BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority
Hereditary Cancer Program

Polyposis Syndromes

Inherited risk for colorectal cancer is associated with a number of polyposis syndromes (genes), some of which are well-defined and others are less common. Identification of an unusual number of polyps and/or unusual polyps should prompt consideration of Hereditary Cancer Program referral for polyposis assessment.

Polyposis syndromes/genes include: Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis (*APC*), Juvenile Polyposis (*SMAD4, BRMP1A*), MutYH-Associated Polyposis (*MutYH*), Polymerase Proofreading-associated syndrome (*POLE/POLD1*), Serrated Polyposis syndrome (formerly Hyperplastic Polyposis), and Mixed Polyposis. Peutz-Jegher syndrome (*STK11*) and Cowden syndrome (*PTEN*) are also associated with specific types of polyps.

Polyposis Referral Criteria

Pathology reports, related operative reports and consult letters must be provided with a request for assessment.

Referral of children is appropriate for some polyposis syndromes because it may inform their medical management.

Referral for polyposis assessment should be considered for any person with:

- personal history of:
  - 10 or more adenomatous polyps, OR
  - 2 or more hamartomatous polyps, OR
  - 5 or more serrated polyps proximal to the sigmoid colon (serrated polyps include: hyperplastic polyps, sessile serrated adenomas/polyps, traditional serrated adenomas) OR
  - multiple polyps of different types (adenomatous, hamartomatous, serrated, hyperplastic)
- family history of:
  - a confirmed mutation in a polyposis gene – refer for carrier testing
  - 1 or more close relatives with polyposis (as defined above)

Personal and family history of polyps, cancer and other clinical features are assessed by Hereditary Cancer Program staff to clarify which genes/syndromes will be considered for genetic evaluation. Specific syndromes are described in more detail on the following pages:

- Cowden syndrome (*PTEN*)
- Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis (*APC*-associated)
- Juvenile Polyposis (*SMAD4*, *BRMP1A*)

- MutYH-Associated Polyposis (*MutYH*)
- Peutz-Jegher syndrome (*STK11*)
- Polymerase Proofreading-associated syndrome (*POLE*/*POLD1*)
- Serrated (hyperplastic) Polyposis syndrome

Additional Information

Comprehensive reviews of this topic are available at:

- https://www.cancer.gov/types/colorectal/hp/colorectal-genetics-pdq
- https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

The following websites offer support and information which may be helpful to people living with polyposis:

- Familial Gastrointestinal Cancer Registry (Mt Sinai Hospital, Toronto): www.mountsinai.on.ca/care/fgicr
- The Cleveland Clinic: www.clevelandclinic.org/registries/inherited/fap.htm
- Familial Adenomatous Polyposis Foundation: http://www.hcctakesguts.org/

Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis (FAP/AFAP) – *APC*-associated conditions

FAP is a hereditary polyposis syndrome that accounts for about 1% of all colon cancers and is associated with pathogenic mutations in the *APC* gene. People with classic FAP develop hundreds to thousands of adenomatous colon polyps, beginning at an average age of 16 (range 7-36 years). By age 35, 95% of individuals with classic FAP will have hundreds of polyps. The average age of colon cancer diagnosis in untreated individuals is 39, with over 90% developing colon cancer by age 50. Attenuated FAP is characterized by fewer colorectal polyps and older average age for colorectal cancer diagnosis.

The majority of individuals with FAP will also develop polyps in the small intestine and about half will develop polyps in the stomach and periampullary region. The lifetime risk of duodenal or periampullary cancer is 4-12%. The following cancers may be more common in families with FAP than in the general population, but the lifetime risk for each of these cancers is likely less than 2%: stomach, pancreatic, thyroid, bile duct, medulloblastoma and hepatoblastoma.

Less common clinical features associated with FAP include: dental abnormalities (e.g. supernumerary teeth), soft tissue tumours on the face, scalp or abdomen (desmoids) and bony growths on the skull or jaw (osteomas). Some people may have a benign freckle of the retina (CHRPE) that does not affect vision. Gardner syndrome is the term formerly used for a clinical FAP presentation that included osteomas, epidermal cysts, and dental abnormalities.

FAP cancer risk management recommendations include:

- sigmoidoscopy/colonoscopy every 1-2 years, beginning at age 10-12
- annual colonoscopy after first polyps are detected, until colectomy
- colectomy is the standard of care, typically completed in the late teens. Delayed colectomy may be considered for those who are age 10-20 and have non-villous adenomas that are smaller than 6 mm.
- esophagogastroduodenoscopy beginning by age 25 and repeated every 1-3 years (depending on the severity of duodenal adenomas). Endoscopic surveillance should include side-viewing endoscopy to ensure medial wall and papilla are assessed.
- annual physical examination, including:
    - assessment for extra-intestinal manifestations
    - palpation of the thyroid, followed by ultrasound and fine-needle aspiration of any thyroid nodules
- after colectomy:
    - If colectomy with ileorectal anastomosis: surveillance of the remaining rectum every 6-12 months, depending on polyp burden
    - If total proctocolectomy with ileal pouch-anal anastomosis or ileostomy: endoscopic surveillance of the ileal pouch or ileostomy every 1-3 years depending on polyp burden. Frequency should be increased to every 6 months for large, flat polyps with villous histology and/or high-grade dysplasia.

Juvenile Polyposis (JPS)

JPS is a rare autosomal dominant condition caused by germline mutations in the *SMAD4* or *BRMP1A* genes. It is characterized by multiple hamartomatous polyps of the colon and rectum.

Juvenile polyps are diagnosed by histologic appearance rather than age of onset, although they are more common in children and young adults. A solitary juvenile polyp in an infant or young child does not confirm JPS.

