GP referral guide for Lynch syndrome risk assessment

Who is this decision aid for?

This guide will help general practitioners (GPs) to understand what Lynch syndrome is.

How will this decision aid help you?

GPs have an important role in identifying patients that are at risk of having Lynch syndrome. This guide will provide GPs with information about Lynch syndrome as well as guidance on when and how to refer a patient to a familial cancer centre for further investigations.

What is Lynch syndrome?

Lynch syndrome (previously known as Hereditary Non-Polyposis Colorectal Cancer or HNPCC) is the most common form of hereditary bowel cancer.

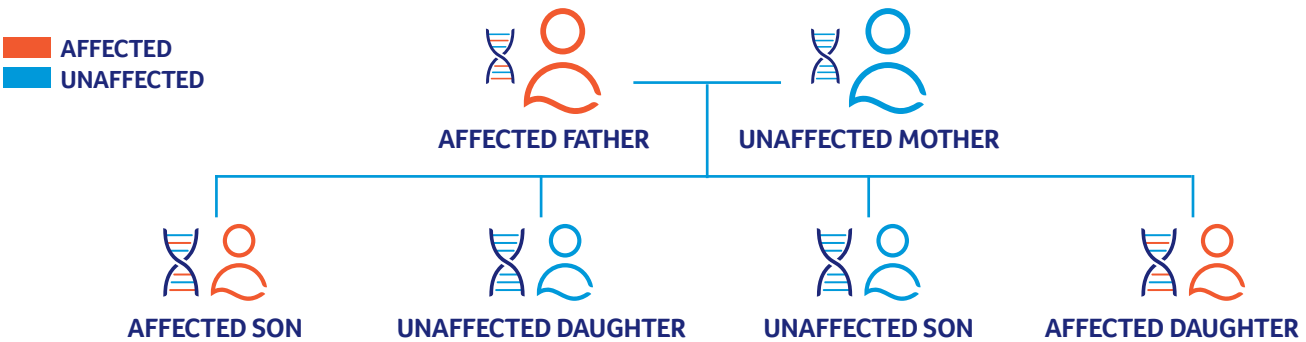
- Lynch syndrome affects approximately 1 in 440 people.[1]
- Lynch syndrome accounts for approximately 4–5% of all colorectal cancer.[2]
- Lynch syndrome is most commonly associated with colorectal cancer but is strongly associated with other cancers (see Table 1).

Table 1: Lynch syndrome related cancers

Common	Large bowel
	Endometrial
Less common	Gastric
	Small bowel
	Renal pelvis (urothelial)
	Bladder
Rare	Ovarian
	Brain (Glioma)
Very rare	Pancreatic

What causes Lynch syndrome?

- Lynch syndrome is caused by pathogenic variants in the following genes: ***MLH1, MSH2, MSH6, PMS2* and *EPCAM***.
  - *MLH1*, *MSH2*, *MSH6* and *PMS2* are mismatch repair (MMR) genes and are involved in detecting errors that occur during DNA replication. Pathogenic variations in MMR genes can lead to the accumulation of mistakes in the DNA, potentially uncontrolled cell growth and possibly cancer.
  - The *EPCAM* gene is located close to the *MSH2* gene and deletions in the *EPCAM* gene can cause the *MSH2* gene to be silenced.
- Lynch syndrome follows an **autosomal dominant inheritance pattern**, meaning that an individual who has a pathogenic variant for Lynch syndrome has a 50% chance of passing on this variant to each of their children.
- However, not all individuals who inherit a pathogenic variant for Lynch syndrome will develop cancer in their lifetime because of **incomplete penetrance**.



Source: www.blueprintgenetics.com/resources/impact-of-inherited-cardiovascular-conditions/

Cancer Council

When do I refer to familial cancer centres?

