Jennifer E. Nuk, MSc, CGC, CCGC, Jennifer J. Telford, MD, MPH, FRCPC, CAGF, FACG

Familial and hereditary colorectal cancer

The BC Hereditary Cancer Program serves individuals with suspected hereditary colorectal cancer syndrome. The BC Colon Screening Program is appropriate for those who have a family history of colorectal cancer among first-degree relatives.

ABSTRACT: A family history of colorectal cancer may increase colorectal cancer risk, and more intensive screening may be indicated. The family history may be classified as familial colorectal cancer, which is multifactorial, or hereditary colorectal cancer, which is due to an inherited germline mutation in a cancer gene. Individuals with familial colorectal cancer may be screened through the BC Colon Screening Program using biennial fecal immunochemical testing; higher-risk individuals may be screened by colonoscopy every 5 years. Individuals with a family history of a hereditary cancer syndrome are referred to the Hereditary Cancer Program for genetic testing and for recommendations on colon screening, which is managed outside the BC Colon Screening Program by their colonoscopy provider.

A significant family history of colorectal cancer may be related to a hereditary syndrome, such as Lynch syndrome, or a familial susceptibility. Hereditary colorectal cancer is associated with a germline pathogenic variant in a hereditary cancer gene and accounts for 5% to 10% of all colorectal cancers. Familial colorectal cancer encompasses a heterogeneous group who may have an increased colorectal cancer risk due to multifactorial genetic and shared environmental risk factors.

Familial colorectal cancer

The risk of future colorectal cancer in an individual with a family history of colorectal cancer depends on several factors. Risk increases based on:

- Older age of the individual.
- Increased number of relatives affected.
- Closeness of the affected relative(s).
- Younger age at diagnosis of the affected relative(s).

The British Columbia guidelines for colon screening in individuals with a family history of colorectal cancer but not a hereditary colorectal cancer syndrome were updated in 2022.[1] The recommendations incorporate an updated review of the literature but remain unchanged from the previous guidelines **[Table 1]**.

In 2018, the Banff Consensus, developed by the Canadian Association of

TABLE 1. BC guidelines for screening individuals with a family history of colorectal cancer.

Family history	Test	Start age	Interval
≥ 2 FDRs* diagnosed with colorectal cancer	Colonoscopy	40 years†	5 years
1 FDR diagnosed with colorectal cancer at < 60 years of age	Colonoscopy	40 years§	5 years
1 FDR diagnosed with colorectal cancer at ≥ 60 years of age	FIT‡	50 years	2 years
≥ 1 SDR(s)§ diagnosed with colorectal cancer	FIT	50 years	2 years
≥ 1 FDR(s) diagnosed with a precancerous lesion	FIT	50 years	2 years

* FDR = first-degree relative.
† Or 10 years younger than the earliest age of diagnosis of the FDRs, whichever is earlier.
‡ FIT = fecal immunochemical test.
§ SDR = second-degree relative.

Ms Nuk is a clinical assistant professor of medicine at the University of British Columbia and practice leader of genetic counseling for the BC Hereditary Cancer Program. Dr Telford is a clinical professor of medicine at UBC, a gastroenterologist at St. Paul's Hospital, and medical director for the BC Colon Screening Program.

This article has been peer reviewed.

Gastroenterology and endorsed by the American Gastroenterological Association, was published as a guideline for screening patients with nonhereditary family history of colorectal cancer or adenoma.[2] The guidelines employed the most rigorous evaluation of the published literature and highlighted the low quality of available evidence to inform decisions regarding screening individuals with a family history of colorectal cancer. The systematic review demonstrated a twofold increased risk of colorectal cancer in individuals with one or more first-degree relatives (parent, sibling, or child) diagnosed with colorectal cancer. The risk was lowest for a single first-degree relative and increased with the number of first-degree relatives affected by colorectal cancer. In addition, as a relative's age of diagnosis increased, the risk decreased in a continuous fashion but always remained elevated compared with those without a family history. Therefore, use of an age cutoff of 50 or 60 years to assign alternative risk-based screening strategies was deemed arbitrary.[2] The group recommended colonoscopy as the preferred screening test for individuals with one or more first-degree relatives with colorectal cancer. Fecal immunochemical testing was recommended as a second-line screening option if an individual prefers fecal immunochemical test over colonoscopy or is at increased risk of colonoscopy-related complications, and to ensure equitable access to colon screening when colonoscopy resources are limited.

