

LYNCH SYNDROME: HEREDITARY COLORECTAL CANCER PREDISPOSITION SYNDROME

Bottom line: Lynch syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is the most common hereditary colorectal cancer predisposition syndrome. It is an autosomal dominant condition that results in an increased lifetime risk of colorectal cancer (CRC) in addition to other cancers. Individuals at high or intermediate risk of LS should be referred for a genetic consultation for consideration of genetic testing. 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 (LS)?

It is estimated that one in 14 men and one in 15 women will develop CRC during their lifetime. CRC is the second deadliest form of cancer, but, with early detection, there is a 90% chance of cure^{1,2}. About 5-10% of colorectal cancer is hereditary.

Lynch syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is the most common inherited cause of CRC³. LS accounts for about 0.7-3.6% of cases of CRC⁴. 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 LS⁴. Having an LS mutation results in an increased lifetime risk of CRC and other Lynch syndrome –related cancers (see [What do the results mean?](#))

Other hereditary CRCs, such as Familial Adenomatous Polyposis [FAP] account for about 1% of CRC. This GEC-KO *Messenger* will focus on LS and will not deal further with FAP.

WHAT DO I NEED TO KNOW ABOUT THE GENETICS OF LYNCH SYNDROME (LS)?

LS is caused by an inherited mutation in one of four mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or in *EPCAM*. Mismatch repair genes play an important role in a cell's ability to repair DNA damage that occurs as a cell grows and divides, by identifying and removing single nucleotide mismatches, insertions and deletion loops. Defects in the MMR pathway lead to an accumulation of mutations in a cell which may result in a malignancy³.

Microsatellite Instability (MSI)

LS is characterized by tumours that exhibit microsatellite instability (MSI). A microsatellite is an area of DNA with a repetitive sequence (i.e. CGCGCGCGC or GAAGAAGAA). These stretches of DNA are susceptible to changes in the number of repeats when a mutation in a MMR gene is present. Cancer arising as the result of a defective MMR gene exhibits an inconsistent number of microsatellite repeats when compared to normal tissue - this is called microsatellite instability (MSI). Approximately 90% of CRCs occurring in individuals with Lynch syndrome exhibit MSI. Approximately 15% of sporadic colorectal cancers (not associated with LS) also exhibit MSI.⁵

PATTERN OF INHERITANCE

LS is an autosomal dominant condition with reduced penetrance and variable expressivity. This means that not all individuals who inherit a mutation in an LS gene will develop cancer (reduced penetrance) and the signs and symptoms/type and onset of cancer will vary between affected family members (variable expressivity).

WHO SHOULD BE OFFERED GENETIC TESTING?

Currently the decision to have genetic testing is made in the setting of a genetics consult at a hereditary cancer program or a general genetics clinic. Click to connect to [your local genetics centre or hereditary cancer program](#).

If possible, the affected individual in the family at highest risk to carry a mutation is offered testing first in order to maximize the likelihood of detecting a mutation. This would usually be a young individual with CRC or another LS-associated cancer.

HOW DO I ASSESS MY PATIENT'S RISK?

LS can be identified by looking for **red flags** in a personal and/or family history.

BOX 1: LYNCH SYNDROME-RELATED CANCERS

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

PERSONAL HISTORY **RED FLAGS** FOR A CRC SYNDROME⁶:

These are general triage 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 suspicious.
- 🔥 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

The Bethesda criteria are those marked with an asterisk. They were developed to identify people at risk of having LS who do not meet the Amsterdam criteria, which are based more on family history than personal history. Patients who meet either Bethesda or Amsterdam criteria are at **high risk** for LS.*

FAMILY HISTORY RED FLAGS FOR A CRC SYNDROME:

Take a three generation family history (your patient's generation and, depending on your patient's age, a prior generation and a subsequent generation, or two prior generations including both maternal and paternal sides of the family); target cancer (all types) and polyps, noting the ages at diagnosis and the primary tumour sites.

