NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Molecular testing for Lynch syndrome in people with colorectal cancer

Final scope

February 2016

1 Introduction

The Medical Technologies Advisory Committee identified PCR-based microsatellite instability testing to help diagnose Lynch syndrome in people with colorectal cancer as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. This final scope was informed by discussions at the scoping workshop held on 14 Dec 2015 and the assessment subgroup meeting held on 11 Jan 2016.

A glossary of terms and a list of abbreviations are provided in appendices B and C.

2 Description of the technology

This section describes the properties of the diagnostic technologies based on information provided to NICE by clinical experts. NICE has not carried out an independent evaluation of these descriptions.

2.1 Purpose of the medical technology

Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer [HNPCC]) is an inherited genetic condition that is associated with an increased risk of colorectal cancer and other cancers. It is most commonly caused by mutations in mismatch repair genes. These genes are involved in recognizing and repairing errors that occur when DNA is copied during cell division (DNA replication). Mutations in these genes can prevent the proper repair of DNA errors and as the cells continue to divide, these DNA mutations are replicated which can lead to uncontrolled cell growth and cancer. Microsatellites are repetitive pieces of DNA that are prone to errors during replication. In tumours of people with mutations in mismatch repair genes,

errors build up causing the microsatellite sequences to be of different sizes. This is called microsatellite instability. The majority of colorectal tumours from individuals with Lynch syndrome genes have 2 distinguishing characteristics:

- Microsatellite instability - expansion or reduction in the length of repetitive DNA sequences (microsatellites) in tumour DNA compared to normal DNA
- Loss of expression or reduced levels of the mismatch repair proteins in the tumour as compared to normal tissue.

Currently, microsatellite instability testing is only done in people considered to be at high risk of having Lynch syndrome, that is, people with a family history of cancer and who are younger than 50 years old at the onset of cancer. Expanding testing to all people with colorectal cancer may increase the detection of Lynch Syndrome in the colorectal cancer population and identify families who could benefit from cascade genetic testing. 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.

2.2 Product properties

2.2.1 Microsatellite instability (MSI) testing

Microsatellite instability (MSI) testing involves PCR (polymerase chain reaction) -based analysis of tissue samples from colorectal cancer tumours to detect a standardised panel of DNA markers. First, the tumour tissue sample is examined by a histopathologist, who distinguishes between the cancerous and non-cancerous cells, and then the tumour tissue is micro-dissected before DNA is extracted.

In the UK, PCR based microsatellite instability testing is carried out by UKAS (United Kingdom Accreditation Service) accredited regional genetics laboratories using in-house tests which are internally validated within the laboratories. One in-house test uses the MSI Analysis System version 1.2 kit from Promega (regulatory approval for research-use only). It includes fluorescently labelled primers for PCR amplification of 7 microsatellite markers, including 5 mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24) and 2 highly polymorphic pentanucleotide repeat markers (Penta C and Penta D). The amplified microsatellite markers are detected using a genetic analyser which displays the size of the microsatellites markers detected. If the size of the microsatellite markers in

the tumour tissue DNA is different to that seen in non-tumour tissue DNA, it shows there is microsatellite instability in the tumour tissue DNA. Tumour samples with microsatellite marker sizes identical to those seen in non-tumour tissue DNA are considered MSI-Stable. Because sporadic (not inherited) colorectal cancer may also show microsatellite instability, further tests may be used to confirm a Lynch syndrome diagnosis.

2.2.2 Immunohistochemistry of mismatch repair proteins (Mismatch repair (MMR) testing)

Mismatch repair (MMR) testing involves using immunohistochemistry (IHC) to detect the presence or absence of mismatch repair (MMR) proteins in colorectal cancer tumours. Mutations in mismatch repair genes can prevent the corresponding proteins being produced by the cells in the tumour tissue so the absence of an MMR protein can suggest a Lynch syndrome diagnosis. The 4 MMR proteins detected by IHC are MSH6, MSH2, MLH1, and PMS2, and these all show nuclear staining and are present in all human tissues. Four immunostains are performed on the colorectal cancer tumour tissue using CE marked monoclonal antibodies for each of the proteins. If staining occurs for all four proteins then this shows that all the MMR proteins are present in the tumour tissue; the tumour is considered mismatch repair proficient. If there is a loss of staining for one or more of the mismatch repair proteins then the tumour is considered mismatch repair deficient. Because sporadic (not inherited) colorectal cancer may also show loss of staining on immunohistochemistry, further tests may be used to confirm a Lynch syndrome diagnosis. Occasionally, some mutations in mismatch repair genes may not lead to a loss of protein expression; however, if MSI testing showed microsatellite instability, further tests for Lynch syndrome are likely to be carried out.

