National Cancer Control Programme

Implementing Lynch syndrome Testing Pathways in Endometrial Cancer, Endometrioid or Clear Cell Ovarian Cancer

Information to support pathologists

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National Cancer Control Programme
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Implementing Lynch syndrome Testing Pathways in Endometrial Cancer, Endometrioid or Clear Cell Ovarian Cancer

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Contents

Note: All information in this booklet is correct at time of publication

1. Universal Testing Pathway for Mismatch Repair (MMR) status using Immunohistochemistry (IHC) in Endometrial Cancer, Endometrioid or Clear Cell Ovarian Cancer

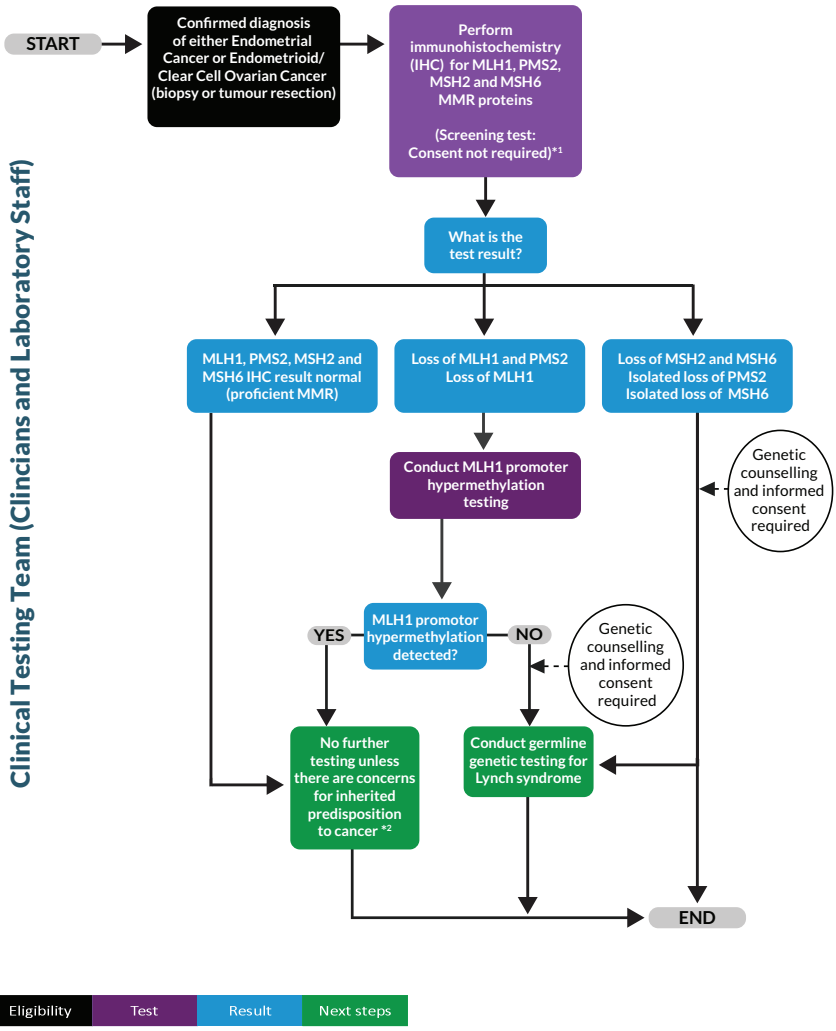
The NCCP[1] recommends universal testing pathways for mismatch repair (MMR) status using immunohistochemistry (IHC) in endometrial.

The *diagnosis and staging of patients with ovarian cancer, National Clinical Guidelines No.20*[2] recommends that all women with a diagnosis of endometrioid or clear cell carcinoma regardless of age should undergo mismatch repair (MMR) protein testing by IHC.

IHC testing is performed on tumour tissue, then MLH1 promoter hypermethylation testing is performed on tumour samples that have loss of MLH1 and PMS2 or loss of MLH1. If the results show that Lynch syndrome is likely, further testing is carried out to confirm this.