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

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

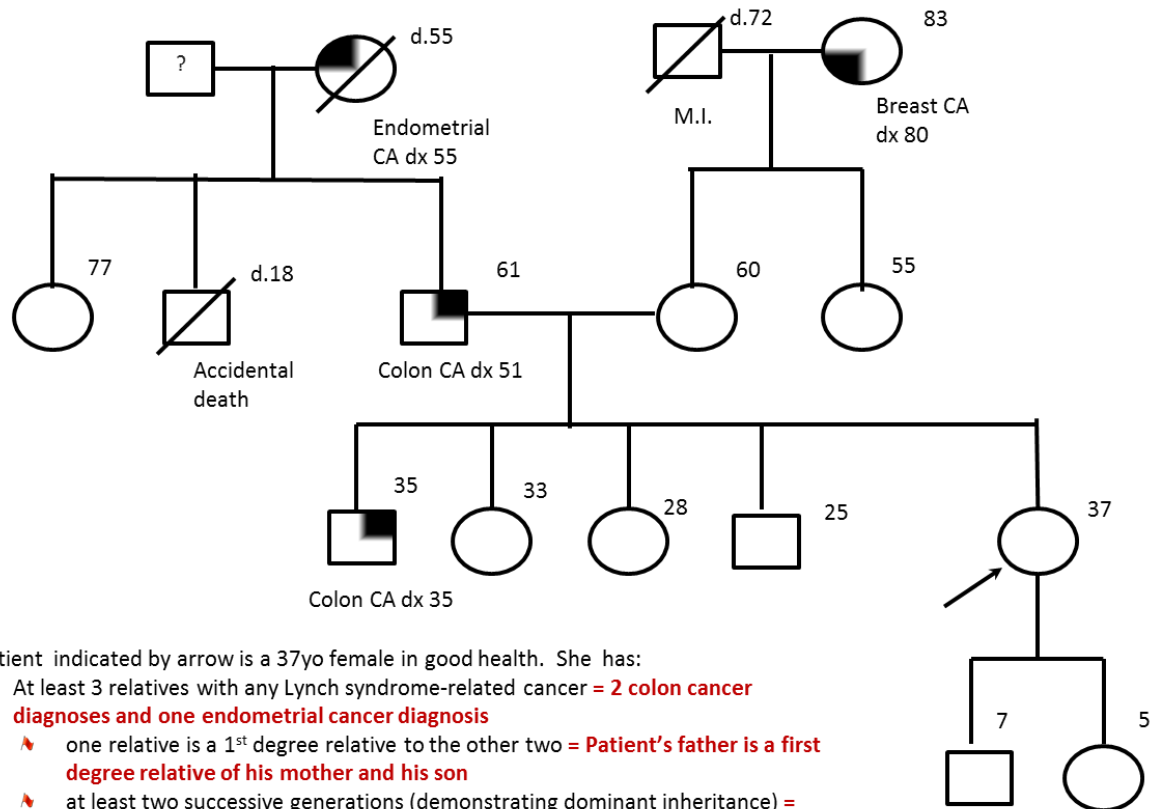
- ✦ Has a known LS causing mutation in the family

Or if he/she meets the revised Amsterdam criteria, meaning he/she⁷ (see Figure 1):

- ✦ 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 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



Patient indicated by arrow is a 37yo female in good health. She has:

- ✦ At least 3 relatives with any Lynch syndrome-related cancer = **2 colon cancer diagnoses and one endometrial cancer diagnosis**
 - ✦ one relative is a 1st degree relative to the other two = **Patient's father is a first degree relative of his mother and his son**
 - ✦ at least two successive generations (demonstrating dominant inheritance) = **Lynch syndrome-related cancer diagnoses are seen in three successive generations**
 - ✦ one diagnosis below age 50 = **The patient's brother**
- AND
- ✦ on the same side of the family = **All Lynch syndrome-related cancer diagnoses are on the patient's paternal side of the family**

Figure 1. Example of a pedigree meeting Amsterdam criteria. The patient (37yo female indicated by the arrow) could benefit from genetic counselling based on her family history; however she would likely not be offered genetic testing because an affected family member (ideally her affected brother) would be most appropriate and informative to test first.

Individuals whose histories may not be appropriate for referral for genetic consultation may still benefit from additional screening as they could be at **increased risk** to develop CRC. See [Table 2](#) in Screening and Surveillance for these criteria and recommendations.

If your patient meets none of the **high** or **increased** risk for CRC criteria, general provincial screening recommendations should be followed.

WHAT DO THE GENETIC TEST RESULTS MEAN?

If your patient has been found to carry a mutation in a Lynch syndrome gene, he/she has an increased lifetime risk to develop certain cancers (Table 1)³. This also means that family members are at risk of carrying the same mutation and of having similar cancer risks. Evidence is emerging from population based studies that these cancer risks are gene specific^{8,9}.