2.3 Further tests to confirm a Lynch syndrome diagnosis

There is considerable local variation in the steps for further testing for Lynch syndrome. Testing strategies include testing that aims to further discriminate between Lynch syndrome tumours and sporadic tumours, and genetic testing that aims to definitively diagnose Lynch syndrome.

2.3.1 Discriminating between Lynch syndrome tumours and sporadic tumours

Microsatellite instability and loss of mismatch repair protein expression in colorectal cancer tumours can occur because of Lynch syndrome but also, sometimes these changes can occur in sporadic colorectal tumours (not inherited). This occurs in around 10-15% of sporadic colorectal cancers.

To identify sporadic changes, tumour samples are tested for the BRAF V600E mutation and MLH1 hypermethylation (switching off of MLH1 expression). These changes are rarely seen in tumours from people with Lynch syndrome so tumour samples that are mutant BRAF V600E or have a methylated MLH1 promoter are likely to be sporadic and no further testing for Lynch syndrome is needed.

2.3.1.1 BRAF V600E testing

Pyrosequence analysis or Sanger sequencing analysis is used to test for the BRAF V600E gene mutation in DNA extracted from the tumour tissue. An antibody specific for the BRAF V600E mutant protein (VE1), allowing direct immunohistochemical testing of a tumour section is also now available. BRAF V600E mutation-positive tumour samples are considered to be from sporadic tumours and receive no further testing. Samples that are wild type BRAF get comprehensive genetic testing.

2.3.1.2 MLH1 promoter hypermethylation testing

MLPA (multiplex ligation dependent probe amplification) or bi-sulphate conversion and pyrosequencing analysis can be used directly to test for MLH1 promoter methylation (switching off of MLH1 expression) in the DNA extracted from the tumour tissue.

Hypermethylated samples (switched off MLH1) are considered to be from sporadic tumours and receive no further testing. Unmethylated samples (switched on MLH1) get comprehensive genetic testing.

2.3.2 Comprehensive genetic analysis - sequencing and multiplex ligation-dependent probe amplification (MLPA)

Comprehensive genetic analysis is considered to be the most complete genetic analysis generally available for Lynch Syndrome within a diagnostic setting and is expected to detect almost all known Lynch syndrome causing mutations. This involves sequencing and MLPA of the mismatch repair genes; MLH, MSH2 MSH6 and PMS2 and also deletions of the EPCAM1 gene. Sequencing detects point mutations and small insertions and deletions in DNA. MLPA detects larger deletions and duplications DNA.

