Screening investigations for Lynch Syndrome

Background

- Lynch syndrome is a relatively common heritable cancer predisposition syndrome associated with a high lifetime risk of gastrointestinal and female gynaecological cancers.
- Lynch syndrome is an important condition to recognise as most of the associated cancers are preventable with available risk management strategies and there may be multiple family members at risk.
- Using family history alone to identify patients with Lynch syndrome is unreliable.
- A germline mutation is a mutation the person was born with, and is present in all the cells of their body. Germline mutations are heritable.
- A somatic mutation is an acquired mutation only present in cancer cells. Acquired somatic mutations are not heritable.
- Lynch syndrome is caused by a germline mutation in one of an individual's two copies of a mismatch repair (MMR) gene: MLH1, PMS2, MSH2 (& EPCAM) or MSH6.
- Immunohistochemistry (IHC) for MMR proteins on tumour tissue is a useful screening test for Lynch Syndrome. IHC for MMR proteins should always be undertaken on colorectal cancers. It is also commonly undertaken on endometrial cancers and sebaceous adenomas. In many cases it is automatically undertaken by the laboratory and in others needs to be ordered by the treating doctor. It can be undertaken on other cancers when there is a clinical suspicion of Lynch syndrome.
- Absence of one (or more) MMR proteins indicates that both copies of a MMR gene have mutations, due to:
    - A germline mutation in one copy and a somatic mutation in the other copy of a MMR gene in an individual with Lynch syndrome.
    - Somatic methylation of the MLH1 Promoter region.
    - Somatic mutations in both copies of a MMR gene in an individual who does not have Lynch syndrome.
- The MLH1 and PMS2 proteins work in pairs. When the MLH1 protein is lost or defective, the PMS2 protein is also lost as it becomes unstable.
- The MSH2 and MSH6 proteins work in pairs. When the MSH2 protein is lost or defective, the MSH6 protein is also lost as it becomes unstable.

Interpreting the results of IHC for MMR proteins

General Information

- The terminology used to report the results of IHC for MMR proteins varies. **If you do not understand the histopathology report, contact the reporting pathologist to clarify the result.**

- Potential outcomes of IHC for MMR proteins include:

    - **The presence of all four mismatch repair proteins.** This is a normal result and makes a diagnosis of Lynch syndrome very unlikely (but does not completely exclude it).

        - Some laboratories initially only perform MSH6 and PMS2 IHC, and if normal, do not undertake further testing. It can be assumed that if MSH6 and PMS2 are present, MSH2 and MLH1 are also present.

        - While rare, it is possible for a patient with Lynch syndrome to have normal IHC as a protein may be present but dysfunctional. Therefore, patients with normal IHC in whom Lynch syndrome is still suspected due to young age of presentation and/or family history, should be referred to genetics.

        - A normal IHC result does not exclude another (non-Lynch) familial cancer predisposition syndrome such as Familial Adenomatous Polyposis.

    - **Absent PMS2 protein with presence of MLH1, MSH2 and MSH6 proteins.** This is an abnormal result and genetics referral is indicated.

    - **Absent MSH6 protein with presence of MLH1, PMS2 and MSH2 proteins.** This is an abnormal result and genetics referral is indicated.

    - **Absence of both MSH2 and MSH6 proteins with presence of MLH1 and PMS2 proteins.** This is an abnormal result and genetics referral is indicated.

    - **Absence of both MLH1 and PMS2 proteins with presence of MSH2 and MSH6 proteins.** This is an abnormal result. However, in the majority of cases this is caused by somatic methylation of the MLH1 promoter region and in a minority of cases by Lynch syndrome. See below for further investigations which can be undertaken on tumour prior to genetics referral.

