NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

Molecular testing strategies for Lynch syndrome in people with colorectal cancer

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

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

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

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

Equality issues

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

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

disabilities.

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

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

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

For further details, see the Diagnostics Assessment Programme manual.

Key dates:

Closing date for comments: 11 November 2016

Second diagnostics advisory committee meeting: 23 November 2016

1 Draft recommendations

1.1 The following molecular testing strategies for Lynch syndrome are recommended:

- Test all colorectal cancers, when first diagnosed, using immunohistochemistry (IHC) for mismatch repair proteins or microsatellite instability testing to identify tumours with deficient DNA mismatch repair, and to guide further testing for Lynch syndrome. Do not wait for the results before starting treatment.
- If the IHC result is abnormal for the mismatch repair proteins MSH2, MSH6 or PMS2, confirm Lynch syndrome by genetic testing of germline DNA.
- If the IHC result is abnormal for the mismatch repair protein MLH1 or the microsatellite instability test result is positive, use *BRAF* V600E testing to differentiate sporadic and Lynch syndrome-associated colorectal cancers. If the result is negative,

do an *MLH1* promoter hypermethylation test. If this result is negative, confirm Lynch syndrome by genetic testing of germline DNA.

1.2 Laboratories doing microsatellite instability testing or IHC for mismatch repair proteins should take part in a recognised external quality assurance programme.

2 Clinical need and practice

The problem addressed

2.1 Testing colorectal tumours using either microsatellite instability (MSI) or immunohistochemistry (IHC) testing for mismatch repair (MMR) proteins can identify people in whom the cancer may have occurred because of Lynch syndrome. Further testing for people at risk of Lynch syndrome can confirm this diagnosis. As well as colorectal cancer, people with Lynch syndrome have an increased risk of other cancers (such as endometrial, ovarian, stomach, small intestine, hepatobiliary tract, urinary tract, brain and skin cancer). After a diagnosis of Lynch syndrome, risk-reducing strategies can be offered to prevent or allow early diagnosis of associated cancers.

2.2 Currently, testing for Lynch syndrome is typically offered to people considered to be at high risk of having Lynch syndrome. Risk factors include a family history of cancer and age younger than 50 years at the onset of colorectal cancer. Expanding testing to all people with colorectal cancer may increase the detection of Lynch syndrome and, because Lynch syndrome is an inherited condition, 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.

2.3 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using molecular testing strategies, which involve MSI testing and IHC for MMR proteins, to assess how likely it is that a person with colorectal cancer has Lynch syndrome.

The condition

2.4 Lynch syndrome is an inherited genetic condition caused by mutation in one of 4 DNA MMR genes; *MLH1*, *MSH2*, *MSH6* or *PMS2*. Mutations in another non-MMR gene, known as *EPCAM*, which is next to the *MSH2* gene, can also cause Lynch syndrome.

2.5 MMR genes encode proteins that are involved in recognising and repairing errors in DNA sequence, which occur when DNA is replicated during cell division. Mutations in MMR genes can lead to impaired functioning of the MMR system and a failure to repair DNA errors. Over time, this allows mutations to accumulate, potentially leading to cancer.

2.6 Lynch syndrome accounts for about 3.3% of colorectal tumours, and the condition is estimated to lead to over 1,100 colorectal cancers a year in the UK. An estimated 175,000 people in the UK have Lynch syndrome, a large proportion of whom will be unaware that they have the condition. In addition to colorectal cancer, people with Lynch syndrome are also at increased risk of other cancers.

The diagnostic and care pathways

Diagnosis

2.7 In current practice, testing for Lynch syndrome in people with colorectal cancer is usually targeted using criteria based on family history and age of cancer onset to determine people at high risk.

2.8 There is currently no NICE guidance on the population to be tested or the testing strategy for Lynch syndrome. The guidelines of the

British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) for colorectal cancer screening and surveillance in moderate and high risk groups (2010) recommend that people with a lifetime risk of between 10% and 100% of developing colorectal cancer are referred to a regional genetics centre for genetic counselling and appropriate mutation analysis.

2.9 In 2009, after a review of Lynch syndrome testing, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group's report on genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives recommended offering laboratory testing to all such people with colorectal cancer, regardless of age or family history. The 2013 European revised guidelines for the clinical management of Lynch syndrome (HNPCC) also recommended systematic testing of all people with colorectal cancer (or at least all those up to the age of 70) for loss of MMR function by testing for MSI in tumour DNA or IHC for MMR proteins.

2.10 The Royal College of Pathologists includes MMR protein IHC as a core dataset item for people under the age of 50 diagnosed with colorectal cancer. The Independent Cancer Taskforce also recommended in its report, Achieving world-class outcomes – a strategy for England 2015–2020, that all people under the age of 50 be offered a genetic test for Lynch syndrome when bowel cancer is diagnosed.

Treating colorectal cancer in people with Lynch syndrome

2.11 The NICE guideline on colorectal cancer provides recommendations on treating colorectal cancer. Clinicians in the NHS also use the European Society for Medical Oncology (ESMO)

guidelines for diagnosis, treatment and follow-up of early colon cancer to guide treatment decisions.

2.12 The 2013 European HNPCC's revised guidelines for the clinical management of Lynch syndrome also note the substantial risk of a second colorectal cancer after partial colectomy and that the quality of life after partial or subtotal colectomy are similar. Therefore, the option of subtotal colectomy, including its advantages and disadvantages, should be discussed with all people with Lynch syndrome and colorectal cancer, especially younger patients.

