Lynch Syndrome Genetic Testing Criteria

Criteria for Mainstream Medicare Funded Testing (MBS Item #73354)

- ❑ A patient with suspected Lynch syndrome* due to mismatch repair immunohistochemistry on tumour tissue# demonstrating a loss of expression of one or more mismatch repair protein (MLH1, MSH2, MSH6, PMS2)

***Lynch syndrome cancers include:** adenocarcinoma of the colorectum, endometrium, small intestine, stomach, ovary, or pancreas, urothelial transitional cell carcinoma, glioblastoma multiforme, and cutaneous sebaceous gland tumours.

 # Germline genetic testing is not indicated in an individual with a single sebaceous adenoma with abnormal mismatch repair immunohistochemistry AND no personal or family history of Lynch syndrome cancers.

Tumour Testing in Lynch Syndrome (see flowchart overleaf):

Tumour testing as outlined below should be undertaken prior to germline genetic testing.

1. Immunohistochemistry of the Mismatch Repair proteins (MMR IHC)

- Loss of expression of one or more of the mismatch repair proteins is relatively common in tumour tissue, occurring in up to 15% of colorectal and 25% of endometrial cancers.
- Usually this reflects somatic (acquired) changes that have arisen in tumour tissue only, most commonly hypermethylation of the MLH1 promoter.

2. MLH1 Promoter Methylation

- The identification of tumour MLH1 promoter methylation is consistent with a somatic cause of abnormal MMR IHC and germline genetic testing is not indicated.
- In colorectal cancer only, the presence of the BRAF V600E variant can be used a surrogate maker for MLH1 promoter methylation. However, if the BRAF V600E variant is not detected, MLH1 promoter methylation testing should still be undertaken.

If not eligible on above criteria, do not offer mainstream genetic testing.
Consider referral to the Adult Genetics Unit for the following patients.

Genetic testing may be offered by the Adult Genetics Unit for patients with a Lynch syndrome cancer* that has normal MMR IHC but is:

- Microsatellite unstable (MSI-high)
- Diagnosed ≤ 40 years
- Diagnosed in an individual with ≥2 Lynch syndrome cancers* with one ≤ 50 years
- Associated with a family history
  - that meets the Amsterdam II criteria OR
  - of ≥ 1 first degree relative with a Lynch syndrome cancer* diagnosed ≤ 50 years OR
  - with limited family history knowledge (i.e. adopted)
- Lynch-like syndrome or other clinical concern for a hereditary cancer syndrome (i.e. colorectal polyposis)

Adult Genetics Unit
Tel: (08) 7074 2697
Fax: (08) 8429 6112
Email: adultgenetics@sa.gov.au