2.4 Potential testing strategies

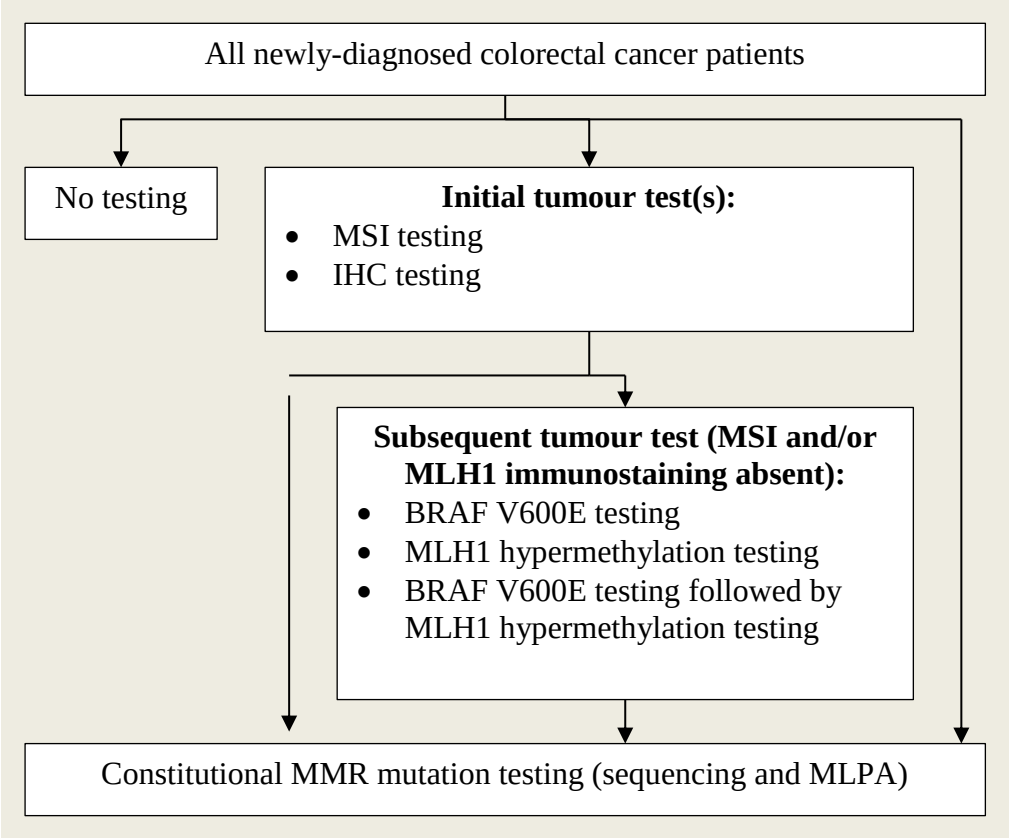

Figure 1. Simplified flow diagram of Lynch syndrome testing strategies

Figure 1 shows simplified flow diagram of possible Lynch syndrome testing strategies. At each stage it is assumed that samples are abnormal and proceed to the next stage of testing. If samples test normal at any stage it is assumed that the sample is more likely to be from a sporadic colorectal tumour and no further testing occurs.

The following are potential genetic testing strategies for diagnosing Lynch syndrome:

1. MSI testing followed by
    a. Comprehensive genetic testing (sequencing and MLPA) if microsatellite instability detected
2. MSI testing, followed by
    a. BRAF **or** MLH1 promoter hypermethylation testing if microsatellite instability detected, followed by:
    b. Comprehensive genetic testing (sequencing and MLPA) for wild type BRAF or unmethylated MLH1 promoter.
3. MSI testing, followed by

   a. BRAF **and** MLH1 promoter hypermethylation testing if microsatellite instability detected, followed by
   b. Comprehensive genetic testing (sequencing and MLPA) for wild type BRAF or unmethylated MLH1 promoter.
4. IHC MMR testing followed by
   a. Comprehensive genetic testing, if MMR deficient
5. IHC MMR testing, followed by
   a. BRAF V600E **or** MLH1 promoter hypermethylation testing if MLH1 deficient.
   b. Comprehensive genetic testing (sequencing and MLPA) is done for any other (not MLH1) deficient MMR result or if wild type BRAF or unmethylated MLH1 promoter.
6. IHC MMR testing, followed by
   a. BRAF V600E and MLH1 promoter hypermethylation testing if MLH1 deficient. Comprehensive genetic testing (sequencing and MLPA) is done for any other (not MLH1) deficient IHC result or if wildtype BRAF or unmethylated MLH1 promoter.
7. Comprehensive genetic testing (sequencing and MLPA).

3 Description of the comparator

The comparator in this assessment is no testing.

4 Target conditions

4.1 Lynch syndrome

Lynch syndrome is an autosomal dominant inherited genetic condition that is associated with an increased risk of colorectal cancer. Lynch Syndrome is also associated with an increased risk of other cancers such as ovarian, endometrial, stomach and brain cancers. People with Lynch syndrome have an estimated 20-80% risk of developing colorectal cancer in their lifetime, compared with an average lifetime risk of 6-7%.