Management and surveillance of Lynch syndrome

2.13 The 2013 European HNPCC's revised guidelines for the clinical management of Lynch syndrome recommend that people with a Lynch syndrome mutation take aspirin because this can reduce the incidence of cancer in Lynch syndrome mutation carriers.

2.14 The 2013 European HNPCC's revised guidelines for the clinical management of Lynch syndrome recommend that people with a Lynch syndrome mutation have a colonoscopy every 1 to 2 years. The BSG and ACPGBI's guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (2010) recommend that people with a Lynch syndrome mutation are offered total colonic surveillance at least every 2 years from the age of 25.

3 The diagnostic tests

The assessment compared tumour testing strategies involving microsatellite instability (MSI) testing, immunohistochemistry (IHC) testing (both with and without further testing to exclude sporadic colorectal cancers), and comprehensive mismatch repair (MMR) gene mutation testing with a single comparator. Comprehensive MMR gene mutation testing was also used as

the reference standard for assessing the accuracy of the tumour testing strategies.

The interventions

Microsatellite instability testing

3.1 Microsatellites are repetitive sequences of DNA that are at increased risk of copying errors during replication. In tumours of people without an effective DNA MMR system, errors in copying microsatellite sequences cause them to vary in length. This is known as microsatellite instability (MSI).

3.2 MSI testing can, therefore, be used to assess whether the DNA MMR system is working effectively by detecting the size of microsatellite regions in tumour samples from people diagnosed with colorectal cancer. Deficiencies in DNA MMR show that a person's cancer may have developed because they have Lynch syndrome.

3.3 MSI testing is a polymerase chain reaction (PCR) based method that amplifies DNA at several microsatellite sites from a person's tumour tissue sample and also a healthy tissue sample. MSI tests can differ in the panel of microsatellite marker sites they assess, both in terms of their number and genetic location.

Immunohistochemistry testing

3.4 Immunohistochemistry (IHC) uses antibodies to detect decreased or abnormal expression of MMR proteins in colorectal tumour tissue samples. Absent or reduced nuclear staining of 1 or more MMR proteins suggests that there may be a pathogenic mutation in a gene encoding these proteins.

3.5 MMR proteins detected by IHC are MLH1, MSH2, MSH6 and PMS2. Laboratories may differ in the source of the antibodies used to carry out these tests.

Tests for sporadic colorectal cancer

3.6 Although deficient DNA MMR systems (identified with MSI testing or IHC) indicate that a person may have Lynch syndrome, they can also be seen in sporadic colorectal cancers (that is, cancers not caused by Lynch syndrome). Sporadic colorectal cancers can show loss of MLH1 protein expression caused by changes in the *MLH1* gene promoter. *MLH1* promoter hypermethylation testing can be used to directly test for these changes, or *BRAF* V600E mutation testing can be used, because this mutation is associated with *MLH1* promoter hypermethylation. Testing for *BRAF* V600E, with or without *MLH1* promoter hypermethylation, can identify sporadic colorectal tumours that are MSI positive or have abnormal MLH1 protein expression in people who are not at risk for Lynch syndrome, and therefore prevent unnecessary further genetic testing.

Comprehensive mismatch repair gene mutation testing

3.7 Comprehensive screening for constitutional mutations in the MMR genes, and also possibly the *EPCAM* gene, is the gold standard for diagnosing Lynch syndrome. This involves gene sequencing to detect point mutations and small insertions or deletions in these genes, and also multiplex ligation-dependent probe amplification (MLPA) to detect larger structural changes to genes, such as deletions, duplications or rearrangements.

3.8 Comprehensive screening for constitutional mutations in MMR genes can identify novel sequence variations in these genes that are of unknown significance, that is, it is unknown whether they are pathological or non-pathological. It can therefore be uncertain as to

whether people with such sequence variants should be diagnosed as having Lynch syndrome or not.

The comparator

3.9 The comparator used in this assessment is no testing to identify Lynch syndrome. That is, all people diagnosed with colorectal cancer are assumed not to have Lynch syndrome.

4 Evidence

The diagnostics advisory committee (section 8) considered several sources of evidence on molecular testing strategies for Lynch syndrome in people with colorectal cancer (section 9). Full details of all the evidence are in the committee papers.

Clinical effectiveness

Diagnostic accuracy

4.1 Ten diagnostic accuracy studies that met the inclusion criteria for the systematic review were identified, 1 of which was based in the UK (Barnetson et al. 2006). One of these studies (Poynter et al. 2008) had 2 distinct samples that were treated separately in the review, so although there were 10 included studies, there were 11 included populations or datasets.

4.2 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 2 separate populations; 1 seemed to be an unselected population with colorectal cancer and 1 was in people at 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 populations with colorectal cancer but specified age limits

in their inclusion criteria. These were people younger than 55, younger than 50, and younger than 45 years respectively. The ages of participants in Poynter et al. (2008) were not reported.

4.3 A further 4 studies (Caldes et al. 2004; Mueller et al. 2009; Overbeek et al. 2007; Shia et al. 2005), plus the second population in Poynter et al. (2008), 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. Studies based on high-risk populations and people known to have Lynch syndrome were only used to inform sensitivity estimates for the index tests.

4.4 Quality appraisal of the included studies was done using the QUADAS-2 tool. The external assessment group (EAG) commented that there was no evidence found to show that the included studies were at high risk of bias.

