Worcestershire Acute Hospitals NHS Trust

Standard Operating Procedure

Lynch Syndrome early diagnosis pathway and mainstreaming: guidance for the gynaecological cancer MDT

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Approved by	**Gynaecology Governance**
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Target Organisation	**Worcestershire Acute Hospitals NHS Trust**
Target Departments	**Gynaecology Oncology Service**
Target staff categories	**All**

SOP Amendments

1. Overview

Lynch Syndrome Early Diagnosis Pathway for Endometrial Cancer

This SOP relates to delivery of the early diagnostic pathway, from diagnosis of endometrial cancer to diagnosis of Lynch Syndrome. The guidance is for the gynaecological cancer MDT. It outlines the diagnostic pathway, and the MDT responsibilities.

Lynch Syndrome (LS) is an inherited condition which results in an increased risk of certain cancer types. The main concerns are colorectal and endometrial cancer. There is also an increased risk to other cancers, but they are less frequent. People with LS have up to an 80% risk of developing colorectal cancer in their lifetime and, in women, up to a 60% risk of developing endometrial cancer.

In total LS affects approximately 1 in 400 people, with 200,000-300,000 people likely to have this condition in the UK. However, it is estimated that only 5% of people with LS in the UK have been diagnosed.

Identifying people with LS provides the opportunity to detect cancers at an earlier stage through enrolment into screening programmes, and prevent cancers through risk reduction techniques including colonoscopy, prophylactic surgery and chemoprophylaxis with aspirin.

A diagnosis of LS can also influence management plans for people who develop cancer, including impacting the surgical approaches chosen and the use of specific immunotherapy and chemotherapy treatments, and may impact access to emerging therapies.

In addition to preventing cancer and maintaining the health and quality of life of patients and families with LS, there is consistent evidence of the cost-effectiveness of a structured diagnostic pathway in patients with LS following a diagnosis of cancer, linked to cascade testing in families. Mainstream testing locally, speeds up the testing and results process for patients, and reduces pressure on the regional genetics team.

Patients with Lynch syndrome may be identified in several ways. Firstly, direct testing of tumour tissue should be performed on all cases of bowel and endometrial cancer (as per NICE guidance) to identify patients who might have a diagnosis of Lynch Syndrome. If immunohistochemistry is abnormal with loss of MLH1, or loss of both MLH1 and PMS2 protein expression, MLH1 promoter hypermethylation testing of tumour DNA should be performed. If MLH1 promoter hypermethylation is not detected, offer germline genetic testing to confirm Lynch syndrome.

If IHC is abnormal with loss of MSH2, MSH6 or isolated PMS2 protein expression, offer germline genetic testing to confirm Lynch syndrome. Germline testing a blood sample from these patients, should be performed to confirm a diagnosis of Lynch Syndrome. Depending on the Lynch gene the patient presents with, the lifetime risk of cancer can exceed 80%.

If Lynch Syndrome is confirmed, the patient should be referred to the regional genetics team for assessment. The family members of these patients should be made aware of this result. They can then choose to have testing themselves – testing unaffected family members (not had a cancer diagnosis) is known as cascade testing. Close relatives of an individual with Lynch Syndrome need to seek a referral to the clinical genetics team via their GP. Finally, patients with a family history of cancer associated with Lynch Syndrome or a confirmed polyposis condition may present to primary care requesting a referral into clinical genetics for assessment.

2. Key messages

The term ‘mainstreaming’, in the context of constitutional (germline) genomic testing, describes pre-test counselling and consent processes being undertaken at the point-of-care by a member of the clinical cancer team caring for the patient.
Referral to a clinical genetics professional is usually reserved for those patients found to have a pathogenic or uncertain variant, or patients with a suspected syndromic cancer predisposition or complex family histories. This mainstream approach saves time, is fiscally advantageous and, importantly, provides continuity of knowledge for both the treating clinicians and the patient.

3. General Principles

a) All newly diagnosed endometrial cancer patients who are identified as likely to have Lynch Syndrome should be referred for genetic testing (either locally or specialised genetics centre) within 62 days of endometrial cancer diagnosis.