    - **Other possible outcomes include:**

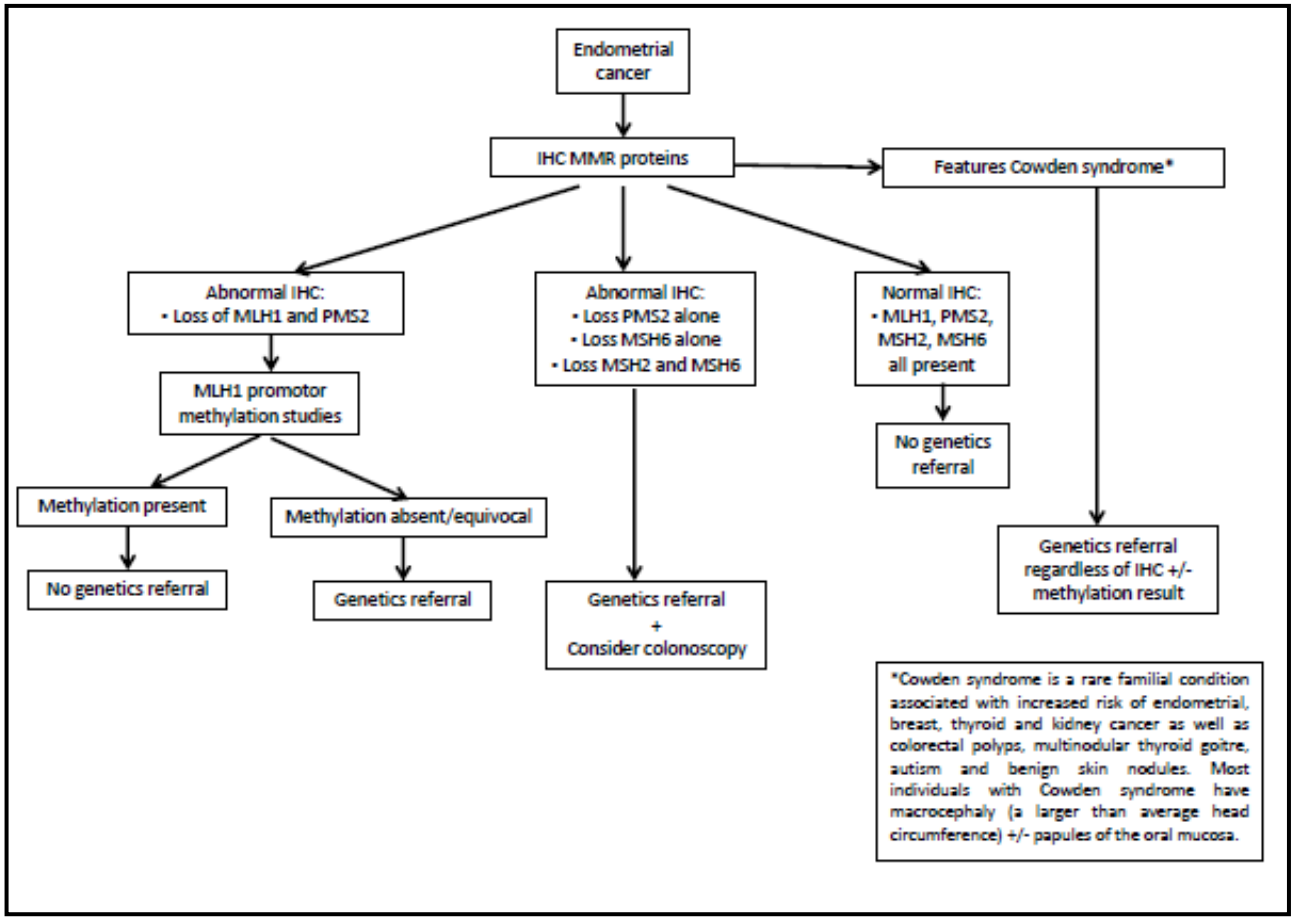
        - Unusual patterns of protein loss such as loss of 3 or all 4 proteins or equivocal staining for one or more proteins. In these situations, the patient should be referred to genetics.

        - In cases with absence of MLH1, PMS2 and MSH6 with presence of MSH2 proteins, BRAF testing (for colorectal cancer) or MLH1 Promoter methylation studies (for endometrial cancer) should be arranged at the same time as the genetics referral.

Interpreting the results of IHC for MMR proteins

Specific information for Endometrial Cancer

Flow chart for patients with endometrial cancer based on the results of IHC for MMR proteins