It is estimated that Lynch syndrome accounts for 2-3% of all colorectal cancers. There were 33,676 new cases of colorectal cancer diagnosed in England in 2013, 18,778 males and 14,898 females. One patient group

estimates that there are approximately 160,000 people with Lynch syndrome in England and only 5000 are aware of it. In 2010, there were 7,170 male deaths from bowel cancer and 5,993 female deaths in England. These represent a rate of 20.9 per 100,000 (male), 12.8 per 100,000 (female) and 16.4 per 100,000 overall. Five-year survival rates have more than doubled over the period of 40 years. Around 57% of people diagnosed with bowel cancer are now expected to survive for at least 10 years and survival rates are as high as 90% if the cancer is detected at an early stage.

Lynch syndrome is cause by mutations in the mismatch repair genes (MLH1, MSH2, MSH6 and PMS2). These genes are involved in recognising and repairing errors that occur when DNA is copied during cell division (DNA replication). Mutations in these genes can prevent the proper repair of DNA errors and as the cells continue to divide, DNA mutations accumulate which can lead to uncontrolled cell growth and cancer. Lynch syndrome is the most common form of hereditary colorectal cancer and accounts for approximately 1-3% of all colorectal cancer cases. Colorectal cancer often presents at an earlier age (mean age of diagnosis is 44 years old) in people with Lynch syndrome.

As Lynch syndrome is a hereditary condition, identification of family members carrying a gene defect is desirable so that colonoscopic surveillance can be offered to allow earlier diagnosis of colorectal cancer. Occasionally, prophylactic surgery, such as removal of parts of the large bowel, may be offered to further reduce the risk of cancer. To identify family members who carry the gene defect, genetic testing must first occur in the family member with colorectal cancer.

There is evidence to suggest that the prognosis is better in colorectal cancer in people with Lynch syndrome than in people with sporadic colorectal cancer. It has also been suggested that people with sporadic colorectal cancer who have tumours with microsatellite instability have a better prognosis than people with sporadic colorectal cancer who have MSI-stable tumours. People with tumours with microsatellite instability may not respond to 5-fluorouracil-based chemotherapy; however the majority of the studies showing this have been in people with sporadic colorectal cancer. Lynch Syndrome tumours are also less likely to metastasize than non-Lynch Syndrome tumours despite the presence of multiple colorectal tumours. Surveillance is very important for people with Lynch syndrome to ensure colorectal cancers are caught early. If a person has a parent with Lynch syndrome, they have a 50% chance of also inheriting Lynch syndrome.

4.2 Diagnostic and care pathway

The diagnosis and management of colorectal cancer is described in several guidelines:

- NICE Clinical Guideline 131: Colorectal cancer: The diagnosis and management of colorectal cancer (November 2011)
- NICE Clinical Guideline 131: Suspected cancer: recognition and referral (June 2015)
- NICE Quality Standard 20: Colorectal cancer (August 2012)

There is currently no NICE guidance on the diagnosis and management of Lynch Syndrome, however the diagnosis and management of Lynch Syndrome is described in several national and international guidelines:

- British Society of Gastroenterology: Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (2010)
- European Guidelines: Revised guidelines for the clinical management of Lynch syndrome (HNPCC). (2013)
- Bethesda Guidelines: Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability (2004)
- Amsterdam II criteria: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. (1999)

4.3 Diagnosing Lynch syndrome

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

The British Society of Gastroenterology: Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (2010) recommends that people with a lifetime risk of between 10-100% of developing colorectal cancer based on family history or clinical symptoms are

referred to a regional genetics centre for genetic counselling and appropriate mutation analysis.

The Amsterdam criteria and Revised Bethesda Guidelines are most commonly used in referring people for Lynch syndrome testing. The Amsterdam criteria were developed to identify Lynch syndrome for research studies but are now used in clinical settings. The Bethesda guidelines were developed to identify patients with colorectal cancer who should get testing for Lynch syndrome. Both guidelines use criteria mainly based on family cancer history and age at onset.