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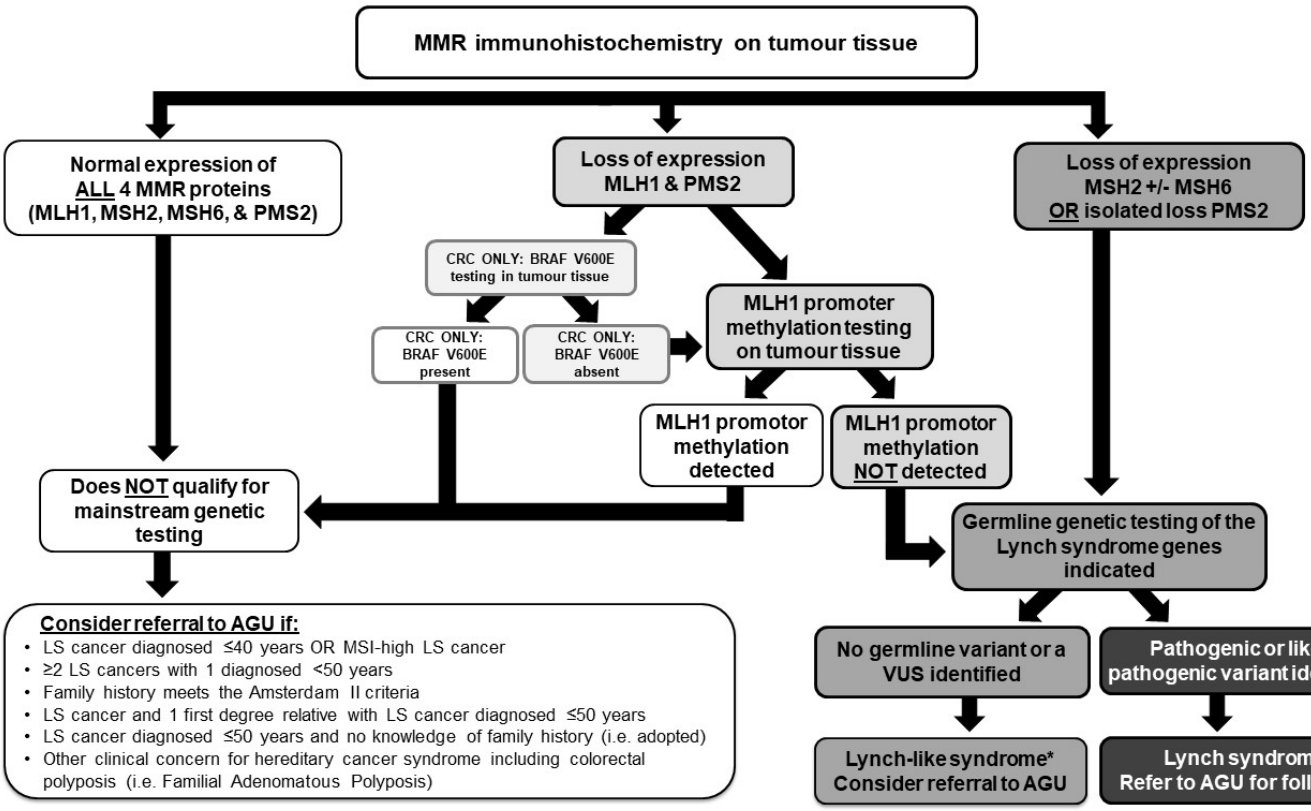
Lynch Syndrome Genetic Testing Flowchart



LYNCH SYNDROME CANCERS INCLUDE: Adenocarcinoma of the colorectum, small bowel, stomach, endometrial, ovary, or pancreas, glioblastoma multiforme, urothelial transitional cell carcinomas and cutaneous sebaceous gland tumours

* Possible explanations for Lynch-like syndrome include a false positive MMR IHC result, a false negative germline result, mosaic Lynch syndrome, or most likely, a sporadic cancer with somatic/acquired MMR gene variants.

MMR: mismatch repair; **CRC**: colorectal cancer; **LS:** Lynch syndrome; **MSI:** microsatellite instability; **AGU:** Adult Genetic Unit; **IHC**: immunohistochemistry.

Amsterdam II Criteria (1998)[1]

A family with ≥ 3 relatives with Lynch syndrome cancers plus **ALL** of the following:

- ≥ 1 affected relative is a first-degree relative of both of the other two AND
- ≥ 2 generations of the family have a Lynch syndrome associated cancer AND
- ≥ 1 of the cases of cancer was diagnosed under the age of 50 AND
- familial adenomatous polyposis should be excluded in colorectal cancer cases; AND
- tumours should be verified by pathological examination.

[1]Vasen HF et al. New clinical criteria for hereditary nonpolyposis colorectal cancer proposed by the International Collaborative group on HNPCC. Gastroenterology 1999; 116:1453.

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Lynch Syndrome
Mainstream Genetic Testing Checklist

Patient name:
DOB:
UR:
EMR Visit:

(or patient label)

- ❑ Patient's family history taken and documented
- ❑ Ensure appropriate tumour testing has been done:
  - ❑ MMR IHC abnormal (absence of ≥1 MMR protein) **AND**
  - ❑ MLH1 promoter hypermethylation absent (if absence of MLH1 and PMS2)
- ❑ Provide patient with genetic testing information leaflets
- ❑ Discuss genetic testing with patient
- ❑ Complete Consent to Genetic Testing form
- ❑ Provide patient with completed SA Pathology request form
  - 4mL blood in EDTA tube
  - Cc: Responsible Consultant
  - Cc: Adult Genetics Unit, Royal Adelaide Hospital
- ❑ Place a copy of consent form and this checklist in patient notes (Paper or scan to EMR)
- ❑ Ensure patient follow-up appointment in 3 months to discuss results (date of appointment _ _ / _ _ / _ _)

MO Signature: _____ Date _ _ / _ _ / _ _

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Consent to Mainstream Cancer Genetic Testing