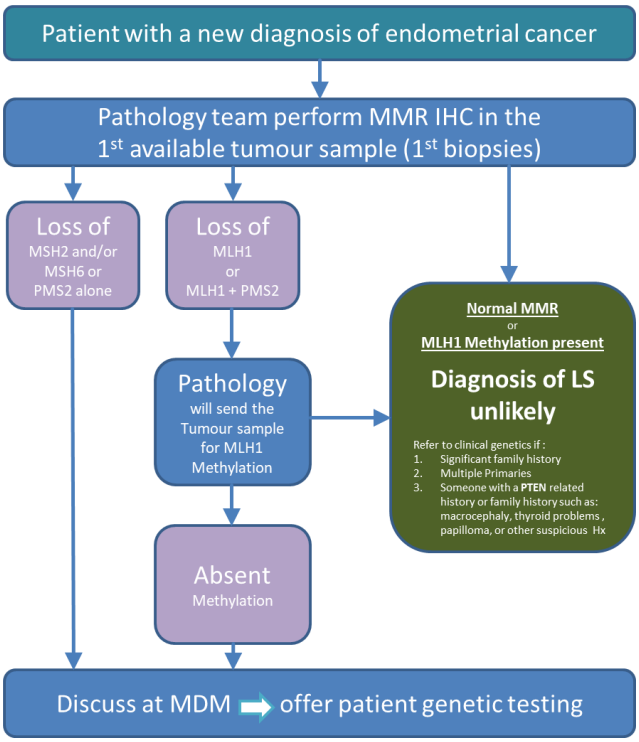
b) Each MDT should identify a responsible local lead for the Lynch diagnostic pathway (a 'Lynch champion'), who may identify specific tasks for others within the MDT.

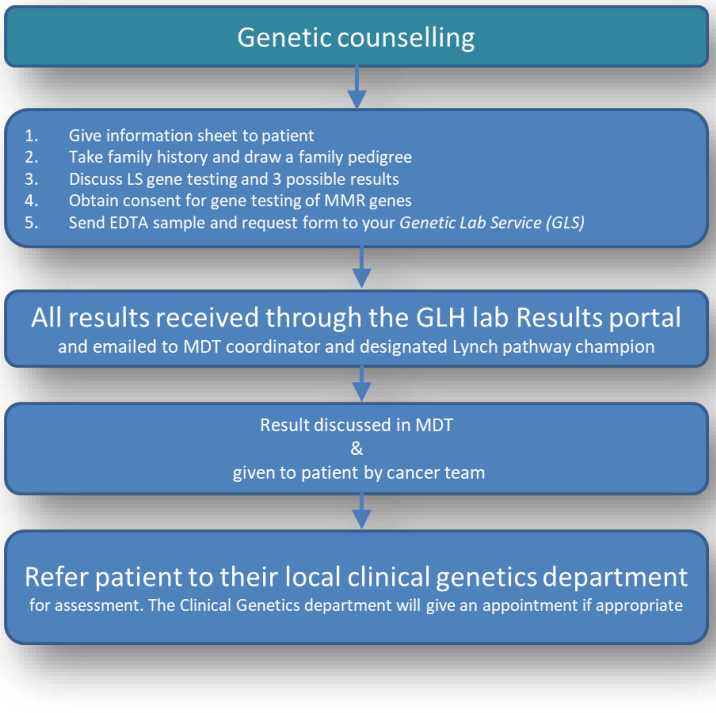
c) Each MDT is responsible for the delivery of the pathway locally. To deliver this pathway each MDT should work with regional genetics centres.

d) Ideally genetic testing should be performed by trained clinicians in mainstream speciality teams (MDT clinician designated by the national testing directory). Or by clinical genetics if mainstream is not currently set up.

e) Each MDT should offer genetic testing via 'mainstreaming'. Thus, local MDTs should aim to achieve either
   - Mainstreaming of genetic result 'in-house'., **or**
   - Timely referral of patients for genetic testing only after the completion of IHC +/- methylation testing.

FLOWCHART





The SOP has been mapped to the:

- *NICE DG42 guideline (DG42 Testing strategies for Lynch syndrome in people with endometrial cancer, 2020)*
- *The NHS England handbook for cancer alliances (2021)*
- *The National Genomic Test Directory (2022*

4. Eligibility Criteria

Part 1: The tumour testing pathway

A. Initial tumour assessment for Lynch Syndrome

- Every patient with a new diagnosis of endometrial cancer should have their first available tumour sample tested for the expression of the four Mismatch Repair (MMR) proteins done by MMR Immunochemistry (IHC).
- IHC should be performed in the first available biopsies but may be performed in surgical resection specimens where biopsies were not available/previously tested.
- MMR IHC results should be discussed and documented during the MDT meeting.