Refer to a familial cancer centre if any of the following features are present:

1. Known presence of a family germline genetic variation causing Lynch syndrome

2. Meets Amsterdam II Criteria:

✔ 3 or more relatives with a Lynch syndrome-related cancer (as per Table 1), with one being a first-degree relative of the other two, that meet the following criteria:

- 2 or more successive generations affected
- 1 or more relatives diagnosed younger than age 50
- No evidence of Familial Adenomatous Polyposis (FAP) (multiple polyps in the large bowel)

3. A person in the family with two or more bowel cancers, or bowel cancer and a Lynch syndrome-related cancer (as per Table 1) (i.e. metachronous)

4. Testing on a cancer in the family has identified a problem (absent expression of MMR proteins on IHC or MSI-H in tumour)

5. Family history indicates >10% risk of having Lynch syndrome gene mutation using predictive models

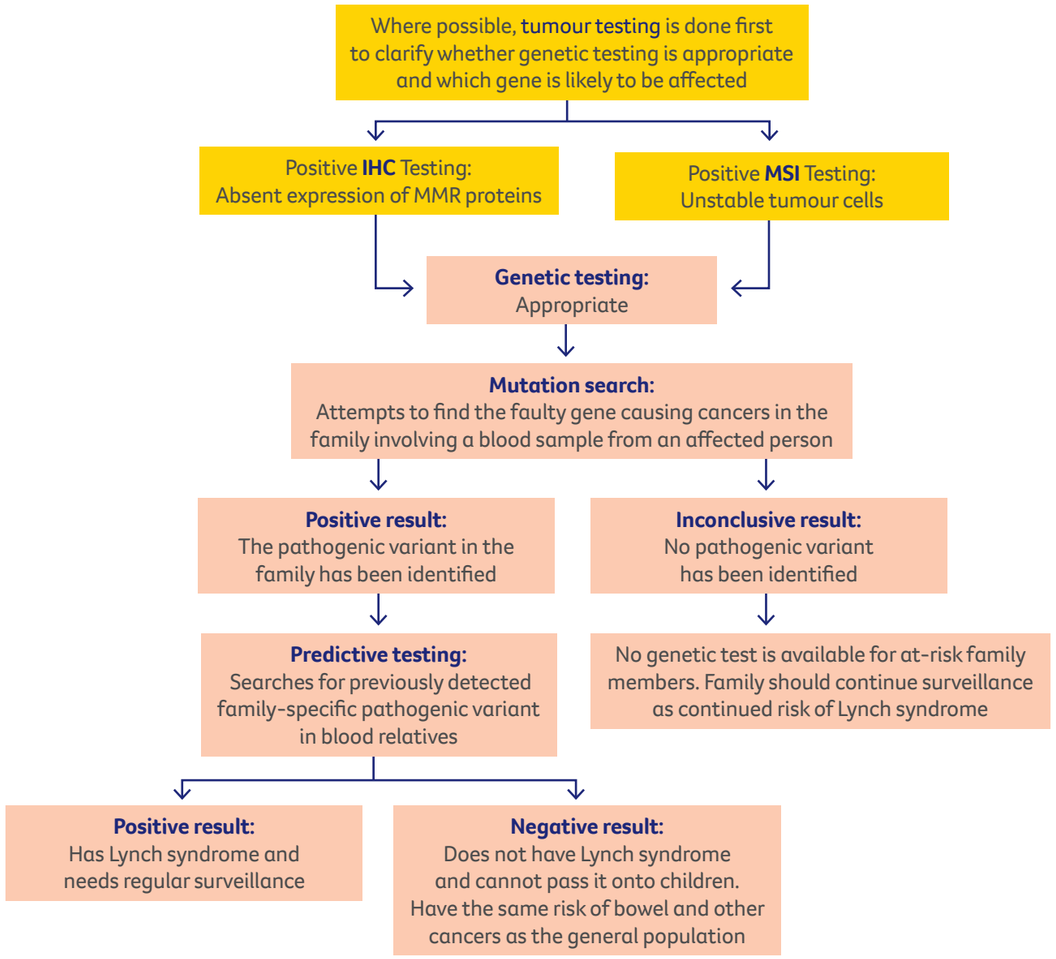
If unsure about the significance of the family history, seek advice from a familial cancer centre regarding referral. Familial cancer centres will assess individual risk and determine utility of genetic testing for Lynch syndrome.

What do I include in the referral?

Checklist:	Including:
☐ I have recorded a detailed family history	• Cancer diagnoses in 3 generations where available • Age of onset of any cancers in the family • Type of cancer (including whether cancer is metachronous) • Ethnicity of patient (as some pathogenic variations are more prevalent in some ethnicities) • Presumed inheritance pattern
☐ I have provided information about the patient's health history	• Any recent investigations (blood results, histopathology reports, operation notes and any diagnostic imaging) • Current medications • Relevant clinical information
☐ I have provided a reason for referral	• Whether it is urgent (give reason) or non-urgent
☐ I have provided contact details	• Contact information for the patient • Your contact details in case there are any questions about the referral

What tests may be offered by the treating surgeon/familial cancer centre?

