (95% CI)	NVP [%] (95% CI)
Single-gate, population-based samples						
Barnetson, 2006	92.6 (76.6, 97.9)	NE[a]	- [b]	- [b]	- [b]	- [b]
Limburg, 2011	85.7 (42.1, 99.6)	91.9 (86.3, 95.7)	10.6 (5.7, 19.7)	0.16 (0.02, 0.95)	33.3 (13.3, 59.0)	99.3 (96.0, 100.0)
Southey, 2005	100.0 (81.5, 100.0)	80.5 (65.1, 91.2)	5.1 (2.8, 9.5)	0.00 (NE)[a]	69.2 (48.2, 85.7)	100.0 (89.4, 100.0)
Single-gate, high-risk samples						
Caldes, 2004	96.4 (81.7, 99.9)	-	-	-	-	-
Overbeek, 2007	87.5 (52.9, 97.7)	-	-	-	-	-
Shia, 2005	80.8 (60.6, 93.4)	-	-	-	-	-
Reference standard positive study sample						
Hendriks, 2003	91.7 (77.5, 98.2)	-	-	-	-	-

[a] Not estimable, [b] analysis not conducted because overall IHC results were only available for reference standard positive participants.
LR+: positive likelihood ratio, LR-: negative likelihood ration, PPV: positive predictive value, NPV: negative predictive value.

The EAG noted that there was no large difference between the sensitivity values from the population-based and high-risk studies. This could be because the 3 population-based studies included are based on age-limited populations and may also be subject to spectrum bias.

Likelihood ratios and positive and negative predictive value estimates were calculated for 2 of the population-based studies (Limburg et al. 2011 and Southey et al 2005). The results suggest that there are differences in the performance of the IHC test in these studies but the EAG noted that Southey et al. (2005) included an assessment of PMS2 in their results whereas Limburg et al. (2011) did not. In addition, the specific techniques and methods used to perform the reference standard differ between the studies and this may affect the results.

Only 2 studies (Caldes et al. 2004 and Hendriks et al. 2003) provided sufficient data to be included in the secondary analyses (where unclassified variants are considered to be positive reference standard results for Lynch syndrome). Only sensitivity estimates were made because Caldes et al. (2004) included people at high-risk of Lynch syndrome and Hendriks et al. (2003) included people known to have Lynch syndrome. The EAG noted that Caldes (2004) showed a reduction in sensitivity (75.0%, 95% CI 57.8, 87.9) compared with the primary analyses where unclassified variants were categorised as negative reference standard tests (96.4%; 95% CI 81.7, 99.9). For Hendriks et al. (2003) sensitivity was only slightly reduced.

The EAG also analysed data according to the individual proteins targeted by the IHC tests. Five studies (the population-based sample in Poynter et al. 2008; Barnetson et al. 2006; Southey et al. 2005; Hendriks et al. 2003; Okkels et al. 2012) made an assessment of whether abnormal expression of a particular MMR protein was an accurate indication of a pathogenic mutation in

the gene encoding that protein. Full details of this analysis can be found in the diagnostic assessment report starting on page 107. Only one study (Hendriks et al. 2003) provided sufficient data for secondary IHC analyses (for individual proteins), where unclassified variants were considered to indicate a positive reference standard test result. Sensitivity estimates in the secondary analysis were very similar to those estimated from data where unclassified variants were considered to be reference standard negatives. Full details of this analysis can be found in the diagnostic assessment report on page 114.

Evidence on end-to-end studies

The EAG carried out searches for relevant end-to-end studies according to the inclusion and exclusion criteria set out in table 20 on page 123 of the diagnostic assessment report. No studies that satisfied these criteria were identified.

2.2 Costs and cost effectiveness

The EAG conducted a search to identify existing studies investigating the cost effectiveness of molecular testing for Lynch syndrome in people with colorectal cancer. The EAG also constructed an economic model to assess the cost effectiveness of molecular testing for Lynch syndrome in people with colorectal cancer.

Systematic review of cost effectiveness evidence

The EAG carried out a systematic review to identify existing studies reporting the cost-effectiveness of using microsatellite instability (MSI) and immunohistochemistry (IHC) testing in strategies to identify Lynch syndrome in people with colorectal cancer. Details of the review are reported in the diagnostics assessment report on page 127 onwards.

Nine separate studies were identified, reported in 10 papers. One study was reported in 2 papers - Snowsill et al. (2014) and Snowsill et al. (2015). Details of the study characteristics are presented in table 22 in the diagnostics assessment report (page 133 onwards). Seven of the included studies were

based in US populations, 1 was based in Germany and took the perspective of a health insurance system and one was based in the UK and took the perspective of the NHS and personal social services. The modelling approach used by the studies was similar. Most included a decision tree to model the diagnosis of Lynch syndrome, and a longer term Markov or individual patient simulation model to estimate the costs and benefits associated with the outcomes of the diagnostic model. Conclusions on which were the most cost-effective strategies varied across these studies and was dependant on the willingness to pay threshold and comparators used in the analysis. No single strategy was consistently seen to be the most cost-effective. When a universal genetic testing strategy was assessed by the studies, strategies that used tumour based tests such as IHC or MSI to select the population undergoing full genetic testing appeared to improve the cost-effectiveness estimates. Most studies agreed that the effectiveness of colonoscopy screening, number of relatives and prevalence of Lynch syndrome were the parameters which had the greatest impact on the cost effectiveness of the testing strategies assessed.

No single study answered the current decision problem in full. Snowsill et al. (2014) was considered the most applicable and was updated for this assessment.

Economic analysis

The External Assessment Group developed an economic model designed to assess the cost effectiveness of molecular testing for Lynch syndrome in people with colorectal cancer. This was based on a previously constructed model, as described in Snowsill et al. (2014) and Snowsill et al. (2015).

Model structure

The model included:

- a decision tree model to investigate the short term outcomes of strategies to identify people with Lynch syndrome, and

- an individual patient simulation model to assess the long term implications of strategies to identify and manage Lynch syndrome.

The model considers longer term outcomes for both colorectal and endometrial cancer.

Decision tree for probands

An overview of the decision tree model is shown in figure 1. The diagnostic pathway was the same for each of the testing strategies included in the decision tree. Descriptions of the testing strategies that are included in the model are shown in table 5. In addition, diagrammatical representations of these strategies are provided in the diagnostics assessment report in figures 10-13 (page 154 onwards).