4.5 The EAG noted that the index tests included in the assessment are highly susceptible to spectrum bias. In particular, the increased presence of mismatch repair (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.

4.6 Because of the methodological and clinical heterogeneity seen, the EAG did not consider meta-analyses to be appropriate, and results were presented as a narrative summary. Most of the included studies assessed microsatellite instability (MSI) testing and immunohistochemistry (IHC); however, because none of the

studies directly compared MSI testing and IHC, results were reported separately for each of the index tests.

Accuracy of microsatellite instability testing

4.7 All of the included studies, except Limburg et al. (2011) and Okkels et al. (2012), assessed MSI testing. There were several differences in the MSI testing procedures used in the included studies. These included variations in the number and types of markers in the panels of MSI markers used and also differences in the categorisation of test results; tumours were categorised using either 2 categories (MSI positive or negative) or 3 categories (MSI-High [MSI-H], MSI-Low [MSI-L] or microsatellite stable [MSS]). Studies also varied in the thresholds used to categorise MSI.

4.8 Sensitivity and specificity values were calculated based on a positive MSI test result for Lynch syndrome being MSI-H alone or either MSI-H or MSI-L, as shown in table 1.

Table 1 Accuracy estimates for 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 et al. 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 et al. 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 et al. 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 et al. 2004[b]	79.4 62.1, 91.3	–	79.4 62.1, 91.3	–
Mueller et al. 2009	91.3 72.0, 98.9	–	93.1 77.2, 99.2	–
Overbeek et al. 2007[b]	90.0 59.6, 98.2	–	90.0 59.6, 98.2	–
Poynter et al. 2008	86.8 71.9, 95.6	–	94.7 82.3, 99.4	–
Shia et al. 2005[b]	100.0 85.8, 100.0	–	100.0 85.8, 100.0	–
Reference standard positive study				
Hendriks et al. 2003	88.0 68.8, 97.5	–	92.0 74.0, 99.0	–

[a] Population-based sample

[b] MSI-L not defined

Abbreviations: CI, confidence interval; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low; MSS, microsatellite stable.

4.9 Secondary analyses were carried out if data allowed, with unclassified variants (variations in the sequence of MMR genes that are of unknown clinical significance) considered as positive reference standard results for Lynch syndrome (as opposed to negative reference standard results, as in primary analyses). The

EAG noted that results were similar to those obtained when unclassified variants were considered as negative.

Accuracy of immunohistochemistry testing

4.10 IHC for MMR proteins was carried out in all of the 10 included studies, although 2 of the studies did not have enough data to be included in the IHC analyses: the high-risk samples in Poynter et al. (2008) and Mueller et al. (2009).

4.11 The accuracy estimates from included studies are shown in table 2. 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; Hendriks et al. 2003), an overall result was given, that is, when abnormal staining of any of the MMR proteins assessed was classed as a positive IHC result. All of these 7 studies assessed MLH1, MSH2 and MSH6 proteins. Southey et al. (2005) and Overbeek et al. (2007) also assessed PMS2. So, for these 2 studies, an abnormal PMS2 result would also be included as a positive index test result.

Table 2 Accuracy estimates for 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 et al. 2006	92.6 (76.6, 97.9)	NE	– [a]	– [a]	– [a]	– [a]
Limburg et al. 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 et al. 2005	100.0 (81.5, 100.0)	80.5 (65.1, 91.2)	5.1 (2.8, 9.5)	0.00 (NE)	69.2 (48.2, 85.7)	100.0 (89.4, 100.0)
Single-gate, high-risk samples						
Caldes et al. 2004	96.4 (81.7, 99.9)	–	–	–	–	–
Overbeek et al. 2007	87.5 (52.9, 97.7)	–	–	–	–	–
Shia et al. 2005	80.8 (60.6, 93.4)	–	–	–	–	–
Reference standard positive study sample						
Hendriks et al. 2003	91.7 (77.5, 98.2)	–	–	–	–	–

[a] Analysis not done because overall IHC results were only available for reference standard positive participants.

Abbreviations: IHC, immunohistochemistry; NE, not estimable; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

4.12 Only 2 studies (Caldes et al. 2004; Hendriks et al. 2003) had enough data to be included in the secondary analyses (in which unclassified variants were considered as positive reference standard results for Lynch syndrome). Only sensitivity estimates could be 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. Caldes et al. showed a reduction in sensitivity (75.0%; 95% confidence interval [CI] 57.8, 87.9) compared with the primary analyses in which unclassified variants were categorised as negative reference standard tests

(96.4%; 95% CI 81.7, 99.9). For Hendriks et al., sensitivity was only slightly reduced from 91.7% (95% CI 77.5, 98.2) to 88.6% (95% CI 76.0, 95.0).

End-to-end studies

4.13 No end-to-end studies meeting the inclusion criteria for the systematic review were identified.

Cost effectiveness

Systematic review of cost effectiveness

4.14 Nine separate studies reporting the cost effectiveness of using MSI and IHC testing in strategies to identify Lynch syndrome in people with colorectal cancer met the inclusion criteria for the systematic review of existing economic evaluations. One study was reported in 2 papers (Snowsill et al. 2014; Snowsill et al. 2015). Seven of the included studies were based in US populations, 1 in Germany and 1 in the UK.

4.15 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 depended on the maximum acceptable incremental cost-effectiveness ratio (ICER) and comparators used in the analysis. No single strategy was consistently most cost effective.