Individuals who have a high risk of Lynch syndrome may be referred to a familial cancer centre for further tumour testing and possibly genetic testing.



Surveillance options and recommendations

It's important that individuals are aware that they have Lynch syndrome because as a GP, it is recommended that you offer the patient tailored surveillance and prevention. This may include:

Annual surveillance, including:

- Having a colonoscopy from 25 years of age
- Transvaginal ultrasound
- Monitoring of cancer of the uterus

Preventative measures, including:

- Taking aspirin to reduce the chance of developing bowel cancer
- Some women may consider having their uterus and ovaries removed (salpingo-oophorectomy) after they have finished having children or are 40 years and over.

Familial cancer services in Victoria

Clayton

Monash Medical Centre
Familial Cancer Centre
Special Medicine Building
246 Clayton Rd, Clayton 3168

Ph: (03) 9594 2009
Fax: (03) 9594 6046
E: familial.cancer@monashhealth.org

Regional clinics:
- Frankston
- Moe

Heidelberg

Austin Hospital
Genetics in the North East
145 Studley Road,
Heidelberg 3084

Ph: (03) 9496 3027
Fax: (03) 9496 4385
E: genetics@austin.org.au

Regional clinics:
- Albury/Wodonga
- Shepparton
- Ballarat

Parkville

The Parkville Familial Cancer Centre

The Royal Melbourne Hospital
Level 2 Centre, Infill Building,
Grattan Street, Parkville 3050

Ph: (03) 9432 7151
Fax: (03) 9342 4267
E: familycancer@mh.org.au

Regional clinics:
- Geelong
- Warrnambool

Peter MacCallum Cancer Centre
Level 1, 305 Grattan Street
Melbourne 3000

Ph: (03) 8559 5322
Fax: (03) 8559 5329
E: familialcancer@petermac.org

Regional clinics:
- Bendigo
- Mildura

Further resources

Cancer Connections
www.cancerconnections.com.au

Cancer Council Australia
www.cancer.org.au

Cancer Council Victoria
www.cancervic.org.au

Cancer Institute NSW
www.cancer.nsw.gov.au/getattachment/learn-about-cancer/cancer-in-nsw/hereditary-cancers/lynch-syndrome/lynch-syndrome-guide.pdf?lang=en-AU

Centre for Genetics Education
www.genetics.edu.au

EviQ Cancer Genetics resources for GPs
www.eviq.org.au/clinical-resources/health-professional-fact-sheets/3077-gp-fact-sheet-cancer-genetics-resources

EviQ GP referral guidelines
www.eviq.org.au/cancer-genetics/referral-guidelines

Lynch Syndrome Australia
www.lynchsyndrome.org.au/

National Health and Medical Research Council
www.nhmrc.gov.au

RACGP Clinical Guidelines:
- www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/red-book
- www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/genomics-in-general-practice

Glossary

- **Immunohistochemistry (IHC)** – a laboratory method that uses antibodies to check for certain antigens (markers) in a sample of tissue, which is used to help diagnose cancer and to tell the difference between different types of cancer.
- **Microsatellite instability (MSI)** – is used to identify tumours caused by defective MMR by comparing the number of nucleotide repeats in a panel of microsatellite markers in normal tissue with the number from tumour tissue from the same individual. Microsatellite instability is present if the number of repeats in the tumour and the normal tissue differs.

References

1. Jenkins MA, Ait Ouakrim D, Boussioutas A, Hopper JL, Ee HC, Emery JD, Macrae FA, Chetcuti A, Wuellner L & St John DJ. (2018), Revised Australian national guidelines for colorectal cancer screening: family history. *Medical Journal of Australia, 209(10)*, 455–60. doi:10.5694/mja18.00142
2. Kohlman W & Gruber S. (2004 [last updated 2018]). Lynch syndrome. In Adam MP, Ardinger HH, Pagon RA, et al., (Eds.), *GeneReviews*. Retrieved from: www.ncbi.nlm.nih.gov/books/NBK1211/?report=printable

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