Figure 1 Lynch syndrome diagnostic pathway

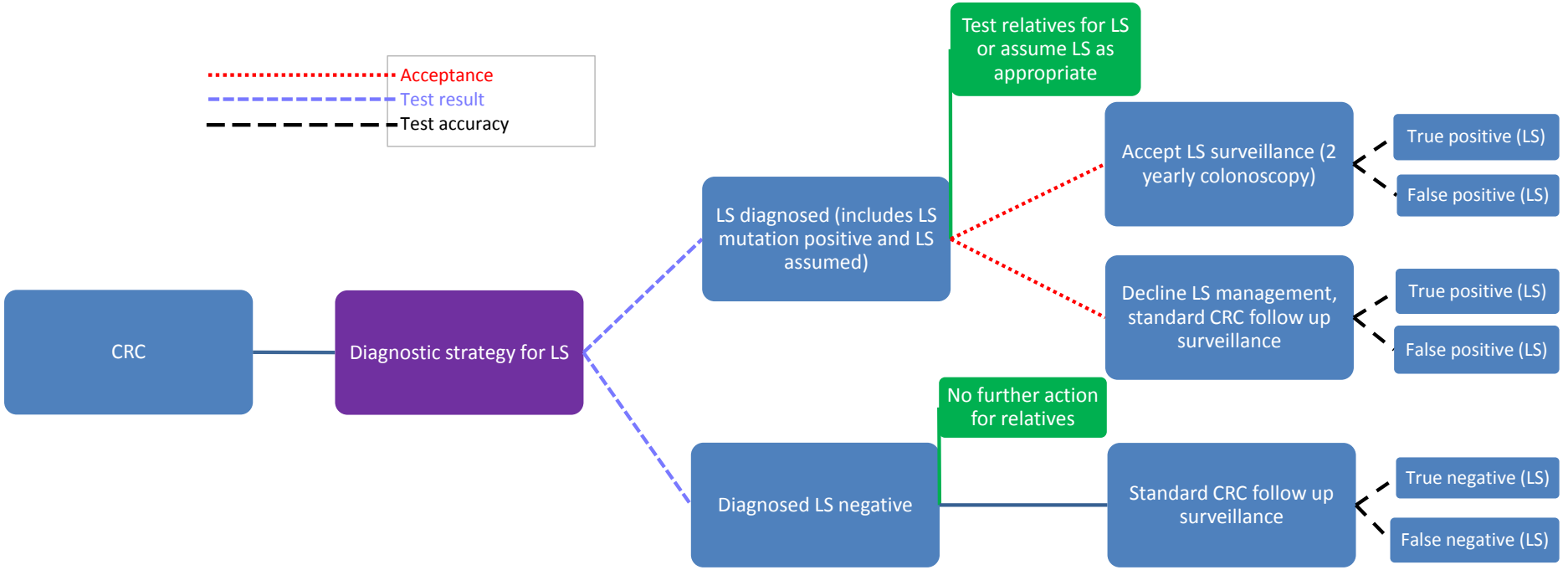


Table 5 Diagnostic strategies for probands

Strategy number	Description
1	No systematic testing to identify LS (all probands assumed to not have LS)
2	IHC four panel test for MLH1, MSH2, MSH6 and PMS2, followed by genetic testing if IHC result abnormal.
3	IHC four panel test for MLH1, MSH2, MSH6 and PMS2, followed by: • Genetic testing for abnormal MSH2, MSH6 or PMS2 abnormal IHC results, or • *BRAF* V600E testing for abnormal MLH1 IHC results. Genetic testing is carried out if the *BRAF* V600E test is negative (negative for V600E, a 'wild type' result).
4	IHC four panel test for MLH1, MSH2, MSH6 and PMS2, followed by: • Genetic testing for abnormal MSH2, MSH6 or PMS2 abnormal IHC results, or • *MLH1* promoter hypermethylation testing for abnormal MLH1 IHC results. Genetic testing is carried out if the *MLH1* promoter hypermethylation test is negative.
5	IHC four panel test for MLH1, MSH2, MSH6 and PMS2, followed by: • Genetic testing for abnormal MSH2, MSH6 or PMS2 abnormal IHC results, or • *BRAF* V600E testing for abnormal MLH1 IHC results. A negative *BRAF* test (negative for V600E), is followed with *MLH1* promoter hypermethylation testing. Genetic testing is carried out if the *MLH1* promoter hypermethylation test is negative.
6	MSI test, followed by genetic testing for positive MSI results.
7	MSI test, followed by *BRAF V600E* testing for positive MSI results. Genetic testing occurs for a negative *BRAF* test (negative for V600E, a 'wild type' result).
8	MSI test, followed by *MLH1* promoter hypermethylation testing for positive MSI results. Genetic testing occurs for a negative *MLH1* promoter hypermethylation test.
9	MSI test, followed by *BRAF* V600E testing for positive MSI results. A negative *BRAF* test (negative for V600E), is followed with *MLH1* promoter hypermethylation testing. Genetic testing is done for a negative *MLH1* promoter hypermethylation test.
10	Universal genetic testing (i.e. as first and only test for all probands)
LS: Lynch syndrome. MSI: microsatellite instability. IHC: immunohistochemistry.	

In the model it is assumed that all patients with colorectal cancer who accept genetic testing will receive testing for all 4 known Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). The exception to this is probands who follow strategies which use IHC followed by either *BRAF* V600E or *MLH1*

promoter hypermethylation testing (in the event of abnormal MLH1 expression, as seen by IHC), who will receive only *MLH1* and *PMS2* germline testing. Mutations related to *EPCAM* are assumed to be identified via the testing for *MSH2*.

The potential results of testing strategies for patients are:

- LS-mutation positive: when a proband receives a positive genetic test.
- LS-negative: where a proband is ruled out of having Lynch syndrome by one of the strategies.

The model also takes account of probands who decline genetic testing for Lynch syndrome, who become “Lynch syndrome-assumed”. The proportion of probands who decline testing in the model is adjusted by age-subgroup.

Results from testing strategies determine the subsequent management of probands, including whether they are offered surveillance for colorectal and endometrial cancer, and aspirin chemoprevention. The effects of these interventions are determined in the longer term model.

