Gastrointestinal cancers and Lynch syndrome

Lynch syndrome

Lynch syndrome is an inherited condition characterised by a mismatch repair (MMR) gene mutation that predisposes carriers to a significant increased risk of a number of cancers; most notably, gastrointestinal and gynaecological cancers. Affected MMR genes include MLH1, MSH2, MSH6, PMS2 and EP-CAM.

Over time, various names have been given to this condition including:

- ➔ Hereditary non-polyposis colon cancer (HNPCC)
- ➔ Family cancer syndrome
- ➔ Muir Torre syndrome (where specific skin cancer and sebaceous adenomas are present)
- ➔ Turcott syndrome (where specific brain tumours are present)

The name 'Lynch syndrome' now replaces each of the above conditions.

Lynch syndrome is extremely under-diagnosed. Although LS is identified in approximately 3-5% of all colorectal cancers (CRCs), it is estimated that >90% of Lynch syndrome carriers are unaware of their LS status. These carriers are therefore unaware of their increased cancer risk and screening needs.

Cancer risks for Lynch syndrome carriers

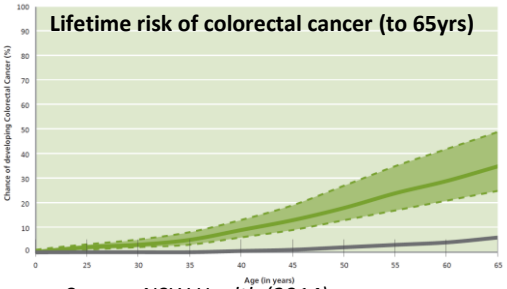
Lynch syndrome predisposes a carrier to a significantly higher risk of cancer than the general population. **Cancer risk for LS carriers varies by the location of cancer and by the affected gene**.

	MLH1	MSH2	MSH6	PMS2
Overall LS cancers risk	50-76%	38-78%	65%	21-53%

Source: Uptodate.com

Cancer risk for LS carriers is also influenced by familial and environmental factors (e.g. some families have extraordinarily high rates of particular LS cancers). Published risk profiles therefore provide a general guide and must be considered in conjunction with a patient's family history of cancer and environmental factors.

Notably, any literature review of LS cancer risk profiles reveal wide variations in information about the magnitude of cancer risks (due to substantially different sampling methodologies). For example,



Source: NSW Health (2014)

	Risk for LS carriers (to age 65 or 70yrs, varies by source)					Risk to age 85
	MLH1	MSH2	MSH6	PMS2	Av. Lynch syndrome	Av. General population
Colorectal	34 - 53%	47 - 68%	22 - 30%	15 - 20 %	38 - 68%	10 %
Endometrial	18 - 60%	30 %	25 %	15 %	33 - 60%	2 – 3 %
Ovarian	8 - 15 %	8 - 15 %	Low	-	9 %	1 – 2 %
Gastric	6 %	0.2 %	0 %	-	6 %	1 %
Biliary/pancreatic	4%	4%				
Urothelial	0.2 %	2.2 %	0.7 %	-	< 3 %	1 %
Small bowel	0.4 %	1.1 %	0	-	< 3 %	0.01 %

Sources: EviQ. (2008) and Uptodate.com (2014) *Data does not consider impact of surveillance / early detection.*

A Lynch syndrome carrier may be identified at colonoscopy, or from their family history:

Where a patients has a family history of cancer, Lynch syndrome may be indicated where the history meets either of the following criteria:

➔ **Amsterdam II criteria**

The patient has:

- At least 3 relatives with Lynch cancers (see below), one of whom is a first degree relative of the other two, and
- At least 2 successive generations are affected, and
- At least one affected relative had a cancer diagnosis under age 50.

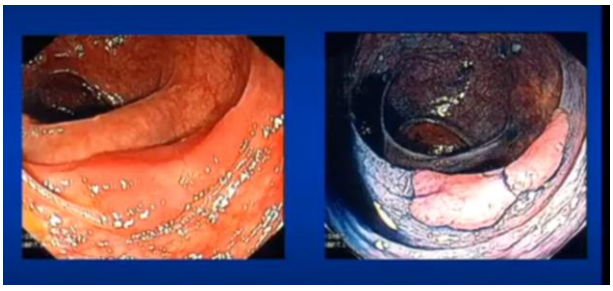
➔ **(Updated) Bethesda criteria**

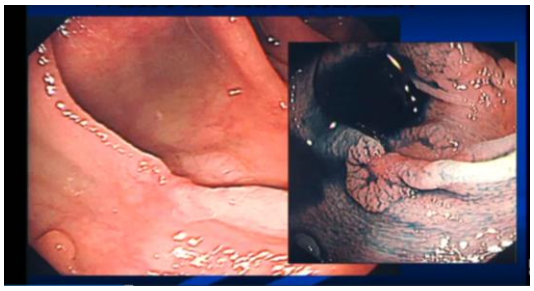
The patient has:

- A Colorectal or uterine cancer under age 50, or
- Synchronous or metachronous CRC (or other Lynch cancer) regardless of age, or
- A CRC with MSI-H / IHC negative histology under age 60, or
- A CRC and one first degree relative also has/had a CRC (or other Lynch cancer) with one of the cancers being diagnosed under age 50, or
- A CRC with two or more first or second degree relatives with CRC (or other Lynch cancers) regardless of age.

Lynch CRC presentation at colonoscopy

➔ CRCs often present on the right side of the colon – important to scope to the terminal ileum;





➔ Bowel polyps are often flat;

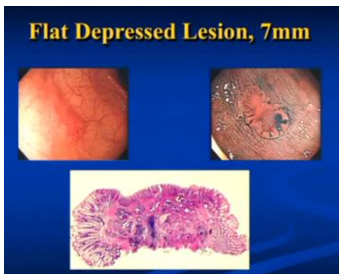
➔ Small adenomas may present with advanced histology;

➔ Polyps exhibit rapid carcinogenesis. Average time from polyp to CRC: Lynch carrier ≈ 35 months, General population ≈ 10 years;

➔ CRCs often present at a much younger age (<25 not unheard of);

➔ Presentation of synchronous CRCs is not unusual;

➔ Increased risk of secondary primary cancer (25-30%).



Photos: Dr M Appleyard

Endoscopy surveillance protocol

➔ Annual colonoscopy is recommended from age 25 (MLH1 or MSH2 gene mutation) or age 30 (MSH6 or PMS2 gene mutation), or 5 years younger than youngest CRC affected relative;

➔ Biennial upper GI endoscopy;

➔ All polyps must be removed, with special attention to the right colon and alertness to flat lesions;

➔ Consider capsule endoscopy for patients with a personal / family history of small bowel cancer.

CRC – Lynch syndrome diagnosis map

Lynch Syndrome Australia

Colorectal cancer - tissue sample

Pathology – Immunohistochemistry (IHC) test **(Medicare item: 72847)**

This staining test looks for loss of proteins associated with mutations in one of the four mismatch repair (MMR) genes associated with Lynch syndrome (i.e. MLH1, MSH2, MSH6, PMS2).

A **negative result** for a gene means the protein is not being made properly and there could be an inherited germline mutation in that gene. Note: the MMR genes work in pairs. For example,

- A mutation in MLH1 will produce a negative staining result for both MLH1 and PMS2.
- A mutation in MSH2 will produce a negative staining result for both MSH2 and MSH6.
- A mutation in PMS2 will produce a negative staining result for PMS2 (only).
- A mutation in MSH6 will produce a negative staining result for MSH6 (only).

Mutations in more than one MMR gene are extremely rare. **Negative results should be actioned**.

Pathology – BRAF test **(follows a negative IHC result for MLH1 gene only)**

If the staining test result is negative for MLH1, then the sample should be subjected to a further elimination test: a BRAF V600E test.

This relatively inexpensive test can distinguish between the germline (hereditary) mutations that occur in the MLH1 gene (e.g. those in Lynch syndrome carriers which can be identified through genetic sequencing) and the far more prevalent somatic changes (e.g. due to environmental influences) that randomly occur in genes over time.

A BRAF test ensures only those patients with a potential germline mutation are referred for genetic sequencing. The BRAF test works only for MLH1 genes.

Patients whose IHC result shows loss of staining MAY have a mutation in an MMR gene associated with LS and should be referred to a the Hereditary Cancer Clinic in your state.

Genetic counsellors at the Hereditary Cancer Clinic will:

- Provide information about Lynch syndrome – the various increased cancer risks associated with the syndrome and the significant cancer prevention / early detection benefits that may be gained from diagnosis and a regular screening program.
- Explain how genetic sequencing is used to confirm a diagnosis of Lynch syndrome by identifying the specific MMR gene mutation. This then enables other family members who may be at risk to be tested (by comparison to the identified mutation).
- Counsel the patient regarding the benefits and consequences of genetic sequencing and seek consent to have the tumour sample tested. If consent is given, the genetic counsellor will arrange for the genetic sequencing to be undertaken (Important: the patient does not pay the costs if the genetic sequencing is requested by a Hereditary Cancer Clinic.