4.16 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 having full genetic testing seemed 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 that had the greatest effect on the cost effectiveness of the testing strategies assessed.

Modelling approach

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

Model structure

4.18 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.

4.19 The decision tree started with people diagnosed with colorectal cancer (called 'probands') who could have one of 10 diagnostic strategies for Lynch syndrome, as described in table 3. As a result of these diagnostic strategies, probands were either diagnosed as LS-positive, LS-negative or LS-assumed (if they refused genetic testing). People who were diagnosed as LS-positive or LS-assumed were offered 2-yearly colonoscopies, which they could either accept or decline. People diagnosed as LS-negative had standard colorectal cancer follow-up and surveillance.

4.20 Decision tree models were also included for relatives of probands. Relatives of probands diagnosed as LS-positive were offered testing (which they could accept or decline). Relatives who tested positive for Lynch syndrome, or who declined testing, were offered

surveillance (which they could either accept or decline). First-degree relatives of probands diagnosed as LS-assumed were also offered surveillance. No further action was taken for the relatives of probands who did not have Lynch syndrome.

Table 3 Diagnostic strategies for probands

Strategy number	Description
1	No systematic testing to identify LS (all probands assumed to not have LS).
2	IHC 4 panel test for MLH1, MSH2, MSH6 and PMS2, then genetic testing if the IHC result is abnormal for one of them.
3	IHC 4 panel test for MLH1, MSH2, MSH6 and PMS2, then: • genetic testing for abnormal MSH2, MSH6 or PMS2 IHC results, or • *BRAF* V600E testing for an abnormal MLH1 IHC result, if negative for V600E (a 'wild type' result) then genetic testing is carried out.
4	IHC 4 panel test for MLH1, MSH2, MSH6 and PMS2, then: • genetic testing for abnormal MSH2, MSH6 or PMS2 IHC results, or • *MLH1* promoter hypermethylation testing for an abnormal MLH1 IHC result, if negative then genetic testing is carried out.
5	IHC 4 panel test for MLH1, MSH2, MSH6 and PMS2, then: • genetic testing for abnormal MSH2, MSH6 or PMS2 IHC results, or • *BRAF* V600E testing for an abnormal MLH1 IHC result, if negative then *MLH1* promoter hypermethylation testing is done, if the *MLH1* promoter hypermethylation test is negative, genetic testing is carried out.
6	MSI test, if positive then genetic testing is done.
7	MSI test, if positive then *BRAF* V600E testing, if negative for V600E (a 'wild type' result) then genetic testing is done.
8	MSI test, if positive then *MLH1* promoter hypermethylation testing, if the *MLH1* promoter hypermethylation test is negative, then genetic testing is done.
9	MSI test, if positive then *BRAF* V600E testing, if negative for V600E then an *MLH1* promoter hypermethylation test is done, if the *MLH1* promoter hypermethylation test is negative, then genetic testing is done.
10	Universal genetic testing (that is, the first and only test for all probands).
Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability; LS, Lynch syndrome.	

4.21 The longer-term model included outcomes relating to surveillance and treatment for both colorectal cancer and gynaecological

(endometrial) cancer. Longer-term outcomes were 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 was a proband or relative
- whether the person had Lynch syndrome
- whether the person had been diagnosed with Lynch syndrome and accepted or declined surveillance
- sex.

4.22 Patients were simulated for 1 year at a time in the model, with the events that happened to them during that year, as well as the life years and quality-adjusted life years (QALYs) they accumulated, being determined by the health state they were in.

Model inputs

4.23 Estimates of test accuracy were taken from available literature identified through the diagnostic-accuracy and cost-effectiveness literature reviews. To estimate the accuracy of MSI and IHC testing, results from studies included in the clinical-effectiveness review were pooled using a multilevel mixed-effects logistic regression analysis. For MSI testing, 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, the results from Limburg et al (2011) and Southey et al. (2005) were pooled.

4.24 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 using various types of previous testing for Lynch syndrome (including MSI and IHC testing). Test accuracy parameters used in modelling are shown in table 4.

Table 4 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	0.960 (0.600, 0.990)
	Specificity	0.760 (0.600, 0.870)
MLH1 promoter methylation	Sensitivity	0.940 (0.790, 0.980)
	Specificity	0.750 (0.590, 0.860)
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
Abbreviations: CI, confidence interval; IHC, immunohistochemistry; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low.		

4.25 Estimates of parameter values relating to acceptance of tests, colorectal cancer surveillance, stage of cancer at diagnosis, gynaecological surveillance, and chemoprevention were taken from identified literature, registry data and clinical expert opinion.

Costs

4.26 Costs of preliminary tumour testing, genetic tests (for both probands and relatives), and genetic counselling were sourced from the UK Genetic Testing Network (2016), Health and Social Care Unit Costs and from personal communication with providers. Further relevant costs came from NHS references costs, identified literature, the British national formulary (BNF) and the NHS drug tariff.

Health-related quality of life and quality-adjusted life year decrements

4.27 Utilities associated with colorectal cancer, endometrial cancer and prophylactic hysterectomy were taken from published literature identified by systematic searches. Disutilities associated with genetic testing used in the model were as previously reported in Snowsill et al. (2014).