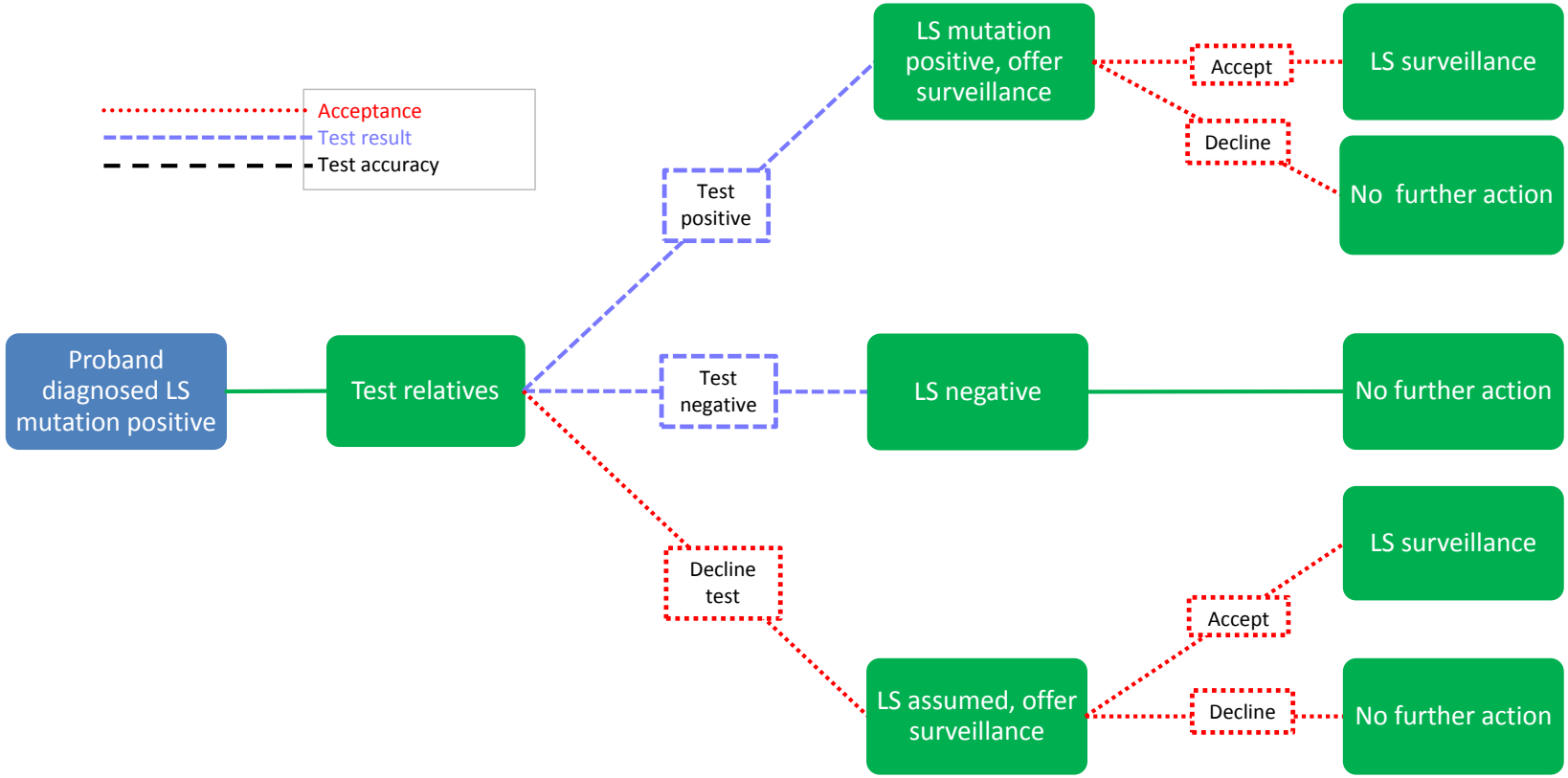
The primary outputs from the diagnostic model that feed into the longer term model are:

- Number of probands with Lynch syndrome who receive surveillance
- Number of probands with Lynch syndrome not receiving surveillance (either people who are diagnosed as Lynch syndrome positive but decline surveillance or people who are incorrectly diagnosed as Lynch syndrome negative)
- Number of probands without Lynch syndrome who are receiving surveillance
- Number of probands without Lynch syndrome who do not receive surveillance (either people who are incorrectly diagnosed as Lynch syndrome positive but decline surveillance or people who are correctly diagnosed as Lynch syndrome negative).

Decision tree for relatives

The model also includes testing for the relatives of probands diagnosed as Lynch syndrome positive. This is summarised in figure 2. For probands categorised as Lynch syndrome assumed, their first-degree relatives are offered Lynch syndrome surveillance (which they can either accept or decline). No further action is taken for the relatives of people who do not have Lynch syndrome.

Figure 2 Diagnostic strategy for relatives of probands diagnosed as Lynch syndrome mutation positive. LS: Lynch syndrome



Further detail on diagnostic testing strategies for relatives is included in the diagnostics assessment report (page 158 onwards).

Longer-term model

The longer term model includes outcomes relating to both colorectal cancer surveillance and treatment and gynaecological (endometrial) cancer surveillance and treatment. Details of the longer-term model, including a simplified diagram, are presented in the diagnostics assessment report on page 159 onwards.

Longer-term outcomes are modelled for all probands and relatives (regardless of the diagnostic path they follow) using an individual patient sampling model to simulate 240,000 patients, distributed across 24 groups, representing all combinations of the following variables:

- whether the person is a proband or relative
- whether the person has Lynch syndrome
- whether the person has been diagnosed with Lynch syndrome and accepted or declined surveillance
- sex

Patients are simulated for 1 year at a time in the model, with the events that happen to them during that year, as well as the life years and quality adjusted life years (QALYs) they accumulate, being determined by the health state they are in. Further details on the health states included in both the colorectal and gynaecological cancer longer-term models can be found starting on page 162 of the diagnostics assessment report.

Model inputs

Summaries of model inputs are presented below. Further details on the identification of the model inputs and their sources are given in the diagnostics assessment report, starting on page 179, and a summary table of all model

parameter values is provided in appendix 5 of the diagnostics assessment report.

