Guidelines for the Management of MMR results in patients with Endometrial Cancer

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Purpose and scope

This document aims to provide guidance for all clinicians involved in the management of mismatched repair (MMR) immunohistochemistry (IHC) results in patients with endometrial cancer.

Key Contributors:

Kathryn Chrystal	Medical Oncologist, Deputy Chair NMGOTS	Auckland DHB
Lois Eva	Clinical Director Gynaecology Oncology & Regional Gynaecology, Chair NMGOTS	Auckland DHB
Ai Ling Tan	Gynaecology Oncologist	Auckland DHB
Cecile Bergzoll	Gynaecology Oncologist	Auckland DHB
Michelle Wilson	Medical Oncologist	Auckland DHB
Jye Lu	Gynaecologist	Waitemata DHB
Cindy Farquar	Gynaecologist	Auckland DHB
Cindy Ooi	Gynaecologist	Auckland DHB
Katherine Sowden	Gynaecologist	Counties Manukau DHB
Tava Mudzamiri	Gynaecologist	Waikato DHB
Anand Gangji	Gynaecologist	Northland DHB
Kathryn Payne	Pathologist	Auckland DHB
Hiba Hameed	Pathologist	Auckland DHB
Jo Moses	Pathologist	Auckland DHB
Archana Pandita	Pathologist	Waikato DHB
Karen Sheath	Genetic Scientist	Auckland DHB
Courtney Forgeng	Genetic Counsellor	Auckland DHB

What is Lynch Syndrome?

Lynch syndrome[1] is an inherited condition that increases the risk of colon cancer, endometrial cancer and several other cancers. Females with Lynch Syndrome have a 28%–60% lifetime risk for endometrial cancer. The lifetime risk of developing colorectal cancer is 20%–52% for females, and 20%–74% for males.

Lynch Syndrome is caused by autosomal dominantly inherited mutations in one of the mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2. First-degree relatives of individuals identified with a Lynch Syndrome gene mutation have a 50% chance of carrying the mutation. [i]

Why screen for Lynch Syndrome?

Endometrial cancer is the first malignancy in 50% of women with Lynch syndrome. These women (2-4% of all those with endometrial cancer) remain at risk of subsequent colorectal cancer and, to a lesser extent, of other Lynch-associated cancers. [ii]

Estimated cancer risks for those with documented Lynch Syndrome vary. The cancer risk after endometrial cancer for women with Lynch syndrome was estimated using data for 127 women from the International Colon Cancer Family Registry. The median age of endometrial cancer diagnosis in this population was 46 years. The major risk was found to be for colorectal cancer, with 10- and 20-year cumulative risks of 20% and 48% respectively; the median time from endometrial cancer diagnosis to colorectal cancer diagnosis was 11 years.[iii]

Screening all women newly diagnosed with endometrial cancer for Lynch syndrome may have clinical utility for the index case and her relatives by alerting them to the benefits of surveillance (particularly for colorectal cancer) and preventive options (in particular for endometrial and ovarian cancer).

What is the process?

See Appendix 1 for the algorithm showing the proposed process for MMR IHC testing in patients with endometrial cancer.

An endometrial sample is taken in General Gynaecology and goes to Pathology for diagnosis. If any type of endometrial cancer is diagnosed, the pathologist performs Tumour Mismatch Repair (MMR) Immunohistochemistry (IHC) to characterise the tumour and to screen for Lynch Syndrome (MMR IHC is not a genetic test; it does not look at genes and does not say that a person has Lynch Syndrome).

If the MMR IHC results show “MLH1 and PMS2 loss of expression”, then the pathologist refers the tissue for methylation testing. If the results of methylation testing show “hypermethylation absent” then referral to Genetic Services is recommended.

If the MMR IHC results show “MSH2/MSH6/Isolated PMS2 loss” then referral to Genetic Services is recommended.

If there is a high clinical suspicion of Lynch Syndrome (significant family or personal history of endometrial, ovarian, colorectal, upper GI, brain or bladder cancer; aged <40 years), then referral to Genetic Services is recommended regardless of the results of MMR testing.

What are the risks associated with abnormal IHC results?

The risk of cancer development (frequency and site) varies depending on which protein is mutated.
For women diagnosed with endometrial cancer, the probability of having a heritable mutation has been reported to be: [iv] [v]

- 13% if the patient has loss of one or more MMR proteins any age,
- 46% if the patient has loss of one or more MMR proteins under age 60 and MLH1 promoter methylation studies show “hypermethylation absent”.