One year after the Banff Consensus was developed, a systematic review and meta-analysis by Roos and colleagues reported on the cumulative risk of developing colorectal cancer by 85 years of age in individuals with a family history of colorectal cancer in Western European and United States populations.[3] The relative risk for patients with at least one first-degree relative with colorectal cancer was lower than previously reported and was not significantly different from individuals without a family history of colorectal cancer: 1.37 (95% CI, 0.76-2.46) in pooled cohort studies. The relative risk increased to 3.26 (95% CI, 2.82-3.77) when the first-degree relative was less than 50 years of age at the time of diagnosis, and to 2.02 (95% CI, 1.59-2.57) when the first-degree relative was less than 60 years of age at diagnosis. However, the colorectal cancer risk among individuals with a first-degree relative who was diagnosed after 50 years of age was similar to the risk when the relative was diagnosed after 60 years of age, which implies that the increased risk to individuals with a first-degree relative who is diagnosed before 60 years of age is driven largely by those with a first-degree relative who is diagnosed before 50 years of age. These findings support screening individuals with a single older first-degree relative who has been diagnosed with colorectal cancer in a fashion similar to that of the average-risk population.

First-degree relative with colorectal cancer

Screening recommendations for individuals with two or more first-degree relatives with colorectal cancer are consistent across different jurisdictions: colonoscopy every 5 years. Conversely, recommendations for those with a single first-degree relative with colorectal cancer vary, although most guidelines recommend an age cutoff at which to intensify colon screening. The most common cutoff is 60 years of age, although the British guidelines use 50 years of age, which is supported by the findings of Roos and colleagues[3] **[Table 2]**.

Second-degree relative with colorectal cancer

Individuals with one or more second-degree relatives with colorectal cancer have a risk similar to that of the general population and should be screened as per the average-risk population.[2,8] However, an individual with multiple second-degree relatives with colorectal cancer and an early death in the connecting first-degree relative may require more intensive screening and, if the second-degree relatives are younger than 50 years of age at the time of diagnosis, a referral to the BC Cancer Hereditary Cancer Program.

First-degree relative with a precancerous lesion

An individual's risk of colorectal cancer may be affected by first-degree relatives who have had precancerous lesions removed; however, the evidence for this is of very low quality. Colonoscopy and resection of precancerous lesions will reduce an individual's risk of colorectal cancer, but there is no mechanism for determining if or when that precancerous lesion would have progressed to colorectal cancer. Therefore, it is unknown whether the individual's first-degree relatives are at increased risk for colorectal cancer. Risk stratification is further complicated by a lack of documentation to confirm the presence of precancerous lesions and whether the lesion was high risk or low risk. Given the uncertain benefit of and the difficulty with family history validation,

TABLE 2. Screening guidelines for individuals with a single first-degree relative with colorectal cancer.

Guideline	Year published	Single first-degree relative age cutoff
BC[1]	2022	Diagnosed at < 60 years of age
Ontario[4]	2017	Diagnosed at < 60 years of age
Canada (Banff Consensus)[2]	2018	Diagnosed at any age
US Multi-Society Task Force[5]	2017	Diagnosed at < 60 years of age
Britain[6]	2020	Diagnosed at < 50 years of age
Asia-Pacific[7]	2022	Diagnosed at < 60 years of age

most screening programs, BC's included, do not distinguish these individuals from the general population for screening.

However, some clinical practice guidelines have made specific recommendations. For instance, the Banff Consensus recommends initiating screening at 40 to 50 years of age or 10 years younger than the age of diagnosis of a first-degree relative with a confirmed high-risk precancerous lesion.[2] Screening with either colonoscopy every 5 to 10 years or fecal immunochemical testing every 1 to 2 years are options.

Screening with the fecal immunochemical test

The fecal immunochemical test is the most common primary screening modality used in programmatic screening. Although the BC Colon Screening Program offers intensified screening for those with a high-risk family history, in accordance with the BC Guidelines,[1] this is not the case in many screening programs. Several studies have also evaluated fecal immunochemical test performance for individuals with a family history. A cohort study in the BC Colon Screening pilot evaluated 1387 individuals who had one or more first-degree relatives with colorectal cancer. The participants were invited to complete both a fecal immunochemical test and colonoscopy. The positive and negative predictive values of the fecal immunochemical test in the detection of colorectal cancer were 4.8% and 100%, respectively.[9] In addition, the Dutch screening program invited nearly 6000 individuals to complete a fecal immunochemical test and a family history questionnaire. If either the fecal immunochemical test was positive or there was a significant family history of colorectal cancer, a colonoscopy was performed. The addition of the family history questionnaire did not increase the detection of advanced neoplasia (a combined outcome of colorectal cancer and high-risk precancerous lesions).[10] Finally, Quintero and colleagues conducted a prospective trial that randomly assigned 1981 first-degree relatives of patients with colorectal cancer to receive colonoscopy or an annual fecal immunochemical test. Follow-up after 3 years showed both screening strategies detected all the colorectal cancers, and there was no difference in the detection of advanced neoplasia.[11]

The BC Colon Screening Program screens individuals with familial colorectal cancer as follows:

- One first-degree relative diagnosed at younger than 60 years of age or two or more first-degree relatives diagnosed at any age:
  - Fill in and fax the colonoscopy referral form to the Colon Screening Program: www.bccancer.bc.ca/screening/Documents/Colonoscopy-Referral-Form.pdf.
  - The patient will be referred for colonoscopy when they are due, at 40 years of age, or 10 years younger than the age of diagnosis of the earliest affected relative.
- One first-degree relative diagnosed at older than 60 years of age:
  - Refer for biennial fecal immunochemical test at 50 years of age: www.bccancer.bc.ca/screening/Documents/Standard-Outpatient-Lab-Requisition.pdf.