Diagnostic accuracy

Estimates of test accuracy (sensitivity and specificity; shown in table 6) were taken from available literature, which were identified via the diagnostic accuracy and cost-effectiveness literature review. To estimate the accuracy of MSI and IHC testing the EAG pooled results from studies included in the clinical effectiveness review using a multilevel mixed-effects logistic regression analysis. For MSI the results from Barnetson et al. (2006), the population-based sample from Poynter et al. (2008) and Southey et al. (2005) were pooled, and for IHC testing results from Limburg et al (2011) and Southey et al. (2005) were pooled. Effect estimates for all other tests included were obtained from the systematic review of existing economic models.

Diagnostic accuracy data for *BRAF* V600E and *MLH1* promoter methylation testing were taken from Ladabaum et al. (2015). This study pooled values from studies reporting test accuracy, with included studies utilising a variety of prior testing for Lynch syndrome (including the use of MSI and IHC testing).

Table 6 Test accuracy parameters used in modelling

Test	Parameter	Parameter value (95% CI)
MSI Base case: MSI test positive=MSI-H	Sensitivity	0.913 (0.426-0.993)
	Specificity	0.837 (0.638-0.937)
MSI Scenario analysis: MSI test positive=MSI-L and MSI-H	Sensitivity	0.973 (0.893-0.994)
	Specificity	0.596 (0.304-0.833)
IHC	Sensitivity	0.962 (0.694-0.996)
	Specificity	0.884 (0.790-0.940)
BRAF	Sensitivity	0.96 (0.60-0.99)
	Specificity	0.76 (0.60-0.87)
MLH1 promoter methylation	Sensitivity	0.94 (0.79-0.98)
	Specificity	0.75 (0.59-0.86)

Diagnostic genetic testing for probands	Sensitivity	*MLH1*, *MSH2*, *MSH6* 0.90 *PMS2* 0.67
	Specificity	0.997
Predictive testing for relatives	Sensitivity	1.00
	Specificity	1.00

Estimates for parameters relating to the acceptance of tests, by either probands or their relatives, were based on values obtained from published literature, expert advice or from Manchester Familial Colorectal Cancer Registry data. Values are shown in table 48 on page 183 of the diagnostics assessment report.

Colorectal cancer surveillance

In the model, surveillance colonoscopy is assumed to lead to improved health outcomes and increased survival by reducing colorectal cancer incidence and by detecting colorectal cancer earlier. Acceptance of colonoscopic surveillance is assumed to be high for probands, and values for the acceptance of surveillance for relatives were based on data from the Manchester Familial Colorectal Cancer Registry. Parameter values related to the stage of colorectal cancer at which a diagnosis is made were based on data from the UK-wide National Cancer Intelligence Network.

Gynaecological surveillance

Insufficient evidence was identified to assess whether gynaecological surveillance had an effect on the incidence of gynaecological cancer, therefore no effect was assumed in the model. A study comparing endometrial cancer cases before and after surveillance was implemented was used to estimate the impact of surveillance on the stage of cancer at diagnosis, and, based on this, the EAG estimated the effect of gynaecological surveillance on overall survival.

Chemoprevention

Parameters relating to the effects of aspirin on reducing the incidence of cancer in people with Lynch syndrome were estimated based on data from the CAPP2 randomised controlled trial. It was assumed that the duration of the protective effect of aspirin was 10 years.

Costs

Resource use in the model is outlined in the diagnostic assessment report on page 200 onwards.

Costs of preliminary tumour testing, genetic tests (for both probands and relatives) and genetic counselling were sourced from the UKGTN (2016), Health and Social Care Unit Costs and from personal communication with providers. These costs are summarised in table 7.

Table 7 Costs of diagnostic tests and genetic counselling

Test		**Patient**	**Base case cost**
MSI		Proband	£202
IHC		Proband	£210
BRAF V600E		Proband	£119
MLH1 promoter methylation testing		Proband	£136
Proband genetic test, all 4 genes		Proband	£1,276
Proband genetic counselling		Proband	£64
Targeted genetic test for relatives	*MLH1*	Relative	£166
	MSH2	Relative	£161
	MSH6	Relative	£161
	PMS2	Relative	£165
Relative genetic counselling		Relative	£64

Unit costs for surveillance colonoscopies, complications arising from colonoscopies and the cost of colorectal cancer surgery (according to the type of surgery performed and whether the person had Lynch syndrome) were

estimated from NHS reference costs. The costs associated with diagnosis, chemotherapy and radiotherapy (including recurrence), surveillance, stoma care and palliative care for colorectal cancer treatment were taken from Trueman et al. (2007).

The following costs were also estimated based on NHS reference costs, where possible:

- gynaecological surveillance (including gynaecological examination, transvaginal ultrasound, endometrial aspiration biopsy and costs of CA125 testing)
- prophylactic gynaecological surgery
- endometrial cancer (surgery and the cost of administering the chemotherapy regimen).

The cost of a course of radiotherapy for endometrial cancer was estimated based on a published study (Havrilesky et al. 2009), and costs of adjuvant chemotherapy for endometrial cancer and aspirin were based on data from the eMit database, the BNF and the NHS drug tariff.

Health related quality of life and QALY decrements

Utilities associated with colorectal cancer, endometrial cancer and prophylactic hysterectomy were taken from the published literature. Full details of the utilities included can be found starting on page 191 of the diagnostics assessment report. Identified studies were used to provide utilities relating to:

- being diagnosed with different stages of colorectal cancer
- colorectal cancer treatment
- colorectal cancer prevention (i.e. colonoscopy surveillance)
- being diagnosed with, and treated for, endometrial cancer
- the psychological impacts of Lynch syndrome testing and management on quality of life.

No studies were identified that provided disutility values for prophylactic hysterectomy. Disutilities associated with genetic testing used in the model are shown in table 8.