Table 1. Lifetime cancer risks for individuals who have inherited a mutation in a Lynch syndrome gene as compared to the general population.³

Cancer type	Lynch syndrome lifetime cancer risk (carrier of a <i>MLH1</i> or <i>MSH2</i> gene mutation)		General Population lifetime cancer risk < 70years-old
	Risk	Mean age of diagnosis	Risk
Colon	52-82%	44-61 years	5.5%
Endometrium	25-60%	48-62 years	2.7%
Stomach	6-13%	56 years	<1%
Ovary	4-12%	42.5 years	1%
Hepatobiliary tract	1-4%	Not yet reported	<1%
Urinary tract (ureter and renal pelvis)	1-4%	55 years	<1%
Small bowel	3-6%	49 years	<1%
Brain/ central nervous system	1-3%	50 years	<1%
Sebaceous neoplasm	1-9%	Not yet reported	<1%
Pancreas	1-6%	Not yet reported	<1%

HOW DO I ORDER THE GENETIC TEST?

Currently the decision to offer genetic testing is made in the setting of a genetics consult at a hereditary cancer program or general genetics clinic. To assess if your patient could be eligible for genetic testing see [Who Should Be Offered Genetic Testing?](#) Click to connect with [your local genetics centre or hereditary cancer program](#) and find their referral criteria. If your patient does not have cancer, genetic testing of a relative with cancer will be recommended as a first step

Once a patient has been referred to a hereditary cancer program/general genetics clinic and genetic testing is offered and accepted, the algorithm for LS testing (Figure 2) is as follows. Ideally testing begins with immunohistochemical (IHC) analysis of a CRC tumour (it is possible to test other tumour types if a CRC tumour is not available) 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. Inherited mutations in *MLH1* result in loss of expression of *MLH1* and *PMS2* and inherited mutations in *MSH2* typically result in loss of expression of *MSH2* and *MSH6*. 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 [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.

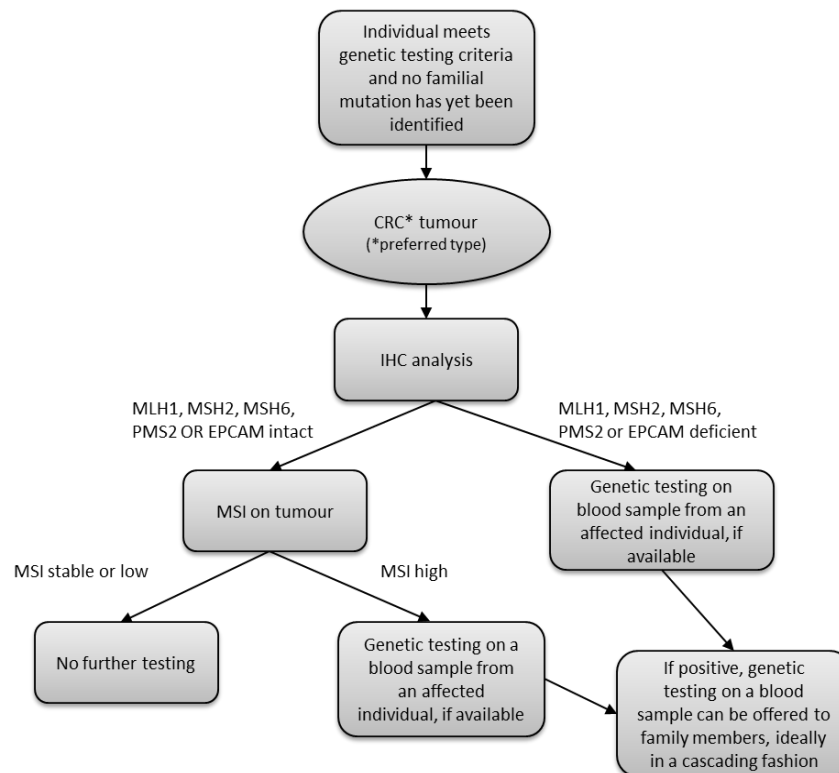


Figure 2. Lynch syndrome testing algorithm

WHERE DO I REFER MY PATIENT?

Click to connect to [your local genetics centre or hereditary cancer program](#).

Note that hereditary cancer programs/general genetics centres vary with regards to the referrals they choose to accept. You may want to contact [your local genetics centre or hereditary cancer program](#) for more information.

Include all relevant information with your referral (e.g. family history, cancer history, pathology results, genetic test results, and results of investigations such as colonoscopies). Encourage your patient to collect this information if you do not have it, to facilitate a productive genetic counselling session and to prevent unnecessary delays when further clarification is needed before an appointment can be booked.