B. Action following MMR IHC results

- MMR IHC assesses the expression of the four MMR proteins: MLH1, MSH2, MSH6, and PMS2. If there is a loss of any of these proteins, further diagnostic tests are indicated.
- All patients with a tumour sample with loss of MMR protein expression except those with loss of MLH1 (see section C) should now be offered germline testing for lynch syndrome genes. This action should be documented in the MDT outcome

C. Further testing for tumour samples with loss of expression of MLH1 or loss of MLH1+PMS2 on MMR IHC

- Tumour samples with loss of MLH1 expression will require further testing with MLH1 promoter Hypermethylation.
- Methylation testing of MLH1 should be ‘reflex’ arranged by the MDT pathologist who reports the IHC MMR.

Once the result is available, the MDT should arrange further MDT discussion.

- If the tumour sample is **absent** of **MLH1 promoter Hypermethylation** the patient may have Lynch Syndrome and should be immediately referred for genetic testing.

- If the tumour sample shows that MLH1 promoter methylation is identified, then it is unlikely that the patient has Lynch syndrome (pathway stops).

- Patients without evidence of Lynch syndrome on tumour testing, but who are diagnosed with endometrial cancer with a high risk family history of cancer or, multiple primaries, or with a *PTEN* related history or family history (such as macrocephaly, thyroid problems, papilloma, etc.) may also be referred to regional expert centres for further genetic assessment.

D. Referral for genetic counselling

- For eligible patients, the MDT should offer testing 'mainstreaming' locally by a trained cancer MDT clinician or Clinical nurse specialist. If not currently set up refer the patient to their local clinical genetics centre.

E. Informing the patient of their genetic result and assessment

- Eligible patients should be informed by an MDT member that they will receive a genetic assessment

Part 2: Mainstreaming: Genetic counselling & testing performed by members of local MDTs

- Before offering 'in-house' mainstream testing, a member of the local MDT should have completed the online training for mainstreaming with certification, and additional practical workshops.
- Contact with the local genetics representative to establish support and a channel of communication is highly recommended.
- The MDT clinician who performed the genetic counselling should contact the patient and give them their genetic test result.
- Patients should then be referred to their local clinical genetics centre for review and further management if:

1. Pathogenic variant **identified**: the regional centre will offer a consultation.
2. Variant of uncertain significance **(VUS)** identified, or **NO** pathogenic variant was found; these patients will be referred to the regional genetic centre by letter and the patient made aware of the referral.

The genetics team will assess all available information:

1. For confirmed Lynch patients, they will offer a consultation to discuss the implication of the results for the patient and their family members.

- The genetics team will register each patient with the National Lynch register.
- Genetics will facilitate referrals for ongoing screening.
- Explain and manage cascade testing for at risk family members.

2. For VUS or negative germline test – genetics will want to perform further tumour testing or segregation studies if possible, to help inform pathogenicity and screening options for this cohort.

In principle, all patients who have had an MMR deficient IHC result and undergone germline testing will be referred to the genetics department, once the patient has been given their result.

5. Patient information

It is important that patients are given the appropriate verbal and written information (Appendix 1), explaining why they have been offered mainstream testing and the benefits and implications they may expect. Patients should be given time to decide if they wish to consent to genetic testing.

6. Booking a Mainstreaming genetic appointment

Following MDT discussion, the consultant will inform the patient of the result and discuss the need for germline testing. Following this, an appointment will be made with the CNS to counsel and consent the patient for testing.

7. GP Communication

The GP will be kept informed of the results by letter.

8. Disclaimer

Clinicians should always use their clinical judgment to determine if an individual patient is suitable for mainstreaming. These consensus recommendations have been produced as guidance and are based on available evidence. Where little evidence existed, expert consensus was agreed.

Appendix 1

Patient leaflet

Lynch-Syndrome_Patient-guide_vs2_digital_FINAL_21.02.23.pdf

Appendix 2

Template genetics results letter for Lynch testing through mainstreaming pathway

MCG LYNCH1 – TUMOUR TISSUES SUGGESTIVE OF LYNCH

Please insert appropriate text into the grey boxes in the template letter below.