[1] Lynch syndrome is previously known as hereditary non-polyposis colorectal cancer (HNPCC), a term no longer recommended as syndromic tumours can be associated with colorectal polyps, and there are important manifestations of Lynch syndrome outside the colorectal setting.

Approximately 52% of endometrial carcinomas that show loss of expression with MMR IHC do not have a demonstrable germ-line mutation when tested by Genetic Services. This population is currently regarded as "Lynch-like" and at a risk of cancer in the future that is intermediate between the normal population and those with documented Lynch Syndrome. Some possible causes for this are:

- defective immunohistochemistry
- failure to screen for EPCAM mutations in the case of MLH2 loss
- somatic double hit mutations (a frequent cause) and
- epigenetic silencing.

This is an area of uncertainty and optimal follow up for this group of patients is currently unclear. In the future, genetic testing will be performed on the tumour itself which will provide clarity.

Guidance for clinicians on managing results

See Appendix 2 for pathway showing guidance for clinicians on the management of MMR IHC results in patients with endometrial cancer.

MMR IHC testing is performed in all cases where there has been a diagnosis of endometrial cancer. The testing is done on a diagnostic sample (not hysterectomy) in the DHB of residence and therefore sits in the realm of general gynaecologists.

The clinician who is looking after the patient is responsible for checking for the MMR result in the pathology report and should follow the recommendations in the pathology report (see **Appendix 3a and 3b for example pathology reports**).

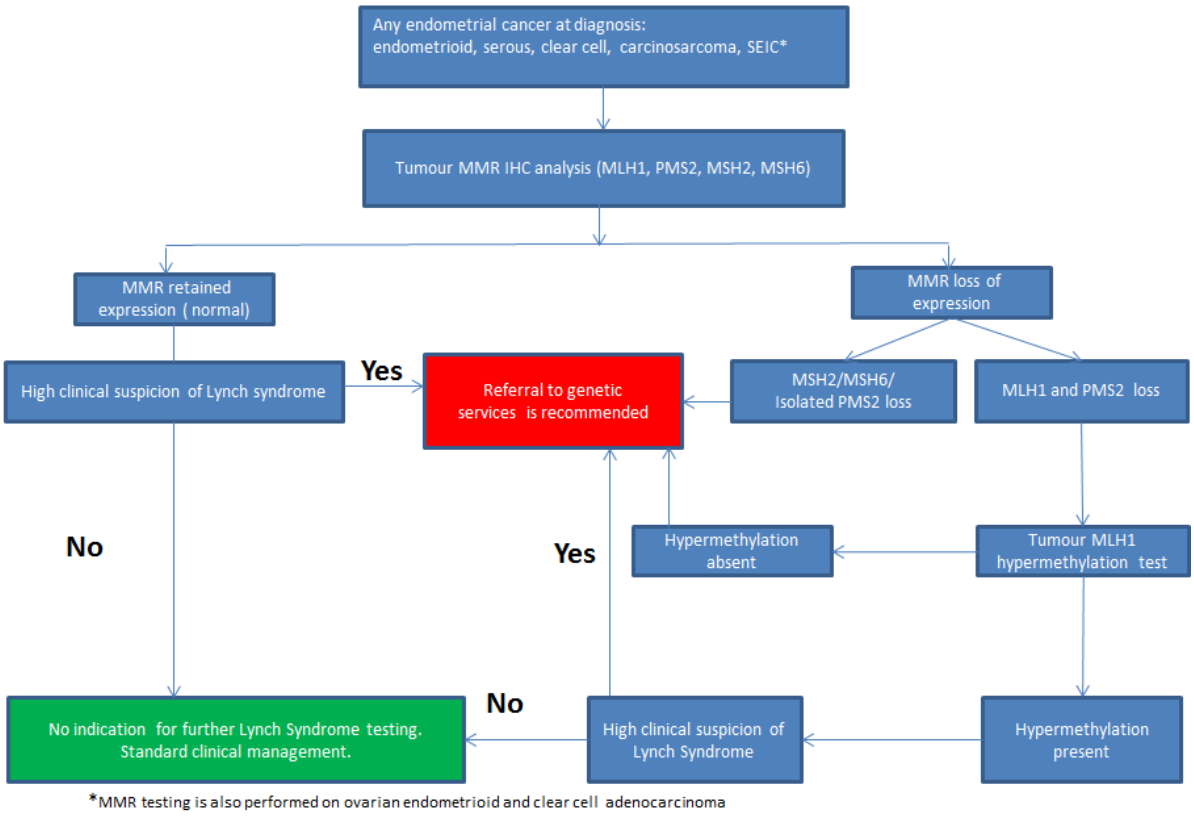
If the pathology report indicates that the tissue will be referred for methylation testing, then a supplementary report will be issued, which the clinician also needs to check for (this supplementary report may take up to a few weeks).