Hereditary colorectal cancer

Identifying an inherited cancer susceptibility in an individual clarifies future cancer risk for both the individual and their family and informs decisions regarding increased screening and surveillance and options for prevention.

The hereditary cancer syndromes that predispose to colorectal cancer and general recommendations for colonoscopy surveillance are outlined in **Table 3**. There is wide variability in overall lifetime cancer risk, age at diagnosis, associated extracolonic cancers, and phenotypic presentation between and within conditions and families. The variability in risk may be related to shared biologic (e.g., genetic risk modifiers), social, and behavioral exposures (e.g., tobacco, alcohol, processed/red meat consumption, physical exercise).

Due to the increased complexity of colorectal screening, as well as the potential need to screen for other gastrointestinal and extraintestinal cancers, individuals with a hereditary colorectal cancer syndrome are not eligible to participate in the BC Colon Screening Program. Rather, they should be evaluated by the BC Hereditary Cancer Program, and their colorectal screening and surveillance should be managed on an individual basis by their colonoscopy provider.

Hereditary colorectal cancer syndromes can be categorized by the histologic subtype of the precancerous lesion and whether polyposis (numerous precancerous lesions), measured cumulatively over time, is a feature. Adenomatous syndromes include Lynch syndrome, which is not usually accompanied by polyposis; familial adenomatous polyposis; attenuated familial adenomatous polyposis; and *MUTYH*-associated polyposis. The hamartomatous polyposis syndromes include Peutz-Jeghers syndrome, juvenile polyposis syndrome, and *PTEN* hamartomatous syndromes. Finally, serrated polyposis syndrome is characterized by numerous serrated lesions.

Adenomatous syndromes

Lynch syndrome

Lynch syndrome is the most common type of hereditary colorectal cancer. It is diagnosed when a pathogenic germline variant is reported in a mismatch repair gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or 3' terminal deletions of *EPCAM* causing epigenetic silencing of *MSH2*).[15,16] The mismatch repair system corrects errors in base pair matching that occur during DNA replication. Lynch syndrome is an autosomal dominant condition whereby an individual will inherit a mismatch repair mutation in one allele and then the second allele is later inactivated. If there are inherited mutations in both alleles, this is termed constitutional mismatch repair deficiency and typically presents with multiple malignancies in childhood.[17]

Lynch syndrome should be suspected in individuals with a personal or family history of colorectal cancer or uterine cancer diagnosed at younger than 50 years of

TABLE 3. Hereditary cancer syndromes predisposing to colorectal cancer.[12-14]

Syndrome	Gene	Population frequency	Percentage of colorectal cancer	Cumulative lifetime colorectal cancer risk*	Average age of colorectal cancer diagnosis (years)	Colonoscopy†
Lynch syndrome		1/279	3%–5%			
	MLH1	1/1 946		50%–60%	44	Every 1–2 years from age 25
	MSH2 (includes *EPCAM*)	1/2 841 (*EPCAM* rare)		50%	44	Every 1–2 years from age 25
	MSH6	1/758		20%	42–69	Every 1–3 years from age 30
	PMS2	1/714		Up to 20%	61–66	Every 1–3 years from age 30
APC-associated polyposis‡	*APC*	1/33 000	1%	Classic FAP§: ~100% Attenuated FAP (AFAP): 70%	Classic: 39 (without colectomy) AFAP: 50	• Classic: every 1–2 years from age 10–15 • AFAP: every 1–2 years from late teens
MUTYH-associated polyposis	Biallelic *MUTYH*	Monoallelic: 1/45 Biallelic: 1/8 000	< 1%	70%–90%	45–59	Every 1–2 years from age 25–30
Peutz-Jeghers syndrome	*STK11*	1/25 000–1/280 000	< 1%	39%	40–45	• Baseline age 8 years • No polyps: every 2–3 years from age 18 • Polyps: at least every 3 years
Juvenile polyposis	*BMPR1A/SMAD4*	1/16 000–1/100 000	< 1%	30%–40%	34	• Baseline age 12–15 years • No polyps: every 3 years from age 18 • Polyps: every 2–3 years
PTEN-hamartoma tumour syndrome	*PTEN*	1/200 000	< 1%	Up to 16%	44–58	Every 5 years from age 35–40
Serrated polyposis syndrome	Multifactorial *RNF43/MUTYH*	Not well known; 0.09%–0.4% in average-risk colonoscopy patients	< 1%	15%–35%	50–60s	• Every 1–2 years from diagnosis • Every 5 years from age 40 for FDRs¶ • Every 1–3 years if polyps found

