NICE National Institute for Health and Care Excellence

Adoption support resource – insights from the NHS

Implementation support

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1 Introduction

This resource has been developed to provide practical information and advice on NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer (CRC).

NICE's adoption team worked with contributors who use molecular testing strategies in NHS trusts to gather learning and experiences.

The purpose of this resource is to support the NHS in adopting and evaluating the impact of adopting these testing strategies as part of a specialist service. It is aimed at providers and commissioners of colorectal cancer services, clinical genetics services and laboratories responsible for doing the molecular tests. It is complementary to the guidance and was not considered by the diagnostics advisory committee when developing its recommendations.

Lynch syndrome is an inherited predisposition to some cancers, including CRC. People with Lynch syndrome also have an increased risk of other cancers, such as endometrial, ovarian, stomach, small intestine, hepatobiliary tract, urinary tract, brain and skin cancer. This is caused by mutations in mismatch repair (MMR) genes which normally correct mistakes when DNA is being replicated. In a person with Lynch syndrome, these mismatch errors happen more often which may result in the development of cancer.

Offering testing of colorectal tumours after surgical resection or biopsy using either microsatellite instability (MSI) or immunohistochemistry (IHC) testing for MMR deficiency can be used to screen for people in whom the cancer may have occurred because of Lynch syndrome. MSI testing is usually carried out in accredited specialist clinical laboratories. The tissue specimens are first assessed by a histopathologist or a molecular pathologist (within molecular or molecular genetic laboratories, or a local histopathology laboratory), who marks out the tumour areas in the tissue and determines the neoplastic cell content. IHC testing can be done in local histopathology laboratories. Further sequential testing for those tumours with a positive MSI result or an abnormal IHC result is needed to make a Lynch syndrome diagnosis. This is usually done in specialist clinical laboratories, although some of these further tests may take place in local laboratories. Further testing includes *BRAF* V600E and *MLH1* promoter hypermethylation (both carried out on tumour tissue) but the final diagnosis, if a negative result is received for these tests, can only be confirmed after genetic testing of germline DNA (carried out on a blood

sample).

Benefits

The benefits of using molecular testing strategies as reported by the NHS staff involved in producing this resource may include:

- Earlier identification of people with Lynch syndrome.
- A more consistent patient pathway to identify all people with CRC who also have Lynch syndrome.
- Reassurance for patients and relatives when testing rules out a diagnosis of Lynch syndrome.
- Prevention or early detection of some of the other types of cancers which people with Lynch syndrome are at higher risk of, through earlier surveillance and preventive treatment.
- Cascade genetic testing of relatives after a positive diagnosis of Lynch syndrome. Identifying other family members with Lynch syndrome will prompt earlier colonoscopy for detecting CRC and other cancer screening, as well as preventive treatment with aspirin. Both of these interventions significantly reduce the risk of developing CRC.

2 Summary of NICE recommendations

NICE recommends that all colorectal cancers be tested, when first diagnosed. This can be done using immunohistochemistry (IHC) for mismatch repair proteins or microsatellite instability (MSI) testing to identify those with deficient DNA mismatch repair, and to guide the offer of further sequential testing for Lynch syndrome. The guidance also recommends not waiting for the results before starting treatment.

Shared decision making puts people at the centre of decisions about their own treatment and care by exploring care or treatment options and their risks and benefits, discussing choices available and reaching a decision about care or treatment, together with their healthcare professional.

In line with these principles, healthcare professionals should ensure that people are informed of the possible implications of test results both for themselves and their relatives. This may be achieved by trained healthcare professionals having sensitive discussions with each person about genetic testing and the risks and benefits of such testing. Relevant support and information should be available to support this.

Laboratories doing IHC or MSI testing, should take part in a recognised external quality assurance programme.

Please see the NICE testing strategies flowchart.