Main assumptions

4.28 The key assumptions applied in the base-case analysis were:

- MSI-L was considered a negative result.
- The sensitivity of MSI and IHC testing did not depend on which MMR gene is mutated.
- All people who accepted genetic testing had testing for all 4 MMR genes, unless they followed a strategy that used IHC in which case either *BRAF* V600E or *MLH1* promoter hypermethylation testing and only MLH1 and PMS2 were tested.
- The average number of relatives per proband was 6 (2.5 of whom were first-degree relatives).
- Surveillance colonoscopies reduced the incidence of colorectal cancer by 61%, and the incidence of metachronous colorectal cancer by 47%.
- Surveillance colonoscopies improved the proportion of people in whom colorectal cancer was diagnosed at an early stage (stage I or II) from 44.6% to 79.1%.
- Colorectal surveillance colonoscopies occurred every 2 years.
- Gynaecological surveillance reduced endometrial cancer mortality by 10%.
- People taking aspirin had a reduced incidence of colorectal and endometrial cancer that lasted for 10 years.
- Disutility was only applied to people with stage IV colorectal cancer.

- No disutility arising from prophylactic hysterectomy was assumed.
- Initial acceptance of colonoscopic surveillance was 97% for probands and relatives who tested positive for Lynch syndrome mutation, and 70% for probands and relatives who were assumed to have Lynch syndrome.

Base-case model results

4.29 The base-case analysis included 238,175 simulated individuals and represents an annual cohort of 34,025 probands with colorectal cancer and 204,150 relatives.

4.30 Pairwise ICERs were calculated for all strategies compared with no testing (strategy 1). Only strategy 10 (universal genetic testing) had an ICER above £20,000 per QALY gained, with ICERs for strategies 2 to 9 all below £14,000 per QALY gained. Comparative (fully incremental) ICERs were also calculated for all strategies. Strategies involving MSI testing were either dominated (that is, they were less effective and more expensive than another option) or extendedly dominated (that is, a combination of other options were more effective and less expensive) by other strategies. The ICER for strategy 3 (IHC plus *BRAF*) was £37,495 per QALY gained and the ICER for strategy 5 (IHC plus *BRAF* and *MLH1* promoter methylation) was £11,008 per QALY gained.

Base-case model results – subgroup analysis

4.31 Subgroup analyses were carried out by restricting the age of probands, who have Lynch syndrome testing strategies, included in the model. The age groups were: under 50 years, under 60 years, under 70 years, and 70 years or over.

4.32 When the proband population was restricted to people under 50 years, all the strategies had ICERs of 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) had ICERs under £20,000 per QALY gained in the fully incremental analysis.

4.33 When the proband population was restricted to people under 60 years, all the strategies had ICERs of 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) had an ICER below £20,000 per QALY gained in the fully incremental analysis.

4.34 When the proband population was restricted to people under 70 years, all the strategies had ICERs of less than £20,000 per QALY gained compared with no testing (strategy 1), except for strategy 10 (universal genetic testing), which had an ICER of £20,528 per QALY gained. Only strategy 5 (IHC plus *BRAF* and *MLH1* promoter methylation; £9,912) had an ICER below £20,000 per QALY gained in the fully incremental analysis.

4.35 When the proband population was restricted to people 70 years or over, strategies 5 (IHC plus *BRAF* and *MLH1* promoter methylation), 7 (MSI plus *BRAF*) and 9 (MSI plus *BRAF* and *MLH1* promoter methylation) had ICERs less than £20,000 per QALY gained compared with no testing (strategy 1). Strategies 5 (£18,839) and 9 (£18,766) had ICERs below £20,000 per QALY gained in the fully incremental analysis.

Base-case model results – scenario analysis

4.36 If both MSI-L and MSI-H test results are assumed to indicate Lynch syndrome (in the base-case analysis only MSI-H is indicative), this effectively lowered the threshold for a positive MSI test result. Only strategies involving MSI testing (strategies 6 to 9) were affected, with ICERs for testing compared with no testing increased relative to 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.

4.37 If aspirin was not included as a risk-reducing component in the model (as it was in the base-case analysis), this resulted 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.

4.38 In the base-case analysis, if gynaecological surveillance was accepted, it reduced 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 that removed gynaecological surveillance from the model (no cost and no benefit). For both scenarios, strategy 5 remained the optimal strategy and the only strategy with an ICER below £20,000 per QALY gained in the fully incremental analysis.

4.39 In the base-case analysis, the quality of life for people with colorectal cancer, except Dukes' stage D, was 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 were used and values were based on Ness et al. (1999). When compared with the base-case analysis, ICER values for all strategies compared with no testing were reduced. Strategy 5 remained the optimal strategy, with an ICER of £9,775 per QALY gained in the fully incremental analysis.

4.40 If colonoscopic surveillance was assumed to have no effect on colorectal cancer incidence, ICERs for all strategies were increased 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

increased to £19,194 per QALY gained (from £11,008 per QALY gained in the base case).

Base-case model results – sensitivity analysis

4.41 Deterministic sensitivity analyses were carried out for several parameters in the model. The ICERs for the testing strategies were sensitive to several parameters. When sensitivity and specificity values for all tumour tests (MSI, IHC, *BRAF* and *MLH1* promoter methylation) were both reduced to their lower 95% confidence interval values, the ICER for strategy 5 compared with no testing increased to £16,036 per QALY gained.

4.42 Altering diagnostic accuracy can also affect which strategy is optimal. When sensitivity was reduced for all tumour tests, strategy 4 became the optimal strategy (IHC followed by *MLH1* promoter methylation). When sensitivity values were increased for all tumour tests (to their upper 95% confidence interval values), MSI testing strategies became optimal, despite MSI testing still having lower sensitivity and specificity values than IHC testing. In addition, when the cost of IHC was doubled, or the cost of MSI testing halved (both relative to base-case values), strategy 7 (MSI followed by BRAF) became the optimal strategy.