Table 8 Base case disutilities resulting from genetic testing

Result of genetic testing	Disutility	
	Males	Females
Proband		
Test declined, risk-reduction not offered	0.04	0.04
Test declined, accept risk-reduction	N/A	0.05
Test declined, decline risk-reduction	N/A	0.11
Test accepted, LS negative	0	0
Test accepted, LS positive, risk-reduction not offered	0.02	0.02
Test accepted, LS positive, accept risk reduction	N/A	0.03
Test accepted, LS positive, decline risk-reduction	N/A	0.09
Relative		
Test declined, risk-reduction not offered	0.04	0.04
Test declined, accept risk-reduction	N/A	0.08
Test declined, decline risk-reduction	N/A	0.11
Test accepted, LS negative	0	0
Test accepted, LS positive, risk-reduction not offered	0.02	0.02
Test accepted, LS positive, accept risk-reduction	N/A	0.06
Test accepted, LS positive, decline risk-reduction	N/A	0.09
Key: LS, Lynch syndrome		

Base-case results

For the purposes of decision making, the ICERs per QALY gained or lost will be considered. The following main assumptions were applied in the base case analysis (a list of assumptions is included in the diagnostics assessment report on page 15 onwards):

- MSI-L is considered a negative result
- The sensitivity of MSI and IHC testing is not dependent on which MMR gene is mutated

- All people who accept genetic testing will receive testing for all 4 MMR genes, unless they follow a strategy which uses IHC followed by either *BRAF* V600E or *MLH1* promoter hypermethylation testing, in which case only *MLH1* and *PMS2* are tested
- The average number of relatives per proband is 6 (2.5 of whom are first-degree relatives)
- Surveillance colonoscopies reduce the incidence of colorectal cancer by 61%, and the incidence of metachronous colorectal cancer by 47%
- Surveillance colonoscopies improve the proportion of people in whom colorectal cancer is diagnosed at an early stage (stage I/II) from 44.6% to 79.1%.
- Colorectal surveillance colonoscopies occur every 2 years
- Gynaecological surveillance reduces endometrial cancer mortality by 10%
- People receiving aspirin have a reduction in the incidence of colorectal and endometrial cancer that lasts for 10 years
- Disutility is only applied to people with colorectal cancer at stage IV
- No disutility arising from prophylactic hysterectomy is assumed.
- Initial acceptance of colonoscopic surveillance is 97% for probands and relatives who are Lynch syndrome mutation positive, and 70% for probands and relatives who are Lynch syndrome assumed.

The results of the base case analysis in full are shown on page 213 onwards in the diagnostics assessment report. The base case includes 238,175 simulated individuals and represents an annual cohort of 34,025 probands with colorectal cancer and 204,150 relatives. Summary cost-effectiveness results for the 10 strategies in the base-case analysis are shown in table 9. Pairwise ICERs are presented for all strategies versus no testing (Strategy 1; in column 4) plus the comparative (fully incremental) ICERs for all strategies (column 6). The optimal strategy (highest incremental net health benefit [INHB] at a willingness to pay threshold of £20,000 per QALY gained) is IHC testing followed by both *BRAF* and *MLH1* promoter methylation testing

(Strategy 5; column 5). The cost-effectiveness plane can be found on page 215 of the diagnostics assessment report.

Table 9 Summary base case cost-effectiveness results

Strategy	QALYs	Cost	ICER vs. no testing (cost per QALY)	INHB £20k/QALY vs. no testing	Incremental ICER (cost per QALY)
1: No test	3,508,052	£743,298,306	—	—	—
2: IHC	3,510,017	£767,955,447	£12,553	731.5	£60,967
3: IHC plus *BRAF*	3,509,977	£765,532,726	£11,553	812.9	£37,495
4: IHC plus *MLH1* promoter methylation	3,509,965	£765,535,788	£11,672	793.3	Dominated by 3
5: IHC plus *BRAF* and *MLH1* promoter methylation	3,509,937	£764,048,240	£11,008	848.0	£11,008
6: MSI	3,509,926	£769,249,096	£13,849	576.3	Dominated by 2
7: MSI plus *BRAF*	3,509,832	£763,660,095	£11,438	762.0	Extended dominated by 8 and 5
8: MSI plus *MLH1* promoter methylation	3,509,796	£763,503,459	£11,589	733.2	Extended dominated by 9 and 7
9: MSI plus *BRAF* and *MLH1* promoter methylation	3,509,721	£761,784,044	£11,076	744.7	Extended dominated by 1 and 5
10: Universal genetic testing	3,509,987	£793,380,127	£25,884	−569.2	Dominated by 2
INHB: incremental net health benefit					

Long term costs (treatment and prevention costs as opposed to diagnostic costs) were the largest cost component for each strategy. When compared with strategy 1 (no testing), all strategies had increased incremental costs for cancer prevention (both colorectal and endometrial) and decreased incremental costs for cancer treatment. The EAG noted that total long term costs appeared broadly similar across all strategies, potentially because any reduction in cost for cancer treatment achieved by using a particular strategy for Lynch syndrome diagnosis are counter-balanced by increases in cost for cancer prevention. The cost of Lynch syndrome diagnosis is therefore one of the main drivers of incremental cost difference between strategies.

Subgroup analyses

Subgroup analyses were carried out by restricting the age of probands included in the model who undergo Lynch syndrome testing strategies. The age groups were: less than 50 years, less than 60 years, less than 70 years and 70 years or older.

The prevalence of Lynch syndrome in probands increases as the age limit of the included population is decreased (from 1.1% in 70 years or older to 8.4% in under 50 year olds). In addition to the prevalence of Lynch syndrome in probands, further parameters were also altered in the subgroup analyses. Details are given in table 71 in the diagnostics assessment report, on page 226. The annual incidence of colorectal cancer changes with each age limit (increasing as the age limit is raised), and the total number of people with colorectal cancer is higher for the age group 70 or over (20,202) than in the under 70 age group (13,823). The number of relatives per proband is not altered by the age of the proband, and the age of the relatives is not linked to the age of the proband.

Summary cost-effectiveness results for the subgroup analyses are presented in the diagnostics assessment report from page 227 onwards. Summaries of the results are provided below.

Proband population aged less than 50 years

All strategies have ICERs less than £13,000 per QALY gained compared with no testing (Strategy 1). Strategies 3 (IHC plus *BRAF*; £19,903) and 5 (IHC plus *BRAF* and *MLH1* promoter methylation; £8,090) have ICERs under £20,000 per QALY gained in the fully incremental analysis.

Proband population aged less than 60 years

All strategies have ICERs less than £17,000 per QALY gained compared with no testing (Strategy 1). Only strategy 5 (IHC plus *BRAF* and *MLH1* promoter methylation; £9,156) has an ICER below £20,000 per QALY gained in the fully incremental analysis.