If a pathology report advises referral to Genetic Services, then the clinician who is looking after the patient should make the referral following discussion with the patient. All results should be sent with the referral.

The clinician should refer to Genetic Services if there is a high clinical suspicion of Lynch Syndrome (significant family or personal history of endometrial, ovarian, colorectal, upper GI, brain or bladder cancer; aged <40 years), regardless of the results of MMR or hypermethylation testing.

Appendix 1

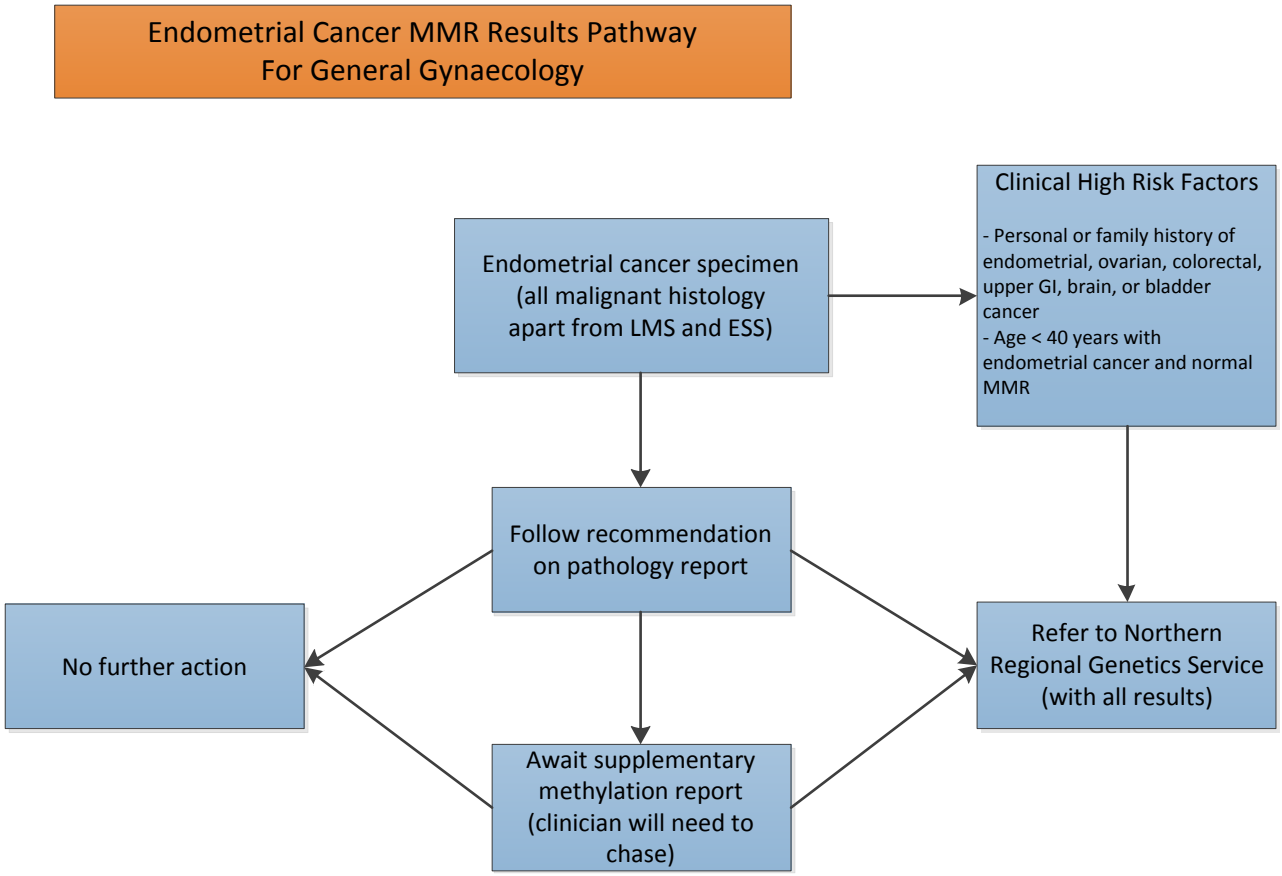
Proposed Algorithm for MMR Testing in Endometrial Carcinoma



*MMR testing is also performed on ovarian endometrioid and clear cell adenocarcinoma