3 Current practice

Testing strategies for Lynch syndrome in people with colorectal cancer (CRC) varies widely (estimated 50% of centres currently providing tests) and some trusts still need to establish a strategy within their service. Contributors to this resource reported that the criteria commonly used to identify people to test include a diagnosis of CRC in people aged under 50 years and a strong family or personal history according to the Bethesda and Amsterdam criteria. Reasons for using such criteria, as stated by contributors to this resource, include alignment with the Royal College of Pathology dataset for CRC histopathology reports, prevention of unnecessary testing and the likelihood of having Lynch syndrome.

Four out of the 5 trusts that helped to develop this document use immunohistochemistry (IHC) testing as the first test to identify tumours with mismatch repair (MMR) deficiency. This can be carried out in local histopathology laboratories. The other trust uses microsatellite instability (MSI) testing as the first test. This test is usually carried out in accredited specialist clinical laboratories.

If the IHC result is abnormal or the MSI result is positive referral to clinical genetics may be needed. Further sequential tests are likely to be requested by clinical genetics, and done at specialist clinical laboratories. Systems must be in place to request sequential tests, transport samples (either tumour tissue for *BRAF* and *MLH1* hypermethylation tests or blood for genetic testing of germline DNA), and to follow-up results. Because of the challenges in setting up robust systems, even those trusts that have a testing strategy do not consistently refer people who need further sequential tests to clinical genetics services to either confirm or rule out Lynch syndrome.

4 Tips for adopting molecular testing strategies

- Ensure the colorectal team, and local histopathology and specialist clinical laboratory staff have the appropriate level of awareness training and education. This is needed to ensure that staff:
  - Request the correct tests for all people who should be tested (either automatically, or according to a protocol).
  - Are able to correctly carry out and interpret the results of the genetic tests.
  - Prepare tumour samples appropriately; see developing local documentation for examples of a letter to a histopathology lab requesting tumour samples for *MLH1* hypermethylation testing and a form describing the material needed for immunohistochemistry testing.
  - Refer patients to clinical genetics services correctly; see developing local documentation for an example letter to support referral to clinical genetics.
  - Are able to provide support and information for people regardless of the testing outcome.
- Communication between colorectal teams, clinical genetics services and patients is important. Attendance at colorectal multidisciplinary team (MDT) meetings is 1 method to support this as is the development of resources such as referral guides, flow charts and patient information sheets (see developing local documentation).
- Ensure laboratory protocols are in place which lead to automatic mismatch repair (MMR) testing and inclusion of results within standard histopathology reports. This protocol should also cover further sequential testing when indicated. Development of such a protocol should involve representatives from the colorectal team, histopathology laboratory, specialist clinical laboratory and clinical genetics to ensure systems are in place for transporting and tracking samples or results and that it is clear who is accountable and responsible for following up results.

5 Insights from the NHS

NICE worked with 5 NHS organisations to share their learning and experiences of adopting molecular testing strategies. One of these currently tests all colorectal cancer (CRC) tumours for mismatch repair (MMR) deficiency and their learning is presented as an example of current practice. It is not presented as best practice but as a real-life example of how this site has managed the introduction of testing. The other 4 organisations are using a testing strategy but are not currently testing all CRCs. Their learning is presented in section 6.

Oxford University Hospitals NHS Foundation Trust

The Oxford Department of Clinical Genetics and Genomics has 14 full- or part-time genetic counsellors who see people with, or at risk of, hereditary forms of cancer as well as people with, or at risk of, other genetic conditions. There are also 2.2 full-time equivalent cancer genetics consultants.

In 2014, the trust started to routinely test all CRCs managed surgically using immunohistochemistry (IHC) to identify mismatch repair deficiency. This decision was made by the Oxford Mismatch Repair group to avoid unnecessary delays and the need for pathological reassessment because most tumours were already being tested. Membership of the group includes the local genetics, oncology, gastroenterology and laboratory teams. This new approach was named the 'MMR management protocol'.