4.43 Decreasing the acceptance by probands of both genetic counselling and testing after counselling (set at 90% and 92.5% respectively in the base-case analysis) to 50%, increased the ICER for strategy 5 compared with no testing to £17,767 per QALY gained (from £11,008 per QALY gained).

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

4.45 In the base-case analysis, people who were diagnosed as LS-assumed because they declined genetic testing were considered as positive for Lynch syndrome. If all LS-assumed probands, and their relatives, were instead considered to be negative for Lynch syndrome, the ICER for strategy 5 compared with no testing decreased to £5,225 per QALY gained.

4.46 Six relatives per proband were assumed in the base-case analysis. If only probands were included in the model (that is, no relatives included), the ICERs for all strategies increased, with strategy 5 compared with no testing increasing to £17,921 per QALY gained. Increasing the number of relatives per proband to 12 decreased the ICERs slightly, with strategy 5 compared with no testing decreasing to £10,068 per QALY gained.

4.47 If the costs of colonoscopy used in the base-case analysis were doubled, all ICERs for strategies compared with no testing increased; for example, for strategy 5, this increased to £16,630 per QALY gained. Reducing the acceptance of colonoscopy surveillance by people with confirmed Lynch syndrome causing mutations from 97% (as in the base-case analysis) to 70% increased the ICERs for strategies compared with no testing (for example, to £12,632 per QALY gained for strategy 5).

4.48 In the base-case analysis, disutility associated with prophylactic hysterectomy and bilateral salpingo-oophorectomy was assumed to be 0. Increasing the disutility value to 0.04 for 1 year increased the ICERs for all strategies compared with no testing, with the value for strategy 5 increasing to £14,441 per QALY gained.

5 Committee discussion

5.1 The committee discussed current practice for assessing the risk of Lynch syndrome in people with colorectal cancer. It heard that

testing is usually only carried out in people with colorectal cancer who are under 50 years at the time of diagnosis. The committee heard from clinical experts that guidelines to target testing for Lynch syndrome, such as the Amsterdam criteria and Revised Bethesda Guidelines, are often not used in current practice because they were developed to identify research populations. Also, required information, such as a detailed family history, is often not available and there are concerns over the sensitivity of these methods to detect Lynch syndrome. The committee also heard that the provision of testing for Lynch syndrome and other inherited colorectal cancers varies widely, with an estimated 50% of centres providing tests to assess the risk of Lynch syndrome in people under the age of 50 who have been diagnosed with colorectal cancer.

5.2 The committee discussed the effect that a diagnosis of Lynch syndrome may have on people with colorectal cancer and their families. It heard from a patient expert that many people are often unaware that their colorectal cancer could be hereditary and therefore do not ask questions about whether they should have further genetic testing, unless this issue is raised by their clinician. It also heard that people who are diagnosed with Lynch syndrome often find that the diagnosis is of benefit to both themselves and their family. The diagnosis can help an individual to be placed on an appropriate pathway for colorectal cancer treatment and make decisions about further surveillance. Family members can also have genetic testing and surveillance to reduce their risk of developing cancer. The committee concluded that assessing the risk of Lynch syndrome in people with colorectal cancer could have substantial benefits for patients and their families.

Clinical effectiveness

5.3 The committee reviewed the available evidence on the clinical effectiveness of using immunohistochemistry (IHC) testing of tumour tissue for mismatch repair (MMR) proteins and microsatellite instability (MSI) to identify tumours with deficient DNA mismatch repair in people with colorectal cancer to assess their risk of having Lynch syndrome.

5.4 The committee discussed the generalisability of data from the studies, which were identified in the clinical review, to the decision problem. It noted that estimates for sensitivity values were taken from all the studies in the review, which included colorectal cancer patients who were identified as being at high risk of Lynch syndrome and age-limited patient populations that would be expected to have a higher prevalence of Lynch syndrome. The committee heard from the external assessment group (EAG) that the incidence of MSI in sporadic colorectal cancer increases with age and that this may alter test accuracy values in different age groups. The committee concluded that although there were differences in the trial populations in identified studies and the population of people with colorectal cancer in the UK, the effect of this on test accuracy was likely to be minimal.

5.5 The committee considered the evidence available on the diagnostic accuracy of MSI and IHC testing for MMR proteins. It noted that no identified studies directly compared MSI and IHC testing. It heard from clinical experts that, in their experience, these tests are comparable in diagnostic accuracy. The committee noted that the tests appeared to be accurate enough for detecting MSI or abnormal expression of MMR proteins, but noted that these findings alone are not enough to diagnose Lynch syndrome without second-line tumour-based testing and subsequent genetic testing. Further it heard that external quality assurance programmes are

used to ensure the accuracy and consistency of testing between laboratories. The committee also heard that both tests are used in current practice in the NHS, and that the choice of test used is often determined by locally available services and expertise. The committee concluded that these tests are broadly comparable in accuracy.

