

LYNCH SYNDROME

Bottom line: Lynch syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is the most common hereditary colorectal (CRC) cancer predisposition syndrome. It is an autosomal dominant condition that causes a significant increased lifetime risk of CRC and endometrial (uterine) cancer in addition to other cancers. Individuals suspected of having LS should be referred for a genetic consultation for consideration of genetic testing. Screening, surveillance and management of CRC and other cancers should be guided by genetic test results and/or family/ personal history. Studies show that conversations between patients and their healthcare providers are the strongest driver of screening participation.

WHAT IS LYNCH SYNDROME?

Lynch syndrome (LS) is an autosomal dominant cancer predisposition syndrome caused by inherited mutations in genes responsible for correcting DNA replication errors, called mismatch repair (MMR) genes. **Individuals with LS have a high risk for colorectal and endometrial cancers** and a moderate risk for other cancers (Box 1 and Table 1). Not all individuals who inherit a mutation in a LS gene will develop cancer (*reduced penetrance*) and the signs and symptoms, type and age of onset of cancer will vary within families (*variable expressivity*).

BOX 1: LYNCH SYNDROME-RELATED CANCERS

- | | | | | | |
|---------------------|------------------------------------|--------------|-----------|-----------|----------|
| ✓ Colorectal | ✓ Endometrial | ✓ Kidney | ✓ Gastric | ✓ Ovarian | ✓ Ureter |
| ✓ Small bowel | ✓ Hepatobiliary | ✓ Pancreatic | | | |
| ✓ Brain | ✓ Sebaceous (adenoma or carcinoma) | | | | |

PREVALENCE

LS accounts for about 0.7-3.6% of cases of CRC. Research on LS-related endometrial cancer is still emerging; current data suggest that in North America between 1.8% and 4.5% of cases are attributed to LS.

PERSONAL HISTORY RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

These are general guidelines to identify patients at **high risk** for LS. You should check with your [local genetics centre or hereditary cancer program](#) for more specific details. Consider referring your patient if he/she has:

- 🔴 An early age of CRC diagnosis (<50 years). Patients diagnosed <35years are much more likely to have LS.
- 🔴 An early age of endometrial cancer diagnosis (<50 years)
- 🔴 Multiple primary LS-related cancer diagnoses, regardless of age
- 🔴 A CRC diagnosis and one or more 1st degree relatives with a LS-related cancer, with one of the cancers being diagnosed <50 years
- 🔴 A CRC diagnosis and two or more 1st or 2nd degree relatives with LS- related cancers regardless of age
- 🔴 A CRC diagnosis <60 years with histological features suspicious for LS (excess infiltrating lymphocytes, mucinous/signet cell features, Crohn's-like reaction), particularly when primary tumour is right-sided

FAMILY HISTORY RED FLAGS TO CONSIDER GENETIC CONSULTATION

You should consider referring your patient to [your local genetics centre or hereditary cancer program](#) for further assessment if he/she is at **high risk** for hereditary CRC syndrome.

A patient is considered to be at **high risk** for LS syndrome if he/she

- ✦ Has a known LS causing mutation in the family

Or if he/she meets the revised Amsterdam criteria, meaning he/she:

- ✦ Has **at least three relatives** with a cancer associated with LS (Box 1); the following criteria should also be present:
 - ✦ One must be a first degree relative of the other two;
 - ✦ At least two successive generations must be affected (autosomal dominant inheritance);
 - ✦ At least one relative with LS-related cancer should be diagnosed before age 50;*Tumours should be verified when possible and other CRC syndromes should be ruled out*

If your patient does not have cancer, genetic testing of a relative with cancer may be recommended as a first step.

If your patient does not meet any of the criteria above, but you are suspicious of a hereditary cancer syndrome, consult [your local genetics centre or hereditary cancer program](#). In general, suspicion of a hereditary cancer syndrome should be raised if:

- ✦ There are multiple family members with cancer
- ✦ Cancers occur on the same side of family
- ✦ Cancer diagnoses occur at a younger than expected age
- ✦ Several generations are affected (demonstrating an autosomal dominant pattern – typical of most hereditary cancer syndromes)
- ✦ Clustering of certain types of cancers is present (for LS, see Box 1)
- ✦ Multiple primary cancers are diagnosed in same individual

HOW IS GENETIC TESTING DONE?