PATIENT LABEL (if available)

Name of person to be tested		**DOB**
Hospital		**UR**
Sample to be collected	☐ Tumour Tissue (somatic) ☐ Blood (germline) ☐ Other (_____)	

I consent to a genetic test for _____

The gene(s)/gene panel being tested is _____

I understand that:

1. The meaning of the result is based on what is known now. This could change in the future.
2. There are limitations to genetic testing:
   - We do not know all the genes that cause cancers.
   - Genetic variants may be found that cannot be interpreted. These are called variants of unknown significance or VUS. A VUS cannot be used to guide clinical care.
3. Rarely, there may be a technical problem with a genetic test. Further sample(s) may be needed.
4. Test results may have implications for both my treatment/cancer risks AND for my family members.

I am aware that:

1. Samples will be stored after testing for at least the period required by laboratory guidelines.
2. I can change my mind about testing at any point before a report is issued.

I consent to the genetic testing described above.
I have had the chance to ask questions and I am satisfied with the answers I have been given.

I give permission for this genetic test result to be retained confidentially by the Adult Genetics Unit and/or given to health care services looking after other members of my family: ☐ Yes ☐ No

Patient signature:..... Date:.....

If I am unable to receive my genetic test result, I nominate the following individual(s) to receive it on my behalf:

Name and Contact Information:.....

Person obtaining consent:..... Signature: .....

Position and specialty of person obtaining consent:.....

Responsible Consultant (please print in capitals): .....

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PATHOLOGY REQUEST FORM

Mainstream Genetic Testing (V1 Nov 2022)

SA PATHOLOGY

AFFIX BARCODE HERE

PERSON BEING TESTED *(all samples must include at least two patient identifiers)*

Family Name	Date of Birth	Sex	Ethnicity *(if known)*	Your Ref

Given Name(s)	Medicare No.	Telephone

Address: *(Number, Street)*	Suburb	Postcode

Patient Status at the time of the service or when the specimen was collected:
☐ a private patient in a private hospital or approved day hospital facility
☐ a private patient in a private recognised hospital
☐ a public patient in a recognised hospital
☐ an outpatient public of in a recognised hospital

Medicare Assignment "Section 20A of the Health Insurance Act 1973"
I offer to assign my right to benefits to the approved pathology practitioner who will render the requested pathology service(s) and any eligible pathologist determinable services(s) established as necessary by the practitioner.

Patient Signature & Date _____

Your doctor has recommended that you use SA Pathology. You are free to choose your own pathology provider. However, if your doctor has specified a particular pathologist on clinical grounds a Medicare rebate will only be payable if that pathologist performs the service. You should discuss this with your doctor.

REQUESTING DOCTOR DETAILS

Requesting Clinician:

Responsible Consultant & provider number:

COPY REPORTS TO

Adult Genetics Unit
Royal Adelaide Hospital
via email: adultgenetics@sa.gov.au

CLINICAL SETTING

☒ Diagnostic test	☐ Predictive test	☒ Affected
☐ Carrier Test	☐ Prenatal *(please tick one)*	☐ Unaffected *(please tick one)*

TEST TYPE *(please tick)*

☐ Common mutation screen ☒ Full gene mutation analysis ☐ Known familial mutation(s)

CLINICAL NOTES

Personal and Family History of

This is a <u>Medicare Funded</u> Mainstream Genetic Test (MBS Item Number 73354)

Consent Obtained ☐ YES ☐ NO

MBS & Mainstream Criteria ☐ YES ☐ NO

Loss of expression of the following proteins on MMR IHC: ☐ MLH1 ☐ PMS2 ☐ MSH2 ☐ MSH6

Additional tumour testing: ☐ MLH1 promoter methylation absent ☐ BRAF V600E variant absent (CRC only)

TESTS REQUESTED

EDTA	BUCCAL SWAB	OTHER

4ml blood in EDTA tube for:

Genetic testing: Mismatch Repair/Lynch Syndrome gene panel analysis (sequencing and del/dup studies)

Doctor's Signature & Date

I have verified FULL NAME, DOB and URN on the sample label and request form verbally with the patient and/or checking the patient's ID band.

Collector's Signature: Specimen Collected: / / : Hrs

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Consumer Information Sheet

Information about Genetic Testing and Cancer

This leaflet was written for people who are thinking about having a genetic test following a cancer diagnosis. This leaflet does not replace a discussion with your managing specialist. If you have any questions or concerns after reading this leaflet, please discuss them with your managing specialist or contact the Adult Genetics Unit.