5.6 The committee discussed the issue of unclassified variants, that is, when genetic testing identifies variations in the sequence of MMR genes which are of unknown clinical significance. This can affect whether results from the reference standard test are classified as positive or negative. The committee noted that relatively few studies identified in the clinical review had enough data to allow alternative analyses when unclassified variants were considered as positive reference standard results for Lynch syndrome. The clinical experts commented that in practice, unclassified variants are investigated further by asking for additional clinical information and testing before a diagnosis is given. The committee also heard that there are ongoing efforts to classify sequence variants in MMR genes and that the number of unclassified variants is therefore decreasing. The committee concluded that unclassified variants are unlikely to have a large effect on diagnosing Lynch syndrome in clinical practice.

Cost effectiveness

5.7 The committee considered the cost effectiveness of the different testing strategies to identify Lynch syndrome in people with colorectal cancer. It noted that 10 strategies had been modelled, each using different combinations of tumour-based tests and genetic testing (see table 3).

5.8 The committee discussed the assumptions about the effectiveness of aspirin as a risk-reducing strategy for people with Lynch

syndrome that were made in the economic model. It heard from the EAG that in the model, the effect of aspirin in reducing the risk of colorectal and endometrial cancer was assumed to occur instantaneously and last for 10 years, after which time the effect was assumed to stop instantaneously. However, the committee heard from the clinical experts that the Colorectal adenoma/carcinoma prevention programme 2 (CaPP2) trial of aspirin prophylaxis in Lynch syndrome reported that there is a lag time in the protective effect after starting therapy and that its effects can continue after people stop taking aspirin. The committee noted that the scenario analysis without the costs and effects of aspirin prophylaxis showed no substantial effect on overall results. The committee concluded that the effect of the assumptions about aspirin prophylaxis was likely to be small.

5.9 The committee discussed the effect estimates of colonoscopic surveillance used in the model. It noted that a study used to estimate the effectiveness of colonoscopic surveillance in people with Lynch syndrome in the model was about 15 years old and questioned whether this represents current practice in the NHS. The committee heard from the clinical experts that recent technological developments in this area and the introduction of standards by the Joint Advisory Group on Gastrointestinal Endoscopy have improved the effectiveness of colonoscopic surveillance. Data from cancer screening programmes have also shown that colonoscopic surveillance can lead to the detection of colorectal cancer at an earlier stage, which could improve patient outcomes. The committee also noted that the effectiveness of colonoscopic surveillance is likely to be influenced not only by the effectiveness of the test, but also by patient uptake and were reassured by the clinical experts that uptake of surveillance was high among people with Lynch syndrome. The committee concluded that colonoscopic surveillance is likely to reduce the risk

of cancer developing in people with Lynch syndrome, and that consequently the effect estimate used in the base-case analysis was appropriate.

5.10 The committee considered the results of the base-case analysis, which suggested that strategies that began with IHC for MMR proteins were more cost effective than those that began with MSI testing, and that overall, strategy 5 appeared to be the most cost effective. The committee discussed the extent to which the results of the model were driven by the sensitivity and specificity parameter values used in the model. It noted that in the base-case analysis, MSI testing was assumed to be both less sensitive and less specific than IHC testing. The committee considered that, given the perceived equivalence of MSI and IHC testing and the absence of direct comparative data, there was not enough evidence to conclude that testing strategies that begin with MSI testing are not cost effective compared with IHC testing for MMR proteins.

5.11 The committee discussed the role of *BRAF* V600E and *MLH1* promoter hypermethylation testing in the modelled strategies. It heard from the clinical experts that some tumours that test positive for MSI, or that have abnormal MLH1 protein expression, are sporadic colorectal cancers. Further, it heard that *BRAF* V600E and *MLH1* promoter hypermethylation testing, particularly in combination, can be used to identify sporadic colorectal cancers and so reduce the number of people who are referred for genetic testing for Lynch syndrome. In addition, the clinical experts advised that testing strategies that aim to decrease the number of false-positive diagnoses for Lynch syndrome reduce the number of people having unnecessary colonoscopic surveillance. The committee concluded that strategies 5 and 9, which include tests to

identify sporadic colorectal cancers, after the initial MSI or IHC testing, are likely to be the most cost-effective options.

5.12 The committee discussed the cost effectiveness of the testing strategies in different age groups. It noted that the age-restricted subgroup analysis had little effect on the overall conclusions, but that referral straight to genetic testing was unlikely to be cost effective in older age groups. The committee heard from the clinical experts that although the prevalence of Lynch syndrome is much higher in younger people with colorectal cancer, it can still be the cause of colorectal cancer in older people. It also heard that despite the lower prevalence of Lynch syndrome in older people, the greater number of colorectal cancer diagnoses in these age groups could mean that the absolute number of people who could benefit from a Lynch syndrome diagnosis may be similar to that in younger age groups. Therefore, the committee considered that there is no clinical reason to treat age groups differently. The committee concluded that all people, regardless of their age, with colorectal cancer should have tumour-based testing to assess the risk of Lynch syndrome.

5.13 The committee considered the joint effect of parameter uncertainty used in the model, and noted that this had not been explored in a probabilistic sensitivity analysis. It heard from the EAG that the univariate deterministic sensitivity analyses did not result in large changes to the incremental cost-effective ratios (ICERs) or the net health benefit values, and that it was unlikely that negative net health benefit values would be seen in a probabilistic sensitivity analysis. The committee considered that parameter uncertainty had been explored sufficiently, and that further analyses were unlikely to substantially change the overall results of the economic modelling. Therefore, the committee concluded that testing all people with colorectal cancer using strategies 5 (IHC plus *BRAF*

and *MLH1* promoter methylation) and 9 (MSI plus *BRAF* and *MLH1* promoter methylation) would be a cost-effective use of NHS resource.