Ideally testing begins with immunohistochemical (IHC) analysis of a CRC tumour for the proteins associated with the LS genes (*MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*). IHC analysis looks at the protein products of the LS genes. If IHC analysis reveals a protein to be deficient, genetic testing can be offered to the affected individual and performed on a blood sample. If IHC analysis does not clearly show protein deficiency, the next step is often microsatellite instability (MSI) testing of the tumour sample. If MSI is stable or low, no further testing is indicated. If MSI is high, genetic testing can be offered to the affected individual and performed on a blood sample. Some centres will arrange IHC or MSI alone; others will carry out both tests at the same time.

WHAT DOES THE GENETIC TEST RESULT MEAN?

If your patient has been found to carry a mutation in a LS gene, a **positive result**, he/she has an increased lifetime risk to develop certain cancers (Table 1 and Box 1). This also means that family members are at risk of carrying the same mutation and of having similar cancer risks.

If a mutation is not identified in someone from a family with a known mutation, this is a **true negative result**. You can provide reassurance to your patient. These individuals may still have modified screening recommendations based on their family history. Consult [your local genetics centre or hereditary cancer program](#).

If a mutation is not identified in an affected patient who has no known familial mutation this result is **uninformative**. A **variant of uncertain significance (VUS)** could be identified, which is a gene change that has not yet been categorized as benign or as pathogenic. In both of these cases, the diagnosis of LS is not confirmed or ruled out, especially in families with a strong history of CRC.

Table 1. Significant lifetime cancer risks for individuals who have inherited a mutation in the LS genes, *MLH1* and *MSH2*, as compared to the general population. *Risks for other LS genes are lower.*

Cancer type	LS lifetime cancer risk in a carrier of a <i>MLH1</i> or <i>MSH2</i> gene mutation		General Population lifetime cancer risk < 70 years
	Risk	Mean age of diagnosis	Risk
Colon	52-82%	44-61 years	5.5%
Endometrium	25-60%	48-62 years	2.7%

SCREENING AND SURVEILLANCE

In general, for **high risk** individuals (*carriers of a mutation in a LS gene and their first degree relatives who have not yet had genetic testing*) screening recommendations are as follows:

Colorectal Cancer: Colonoscopy every 1-2 years beginning between ages 20 and 25 or 2-5 years prior to the earliest diagnosis *if* that diagnosis was made before age 25 years, whichever is earlier.

Endometrial and Ovarian cancer: Screening for endometrial or ovarian cancer may include annual transvaginal ultrasound and endometrial biopsy, however, there is little evidence of the effectiveness of these tests. Most importantly, women should be educated about the symptoms of endometrial cancer. Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option that LS women who have completed childbearing can consider.

Individuals who have **tested negative** for a known familial LS gene should follow provincial guidelines for population risk CRC screening, i.e. Fecal Occult Blood Test every two years from age 50. For those individuals who have a family history of CRC unrelated to the mutation in their family (i.e. on the other side of the family), screening recommendations would be based on the family history. Consult [your local genetics centre or hereditary cancer program](#).

For individuals where **no mutation** was identified and there was **no known familial mutation** (*uninformative result*) or when a **variant of uncertain significance (VUS)** was identified, screening recommendations will be based on a combination of factors, such as family history and in cases where a VUS was identified, information about the VUS.

CRC screening for **intermediate risk** individuals is dependent on family history. For a person with a:

- 1st degree relative with CRC diagnosis <50 years or two 1st degree relatives with CRC at any age → Colonoscopy at age 40 or 10 years younger than the youngest CRC diagnosis, repeat 3-5 yearly
- 1st degree relative with CRC diagnosis ≥50 years → Colonoscopy at age 50 or 10 years younger than the youngest CRC diagnosis, repeat 5 yearly
- 2nd degree relative with CRC diagnosis <50 years → Colonoscopy at age 50, repeat dictated by findings

See www.geneticseducation.ca for the full GEC-KO *Messenger* on LS for more details. For general guidelines on CRC management: National Comprehensive Cancer Network (NCCN) Guidelines for colorectal cancer screening V.2.2013 [Login required – no fee]

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