Modified from Buchanan DD et al. Journal of Clinical Oncology 2014; 32:90-100

Appendix 2


Endometrial Cancer MMR Results Pathway
For General Gynaecology
Endometrial cancer specimen (all malignant histology apart from LMS and ESS)
Clinical High Risk Factors
- Personal or family history of endometrial, ovarian, colorectal, upper GI, brain, or bladder cancer
- Age < 40 years with endometrial cancer and normal MMR
Follow recommendation on pathology report
No further action
Refer to Northern Regional Genetics Service (with all results)
Await supplementary methylation report (clinician will need to chase)

Appendix 3a

MMR IHC Typical Expression Patterns

1) Retained MMR expression

MMR immunohistochemistry

MLH1 - Retained expression in tumour cells
PMS2 - Retained expression in tumour cells
MSH2 - Retained expression in tumour cells
MSH6 - Retained expression in tumour cells

Comment

The tumour shows retained (normal) MMR protein expression.
In the absence of clinical criteria, there is no indication for further Lynch syndrome testing.

2) MLH1 and PMS2 complete loss

MMR immunohistochemistry

MLH1 - Loss of expression in tumour cells
PMS2 - Loss of expression in tumour cells
MSH2 - Retained expression in tumour cells
MSH6 - Retained expression in tumour cells

Comment

The tumour shows loss of MLH1/PMS2 protein expression indicating a MLH1 gene alteration.
Tissue will be referred for MLH1 promoter methylation testing.
A supplementary report will be issued with the result.

3) MSH6 and MSH2 complete loss

MMR immunohistochemistry

MLH1 - Retained expression in tumour cells
PMS2 - Retained expression in tumour cells
MSH2 - Loss of expression in tumour cells
MSH6 - Loss of expression in tumour cells

Comment

The tumour shows loss of MSH2/MSH6 protein expression indicating a MSH2 gene alteration.
This suggests an increased risk of Lynch syndrome. Referral to genetic services is recommended.

4) Isolated complete loss of MSH6

MMR immunohistochemistry

MLH1 - Retained expression in tumour cells
PMS2 - Retained expression in tumour cells
MSH2 - Retained expression in tumour cells
MSH6 - Loss of expression in tumour cells

Comment

The tumour shows loss of MSH6 protein expression, indicating a MSH6 gene alteration.
This suggests an increased risk of Lynch syndrome. Referral to genetic services is recommended.

5) Isolated complete loss of PMS2

MMR immunohistochemistry

MLH1 - Retained expression in tumour cells
PMS2 - Loss of expression in tumour cells
MSH2 - Retained expression in tumour cells
MSH6 - Retained expression in tumour cells

Comment

The tumour shows loss of PMS2 protein expression, indicating a PMS2 gene alteration.
This suggests an increased risk of Lynch syndrome. Referral to genetic services is recommended.

Appendix 3b

MLH1 Methylation test result

MLH1 promoter methylation testing has been performed on the tumour by the Diagnostic Genetics Department, LabPlus, Auckland City Hospital.

RESULT: **Hypermethylation Present**

Comment

Presence of MLH1 methylation suggests that the tumour is sporadic, and in the absence of clinical criteria, there is no indication for further Lynch syndrome testing.

OR

RESULT: **Hypermethylation Absent**

Comment

Absence of MLH1 methylation suggests an increased risk of Lynch syndrome. Referral to genetic services is recommended.

References

[i] Lynch Syndrome Screening Network. Available at https://www.lynchscreening.net/development/

[ii] Stewart, A. (2013). Genetic Testing Strategies in Newly Diagnosed Endometrial Cancer Patients Aimed at Reducing Morbidity or Mortality from Lynch Syndrome in the Index Case or Her Relatives. *PLoS Currents*, *5*, http://doi.org/10.1371/currents.eogt.b59a6e84f27c536e50db4e46aa26309c

[iii] Win AK et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. *J Clin Oncol*. 2012 Mar 20; 30(9): 958-64.

[iv] NSW EVIQ. Available at https://www.eviq.org.au/cancer-genetics/genetic-testing-for-heritable-mutations/619-genetic-testing-for-hereditary-mutations-in-th#65540

[v] Buchanan, D. D., Y. Y. Tan, M. D. Walsh, et al. 2014. "Tumor mismatch repair immunohistochemistry and DNA MLH1 methylation testing of patients with endometrial cancer diagnosed at age younger than 60 years optimizes triage for population-level germline mismatch repair gene mutation testing." J Clin Oncol 32(2):90-100