* Estimates typically reflect risk without surveillance.
† May be adjusted based on personal and/or family history of cancer/polyps.
‡ Includes familial adenomatous polyposis and attenuated familial adenomatous polyposis.
§ FAP = familial adenomatous polyposis.
¶ FDR = first-degree relative.

age, synchronous colorectal cancer (more than one colorectal cancer occurring at the same time), metachronous colorectal cancer (more than one colorectal cancer over an individual's life), and multiple Lynch syndrome–associated cancers. The Amsterdam Criteria and revised Bethesda Criteria have largely been replaced by more sensitive clinical prediction models.[15] The use of universal tumour screening of all colorectal cancers for evidence of mismatch repair deficiency will improve detection of Lynch syndrome in cases where it might otherwise go unrecognized. This is described in more detail in the "New colorectal cancer diagnosis" section.

In addition to colorectal cancer, individuals with Lynch syndrome are at increased risk for endometrial cancer (*MLH1*: 40%, *MSH2*: 50%, *MSH6*: 40%, *PMS2*: 13% to 26%), with an average age of diagnosis between 45 and 50 years of age. Depending on the genetic mutation, there is also a risk of ovarian cancer. Prophylactic hysterectomy with bilateral salpingo-oophorectomy is recommended, once childbearing has been completed, from 40 years of age.[18]

Other Lynch syndrome–associated cancers include gastric, hepatobiliary, urinary tract, small intestine, pancreas, brain, and sebaceous carcinomas, with an absolute lifetime risk of less than 5% to 20%, depending on the genetic mutation. Individual

recommendations regarding screening for these cancers depend on the affected gene and which cancers have occurred in a particular family.[18] The terms Turcot syndrome and Muir-Torre syndrome, once used to describe patients who developed glioblastoma and sebaceous skin lesions, respectively, are outdated. Any patient with Lynch syndrome can develop these tumors.

Primary prevention strategies are an important component of Lynch syndrome management. Both excess body weight and smoking are associated with colorectal adenomas in Lynch syndrome individuals.[15] Supporting patients in smoking cessation, exercise, and a healthy diet may reduce their risk. Chemoprevention of colorectal cancer using ASA in individuals with Lynch syndrome was demonstrated in an international randomized controlled trial; the hazard ratio for the per-protocol analysis was 0.65 (95% CI, 0.43-0.97).[19] The benefit was seen at 5 years in subjects who had taken ASA for at least 2 years. The adverse event rate was similar in the treatment and placebo groups. To date, only high-dose ASA, 600 mg daily, has been studied in individuals with Lynch syndrome; however, a trial is underway to examine the use of lower doses of ASA in this population.

APC-associated polyposis

Germline mutations in the tumor suppressor gene *APC* are inherited in an autosomal dominant fashion and result in familial adenomatous polyposis and attenuated familial adenomatous polyposis.[15,20] Individuals with classic familial adenomatous polyposis develop hundreds to thousands of colorectal adenomas in their teenage years and will develop colorectal cancer by 30 years of age unless colectomy is performed. In attenuated familial adenomatous polyposis, individuals develop fewer than 100 adenomas (average 30 adenomas), particularly in the right colon, and have an age of onset between 40 and 60 years of age.[20] Most individuals with familial adenomatous polyposis have a family history consistent with the syndrome, but approximately one-third do not, thus representing either a new germline mutation in that individual or genetic mosaicism.[15]

Small intestinal adenomas are common in familial adenomatous polyposis and attenuated familial adenomatous polyposis, usually in the periampullary region of the duodenum, as well as adenomatous changes in the ampulla of Vater, which results in a lifetime risk of duodenal or periampullary cancer of 4% to 12%. Screening for and resection of any small intestinal adenomas is recommended. Additional familial adenomatous polyposis–associated cancers and attenuated familial adenomatous polyposis–associated cancers include gastric, pancreatic, thyroid, bile duct, medulloblastoma, and hepatoblastoma, all at low absolute lifetime risk. Other features include dental abnormalities, such as supernumerary teeth; soft tissue tumours on the face, scalp, or abdomen (desmoids); osteomas on the skull or jaw; and congenital hypertrophy of the retinal pigment epithelium. These extraintestinal features occur less frequently in attenuated familial adenomatous polyposis.[20]

MUTYH-associated polyposis

MUTYH-associated polyposis is an autosomal recessive syndrome that results from a biallelic germline mutation in the repair gene *MUTYH*, a gene that is critical in repairing oxidative damage to the *APC* gene, among others.[15,20] The phenotype of *MUTYH*-associated polyposis is similar to familial adenomatous polyposis but with a later age of onset, 40 to 50 years of age, and fewer adenomas. The clinical presentation is variable and ranges from early-onset colorectal cancer in the absence of polyposis to mild polyposis (10 to 50 polyps) and, less commonly, to more than 100 polyps. Individuals with *MUTYH*-associated polyposis can also have a mixture of adenomas and serrated lesions.