Dear [patient],

This letter follows your recent clinic appointment where we explained that initial testing of your cancer (tumour) suggested it might be due to an inherited condition called Lynch syndrome. We have offered you a genetic blood test to help determine whether you have Lynch syndrome.

We discussed how the result of your genetic blood test could have implications for your cancer treatment and/or follow-up. It could also have implications for your future health and may have implications for your relatives.

We enclose an information sheet with further information about Lynch syndrome. It also explains the possible results.

Your results should be ready in approximately 2-3 months. A copy of this letter has been sent to your GP so as they are aware of this initial result and that you are proceeding

Appendix 3

Template genetics results letter for Lynch testing through mainstreaming pathway

MCG LYNCH2 –PATHOGENIC VARIANT IDENTIFIED

Please insert appropriate text into the grey boxes in the template letter below.

Dear [patient],

This letter follows your recent clinic appointment where we discussed the result of your recent genetic test. You had a test to look for the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2), following your diagnosis of cancer. This letter is to provide you with written documentation of the result of this test.

A genetic change was identified in a gene called [MLH1/ MSH2/ MSH6/ PMS2/ EPCAM]. This genetic change is considered pathogenic (disease-causing). This confirms that you have a diagnosis of Lynch syndrome, and gives us an explanation for why you developed endometrial cancer. We discussed how this result may have implications for your cancer treatment and/or follow-up.

Having Lynch syndrome increases an individual's risk of developing bowel and other cancers. It is important to know that you have Lynch syndrome as there are techniques that can be used to manage this risk. This includes the use of aspirin which has been shown to decrease an individual's chance of developing a Lynch syndrome related cancer. Other screening techniques, such as bowel screening, can help to ensure that any bowel changes are detected at an early stage where treatment is likely to be much more successful. Your result therefore has implications for protecting your future health and may have implications for your relatives.

We have requested that an appointment is made for you with a member of the Clinical Genetics team to discuss these results in more detail. You should receive an appointment letter from them in the post in the coming weeks.

After your appointment with Clinical Genetics you will be given a letter to pass to relevant family members, so they can arrange an appointment to discuss genetic testing for themselves, should they wish to.

Please continue to attend your standard appointments with your cancer treatment team.

If you would like further information prior to your genetics appointment, you may wish to read the patient information webpage, https://rmpartners.nhs.uk/lynch-syndrome-information/. Alternatively, if you have any further clinical questions, or queries about this result, please contact us on the above details. A copy of this letter has been sent to your GP so that they are aware of this result.

Appendix 4

Template genetics results letter for Lynch testing through mainstreaming pathway

MCG LYNCH3 – VARIANT OF UNKNOWN SIGNIFICANCE

Please insert appropriate text into the grey boxes in the template letter below.

Dear [patient],

You recently had a genetic test for the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, EPCAM), following your diagnosis of cancer. This letter is to inform you of the result of this test.

Your results show that you have a variant of unknown clinical significance in the [MLH1/ MSH2/ MSH6/ PMS2] gene which requires further evaluation.

This variant is simply a change in the gene which has not been seen before or for which the laboratory has only limited information. At present we cannot tell if this is related to the cause of your cancer or if this variant occurs in the general population and is not linked to your cancer diagnosis. This gene variant cannot be used to offer genetic testing to other family members or to clarify their own risk of cancer.

We have referred you to your local Clinical Genetics department in Birmingham for further assessment. Please complete and return the family history form enclosed with this letter (please return to the address on the form. The Clinical Genetics team require this completed form so that they can assess if any further testing is available and if any cancer screening is recommended to you or your family. Dependent on the outcome of their assessment, the clinical genetics department will either be in touch with an appointment for further discussion or with an advice letter in the post.

Please continue to attend your standard appointments with your cancer treatment team.

If you have any further questions regarding this, while you are awaiting contact from the Clinical Genetics team, please contact us on the above details. A copy of this letter has been sent to your GP so that they are aware of this result.

Appendix 5

Template genetics results letter for Lynch syndrome germline testing through mainstreaming pathway

MCG LYNCH4 – NO VARIANT IDENTIFIED

Please insert appropriate text into the grey boxes in the template letter below.