Refer to a flowchart of the pathway on Page 5, followed by a summary of the interpretation of IHC results on Page 6 and 7.

Figure 1: Universal Testing Pathway for Mismatch Repair (MMR) status using Immunohistochemistry (IHC) in Endometrial Cancer, Endometrioid or Clear Cell Ovarian Cancer



*1 PCR/molecular testing may be indicated if MMRP IHC is equivocal.

*2 A referral to the Specialist Cancer Genetics Services should be considered if you have concerns for inherited predispositions to cancer on the basis of multiple primary cancers or a strong family history of cancer, such as multiple relatives with colon and/or endometrial cancers or meeting Amsterdam or revised Bethesda criteria.

2. Summary of the Interpretation of IHC MMR results

MMR result	Recommended report	Action[1, 3, 4]
Normal, MLH1, PMS2, MSH2 and MSH6 tested	**MMR IHC Normal:** The tumour cells show normal nuclear staining for MLH1, PMS2, MSH2 and MSH6. Conclusion: There is no immunohistochemical evidence of a mismatch repair deficiency or Lynch syndrome*.	No action*
Abnormal, MLH1 and PMS2 loss Or MLH1 loss	**MMR IHC Abnormal, MLH1 and PMS2 loss MLH1 loss:** The tumour cells show loss of expression of the mismatch repair proteins MLH1 and PMS2 (with normal nuclear staining for MSH2 and MSH6). Conclusion: This mismatch repair deficiency requires MLH1 promoter hypermethylation testing.	**MLH1 promoter hypermethylation testing** **If MLH1 promoter hypermethylation not detected, referral for germline testing for Lynch syndrome** **If MLH1 promoter hypermethylation detected, no germline testing needed***
Abnormal, PMS2 loss	**MMR IHC Abnormal, PMS2 loss:** The tumour cells show loss of expression of the mismatch repair protein PMS2 (with normal nuclear staining for MLH1, MSH2 and MSH6). Conclusion: This mismatch repair deficiency is associated with Lynch and related syndromes.	Referral for germline genetic testing for Lynch syndrome
Abnormal, MSH2 and MSH6 loss	**MMR IHC Abnormal, MSH2 and MSH6 loss:** The tumour cells show loss of expression of the mismatch repair proteins MSH2 and MSH6 (with normal nuclear staining for MLH1 and PMS2). Conclusion: This mismatch repair deficiency is associated with Lynch and related syndromes.	Referral for germline genetic testing for Lynch syndrome

MMR result	Recommended report	Action[1, 3, 4]
Abnormal, MSH6 loss	**MMR IHC Abnormal, MSH6 loss:** The tumour cells show loss of expression of the mismatch repair protein MSH6 (with normal nuclear staining for MLH1, PMS2, and MSH2). Conclusion: This mismatch repair deficiency is associated with Lynch and related syndromes.	Referral for germline genetic testing for Lynch syndrome