The extracolonic malignancies are similar to familial adenomatous polyposis but also include ovarian, bladder, skin, and breast cancers. In addition to intensive screening for colorectal cancer, screening for small intestinal adenomas is recommended.

Colonic adenomatous polyposis of unknown etiology

Individuals with 10 or more cumulative colorectal adenomas are considered to have polyposis and are eligible for genetic testing through the BC Hereditary Cancer Program. The pathogenic variant detection rate in this group is 5% or higher, irrespective of age, and there is an increasing likelihood of a genetic mutation in patients with higher polyp counts at younger ages.[21]

People who have 10 or more adenomas in the colon but no pathogenic variants found in hereditary cancer genetic testing are considered to have colonic adenomatous polyposis of unknown etiology.[12] These patients should have their ongoing colon surveillance guided by their colonoscopist based on their prior colonoscopy findings.

Other hereditary adenomatous syndromes

In recent years, a moderate increase in colorectal cancer risk has been associated with genes such as *CHEK2* and *TP53* (Li-Fraumeni syndrome). Preliminary data are available for genes that are associated primarily with rare forms of polyposis, such as *GREM1* (hereditary mixed polyposis syndrome), *POLE/POLD1* (polymerase proofreading–associated polyposis), *AXIN2* (gastrointestinal polyposis and ectodermal dysplasia), *NTHL1* (attenuated polyposis phenotype with biallelic pathogenic variant), *MSH3* (polyposis with biallelic pathogenic variant), *GALNT12* (attenuated polyposis phenotype), and *RPS20* (early-onset colorectal cancer in a single Finnish family with multigenerational colorectal cancer).

Hamartomatous colorectal cancer syndromes[22]

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is associated with a histologically distinct hamartoma. It is diagnosed when an *STK11* pathogenic variant is found in germline genetic testing and/or is based on two or more of the following features in an individual:[23]

- Two or more Peutz-Jeghers-type hamartomas of the gastrointestinal tract.
- Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or finger.
- Family history of Peutz-Jeghers syndrome.

Hamartomas occur throughout the gastrointestinal tract, but data on lifetime cancer risks are limited. Associated extraintestinal cancers include female breast, pancreas, lung, ovary, uterus, and testicular.[12,23] Women with Peutz-Jeghers syndrome can be followed for breast cancer (and other) surveillance through the BC Cancer Hereditary Cancer Program High Risk Clinic.

Juvenile polyposis syndrome

Sporadic juvenile polyps occur in 1% to 2% of children and are not associated with an increased risk of cancer. Juvenile polyposis syndrome is characterized by a pathogenic variant in *BMPR1A* or *SMAD4* in approximately half of people who have a clinical diagnosis of juvenile polyposis syndrome based on at least one of the following:[23]

- Five or more juvenile hamartomatous polyps of the colon.
- Multiple juvenile polyps found throughout the gastrointestinal tract.
- Any number of juvenile polyps in an individual with a family history of juvenile polyposis syndrome.

Adenomas and adenocarcinomas develop within hamartomas that occur throughout the gastrointestinal tract, most commonly in the rectosigmoid. Individuals with a *SMAD4* pathogenic variant should be screened at time of diagnosis for vascular lesions associated with *SMAD4*-related juvenile polyposis syndrome–hereditary hemorrhagic telangiectasia.[12,24]

PTEN hamartoma tumor syndrome

PTEN hamartoma tumor syndrome, including Cowden syndrome, is caused by inactivation of the tumor-suppressor gene *PTEN* and is characterized by a mixed polyposis phenotype, including hamartomas, serrated lesions, adenomas, and ganglioneuromas.[23] *PTEN* hamartoma tumor syndrome is associated with an increased risk of breast, endometrial, thyroid, renal, and melanoma skin cancers. Benign features may include macrocephaly, benign skin tumors, multinodular goiter, and, rarely, dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease).[25] Women with *PTEN* hamartoma tumor syndrome can be followed for breast cancer (and other) surveillance through the BC Cancer Hereditary Cancer Program High Risk Clinic.

Serrated polyposis syndrome

A clinical diagnosis of serrated polyposis syndrome is made based on World Health Organization 2019 criteria and a cumulative count of serrated lesions.[26] This includes sessile serrated lesions (previously sessile serrated adenomas/polyps) with or without dysplasia, traditional serrated adenomas, and hyperplastic polyps.

Serrated polyposis syndrome is diagnosed when one of the following is met:

- Five or more serrated lesions proximal to the rectum, all at least 5 mm, and two or more lesions at least 10 mm.
- More than 20 serrated lesions of any size and five or more proximal to the rectum.