Before the new protocol was adopted, CRCs from people under 50 years were automatically being tested using MMR testing, in line with the Royal College of Pathology dataset for CRC histopathology reports. Approval for this test request was gained at the colorectal multidisciplinary team meeting (MDT). CRCs in people over 50 years were only tested if requested by the oncology service.

The trust carried out 256 primary CRC resections in the 12 months before implementing the new protocol:

- 130 people were aged 70 or under, of these 113 (87%) were tested using IHC.

- 126 people were over 70 and although testing for this group was only being offered on a case-by-case basis, 120 (81%) had IHC testing requested by the MDT.

IHC testing is carried out within the hospital's histopathology laboratory, at the time of (or very shortly after) surgery. This means that results are reported to the oncology team within 10 days of surgery. This has saved time and money because tumour sample blocks no longer need to be retrieved from storage for retrospective testing.

If the IHC test result suggests loss of any of the MMR proteins (abnormal result), the pathology report recommends that the patient is referred to the clinical genetics services for review and the tumour sample and copy of the IHC report is sent to the molecular genetics laboratory. During the clinical genetics appointment, the person's family history is explored and the appropriate further molecular genetics tests are requested.

In the 12 months before adoption of the MMR management protocol, only 30% of people whose CRC had MMR deficiency were referred to clinical genetics services. After adoption of the protocol, all the people aged under 70 with CRCs identified as having MMR deficiency have been either referred directly to clinical genetics services, or informed of the need to consider this when their ongoing treatment is complete. The genetics team has spent 2 years working with pathology staff to ensure this change is implemented. Despite this, referrals to clinical genetics services for people over 70 still varies and this is dependent upon clinical judgement. The management protocol is supported by an information pack that includes a patient information resource, pro forma referral letter, guidance flow chart and referral criteria (see developing local documentation).

In Oxford, a strong collaboration between the cancer MDT, histopathology, genetics laboratories, and clinical genetics departments was necessary to develop and optimise the pathways for these patients. Implementation of plans for the centralisation of molecular diagnostic laboratory services in England as outlined in Building On Our Inheritance: Genomic Technology in Healthcare needs to ensure that these close relationships remain.

6 How to implement this guidance

NHS contributors to this resource have worked with NICE to develop practical suggestions for how to consider implementing NICE guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer. Local organisations will need to assess their applicability taking into consideration the time, resources and costs of an implementation programme in the context of their current practice.

Project management

Molecular testing strategies can be best adopted using a project management approach. NICE has produced the into practice guide which includes a section on what organisations need to have in place to support the implementation of NICE guidance in this way.

Project team

The first step is to form a local project team who will work together to support implementation and manage any changes in practice.

Individual NHS organisations will determine the membership of this team. Consider the following membership of the team:

- Clinical champion(s): could be a clinician within the colorectal MDT, for example, a colorectal surgeon or gastroenterologist. They should have the relevant knowledge and understanding to be able to drive the project, answer any clinical queries and champion the project at a senior level. It may be helpful to have a clinical geneticist to support this role.
- Project manager: could be someone in a clinical or managerial role who will be responsible for the day-to-day running of the project, co-ordinating the project team and ensuring the project is running as planned. Examples of roles that may act as project managers include pathologists and clinical scientists. Depending on current service provision, a dedicated project manager may be needed to support adoption of this guidance.

- Management sponsor: will be able to help assess the financial viability of the project, drive the formulation of a business case and help to show the benefits achieved. This member of the team may be based in a laboratory or clinical genetics service because this is where the costs will be incurred.
- Genetic counsellors, colorectal nurses, histopathology laboratory staff and molecular genetics laboratory staff: will be valuable members of the project team because they will be providing the service.
- Clinical audit facilitator: to help set up mechanisms to ensure that every patient is tested and that their test results are discussed as well as collecting and analysing local data related to the project metrics and audit needs.