Other considerations

5.14 The committee discussed the timing of testing for Lynch syndrome in people who have been diagnosed with colorectal cancer. It heard from the clinical experts that knowing a person's MMR gene status may be useful in determining treatment options for colorectal cancer; for example, to direct chemotherapy or surgical decisions. However, it noted that it is very unlikely that definitive genetic testing will be completed before treatment for colorectal cancer begins. The committee concluded that testing to assess the risk of Lynch syndrome should be started as soon as colorectal cancer is diagnosed, but should not delay the start of treatment.

5.15 The committee noted that Lynch syndrome is not the only inherited condition that increases the risk of colorectal cancer. It heard from the clinical experts that other inherited causes of colorectal cancer include familial adenomatous polyposis. The clinical experts also emphasised that it is important that these additional inherited conditions are considered if someone is found not to have Lynch syndrome but the clinician suspects that the person's family history suggests that a genetic cause is likely. The committee concluded that clinical judgement should be used to determine whether a referral to clinical genetics is appropriate when Lynch syndrome has been ruled out by tumour-based testing, but other genetic causes are suspected.

5.16 The committee considered ongoing developments in genetic testing technologies. It noted that in the future, broad-range genetic sequencing or specific cancer panels using next-generation sequencing technology may be considered for diagnosing Lynch

and other inherited colorectal cancer syndromes. The committee concluded that these advances may identify alternative and more rapid methods for diagnosing Lynch syndrome.

Research considerations

5.17 The committee discussed the value of developing research recommendations for tumour testing for Lynch syndrome. It considered that further research was unlikely to change its recommendations on molecular testing strategies for Lynch syndrome.

5.18 The committee heard that good communication between colorectal cancer multidisciplinary teams and genetics or pathology laboratories is important for implementing tumour-based testing for Lynch syndrome. The committee noted that similar systems are embedded in breast cancer care pathways, in which reflex testing for human epidermal growth factor receptor 2 (*HER2*) and *BRCA* are done as part of the first assessment. The committee therefore wished to encourage centres adopting Lynch syndrome testing strategies to audit and publish their clinical and diagnostic outcomes to ensure that assessment of Lynch syndrome is timely and appropriate.

5.19 The committee heard from the clinical experts that centres already offering tumour-based testing for Lynch syndrome often carry out both MSI and IHC testing on samples. The committee encouraged these centres to publish their previously generated comparative results.

6 Implementation

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

7 Review

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

Adrian Newland
Chair, diagnostics advisory committee
October 2016

8 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland

Chair, diagnostics advisory committee

Dr Mark Kroese

Vice Chair, diagnostics advisory committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst

Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Mr John Bagshaw

In-vitro Diagnostics Consultant

Dr Phil Chambers

Research Fellow, Leeds Institute of Cancer and Pathology, University of Leeds

Dr Sue Crawford

GP Principal, Chillington Health Centre

Professor Erika Denton

Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Dr James Gray

Consultant Microbiologist, Birmingham Children's Hospital

Mr John Hitchman

Lay member

Mr Patrick McGinley

Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells NHS Trust

Dr Michael Messenger

Deputy Director and Scientific Manager, National Institute for Health Research (NIHR) Diagnostic Evidence Co-operative, Leeds

Mrs Alexandria Moseley

Lay member

Dr Peter Naylor

GP, Chair Wirral Health Commissioning Consortia

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Dr Simon Richards

VP Regulatory Affairs, EME, Alere Inc

Dr Deirdre Ryan

Consultant Cellular Pathologist, Royal London Hospital

Professor Mark Sculpher

Professor of Health Economics, Centre for Health Economics, University of York

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation Trust

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, St Thomas Hospital

Specialist committee members

Dr Andrew Latchford

Consultant Gastroenterologist, St Mark's Hospital

Miss Demetra Georgiou

Genetic counsellor, St Mark's Hospital

Dr Fiona Lalloo

Consultant in Clinical Genetics and Clinical Director of Manchester Centre for Genomic Medicine, Manchester Centre for Genomic Medicine/St Mary's Hospital

Dr Kevin Monahan

Consultant Gastroenterologist, Imperial College London

Professor Mohammed Ilyas

Professor of Pathology (Honorary Consultant) and Head of Division, Queens Medical Centre, University of Nottingham

Dr Pauline Skarrott

Lay specialist committee member

Dr Robert Glynne-Jones

Consultant Clinical Oncologist, Mount Vernon Hospital

Dr Yvonne Wallis

Consultant Clinical Scientist, West Midlands Regional Genetics Laboratory

NICE project team

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

Brendan Mullaney

Topic Lead (until February 2016)

Thomas Walker

Topic Lead (from March 2016)

Sarah Byron

Technical Adviser (until March 2016)

Rebecca Albrow

Technical Adviser (from April 2016)

Robert Fernley

Project Manager

9 Sources of evidence considered by the committee

The diagnostics assessment report was prepared by Peninsula Technology Assessment Group (PenTAG).

- Snowsill T, Coelho H, Huxley N et al. Molecular testing for Lynch syndrome in people with colorectal cancer. August 2016.

Registered stakeholders

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

Manufacturers of technologies included in the final scope:

- None

Other commercial organisations:

- Promega UK Ltd

Professional groups and patient/carer groups:

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

Research groups:

- None

Associated guideline groups:

- None

Others:

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