Proband population aged less than 70 years

With the exception of strategy 10 (universal genetic testing), which has an ICER of £20,528 per QALY gained, all strategies have ICERs less than £20,000 per QALY gained compared with no testing (Strategy 1). Only strategy 5 (IHC plus *BRAF* and *MLH1* promoter methylation; £9,912) has an ICER below £20,000 per QALY gained in the fully incremental analysis.

Proband population aged 70 years or older

Strategies 5 (IHC plus *BRAF* and *MLH1* promoter methylation), 7 (MSI plus *BRAF*) and 9 (MSI plus *BRAF* and *MLH1* promoter methylation) have ICERs less than £20,000 per QALY gained compared with no testing (strategy 1). Strategies 5 (£18,839) and 9 (£18,766) have ICERs below £20,000 per QALY gained in the fully incremental analysis. The EAG commented that the lower ICER values for these strategies is because the use of multiple tests in sequence in these strategies reduces the number of people without Lynch syndrome (false positives) who receive genetic testing, which reduces diagnostic costs.

Larger total costs and QALYs were reported for subgroups with a higher maximum age limit. The EAG noted that this is largely driven by the size of modelled cohort (both probands and relatives). When compared with the base case analysis, ICERs are reduced for subgroups with an upper age limit (50, 60 and 70 years) but increased in the subgroup analysis for people aged 70 years or older. The EAG commented that this is because subgroups comprised of probands with lower ages have a higher prevalence of Lynch syndrome.

Analysis of alternative scenarios

Several scenario analyses were carried out by the EAG, as described in the diagnostic assessment report on page 231 onwards.

Scenario 1: MSI-L corresponds to a Lynch syndrome positive MSI result

In this scenario, MSI-L and MSI-H are assumed to indicate Lynch syndrome (in the base case analysis only MSI-H is indicative). This lowers the threshold for microsatellite instability, effectively increasing sensitivity and reducing specificity, as described on page 232 in the diagnostics assessment report. Only strategies involving MSI testing (strategies 6-9) are affected, with ICERs versus no testing increased compared with the base case analysis. As for the base case analysis, strategy 5 is the only strategy with an ICER below £20,000 cost per QALY gained (unchanged at £11,008) in the fully incremental analysis.

Scenario 2: Aspirin removed from the model

In this scenario, aspirin was not included as a risk-reducing component in the model (as it was in the base-case analysis). This results in a marginal increase in ICER values, with strategy 5 remaining the optimal strategy with an ICER of £11,659 per QALY gained in the fully incremental analysis.

Scenarios 3 and 4: Gynaecological surveillance assumed to have no benefit or is not included

In the base case analysis, where gynaecological surveillance is accepted it reduces the risk of mortality from endometrial cancer. Two scenarios were considered, 1 assuming that gynaecological surveillance has no benefit (but still has a cost) and another which removed gynaecological surveillance from the model (no cost and no benefit). For both scenarios, strategy 5 remains the optimal strategy, and remains the only strategy with an ICER below £20,000 cost per QALY gained in the fully incremental analysis.

Scenario 5: Altered colorectal cancer disutility values

In the base case analysis the quality of life for people with colorectal cancer, except Dukes' stage D, is assumed to be similar to the general population (that is, a disutility value of 0). In this scenario analysis, increased disutility values for all colorectal cancer stages are used. These values are based on Ness et al. (1999) and are described in the diagnostics assessment report on page 242 onwards. When compared with the base case analysis, ICER values for all strategies compared with no testing are reduced. Strategy 5 remains the optimal strategy, with an ICER of £9,775 per QALY gained in the fully incremental analysis.

Scenario 6: Colonoscopic surveillance assumed to have no impact on colorectal cancer incidence

The EAG noted that there is evidence that colonoscopic surveillance may not be as effective at reducing the incidence of colorectal cancer as assumed in the base case analysis (discussed in the diagnostic assessment report on page 182 onwards). A 'worst case' scenario was therefore modelled, where colonoscopic surveillance was assumed to have no effect on reducing colorectal cancer incidence. This increased ICERs for all strategies compared with no testing (strategy 1), with only 3 strategies remaining, marginally, below £20,000 per QALY gained. Strategy 5 remained the only strategy with an

ICER below £20,000 per QALY gained in the fully incremental analysis; however, this value increases to £19,194 per QALY gained (from £11,008 per QALY gained in the base case).

Sensitivity analyses

Deterministic sensitivity analyses were carried out for several parameters in the model. Summary results for all analyses are in table 86 in the diagnostics assessment report at page 248 onwards.

The ICERs for the testing strategies were sensitive to several parameters, which are discussed below.

Diagnostic testing

Reducing the sensitivity and specificity (individually or jointly) of the tumour tests (MSI, IHC, *BRAF* and *MLH1* promoter methylation) to their lower 95% confidence interval values reduces the INHB for strategies that use these tests. When sensitivity and specificity are both reduced, the ICER for strategy 5 versus no testing increases to £16,036 per QALY gained. Altering diagnostic accuracy can also affect which strategy is optimal (compared with the base case, where strategy 5 is optimal). When sensitivity is reduced for all tumour tests, strategy 4 becomes the optimal strategy (IHC followed by *MLH1* promoter methylation). When sensitivity values are increased for all tumour tests (to their upper 95% confidence interval values), MSI testing strategies become optimal, despite MSI testing still having lower sensitivity and specificity values than IHC testing.

In addition, where the cost of IHC is doubled, or cost of MSI testing halved (both relative to base case values), strategy 7 (MSI followed by *BRAF*) becomes the optimal strategy.

Acceptance of genetic counselling and testing

Decreasing the acceptance of both genetic counselling and testing following counselling by probands (set at 90% and 92.5%, respectively, in the base

case analysis) to 50% increases the ICER for strategy 5 versus no testing to £17,767 per QALY gained (from £11,008 per QALY gained).

Incidence of colorectal cancer

Increasing the incidence of colorectal cancer in people with Lynch syndrome in the model decreased the ICER versus no testing for strategy 5 to £6,689 per QALY gained, whereas decreasing the incidence of colorectal cancer increased this value to £19,300 per QALY gained.

Diagnosis of LS assumed

In the base case analysis, people who are diagnosed as "LS assumed" because they decline genetic testing are considered as positive for Lynch syndrome. If all LS assumed probands, and their relatives, are instead considered to be Lynch syndrome negative, the ICER for strategy 5 versus no testing decreases to £5,225 per QALY gained.