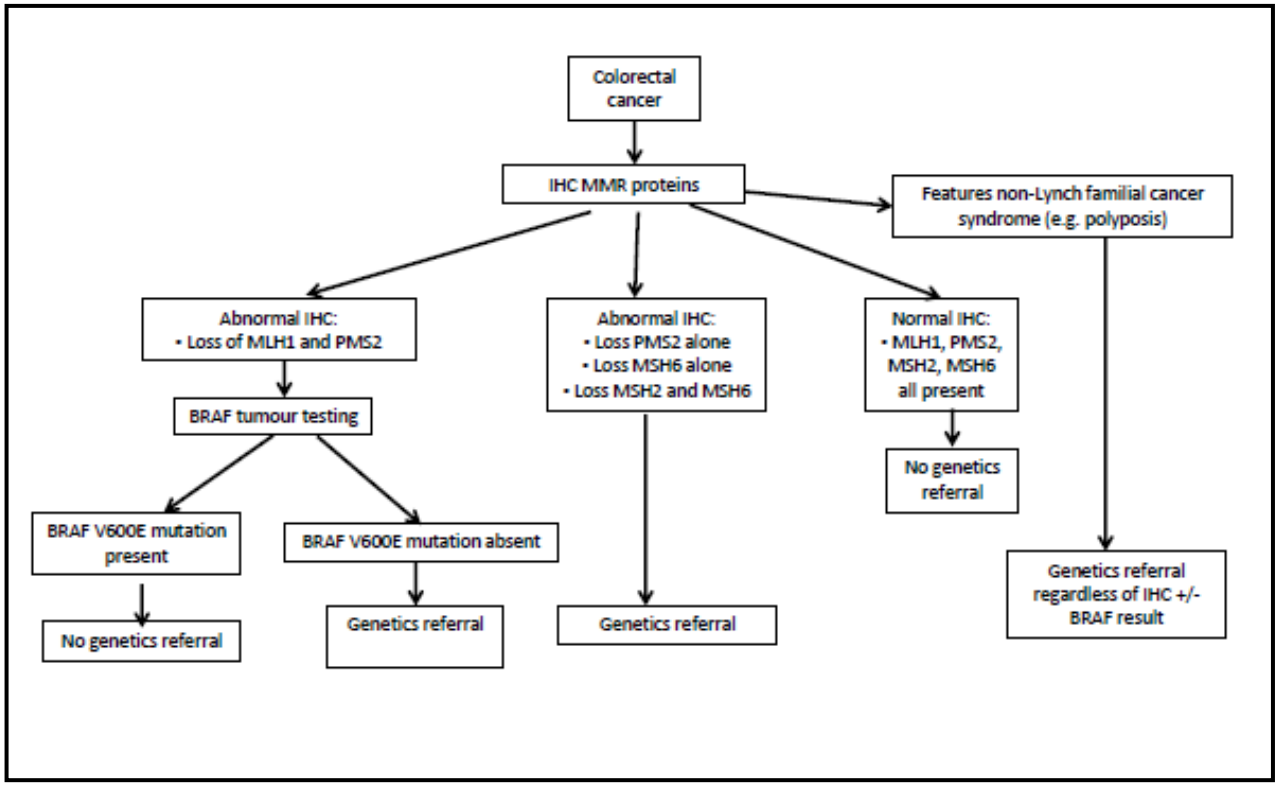


Comments:

- A patient with normal IHC for MMR proteins in whom there is a clinical suspicion of Lynch syndrome should be referred to genetics
- For patients with MLH1 deficient endometrial cancer, tumour MLH1 promoter methylation studies should be arranged prior to referral to genetics (Link to instructions)
- In very rare cases, germline methylation of the MLH1 promoter has been described. If methylation is present and there is a strong clinical suspicion of Lynch syndrome, the patient should be referred to genetics.
- Testing of tumour for the BRAF V600E mutation is NOT a useful test for MLH1 deficient endometrial cancer.

Interpreting the results of IHC for MMR proteins
Specific information for Colorectal Cancer

Flow chart for patients with colorectal cancer based on the results of IHC for MMR proteins



Comments:

- A patient with normal IHC for MMR proteins in whom there is a clinical suspicion of Lynch syndrome should be referred to genetics
- For patients with MLH1 deficient colorectal cancer, BRAF testing of tumour should be arranged prior to referral to genetics. Molecular BRAF testing is available at Pathology Queensland
- A patient with loss of MLH1 and PMS2 MMR proteins and the BRAF V600E mutation is present should be referred to genetics if a non-Lynch cancer predisposition syndrome is suspected (e.g. serrated polyposis syndrome)

Interpreting the results of IHC for MMR proteins
Specific information for Colorectal Polyps

- A patient with abnormal IHC for MMR proteins should be managed as per the flow chart for patients with a colorectal cancer
- IHC for MMR proteins is NOT a reliable screening test for Lynch syndrome when performed on colorectal polyps with no dysplasia or low grade dysplasia. A normal result should not be interpreted as reliable evidence against a diagnosis of Lynch syndrome in this situation.

Specific information for Other Tumours or Cancers

- Patients with loss of one or more MMR proteins should be referred to genetics