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

If a mutation is identified (a positive test result):

- Appropriate surveillance and management can improve outcome
 - High compliance with screening leads to no increase in mortality for individuals with Lynch syndrome over their mutation-negative relatives^{3,11}
 - When detected early, colorectal cancer has a 90% cure rate¹
 - Studies show that conversations between patients and providers are the strongest driver of screening participation^{1,2}
- Other at risk family members can be identified¹²
- Positive health behaviours can be reinforced¹²

If a mutation is not identified and testing was for a known familial mutation (true negative):

- Your patient is not considered to be at increased risk of developing hereditary cancer but may still be at increased risk of cancer depending on family history
- You can provide reassurance to your patient

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

If a mutation is identified (a positive test result)¹²:

- Your patient may experience psychological distress knowing he/she is at increased risk to develop cancer, and/or over the possibility he/she may have passed the mutation to his/her children
- Family issues such as confidentiality concerns may inhibit the transfer of information between relatives
- Your patient may face insurance (life, disability, long-term) or job discrimination, although the increased risk over and above that associated with a strong family history of cancer may be small
- Incomplete penetrance – being identified as having a mutation does not mean one will develop cancer

If a mutation is not identified in an unaffected patient and testing was for a known familial mutation (true negative)^{12,13,14}:

- Depending on family dynamics (some siblings may have tested positive while some have not) or family history of extensive cancer, your patient may experience psychological distress such as ‘survivor guilt’ or ‘identity loss’
- Your patient may develop a complacent attitude to health and screening

If no mutation is identified in an affected patient who has no known familial mutation (uninformative result) or when a variant of uncertain significance (VUS) is identified^{12,14}:

- The diagnosis of Lynch Syndrome is not confirmed or ruled out, even in families with a strong history of CRC
- 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
- Please consult your patient’s geneticist, also see surveillance and management

SURVEILLANCE AND MANAGEMENT

In general, for **high risk** individuals (*carriers of a Lynch syndrome gene mutation and their first degree relatives who have not yet had genetic testing*):

COLORECTAL CANCER

Current recommendations for those with *LS* mutations are colonoscopy every 1-2 years beginning between ages 20 and 25, or 2-5 years prior to the earliest colon cancer in the family *if* that diagnosis was made before age 25 years, whichever is earlier.^{3,10,14} Recommendations may vary depending on the specific mutation.^{3,10}

Because routine colonoscopy is an effective preventive measure for colorectal cancer, prophylactic colectomy is generally not recommended for individuals with Lynch syndrome.³

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 tests¹⁴. Most importantly, women should be educated about the symptoms of endometrial cancer because many endometrial cancers can be diagnosed at early stages on the basis of symptoms.^{3,10} Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option that *LS* women who have completed childbearing can consider.^{3,10,14}

OTHER EXTRACOLONIC CANCERS¹⁰

There is no clear evidence to support additional screening for gastric, duodenal, small bowel, central nervous system or breast cancer. Annual health examination is recommended.

However, for some individuals, depending on family history or ancestry (Asian), upper endoscopy surveillance with extended duodenoscopy can be used to screen for cancer of the stomach.

Screening for urothelial cancer by urinalysis starting at age 25-30 years may also be considered, if there is a family history of these cancers.

Individuals who have tested negative for a known familial *LS* gene should follow provincial guidelines for population risk CRC screening (see below). 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 will be based on that 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.

INCREASED RISK FOR CRC¹⁰

Table 2. Screening recommendations for individuals at increased risk to develop CRC who do not meet high risk, LS criteria.

Criteria	Recommendation
One 1 st degree relative with a CRC diagnosis less than age 50 (older than age 35) OR Two 1 st degree relatives with CRC diagnoses at any age	Colonoscopy beginning at age 40 <u>OR</u> 10 years younger than the youngest CRC diagnosis. Repeat every 3-5y depending on family history and findings.
A 1 st degree relative with a CRC diagnosis at age 50 or older	Colonoscopy beginning at age 50 <u>OR</u> 10 years younger than the earliest CRC diagnosis. Repeat every 5 years, depending on family history and findings.
One 2 nd degree relative with a CRC diagnosis less than age 50	Colonoscopy beginning at age 50. Repeat depending on findings.
A 1 st degree relative with advanced adenomas	Colonoscopy beginning at age 50 <u>OR</u> at age of detection, whichever is first. Repeat depending on findings.
A personal history of colorectal adenomatous polyps	Colonoscopy repeated every 3-5years depending on findings.
A personal history of inflammatory bowel disease	Initiate screening 8-12 years after onset of symptoms (consult specialist), with colonoscopy every 1-2 years. Management is dependent upon findings.