Number of relatives

The EAG noted variation in the number of relatives per proband reported in identified published and unpublished sources (discussed in the diagnostics assessment report on page 148). Six relatives per proband is assumed in the base case analysis. If only probands are included in the model (that is, no relatives included), ICERs for all strategies increase, with strategy 5 versus no testing increasing to £17,921 per QALY gained. Increasing the number of relatives per proband to 12 decreases ICERs slightly, with strategy 5 versus no testing decreasing to £10,068 per QALY gained.

Cost and acceptance of colonoscopy

If the costs of colonoscopy used in the base case analysis are doubled, all ICERs for strategies versus no testing increase; for example, for strategy 5 this increase is to £16,630 per QALY gained. Reducing the acceptance of colonoscopy surveillance by people with confirmed Lynch syndrome causing

mutations from 97% (as per the base case analysis) to 70% increases ICERs for strategies versus no testing (to £12,632 per QALY gained for strategy 5).

Disutility associated with prophylactic H-BSO

In the base case analysis, disutility associated with prophylactic hysterectomy and bilateral salpingo-oophorectomy (H-BSO) is assumed to be 0. Increasing the disutility value to 0.04 for 1 year increases the ICERs for all strategies versus no testing, with the value for strategy 5 increasing to £14,441 per QALY gained. The EAG noted uncertainty for this disutility value because no literature was identified to provide estimates.

3 Summary

Ten studies (with 11 sample populations) were included in the review of diagnostic accuracy for MSI and IHC testing. Only 1 of these studies recruited people from an unselected colorectal cancer population, with other studies either recruiting people from age-limited populations, people considered at high-risk of having Lynch syndrome or people who were already diagnosed as having Lynch syndrome. It is therefore not certain how generalisable the results of the diagnostic accuracy review are to the decision problem for this assessment, which includes an unselected colorectal cancer population. No studies made a direct comparison of MSI and IHC testing and results were reported separately for each of the tests. There was also substantial heterogeneity between the included studies.

The range of sensitivity values for MSI testing derived from included studies varied depending on how MSI-L results were interpreted. When MSI-L was considered to be negative for Lynch syndrome, this range was 66.7-100%, and when MSI-L was considered positive, sensitivity increased to 79.4-100%. Specificity ranges also varied, from 61.1-92.5% when MSI-L was a negative result, to 29.5-84.5% when MSI-L was considered positive for Lynch syndrome. Sensitivity values from studies reporting IHC testing varied between 80.8 and 100%, with the corresponding range of specificity values

being 80.5-91.9%. Secondary analysis conducted on 2 studies resulted in reduced sensitivity values in both, from 96.4% to 75.0% in one study, and from 91.7% to 88.6% in the other.

An economic model was developed to assess the cost-effectiveness of Lynch syndrome testing strategies in people with colorectal cancer. In the base case analysis, all strategies produced increased QALYs and increased costs compared to strategy 1 (no testing). With the exception of strategy 10 (universal genetic testing), all strategies had ICERs less than £20,000 per QALY gained compared with no testing. Strategy 5 was the optimal strategy (IHC testing followed by both *BRAF* and *MLH1* promoter methylation testing). All analyses were deterministic with no probabilistic analyses. The results of the model were robust to many of the assumptions investigated in sensitivity and scenario analyses. Changing assumptions for the following parameters had some impact on the results, although strategy 5 generally remained the most cost effective option in the fully incremental analyses:

- age of the probands
- effect of colonoscopic surveillance
- accuracy of the tumour based tests
- acceptance of genetic testing and counselling
- removal of testing for relatives
- incidence of colorectal cancer
- increased costs for colonoscopy
- disutility associated with prophylactic H-BSO.

The results of the analyses suggest that testing for Lynch syndrome could be cost effective compared to no testing, provided that testing strategies which select the population receiving universal genetic testing by using tumour based testing are implemented. However, because there is no direct comparative evidence for the modelled test strategies it is not certain whether any of the strategies are significantly more accurate or cost effective than another.

4 Issues for consideration

Clinical effectiveness

The EAG identified 10 studies (with 11 sample populations) reporting test accuracy that met the inclusion criteria. Five of these studies included people with colorectal cancer who were considered to be at high-risk of having Lynch syndrome, and 2 studies included people with colorectal cancer who were known to have Lynch syndrome. Because of concern that an increased prevalence of Lynch syndrome in the study population (when compared to unselected colorectal cancer patients) would affect test accuracy, these studies were only used to estimate the sensitivity of index tests. The inclusion of high-risk population studies in this assessment could introduce spectrum bias to sensitivity estimates. The EAG commented that they did not observe large differences between sensitivity values obtained from these high-risk studies and values obtained from included studies which recruited people with colorectal cancer without considering their risk of having Lynch syndrome.

Four included studies assessed index test accuracy in colorectal cancer patient populations that were not considered to be at high-risk of Lynch syndrome. However, 3 of these studies used age-limited populations (under 45, 50 or 55 years old). This may result in spectrum bias, because the prevalence of Lynch syndrome is higher in cohorts of colorectal cancer patients with lower upper-age limits.

The EAG commented that the generalisability of results from the included studies to the general colorectal cancer population was a potential area of uncertainty. Only one study (Poynter et al. 2008) included participants from an unselected colorectal cancer population; with other included studies either using age-limited populations or people identified as being at high-risk of Lynch syndrome.

Methodological heterogeneity was observed across the included studies. The reference standard used differed between studies, in terms of the testing method used and also whether unclassified variants were investigated.

There was also variation in the methodology of index testing in the included studies. For MSI testing, the panel of microsatellite sites used, and the number of sites used, varied between studies. In addition, studies differed in how they defined microsatellite instability and in the techniques of microdissection used to obtain tumour tissue. There is also uncertainty concerning what threshold should be used in MSI testing (that is, does MSI-L constitute a positive or negative test for Lynch syndrome) which affects the cost-effectiveness of MSI testing strategies. For IHC testing, studies differed in whether they included PMS2 in assessment (alongside MLH1, MSH2 and MSH6).