According to the Amsterdam criteria, people that fulfil any of the following criteria should be offered further testing for Lynch syndrome:

- 3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis);
- 2 or more successive generations affected;
- 1 or more relatives diagnosed before the age of 50 years;
- 1 should be a first-degree relative of the other two;
- Familial adenomatous polyposis should be excluded in cases of colorectal carcinoma;
- Tumours should be verified by pathologic examination

The Revised Bethesda Guidelines state that tumours from people should be tested for microsatellite instability in the following situations:

- Colorectal cancer diagnosed in a patient who is less than 50 years old;
- Presence of synchronous (at the same time) or metachronous (at another time i.e.- a re-occurrence of) colorectal cancer or other Lynch syndrome-associated tumours, regardless of age;
- Colorectal cancer with high microsatellite instability histology diagnosed in a patient less than 60 years old;
- Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch syndrome-associated tumour, with one of the cancers being diagnosed at less than 50 years of age;

- Colorectal cancer diagnosed in two or more first-degree or second-degree relatives with Lynch syndrome-associated tumours, regardless of age

It should be noted that all Amsterdam criteria must be met whereas only 1 of the Bethesda criteria need to be met. It is widely accepted that these methods are unlikely to be sensitive enough to detect all patients with Lynch syndrome because family history is not always reliable or available, and some people with Lynch syndrome may not meet all the Amsterdam criteria. This also means that the family of people with Lynch syndrome may also go undiagnosed and remain at high risk of colorectal cancer with no surveillance. There is currently no NICE guidance on the population to be tested or the testing strategy for Lynch syndrome and as a result there is considerable variation in clinical practice.

In 2009 the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Groups report "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 newly diagnosed patients with colorectal cancer, regardless of age or family history following a review of Lynch syndrome testing. Also the 2013 European Guidelines: Revised guidelines for the clinical management of Lynch syndrome (HNPCC), recommends systematic testing of all patients with colorectal cancer (or all individuals with colorectal cancer up to the age of 70) for loss of mismatch repair function by means of microsatellite testing of tumour DNA or immunohistochemistry of mismatch repair proteins. The Royal College of Pathologists (RCPath) colorectal cancer dataset for the reporting of bowel cancer, published in July 2014, lists mismatch repair immunohistochemistry as a core dataset item for patients under 50 years at time of diagnosis and suggests there is a strong evidence base for looking for mismatch repair defects in all bowel cancer tumours, but do not list it as a core dataset due to resource implications.

The Independent Cancer Taskforce recommended in the report Achieving world-class outcomes –A strategy for England 2015-2020 that all patients under the age of 50 receiving a bowel cancer diagnosis are offered a genetic test for Lynch Syndrome.

There is currently no NICE guidance on the population to be tested or the testing strategy for Lynch syndrome and as a result there is considerable variation in clinical practice. The results of 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:

- Among the trusts testing all patients for Lynch syndrome, a wide variety of approaches to testing were reported:
  - Reflex testing (all patients under 50)
  - Multidisciplinary Team (MDT) discussion followed by MMR IHC testing
  - MDT discussion, followed by genetics referral, then MMR IHC testing
  - MDT discussion, followed by GP referral, followed by genetics referral, then IHC testing
- Among the trusts testing all patients for Lynch syndrome, IHC was the initial test in the majority of cases, but microsatellite instability, BRAF mutation analysis and next generation sequencing were also reported.

The survey highlighted that there is variability in who is getting testing and that there are a number of differing possible testing strategies for diagnosing Lynch syndrome.

Cascade testing

In families with Lynch Syndrome first degree relatives of a Lynch syndrome mutation carrier have a 50% risk of inheriting the mutation. Therefore where the familial mutation has been identified, cascade testing should be offered to at risk relatives and is done by either Sanger sequencing or MLPA for the familial mutation identified in the proband. This should include at least the first and second and, when possible, third-degree biological relatives.

4.3.1 Management

Treatment of colorectal cancer in people with Lynch syndrome

In the NHS, colorectal cancer in Lynch Syndrome patients is generally treated as per NICE Clinical Guideline 131: Colorectal cancer: The diagnosis and management of colorectal cancer (November 2011).

The European Society for Medical Oncology guidelines,'Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up' are also used by clinicians in the NHS to guide treatment decisions. The guidelines state that "MSI/MMR may be useful to identify a small (10%– 15%) subset (those with microsatellite instability) of stage II colorectal cancer patients who are at a very low risk of recurrence and in whom the benefits of chemotherapy are very unlikely". These patients would not be given 5 fluorouracil based chemotherapy.