GENERAL POPULATION RISK FOR CRC

For patients who are at general population risk for CRC, recommendations should follow provincial guidelines. In Ontario, these can be found at [Cancer Care Ontario](#) under the [ColonCancer Check](#) program. General population screening guidelines are for individuals who have no symptoms of CRC and no family history of CRC, or who test negative for a known LS gene mutation in the family.

For all average risk adults 50 years and older, recommended screening for CRC is Fecal Occult Blood Testing (FOBT) every two years.

RESOURCES FOR HEALTH PROFESSIONALS

- [1] Cancer Care Ontario (CCO). <https://www.cancercare.on.ca/> [Accessed October 2013]
- [2] ColonCancerCheck (CCC) <http://www.health.gov.on.ca/en/pro/programs/coloncancercheck/> [Accessed October 2013]
- [3] Kohlmann W, Gruber SB. Lynch Syndrome. 2004 Feb 5 [Updated 2012 Sep 20]. In: Pagon RA, Adam MP, Bird TD, *et al.*, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1211/> [Accessed December 19th, 2013]
- [4] Egoavil C *et al.*, Prevalence of Lynch syndrome among patients with newly diagnosed endometrial cancers. *PLoS One* 2013; 8(11):e79737
- [5] Zhang X and Li, J. Era of universal testing of microsatellite instability in colorectal cancer. *World J Gastrointest Oncol* 2013; 5(2): 12-19
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- [7] Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. *J Clin Oncol* 2000; 18(21 Suppl):81S-92S
- [8] Bonadona V *et al.*, Cancer risk association with germline mutations in MLH1, MSH2 and MSH6 genes in Lynch syndrome. *JAMA* 2011; 305(22): 2304-2310.
- [9] Dowty JG *et al.*, Cancer risks for MLH1 and MSH2 mutation carriers. *Human Mutation* 2012; 34(3): 490-497
- [10] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colorectal Cancer Screening V.2.2013© National Comprehensive Cancer Network, Inc 2013. All rights reserved. Accessed [04/09/2014]. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.
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- [13] Valverde K. Why me? Why not me? *J Genet Counsel* 2006; 15(6): 461-463
- [14] Vasen HF *et al.*, Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 2013; 62:812-823.

ADDITIONAL RESOURCES:

- National Coalition for Health Professional Education in Genetics (NCHPEG). Hereditary Colorectal Cancer Resources. http://www.nchpeg.org/index.php?option=com_content&view=article&id=417&Itemid=287
- Ahnen, DY and L Axell. Clinical features and diagnosis of Lynch syndrome (hereditary nonpolyposis colorectal cancer). In *Up To Date*, LaMont, JT (Ed), **UpToDate**, 2013
- Bonis PA, DJ Ahnen and L Axell. Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and management of patients and families. In **UpToDate**, J Thomas LaMont, JT and B Goff (Ed), 2013
- Leddin D *et al.*, Canadian Association of Gastroenterology and Canadian Digestive Health Foundation: Guidelines on colon screening. *Can J Gastroenterol* 2004; 18(2): 93-99
- Lynch HT *et al.*, Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. *Clin Genet* 2009; 76(1):1-18

RESOURCES FOR PATIENTS AND THE PUBLIC

ColonCancerCheck (CCC) <http://www.health.gov.on.ca/en/public/programs/coloncancercheck/>

Canada's first province-wide, population-based colorectal cancer screening program -- ColonCancerCheck -- launched in Ontario in 2008. The program is a partnership between the Ministry of Health and Long-Term Care and Cancer Care Ontario.

Canadian Cancer Society (CCS) <http://www.cancer.ca/en/?region=on>

Lynch Syndrome International (LSI) <http://www.lynchcancers.com/>

An all-volunteer organization founded and governed by Lynch syndrome survivors, their families, and health care professionals who specialize in Lynch syndrome. The primary mission is to focus on providing support for individuals affected by Lynch syndrome, creating public awareness of the syndrome, educating members of the general public and health care professionals and providing support for Lynch syndrome research endeavours.

Authors: S Morrison MS CGC, JE Allanson MD FRCPC, E Tomiak MD FRCPC, K Semotiuk MS (C)CGC and JC Carroll MD CCFP

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