



☆ Topic: Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

☆ **Summary:** One in 16 Canadians will develop colorectal cancer (CRC) for a lifetime risk of 6%. Less than 10% of CRC is hereditary and increasing age is the main risk factor. The most common form of hereditary CRC, hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch Syndrome, can cause up to an 80% lifetime risk for CRC and substantially increases the risk for of endometrial, ovarian, and stomach cancers.

☆ **Bottom line:** Individuals with “high risk” family histories of colorectal, endometrial and other HNPCC-related cancers, particularly in close relatives, should be offered referral for genetics services. Increased surveillance by annual colonoscopy, beginning at 20-25 years of age, is an effective preventive measure for individuals with HNPCC/Lynch syndrome gene mutations. Individuals at moderate risk for CRC should be offered colonoscopic screening beginning 10 years younger than the youngest CRC diagnosis or no later than age 40, while average risk individuals can follow general population guidelines.

✓ The Disease

- ~20% of colorectal cancer is familial (family history of CRC).
- 5-10% is hereditary – an inherited mutation in a single gene that increases risk for cancer.
- The most common hereditary form of CRC is Lynch Syndrome or HNPCC which accounts for 1-5% of all CRC.
- Other inherited CRC susceptibility syndromes account for less than 1% of colorectal cancer and include Familial Adenomatous Polyposis (FAP), *MYH*-associated polyposis, Juvenile Polyposis syndrome, Peutz-Jeghers syndrome.
- The remaining 10-15% of CRC is due to a combination of other genetic and non-genetic factors in the family, which could include the environment, chance, undiscovered gene mutations, several low penetrance genes.

✓ The Genes

- Four main HNPCC/Lynch Syndrome genes have been discovered so far: *MSH2*, *MLH1*, *MSH6*, and *PMS2*.
- 90% of HNPCC/Lynch Syndrome families have a mutation in *MSH2* or *MLH1*.
- Over 400 different mutations are known.
- Autosomal dominant inheritance
- Carrier frequency of HNPCC/Lynch Syndrome mutations is ~1/200-1/1000 in general population.
- The Lynch Syndrome genes are mismatch repair genes: serve to repair damaged DNA.
- Mutation leads to:
 - Inability to correct acquired mutations caused by errors in replication or toxins.
 - Accumulation of mutations in the cell, which can result in cancer.

✓ **Consequences of having an HNPCC/Lynch Syndrome gene mutation**

*HNPCC tumour sites	Estimated risk in HNPCC gene mutation carriers (by age 70)	In General Population
Colorectal Cancer	70- 80%	6%
Endometrial Cancer	20 - 60%	2.7%
Stomach Cancer	13-19%	<1%
Ovarian Cancer	9-12%	1.6%
Hepatobiliary Tract	2-7%	<1%
Urinary Tract	4-5%	<1%
Small bowel	1-4%	<1%
Brain	1-2%	<1%

✓ **Who should be offered referral for genetic counselling? (specific criteria may vary by province)**

Patients with:

- 1st or 2nd degree relative with colorectal cancer (CRC) ≤ age 35 **or**
- 1st or 2nd degree relative with 2 or more HNPCC/Lynch Syndrome-related cancers* (see table) **or**
- 2 or more 1st or 2nd degree relatives on same side of family with CRC diagnosed < age 50 **or**
- 3 or more relatives with any HNPCC/Lynch Syndrome-related cancers at any age, on same side of family, at least 1 of whom has CRC **or**
- Family member with an identified HNPCC/Lynch Syndrome mutation

If there is a strong family history of polyps, consider referral for hereditary adenomatous polyposis syndromes (Familial Adenomatous Polyposis syndrome (FAP), MYH- Associated Polyposis syndrome) when multiple individuals have >10 adenomatous colorectal adenomas, or Cowden syndrome, Peutz-Jeghers Syndrome and Juvenile Polyposis Syndrome, when multiple family members have hamartomatous type gastrointestinal polyps.

✓ **Testing - for mutations in HNPCC/Lynch Syndrome genes**

- TWO parts
 1. Tumour testing first on a sample of colorectal cancer tumour (immunohistochemistry and microsatellite instability) – other tumours can be used if CRC tumour not available
 2. Blood test – gene analysis usually only performed if tumour testing is suggestive of HNPCC/Lynch Syndrome, except in the highest risk families when it can be done if no tumour tissue is available
- MLH1, MSH2 and MSH6 gene analysis is currently available at regional genetic centres.
- Covered by provincial insurance if criteria met.
- Testing eligibility criteria reflect a 10% or higher probability of mutation.
- Test highest risk *affected* individual first. Genetic testing is generally NOT offered to unaffected individuals unless a mutation has been identified in the family.

✓ **Benefits of genetic testing**

Positive test result

- Clinical intervention can improve outcome:
 - Colonoscopy every 1-2 years beginning at age 20-25 years or 10 years younger than the youngest diagnosis in the family, whichever comes first, reduces morbidity and mortality of

colorectal cancer.^{1,2}

- Consideration of prophylactic removal of the uterus and ovaries after childbearing is complete or near age 40.
- Attention to symptoms of endometrial cancer with option of annual endometrial screening beginning at age 30-35 years (Level of evidence: expert opinion)
- Family members at risk can be identified.
- Positive health behaviours can be reinforced.

Negative test result for a known family mutation

- Reassurance of individuals in the family who do not carry the mutation
- Can follow general population screening guidelines

✓ Harms/limitations of genetic testing

Positive test result

- Adverse psychological reaction, family issues/distress
- Incomplete penetrance – having the mutation does not necessarily mean the patient will get the disease
- Insurance/job discrimination, confidentiality issues – especially among family members

Negative test result for a known family mutation

- Adverse psychological reaction (survivor guilt)
- Complacent attitude to health

Uninformative test results and variants of unknown significance. In these cases, testing for HNPCC/Lynch Syndrome does not confirm this diagnosis, even in families with a strong history of CRC. Screening should still be based on family history (see Canadian Association of Gastroenterology guidelines).

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★Web Resources:

- www.geneclinics.org *Lynch Syndrome*
- National Cancer Institute: *The Genetics of Colorectal Cancer PDQ*
www.cancer.gov/cancertopics/pdq/genetics/colorectal/healthprofessional
- NCCN Clinical Practice Guidelines in Oncology - *Colorectal Cancer Screening* 2010 www.nccn.org
- Ontario Medical Review – November 2001 www.oma.org/pcomm/OMR/nov/01genetics.htm

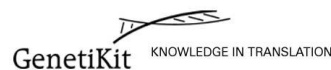
★References:

1. Leddin D, Hunt R, Champion M, et al. Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: Guidelines on colon cancer screening. *Can J Gastroenterology* 2003;17:133-134.
2. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000; 118: 829–34.

For a listing of cancer genetics clinics in Canada, along with their respective contact and referral information, visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca.

"Gene Messenger" is for educational purposes only and should not be used as a substitute for clinical judgement. The "GenetiKit" team aims to aid the practicing clinician by providing informed opinions regarding genetic services that have been developed in a rigorous and evidence-based manner. Physicians must use their own clinical judgement in addition to published articles and the information presented herein. The members of the GenetiKit research team assume no responsibility or liability resulting from the use of information contained on "Gene Messenger."

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