While most patients with serrated polyposis syndrome are not found to have a single genetic pathogenic variant, a rare few have a pathogenic variant identified in *RNF43* (1.4%) and biallelic pathogenic variants in *MUTYH* (2.5%), often with mixed serrated/adenoma phenotype.[27]

Assessing for hereditary colorectal cancer

Personal or family history

Once an individual with a personal or family history of an inherited syndrome is identified, referral to the BC Hereditary Cancer Program is recommended.

- What to ask when taking a family history:
  - Is there a history of cancer in your biological relatives?
    - How are they related to you?
    - What age were they when they were diagnosed?
  - Has anyone had more than one cancer?
  - Has anyone in your family had genetic testing because of the family history?
  - Are any of your relatives biologically related (first cousins to each other)?
- How to refer to the Hereditary Cancer Program (www.bccancer.bc.ca/hereditary):
  - Current referral criteria are listed on the referral form.
  - If the patient meets any of these criteria, complete the referral form and submit it to the Hereditary Cancer Program.
  - The family history form is required only for patients who do not meet the referral criteria based on their own diagnosis.
  - Contact the Hereditary Cancer Program for answers to any questions (hereditarycancer@bccancer.bc.ca).

The Hereditary Cancer Program offers publicly funded hereditary cancer risk assessment and genetic testing to residents of BC and Yukon. To improve access to genetic testing and reduce wait times, the program has embraced multiple alternative models of service delivery, such as group counseling, mainstreaming (testing ordered directly by providers, with patients referred to the program for abnormal results), and employing genetic counseling assistants. In spring 2022, an online platform was developed to provide a patient-led approach to receiving information and consenting to genetic testing. To increase support for patients and families living with hereditary cancer risk, a follow-up service has been integrated into the Hereditary Cancer Program care pathway for individuals with a germline mutation. It provides annual check-ins for medical care and access to recommended surveillance and prevention and addresses any other support needs.

What to expect from the Hereditary Cancer Program:

- Hereditary cancer risk assessment.
- Publicly funded genetic testing.
- Surveillance and prevention recommendations for the patient and their close relatives.

- Family support for cascade carrier testing.
- Continuing education for providers and the public.

New colorectal cancer diagnosis

For an individual with a new diagnosis of colorectal cancer, universal tumor screening for mismatch repair deficiency is recommended, regardless of age, to improve detection of Lynch syndrome and to identify those who may benefit from immunotherapy **[Figure 1]**.[12,14,28] Screening involves using immunohistochemical staining of the tumor to detect the absence of one of the mismatch repair proteins or to detect microsatellite instability. Microsatellite instability refers to the tendency of uncorrected DNA errors in base pair matching to cluster in repetitive sequences, or microsatellites, which create genetic instability. Approximately 15% to 20% of colorectal cancers have high levels of microsatellite instability, or at least one mismatch repair protein is absent. Most mismatch repair–deficient tumors are related to acquired *MLH1* promoter hypermethylation, which inactivates *MLH1*, and can be inferred by testing tumors for the *BRAF* mutation. If the *BRAF* mutation is not present in the tumor, methylation is less likely, and blood testing for genetic sequencing is performed to assess for Lynch syndrome. Likewise, if the tumor demonstrates loss of *MSH2*, *MSH6*, and/or *PMS2*, germline genetic testing is indicated **[Figure 2]**. Although many pathology departments in BC have adopted universal screening for Lynch syndrome in individuals with a newly diagnosed colorectal cancer, this approach is not yet available in all areas.

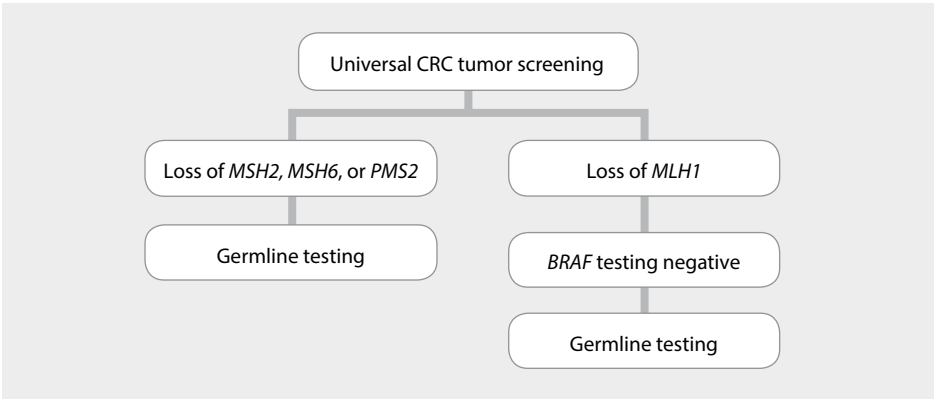

FIGURE 1. Universal screening for Lynch syndrome in colorectal cancer (CRC).