The 2013 European Guidelines: Revised guidelines for the clinical management of Lynch syndrome (HNPCC) suggest that because of the substantial risk of a second colorectal cancer after partial colectomy and similar quality of life after partial and subtotal colectomy, the option of subtotal colectomy including its advantages and disadvantages should be discussed with all Lynch syndrome patients with colorectal cancer, especially younger patients.

Management and surveillance of people who have Lynch syndrome

The 2013 European Guidelines: Revised guidelines for the clinical management of Lynch syndrome (HNPCC), recommends that people who have been identified as having a Lynch syndrome mutation take low dose aspirin as this has been shown to reduce the incidence of cancer in Lynch syndrome mutation carriers.

The 2013 European Guidelines: Revised guidelines for the clinical management of Lynch syndrome (HNPCC), recommend that people who have been identified as having a Lynch syndrome mutation have a colonoscopy every 1-2 years. The British Society of Gastroenterology: Guidelines for colorectal cancer screening and surveillance in moderate and

high risk groups (2010) recommend that people who have been identified as having a Lynch syndrome mutation are offered total colonic surveillance at least every 2 years from the age of 25. People from a family with Lynch syndrome who test negative for their family's Lynch syndrome mutation do not need increased colonoscopic surveillance. Additional screening and surveillance measures should be recommended due to the increased risk of extracolonic tumours, particularly gynecologic tumours like endometrial or ovarian cancer

4.4 Patient issues and preferences

There is considerable anxiety and distress associated with genetic testing for hereditary cancer syndromes. Being diagnosed with Lynch syndrome, or being at risk of it, can be very difficult to cope with. The knowledge of being at an increased risk of cancer but not knowing if cancer will develop can cause considerable anxiety. Parents of children with Lynch syndrome can feel guilty about passing on Lynch syndrome to their children. Many people have concerns about genetic testing, screening or whether to have risk-reducing surgery. Genetic counselling is very important for people with Lynch syndrome or who are at risk of having Lynch syndrome because it can help people understand whether genetic testing is appropriate or not. Genetic counselling helps explain what a positive or negative result means and what the implications are for the person and their extended family. It can also help people understand the importance of informing extended family about their risk of having Lynch syndrome and the benefits of being tested (www.macmillan.org, www.lynch-syndrome-uk.org, www.ihavelynchsyndrome.com/). Once people fully understand the implications of being diagnosed with Lynch syndrome for them and their family, the associated anxiety may substantially reduce.

The Hunter et al. (2015) study Universal Tumor Screening for Lynch Syndrome: Assessment of the Perspectives of Patients With Colorectal Cancer Regarding Benefits and Barriers" looked at patient issues and preferences in universal testing of tumours from people with colorectal cancer Lynch syndrome using MSI testing. It looked at the benefits and barriers to testing. The main findings of the study were:

- Most patients with CRC endorse the benefits of universal tumour screening for Lynch syndrome.
- Most patients reported minimal distress associated with tumour screening, and distress was not associated with age or stage of disease.
- Most patients were not concerned about the potential loss of health insurance.
- Most patients recognised the importance of sharing their tumour screening results with their health care providers.
- Health care providers and patients should be educated that a lack of family history of CRC does not rule out Lynch syndrome.
- Health care providers should educate female patients regarding the association between Lynch syndrome and endometrial cancer and facilitate appropriate clinical care.
- Health care providers and/or health plans should be prepared to provide information to patients regarding the potential costs of additional genetic counselling and testing associated with a positive tumour screen.

5 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
Intervention	1. MSI testing followed by a. Comprehensive genetic testing (sequencing and MLPA) if microsatellite instability detected 2. MSI testing, followed by a. BRAF **or** MLH1 promoter hypermethylation testing if microsatellite instability detected, followed by: b. Comprehensive genetic testing (sequencing

	and MLPA) for wild type BRAF or unmethylated MLH1 promoter. 3. MSI testing, followed by a. BRAF **and** MLH1 promoter hypermethylation testing if microsatellite instability detected, followed by b. Comprehensive genetic testing (sequencing and MLPA) for wild type BRAF or unmethylated MLH1 promoter. c. occurs regardless of IHC result. 4. IHC MMR testing followed by a. Comprehensive genetic testing, if MMR deficient 5. IHC MMR testing, followed by a. BRAF V600E **or** MLH1 promoter hypermethylation testing if MLH1 deficient. b. Comprehensive genetic testing (sequencing and MLPA) is done for any other (not MLH1) deficient MMR result or if wild type BRAF or unmethylated MLH1 promoter. 6. IHC MMR testing, followed by a. BRAF V600E and MLH1 promoter hypermethylation testing if MLH1 deficient. Comprehensive genetic testing (sequencing and MLPA) is done for any other (not MLH1) deficient IHC result or if wildtype BRAF or unmethylated MLH1 promoter. 7. 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.