Care pathway development

Care pathway stages that may need to be considered or developed are as follows:

- Attendance at colorectal cancer MDT meetings or liaising with people who attend them. Representatives from the local pathology laboratory, specialist clinical laboratory and clinical genetics services may organise regular communication with a lead member of the MDT. Contributors advised that attendance at weekly MDT meetings was helpful at the start of the project. After this, electronic communication and attendance at the annual MDT meeting is enough.
- Automatic MMR testing of all CRCs (if service capacity allows) using either immunohistochemistry (IHC) or microsatellite instability (MSI) and inclusion of this in the standard pathology report requested by oncology. If service capacity will not allow for MMR testing of all CRCs, a decision may need to be made on those to prioritise in the early stages of implementing a strategy (phased introduction). If a phased introduction to testing is deemed appropriate locally, plans should be in place to expand this to testing all CRCs in the future.
- Identifying when people with abnormal results for MMR testing should be referred to a clinical genetics service and establishing robust referral mechanisms for this. The MDT may be best placed to make this referral after collation of all test results.
- The point at which to get patient consent for genetic testing and for sharing information with relatives.

- Providing further sequential testing within a regional molecular genetics laboratory or other specialist service depending on results.
- Feedback of test results to all services involved and to patients.

Measuring success

In order to show the benefits of adopting molecular testing strategies it is important to take measurements before, during and after implementation. Some of these measures will not be routinely collected and trusts should consider a data-collection methodology that is appropriate to the service. Inclusion within local and regional audit linked to peer review may help with this. Suggested measures from the sites involved in developing this resource are:

- Proportion of people with CRCs having MMR testing carried out.
- Proportion of people with CRCs that have an MMR deficient result. If this is over 40%, there may be an issue with laboratories reporting false positives.
- Number of further sequential tests that are carried out in people with a positive MSI or an abnormal IHC result.
- Proportion of patients that have an MMR deficient result that are referred to clinical genetics services either at this point or following further sequential tests (depending on point of referral in the local patient pathway).
- Proportion of patients who attend their appointment when referred to clinical genetics services.
- Number of people with CRC who are diagnosed as having Lynch syndrome.
- Number of relatives tested for Lynch syndrome.
- Longer term: number of surveillance detected cancers in patients and relatives diagnosed with Lynch syndrome.

Overcoming implementation challenges

This section shows the challenges which contributors to this resource reported may be experienced by NHS sites when implementing molecular testing strategies.

Capacity

The volume of requests to pathology and specialist clinical laboratories for tests will increase and more clinical genetics appointments will be needed.

- Prepare a business case including full cost considerations of the increased capacity needed for testing all CRCs compared with the current service model. Depending on the current service model, a phased introduction may need to be considered possibly focussing on the highest risk in the first instance. The infrastructure of the service should be designed to ensure equity of access to consistent and quality assured testing strategies. Consolidation of service models may help to achieve this and ensure smaller organisations are able to offer testing to patients.

Quality assurance

It is vital to ensure the tests are done and interpreted correctly.

- Staff in laboratories doing MSI or IHC testing should have training on how to carry out and interpret results and should take part in a recognised external quality assurance programme.

Governance

Testing involves multiple steps that may occur at different sites. It is crucial that there is clear ownership of testing and results at each stage.

- Establish champions (named individuals with a specialist interest and up-to-date knowledge) in each department and within each colorectal cancer MDT to whom questions and requests can be addressed.
- When testing is carried out in more than 1 laboratory, arrange to contact the colorectal MDT lead electronically or set up a service delivery group to discuss collated test results. This can help with decisions on further sequential testing and referral.

- Ensure that the correct samples are sent from histopathology laboratories to specialist clinical laboratories for testing. This could be done by clarifying what is needed on export request forms and by raising awareness in histopathology laboratories about the tissues and formats needed to carry out relevant tests (see developing local documentation and Central Manchester University Hospitals NHS Foundation Trust's website for example letters to pathology detailing how tumour samples need to be prepared and labelled for testing).