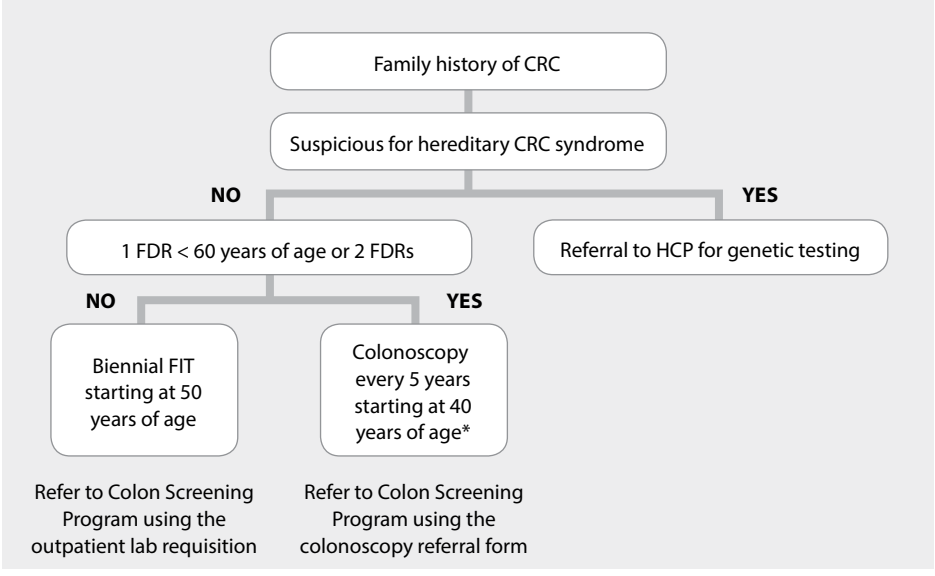

FIGURE 2. Approach to an individual with a family history of colorectal cancer (CRC).

FDR = first-degree relative; HCP = Hereditary Cancer Program; FIT = fecal immunochemical test.
*Or 10 years earlier than the age of diagnosis of the youngest affected relative.

Genetic testing

The Hereditary Cancer Program arranges genetic testing for the following:

- Mismatch repair–deficient colorectal cancer.
- Colorectal cancer diagnosed at 40 years of age or younger.
- Colorectal cancer diagnosed at 50 years of age or younger and no family history known due to adoption.
- Colorectal cancer diagnosed at 50 years of age or younger, plus five or more precancerous lesions.
- Two Lynch syndrome–related diagnoses, at least one at 50 years of age or younger.
- Two or more colorectal adenomas diagnosed at 40 years of age or younger.
- Ten or more cumulative colorectal precancerous lesions.
- Two or more cumulative gastrointestinal hamartomas.
- Five or more serrated lesions proximal to the rectum (all ≥ 5 mm; at least two ≥ 10 mm) or more than 20 serrated lesions of any size throughout the large bowel, with five or more proximal to the rectum.
- Two close relatives (can include the patient) with Lynch syndrome cancer, both 50 years of age or younger.
- Three or more relatives (can include the patient) with Lynch syndrome cancers, at least one diagnosed at 50 years of age or younger.
- Known pathogenic or likely pathogenic variant in a family member.

Individuals who are not eligible for publicly funded services or those who want to access testing as soon as possible may

consider private pay genetic testing through an accredited laboratory. If a pathogenic variant is found in a hereditary cancer gene, the patient should be referred to the Hereditary Cancer Program. In addition, confirmatory germline testing through an accredited laboratory is recommended when a potential pathogenic variant is identified by commercial entities that provide ancestry (and sometimes health) information. These tests typically use microarray-based single nucleotide polymorphism testing, which has not been validated for clinical use and can have a high degree of error.[29]

Summary

In evaluating an individual's risk of familial or hereditary colorectal cancer, a comprehensive family history is essential. If the presence of a hereditary colorectal cancer syndrome is suspected, the Hereditary Cancer Program is an excellent resource for genetic testing and guidance on screening for colorectal cancer and other at-risk cancers. While waiting for a Hereditary Cancer Program appointment, it may be appropriate to refer for colonoscopy. For those who do not appear to have an inherited syndrome but who have a family history of colorectal cancer among first-degree relatives, screening within the BC Colon Screening Program is appropriate **[Figure 2]**. ■

Competing interests

Dr Telford received a sessional fee from the Guidelines and Protocols Advisory Committee in 2021–2022 for her contributions to the colon screening guidelines.