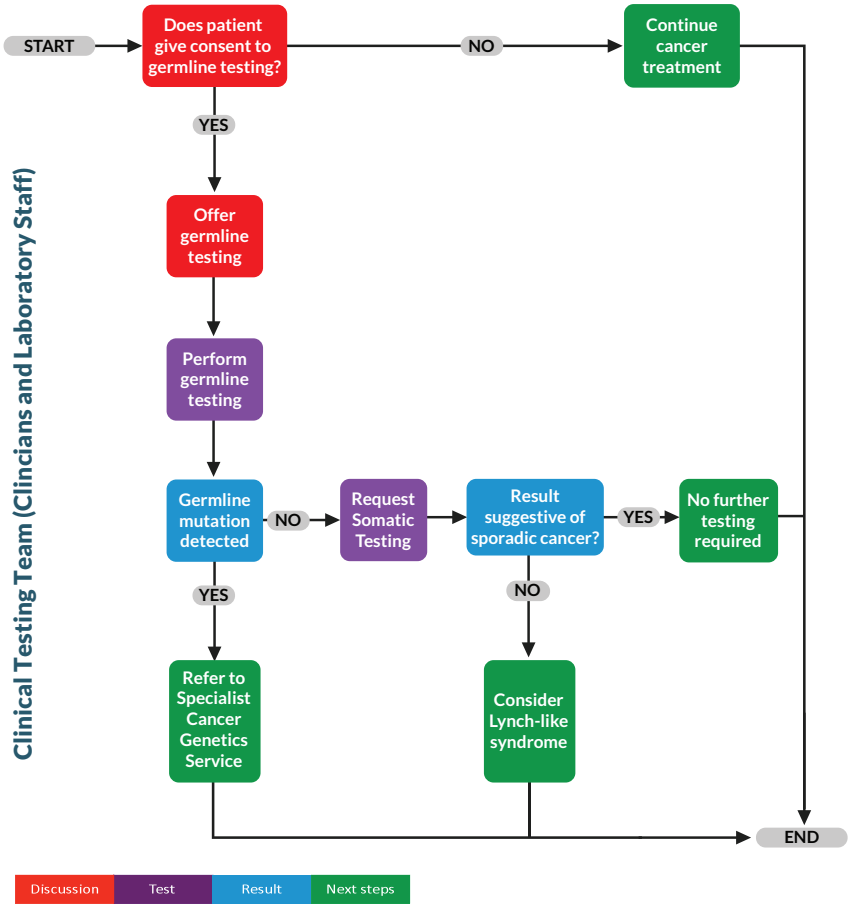
***Despite this result, if there is a strong family history/clinical history suggestive of Lynch syndrome and related syndromes referral to Specialist Cancer Genetics Service should be considered.**

3. Genetic testing following Immunohistochemistry (IHC) testing for Mismatch Repair (MMR) Status in Endometrial Cancer, Endometrioid or Clear Cell Ovarian Cancer

Germline testing should be part of a mainstreaming approach, whereby diagnostic genetic testing is offered to patients outside of Specialist Cancer Genetics Service, as part of standard cancer care and in line with nationally agreed criteria and protocols. If the germline test is negative but the patient has a significant family history, for example, has multiple primary cancers or a strong family history of cancer, such as multiple relatives with colon and/or endometrial cancers or meeting Amsterdam or revised Bethesda criteria, consider referral to the Specialist Cancer Genetics Service.

Refer to the Genetic testing pathway for Lynch syndrome following IHC testing on Page 8.

Figure 2: Genetic testing following Immunohistochemistry (IHC) testing for Mismatch Repair (MMR) Status in Endometrial Cancer, Endometrioid or Clear Cell Ovarian Cancer



Additional Resources

- Royal Marsden website for training pathologists and guidance for requesting and reporting;
  https://rmpartners.nhs.uk/our-work/improving-diagnostic-treatment-pathways/lynch-syndrome-quality-improvement-project/lynch-syndrome-early-diagnosis-pathway-endometrial/

- Lynch syndrome screening (endometrial cancer): Guidance for requesting and reporting;
  https://rmpartners.nhs.uk/wp-content/uploads/2022/05/Endometrial-Cancer-Lynch-screening-v3.pdf

References

1 Implementing a universal testing pathway for Lynch syndrome in colorectal, endometrial and endometrioid or clear cell ovarian cancer, HSE National Cancer Control Programme, 2024;
https://www.hse.ie/eng/services/list/5/cancer/profinfo/hereditary-cancer-genetics/

2 Diagnosis and Staging of patients with ovarian cancer. National Clinical Guideline No. 20, August 2019;
https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/diagnosis-and-staging-of-patients-with-ovarian-cancer.pdf

3 Testing strategies for Lynch syndrome in people with endometrial cancer. Diagnostic Guidance [DG42], 28thOctober 2020;
https://www.nice.org.uk/guidance/dg42

4 British Association of Gynaecological Pathologists (BAGP) guidance document;
https://www.thebagp.org/wp-content/uploads/download-manager-files/BAGP%20BGCS%20NICE%20MMR%20pathway.pdf

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