Dear [patient],

You recently had a genetic test for the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, EPCAM), following your diagnosis of cancer. This letter is to inform you of the result of this test.

No genetic changes were identified in the Lynch syndrome genes. This makes it less likely that your cancer is caused by an inherited condition, but it does not rule this out completely.

We have referred you to your local Clinical Genetics department for further assessment. Please complete and return the family history form enclosed with this letter and return to the address on the form The Clinical Genetics team require this completed form so that they can assess if any further testing is available and if any cancer screening is recommended to you or your family. Dependent on the outcome of their assessment, the clinical genetics department will either be in touch with an appointment for further discussion or with an advice letter in the post.

Please continue to attend your standard appointments with your cancer treatment team.

If you have any further questions regarding this, while you are awaiting contact from the Clinical Genetics team, please contact us on the above details. A copy of this letter has been sent to your GP so that they are aware of this result.

Yours sincerely,

Appendix 6

Worcestershire NHS
Acute Hospitals NHS Trust

CONSENT FOR LYNCH SYNDROME GENETIC TESTING

Requesting DNA analysis for the condition(s):
Lynch Syndrome
The intended purpose is:
Diagnostic genetic testing

Details of the person whose sample is to be tested

Surname	Hospital No
Forename	NHS No:
Date of Birth	
Address	
Post Code:	*Affix Label*

Consultant: _____

Ward/Dept.:_____

Telephone No:_____

I consent to my genetic material being tested for Lynch Syndrome.

Clinical implications

- The test will be specific only for the condition named above and will not detect other genetic/health conditions.
- Genetic testing may be performed on my blood sample or saliva, as well as tissue (cancerous and non-cancerous).
- The results of my test may confirm I have a genetic condition and, in this scenario, would be recommended ongoing clinical management (e.g. colonoscopic surveillance, surgery, medication etc).
- The test may not be able to identify a genetic diagnosis or may not provide a clear answer

Uncertainty

The results of this test *may* reveal genetic variants of uncertain significance. Establishing whether such variants are significant may require (inter)national comparisons. I acknowledge that interpretation of the results may change over time as our understanding increases.

Family implications

The results of my test may have implications for other members of my family. I acknowledge that my results may be shared with other genetic centres to inform the appropriate healthcare of others.

I am happy for results to be shared that identify me if necessary: Yes/No

DNA and data storage

Normal laboratory practice is to store the DNA extracted from my sample even after the current testing is complete. My sample might be used as a 'quality control' for other testing, for example, that of family members.

Data from my test will be stored so it can be looked at again in the future if necessary.

Health records

Results from my test and test report will be part of my patient health record.

Insurance

The results of this test may have implications for insurance. Please refer to the UK Code on Genetic Testing and Insurance for further guidance.

Referrals

Depending on the result, referral to the clinical genetics department may be necessary.

Other specific issues discussed:

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……

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……..

I have been given the opportunity to discuss these implications, to ask questions and to receive verbal and written information regarding my condition and any test currently available.

I will be informed of the results by _____*(telephone, post, in person)*	
I give my consent for my doctor to be informed of the results.	*Yes / No
I give my consent for the results to be shared with other members of the medical community for the benefit other members of the family, if appropriate.	*Yes / No
I give my consent for the results to be shared with other members of the family, if appropriate.	*Yes / No

Patient

Signature of Person giving consent_____

Print_____

Date_____

Interpreter (If consent is given via an interpreter they should sign this section**)**

I confirm I have accurately translated all the information provided by the consenting Clinician/Specialist Nurse to the above patient.

Signature_____Print_____Date_____

Professional

I the undersigned confirm that I am trained to consent for genetic testing, I have explained the nature and implications of genetic testing for Lynch syndrome to the above patient and have given them an information booklet. ☐

Name of clinician obtaining consent_____

GMC/NMC No_____

Signature_____Print_____Position_____

Date:_____

Copy: 1. Patient 2. Patient File 3. Enclose a copy with the patient's blood sample for the Genetics lab.

References

NICE DG42 guidance 'Testing strategies for Lynch syndrome in people with endometrial cancer'

The NHS England handbook: Implementing Lynch syndrome testing and surveillance pathways (2021)

Lynch syndrome quality improvement project

Lynch syndrome training website

Lynch syndrome training supporting documents

The National Genomic Test Directory (2021)

Lynch syndrome patient information website