Raising awareness

People with Lynch syndrome may not be identified because of a lack of awareness among healthcare professionals both of the condition and the referral mechanism to clinical genetics services. To raise awareness:

- Clinical genetics specialists may want to liaise with the colorectal cancer MDT lead within their local services.
- Develop a clear flow diagram that shows what testing and onward referral is needed and signposts to whom that referral should go to at local level.
- Identify clinical champion(s) for education who can offer training and awareness-raising initiatives, particularly to colorectal surgeons and specialist cancer nurses to increase their identification of people who may have Lynch syndrome.
- Use the resources to support awareness raising developed by Lynch Syndrome UK.

Laboratory staff training

- Laboratory staff may need training on how to carry out and interpret the tests covered by this guidance. The sites that have contributed to this resource reported that colleagues with experience of doing these tests may be able to help with this.
- Consider providing training for pathologists as part of a molecular pathology attachment done during their training period, which could include correct preparation and marking of tumour samples.

Information for patients

People need to make informed decisions about both testing and further screening and

treatment.

- Develop resources and information for patients that explain why they have been referred to clinical genetic services because of the results of their tumour tests (see developing local documentation).
- At the review appointment with the oncologist or colorectal surgeon, explain the benefits both for them and possibly their relatives.

Business case

Developing a business case should be a priority for the implementation team. Local arrangements for developing and approving business plans will vary from trust to trust, and each organisation is likely to have its own process in place.

In developing a business case for molecular testing strategies, consider the following:

- The need to develop this in co-ordination with all services involved because the adoption of this guidance is likely to have benefits at hospital and societal level as a result of earlier identification of some associated cancers and cancers in relatives.
- Clinical rationale for testing all people with CRC: include an evidence summary showing treatment pathways, clinical outcomes and reduction in mismanaged patients.
- The increased cost of staff and resources needed in histopathology and specialist clinical laboratories and clinical genetics services to comply with the NICE recommendation to test all people with CRC. For an example approach to histopathology reporting and invoicing, see the Central Manchester University Hospitals Trust website. Take into account that this trust was not testing all CRCs at the time of writing this resource.
- The increased cost of testing relatives and of the screening they may have if diagnosed with Lynch syndrome. See the NICE resource impact report and template to help identify the resource implication within your organisation.
- Potential benefits because of the prevention of early onset of associated cancers and of CRC for relatives of people diagnosed with Lynch syndrome.

Resource Impact

A resource impact report and template have been prepared to support the implementation of the guidance. The guidance may have resource implications at a local level because of variation in clinical practice across the country. Therefore, organisations are encouraged to evaluate their own practice against the recommendations in the NICE guidance and assess resource impact locally.

Developing local documentation

These are examples of tools developed by NHS services using molecular testing strategies, which can be used to inform the development of local documentation. They have not been produced, commissioned or sanctioned by NICE. Take into account that some of these trusts were not testing all CRCs at the time of writing this resource.

Oxford University Hospitals NHS Foundation Trust – Information pack for specialist team to support referral to clinical genetics

Oxford University Hospitals NHS Foundation Trust – Abnormal MMR management flow chart

Cambridge University Hospitals NHS Foundation Trust – Letter to pathology laboratory requesting tumour samples for MLH1 methylation studies

Leeds Teaching Hospitals NHS Trust – Letter to pathology laboratory detailing how tumour samples need to be prepared and labelled for MSI testing

London North West Healthcare NHS Trust – Letter for first degree relatives of patients with CRC who have a normal IHC result

Cambridge University Hospitals NHS Foundation Trust – Information for people with a family history of bowel cancer

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8 About this resource

This resource accompanies NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer. It was developed using NICE's process guide for adoption support resources for health technologies. It is an implementation tool and discusses and summarises the experiences reported by NHS sites which have adopted this technology and shares the learning that took place.

It is the responsibility of local commissioners and providers to implement the guidance at a local level, being mindful of their duty to advance equality of opportunity and foster good relations. Nothing in this document should be interpreted in a way that would be inconsistent with this.

More information about the adoption team.

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