What are genes?

The human body is made up of millions of cells. Each cell contains DNA. DNA spells out the genetic instructions (genes) the cells need. Some genes tell cells how to grow, divide and work properly. Some genes help keep DNA healthy. Other genes tell worn-out cells when to self-destruct (die). These genes work together to control cell growth.

What is cancer?

The DNA in our cells is continually damaged by the things we are exposed to in our environment, for example UV light or cigarette smoke, and the process of aging. This DNA damage is usually repaired but the repair process is not perfect. This means that damage can build up in our DNA. If a cell has too much DNA damage it normally dies.

Cancer occurs when abnormal cells do not die and start to grow in an uncontrolled way. These abnormal cells can damage or invade the nearby tissues or spread to other parts of the body; this is called a cancer.

What is familial cancer?

Rarely, a person is born with a genetic error (called a variant or mutation) in a cell growth-control gene or a DNA-repair gene. These genetic errors increase the chance of developing a cancer. Usually, the genetic error has been inherited from the person's mother or father. If a genetic error is inherited, other blood relatives may also have an increased chance of developing cancer. This is called familial or hereditary cancer.

What is a genetic test?

A genetic test involves collecting a sample, usually blood. Genetic material (DNA) is extracted from the sample and analysed looking for genetic errors or variants.

- Everyone's genes have differences or variants, this makes us each unique.
- Most genetic variants are harmless and do not cause problems.
- Some genetic variants change how a gene works and **do** cause a problem, like an increased risk of developing a cancer.
- The names for a variant that causes a medical problem include a disease-causing variant, mutation, genetic error or genetic fault.
- Most genetic tests analyse a number of genes that are all known to cause a particular health problem, like an increased risk of cancer. This is called a gene panel test.
- Genetic testing is part of the standard care for patients with certain types of cancer. This genetic testing is not research based or part of a clinical trial.

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Consumer Information Sheet

Why have a genetic test?

There are many reasons a doctor may suggest having a genetic test in the setting of a cancer diagnosis, including:

- To help identify the best treatments for some types of cancer.
- To understand the chance of developing another cancer.
- To help family members understand their cancer risks.
- To help family members manage and reduce their cancer risks through early cancer screening tests and other management options.

What are the possible outcomes of a genetic test?

1. No genetic variants are found. This is the most common result and is called a negative or uninformative test. This may mean that the cancer did not have an inherited genetic cause or that an inherited genetic cause cannot be found using the currently testing technology.
2. A genetic variant that explains the cancer is found. This is a less common result. This may influence cancer treatments. It also means that other family members may have the variant and can choose to have their own genetic test.
3. A variant that is not understood is found. This is an uncommon result and is called a variant of unknown significance or VUS. A VUS is neither good nor bad; its meaning is just not known yet. Sometimes more testing can help to understand the meaning of a VUS, or the meaning may become clearer overtime. A VUS cannot be used to influence cancer treatments or offer testing to other relatives.
4. An unexpected variant is found. This is a rare result called an incidental finding. It occurs when a genetic variant that causes a different medical problem is found.

What do I tell my family about genetic testing?

A genetic variant found in you may be relevant for your blood relatives. Genetic variants can occur in both sexes and both sexes can pass a genetic variant down to their children. Telling your family members about a genetic variant can be difficult but may help them understand and manage or reduce their cancer risks.

What about genetic tests and insurance?

A genetic test result is part of a person's health history. In Australia, premiums for private health insurance do **not** depend on health history. Previously, other types of insurance like income protection and life insurance could have been impacted by genetic testing. However, the laws have recently changed and there is now more protection from genetic discrimination by insurance companies. A genetic test should not impact insurance for a person with a cancer.

Where can I get more information or support?

- **Watch Our Video** (scan the QR code or use the link) https://t2m.io/zr5HM4O0
- NSW Centre for Genetics Education https://www.genetics.edu.au/
- Inherited Cancers Australia https://www.inheritedcancers.org.au/
- Adult Genetics Unit, Royal Adelaide Hospital Tel: 08 7074 2697

The information contained within this leaflet does not constitute medical advice and is for general information only. Readers should always seek independent, professional advice where appropriate.

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