References

1. Guidelines and Protocols Advisory Committee. Colorectal cancer part 1. Part 1: Screening for the purposes of colorectal cancer prevention and detection in asymptomatic adults. BC Guidelines. April 2022. Accessed 26 April 2023. https://alpha.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/colorectal-cancer-part1.
2. Leddin D, Lieberman DA, Tse F, et al. Clinical practice guideline on screening for colorectal cancer in individuals with a family history of nonhereditary colorectal cancer or adenoma: The Canadian Association of Gastroenterology Banff Consensus. Gastroenterology 2018;155:1325-1347.e3.
3. Roos VH, Mangas-Sanjuan C, Rodriguez-Girondo M, et al. Effects of family history on relative and absolute risks for colorectal cancer: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:2657-2667.e9.
4. Cancer Care Ontario. Colorectal cancer screening recommendations summary. Accessed 21 December 2022. www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/resources-healthcare-providers/colorectal-cancer-screening-summary.
5. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: Recommendations for physicians and patients from the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2017;112:1016-1030.
6. Rutter MD, Chattree A, Barbour JA, et al. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. Gut 2015;64:1847-1873.
7. Sung JJY, Chiu HM, Lieberman D, et al. Third Asia-Pacific consensus recommendations on colorectal cancer screening and postpolypectomy surveillance. Gut 2022;71:2152-2166.
8. Kim NH, Yang H-J, Park S-K, et al. The risk of colorectal neoplasia can be different according to the types of family members affected by colorectal cancer. J Gastroenterol Hepatol 2018;33:397-403.
9. Moosavi S, Gentile L, Gondara L, et al. Performance of the fecal immunochemical test in patients with a family history of colorectal cancer. J Can Assoc Gastroenterol 2019;3:288-292.
10. Roos VH, Kallenberg FGJ, van der Vlugt M, et al. Addition of an online, validated family history questionnaire to the Dutch FIT-based screening programme did not improve its diagnostic yield. Br J Cancer 2020;122:1865-1871.
11. Quintero E, Carrillo M, Gimeno-García AZ, et al. Equivalency of fecal immunochemical tests and colonoscopy in familial colorectal cancer screening. Gastroenterology 2014;147:1021-1030.e1.
12. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. NCCN Guidelines. Accessed 21 December 2022. www.nccn.org/guidelines/guidelines-detail?category=2&id=1436.
13. Cancer Institute NSW. Risk management. Accessed 21 December 2022. www.eviq.org.au/cancer-genetics/adult/risk-management.
14. Heald B, Hampel H, Church J, et al. Collaborative Group of the Americas on Inherited Gastrointestinal Cancer position statement on multigene panel testing for patients with colorectal cancer and/or polyposis. Fam Cancer 2020;19:223-239.
15. Kastrinos F, Syngal S. Inherited colorectal cancer syndromes. Cancer J 2011;17:405-415.
16. Rubenstein JH, Enns R, Heidelbaugh J, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology 2015;149:777-782.
17. Holter S, Hall MJ, Hampel H, et al. Risk assessment and genetic counseling for Lynch syndrome—Practice resource of the National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer. J Genet Couns 2022;31:568-583.
18. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: Findings from the Prospective Lynch Syndrome Database. Genet Med 2020;22:15-25.
19. Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: A double-blind, randomised, placebo-controlled trial. Lancet 2020(10240);395:1855-1863.
20. Yen T, Stanich PP, Axell L, Patel SG. APC-associated polyposis conditions. GeneReviews. Last updated 12 May 2022. Accessed 28 April 2023. www.ncbi.nlm.nih.gov/books/NBK1345/.
21. Stanich PP, Pearlman R, Hinton A, et al. Prevalence of germline mutations in polyposis and colorectal cancer–associated genes in patients with multiple colorectal polyps. Clin Gastroenterol Hepatol 2019;17:2008-2015.e3.
22. Boland CR, Idos GE, Durno C, et al. Diagnosis and management of cancer risk in the gastrointestinal hamartomatous polyposis syndromes: Recommendations from the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2022;117:846-864.
23. McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers syndrome. GeneReviews. Last updated 2 September 2021. Accessed 28 April 2023. www.ncbi.nlm.nih.gov/books/NBK1266/.
24. Larsen Haidle J, MacFarland SP, Howe JR. Juvenile polyposis syndrome. GeneReviews. Last updated 3 February 2022. Accessed 28 April 2023. www.ncbi.nlm.nih.gov/books/NBK1469/.
25. Hendricks LAJ, Hoogerbrugge N, Schuurs-Hoeijmakers JHM, Vos JR. A review on age-related cancer risks in PTEN hamartoma tumor syndrome. Clin Genet 2021;99:219-225.
26. Dekker E, Bleijenberg A, Balaguer F, et al. Update on the World Health Organization criteria for diagnosis of serrated polyposis syndrome. Gastroenterology 2020;158:1520-1523.
27. Terradas M, Munoz-Torres PM, Belhadj S, et al. Contribution to colonic polyposis of recently proposed predisposing genes and assessment of the prevalence of NTHL1-and MSH3- associated polyposes. Hum Mutat 2019;40:1910-1923.
28. Eikenboom EL, van der Werf–'t Lam A-S, Rodríguez-Girondo M, et al. Universal immunohistochemistry for Lynch syndrome: A systematic review and meta-analysis of 58,580 colorectal carcinomas. Clin Gastroenterol Hepatol 2022;20:e496-e507.
29. Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 2018;20:1515-1521.