6 Modelling approach

The aim and structure of the economic model will depend upon the final scope.

6.1 Existing models

Snowsil et. al. (2014), reported a National Institute for Health Research Health Technology Assessment Programme Systematic review and economic evaluation of diagnostic strategies for Lynch syndrome modelled 8 testing strategies for diagnosing Lynch syndrome in people with colorectal cancer less than 50 years of age. On the whole, strategies that identified Lynch syndrome were found to be cost-effective in comparison to no Lynch syndrome testing, with ICERs of less than £10,000 per QALY gained. When the age limit for proband testing was raised to 60 or 70 years, strategies became less cost effective versus no testing compared with the base case. At the age limit of 60 years, all ICERs compared with no testing remained below £20,000-per-QALY, but at age 70 years the ICER for one strategy was above £20,000-per-QALY.

7 Potential equality issues

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

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.

8 Potential implementation issues

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:

- It is vital that clinicians are accountable for patient results and aware of their responsibilities throughout the care pathway if implementation is to be successful.
- Ensuring sufficient resource is available to conduct the screens is pertinent to avoid unnecessary delays.
- If MSI screening 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.
- Quality assurance is vital to ensure tests are conducted and interpreted correctly.

Appendix A Glossary of terms

Bi-sulphate treatment

Converts unmethylated cytosine to uracil

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

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 region it can supress gene expression.

Mutant

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

Proband

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

Unmethylated

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

Wild type

The normal or most common DNA sequence in an organism

Appendix B Abbreviations

CPA Clinical Pathology Accreditation

EQA external quality assurance

MMR Mismatch repair

MSI Microsatellite instability

NCI National Cancer Institute

PCR polymerase chain reaction

Appendix C Related guidance

NICE guidance

Colorectal cancer (2011) NICE guideline (CG131)

Improving outcomes in colorectal cancer (2004) NICE guideline (CSGCC)

Suspected cancer (2015) NICE guideline (NG12)

All other NICE guidance and advice products

Colorectal cancer (2012) NICE quality standard 20

Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (2014) NICE technology appraisal 307

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (2007) NICE technology appraisal

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (2010) NICE technology appraisal 212

Cetuximab for the first-line treatment of metastatic colorectal cancer (2009) NICE technology appraisal 176

Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (2012) NICE technology appraisal 242

Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (2003) NICE technology appraisal 61

Laparoscopic surgery for colorectal cancer (2006) NICE technology appraisal 105

NICE pathways

Colorectal Cancer (2015) NICE pathway

NICE guidance underdevelopment

Referral for suspected cancer. NICE quality standard. Publication expected May 2016

Colon cancer (adjuvant) – irinotecan. NICE technology appraisal. Publication date to be confirmed.

Colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line) ID794. NICE technology appraisal. Publication expected April 2016

NICE pathways

The genetic testing for Lynch syndrome guidance will be included in several NICE pathways, for example: colorectal cancer

In some of the pathways, it may be appropriate to include the full recommendations of the guidance, in others it will only be necessary to give a link to the guidance.

Relevant guidance from other organisations

British Society of Gastroenterology: Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (2010)

Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96:261–268.

Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology. 1999;116:1453–1456.

Appendix D References

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Hughes et al (2004),Colon Cancer Screening Practices Following Genetic Testing for Hereditary Nonpolyposis Colon Cancer (HNPCC) Mutations

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Patient UK: Screening for the early detection of colorectal cancer

Cancer Research UK (2015) Lifetime risk of cancer

Public Health England (2015), National Cancer Intelligence Network Cancer and equality groups: key metrics 2015 report

National Bowel Screening Programme, Bowel Cancer