The categorisation of unclassified variants is a further possible area of uncertainty. Because the pathogenicity of these variants is unknown, there is uncertainty as to whether people in whom these variants are identified should be considered Lynch syndrome positive or negative. The EAG carried out separate analysis of MSI and IHC testing considering unclassified variants as negative (primary analysis) or positive (secondary analysis) reference standard results. However, most studies did not provide sufficient data to conduct secondary analysis, and the only studies with the required data were based on either a high-risk population or were a reference standard positive study; consequently, only sensitivity could be calculated in secondary analysis.

Cost effectiveness

The base case analysis suggests that IHC-based testing is more cost-effective than MSI-based testing. This is in contrast to results reported in Snowsill et al. (2014), which uses an economic model that has been adapted for this assessment. The EAG suggested that this is because different values for the sensitivity of IHC testing (higher) and specificity of MSI testing (lower) were used in the base case analysis. This is potentially because different inclusion criteria were used to identify studies for Snowsill et al. (2014); inclusion criteria required people with colorectal cancer who were considered

at risk of Lynch syndrome, for example because they were under 50 years at diagnosis, or due to family history indicators or clinical criteria.

The EAG also commented that there is no direct comparative evidence that either test (MSI or IHC) is more accurate. Values for sensitivity and specificity in the base case analysis model for both IHC and MSI testing were obtained by pooling data from studies identified in the systematic review of test accuracy studies. However, in the systematic review a meta-analysis was not considered appropriate, because of substantial heterogeneity between studies.

No data on the accuracy of testing strategies as a whole were available for the model. Accuracy data for each of the individual tests (MSI, IHC, *BRAF* and *MLH1* promoter hypermethylation testing) were combined to model the likely performance of the tests when they are used in combination. Tests may perform differently in practice when they are used in unselected populations and in populations that have been selected by previous testing.

There is potential uncertainty about the risk of colorectal cancer in people with Lynch syndrome and also the effect of colonoscopic surveillance in reducing this risk. The effectiveness of colonoscopic surveillance used in the base case analysis was based on results from a Finnish study (Jarvinen et al. 2000) and it is possible that surveillance in the NHS may have different effectiveness. Scenario analysis that assumed no benefit for colonoscopic surveillance increased ICERs for all strategies compared with no testing, with the ICER for optimal strategy 5 increasing to marginally below £20,000 per QALY. The model also showed sensitivity to the incidence of colorectal cancer in people with Lynch syndrome in deterministic sensitivity analysis. While univariate analysis was conducted for both these parameters (incidence of colorectal cancer and effectiveness of colonoscopic surveillance), a two-way sensitivity analysis in which they were both varied simultaneously was not carried out.

Probabilistic sensitivity analysis was not conducted, with uncertainty in parameter values being investigated using scenario and deterministic

sensitivity analyses. This means that only a small number of parameters in the model were varied simultaneously in analyses and consequently the joint uncertainties in all included parameters has not been quantified, that is there are no confidence intervals provided for incremental costs, QALYS or ICERs and the probability of the strategies being cost effective has not been computed using cost effectiveness acceptability curves.

The model only includes outcomes associated with colorectal and endometrial cancer. Other cancers are also more likely in people with Lynch syndrome and may affect the cost-effectiveness of testing strategies. For example, consideration of ovarian cancer may improve cost-effectiveness, because the costs of risk-reduction are already included in the model (because they are the same as for endometrial cancer) but the benefits of reduced ovarian cancer incidence are not included.

5 Equality considerations

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

People with cancer are protected under the Equality Act 2010 from the point of diagnosis.

Women with Lynch syndrome have an increased incidence of gynaecological cancers.

Older people have an increased risk of colorectal cancer and other Lynch syndrome associated cancers. Microsatellite instability is more common in colorectal cancer tumours in older people.

6 Implementation

A 2015 Bowel Cancer UK survey on Reflex testing for Lynch syndrome in people diagnosed with bowel cancer under the age of 50 reported that 49% of

NHS trusts in England screen bowel cancer patients under the age of 50 for Lynch syndrome. Reasons stated for not implementing testing were lack of funding; potential impact on patients and some stated they were awaiting NICE guidance.

The following are key adoption issues which the adoption team highlighted in their adoption scoping report:

- If MSI or IHC testing is to be successfully implemented training and education need to be provided to increase awareness and identify patients to be screened.
- There needs to be local agreement on commissioning arrangements to achieve consistent access to the screens for all patients.

7 Authors

Thomas Walker
Topic Lead

Rebecca Albrow
Technical Adviser

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

A. The diagnostics assessment report for this assessment was prepared by Peninsula Technology Assessment Group (PenTAG):

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling I, Hyde C. Molecular testing for Lynch syndrome in people with colorectal cancer: 2016, Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School (Report for NICE).

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

Manufacturer(s) of technologies included in the final scope:

- N/A

Other commercial organisations:

- Promega UK Ltd

Professional groups and patient/carer groups:

- British Society of Gastroenterology
- Cancer Genetics Group
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Bowel Cancer UK
- Genetic Alliance
- Lynch syndrome UK

Research groups:

None.

Associated guideline groups:

None.

Others:

- Cardiff and Vale University Health Board
- Department of Health
- Healthcare Improvement Scotland
- NETSCC
- NHS England
- UK NEQAS for Molecular Genetics
- Welsh Government
- Bristol Genetics Laboratory
- Manchester Centre for Genomic Medicine
- Manchester Royal Infirmary
- Northern Molecular Genetics Service
- Oxford Radcliffe Hospitals NHS Foundation Trust
- Sheffield Diagnostic Genetics Service

Appendix B: Glossary of terms

BRAF V600E

Also known as c.1799T>A (p.Val600Glu), a change from valine to glutamic acid at amino acid position 600 in the BRAF protein

Cascade testing

The identification of close relatives of an individual with a disorder to determine whether the relatives are also affected or are carriers of the same disorder.

Hypermethylation

An increase in the epigenetic methylation of cytosine and adenosine residues in DNA

Microsatellite instability

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

Methylated

DNA which is altered by the addition of a methyl group. When this happens in promoter regions it can supress gene expression.

Mutation

A change in the DNA sequence from the wildtype or common sequence

Proband

A person who is diagnosed with colorectal cancer and for whom different strategies can be employed to detect Lynch syndrome.

Unmethylated

DNA which has not been modified by the addition of a methyl group.

Wild type

The normal or most common DNA sequence in an organism