A clinical JPS diagnosis requires 1 of the following:

- at least 3-5 juvenile polyps of the colon
- multiple juvenile polyps in other parts of the GI tract
- at least 1 juvenile polyp and family history of JPS

The lifetime colorectal cancer risk with JPS is estimated to be 30-40% and the gastric cancer risk may also be increased.

If there is a confirmed *SMAD4* mutation in a family, genetic testing should be done within the 1st 6 months of life due to the associated risk of hereditary hemorrhagic telangiectasia (HHT). Surveillance and treatment of HHT complications is required for all *SMAD4* mutation carriers.

JPS Cancer Risk Management

- because this is a rare condition, referral to a specialized team is recommended
- the need for thorough assessment of any symptoms should be reinforced
- screening colonoscopy to start at about age 15. Repeat annually if polyps are found, and every 2-3 years if no polyps. May decrease frequency after age 35 if no polyps.
- upper endoscopy to start at about age 15. Repeat annually if polyps are found, and every 2-3 years if no polyps. May decrease frequency after age 35 if no polyps.

MutYH-Associated Polyposis (MAP)

MAP is an autosomal recessive hereditary syndrome associated with attenuated polyposis and colorectal cancer. As a recessive condition, it is caused by inheriting a *MutYH* gene mutation from each parent, which is different from most hereditary cancer syndromes.

MAP is characterized by multiple polyps (usually 10s to a few hundred) throughout the colon. Colonic polyps related to MAP are most often adenomatous but may include hyperplastic, sessile serrated, traditional serrated and mixed hyperplastic/adenomatous pathologies. Some people with MAP develop colorectal cancer without polyposis, and the number of polyps does not appear to correlate with colorectal cancer risk.

Colorectal cancer risk for an unscreened individual with MAP is currently estimated to be: 12% by age 40, 20-40% by age 50, 43-63% by age 60, and 86% by age 70 years (compared to 2-3% by age 70 in the general population). Mean age of colorectal diagnosis is 48-53 years.

Duodenal adenomas are found in 18-25% of people with MAP and the lifetime risk of duodenal cancer is approximately 4%.

Cancer outside the GI tract is about twice as common for a person with MAP compared to the general population, but not at younger than usual ages. Cancers that may be more common with MAP include: ovarian, bladder and skin cancers (melanoma, squamous epithelial carcinoma, basal cell carcinoma), as well as sebaceous gland tumours. More research is required to clarify the cancer risks associated with this syndrome.

Cancer Risk Management for *MutYH*-Associated Polyposis

Colorectal Cancer:

- colonoscopy starting at age 20 and repeated every 2 years until polyps are detected
- subsequent colon screening should be guided by the polyp burden (number, size, histology, location) with counselling about surgical options as appropriate

Upper Gastrointestinal:

- upper endoscopy and side-viewing duodenoscopy including complete visualization of the ampulla of Vater, starting at age 25 and repeated every 1-4 years based on polyp burden

Other Cancers:

- baseline dermatological evaluation
- general population screening guidelines

Individuals who inherit a single *MutYH* mutation may have a moderately increased colorectal cancer risk although study results are conflicting. At this time, carriers of a single MutYH mutation without a significant personal history of polyposis or colorectal cancer may consider colonoscopy every 5 years, beginning at age 40 or 10 years younger than the age of colorectal cancer diagnosis in a first degree relative, whichever is younger. Frequency may be increased based on colonoscopy results or review by a GI specialist.

Polymerase Proofreading-associated syndrome (*POLE*/*POLD1*)

Polymerase Proofreading-associated syndrome is characterized by the presence of colonic oligopolyposis. Germline mutations in the associated *POLE* and *POLD1* genes have been identified in some people with personal/family history of adenomas, colorectal cancer and endometrial cancer that may not meet criteria for other hereditary cancer syndromes, or where no mutation was identified.

The risks for duodenal adenomas, gastric fundic gland polyps, colorectal cancer and endometrial cancer (*POLD1*) for unaffected gene mutation carriers are increased but not yet defined.

In the absence of syndrome-specific guidelines, it is reasonable to consider the following general approach to **cancer risk management**:

- screening colonoscopy to start at age 25 and repeat annually if polyps found or every 2-3 years if no polyps
- consider colectomy if suggested by polyp burden
- upper endoscopy to start at age 25 and repeat every 3 years or as directed by polyp load
- prompt investigation into any unusual bleeding between menstrual periods or after menopause (*POLD1*). No evidence to support endometrial cancer screening.

Serrated Polyposis syndrome (previously known as hyperplastic polyposis)

Serrated polyps (SP) include hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas. These polyps are flat or slightly raised, usually occur on the right side of the colon, are more difficult to detect during colonoscopy, and progress to cancer via different pathways than adenomas.

Serrated polyposis syndrome (SPS) is defined by the occurrence of multiple serrated polyps in the large intestine, and is associated with increased (25-40%) colorectal cancer risk. The genetic basis for SPS is not yet unknown. Up to 40% of people with SPS have a family history of colorectal cancer.

Referral for SPS assessment is suggested for a person with:

- 5 or more SPs proximal to the sigmoid colon, 2 of which are bigger than 10 mm, OR
- any number of SPs proximal to the sigmoid colon and a close relative with SPS, OR
- 20 or more SPs of any size distributed throughout the colon

Surveillance for a person with SPS should include colonoscopy with polypectomy until all polyps larger than 5 mm are cleared, and then every 1-3 years depending on number and size of polyps. Consider surgical referral if polyp burden cannot be effectively managed via colonoscopy.

The colorectal cancer risk for close relatives of a person with SPS is unclear. They could consider starting colonoscopy screening at age 40, or earlier if suggested by the youngest age of SPS/colorectal cancer diagnosis in the family.

References available on request.
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