

APC-Associated Polyposis - Cancer Risks and Management

Overview

APC-associated polyposis is a spectrum that includes classical Familial Adenomatous Polyposis (FAP), attenuated FAP (AFAP) and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).

People with a pathogenic variant in the *APC* gene have a higher chance of developing colon polyposis and certain types of cancer, often at younger ages than the general population.

This page summarizes the cancer risks and management recommendations for individuals with a pathogenic variant in the *APC* gene. Recommendations (i.e. whether to follow FAP, aFAP vs GAPPS) are dependent on a person's personal or family history of cancer and colon polyposis.

Familial Adenomatous Polyposis (FAP)

FAP is a hereditary polyposis syndrome which accounts for about 1% of all colon cancers. Individuals with classic FAP develop hundreds to thousands of adenomatous colon polyps. The average age for polyps to begin developing is 16 years (range 7 to 36 years). By age 25, 95% of individuals with classical FAP will have hundreds of polyps. The average age of colon cancer diagnosis in untreated individuals is 39 years, with over 90% developing colon cancer by age 50.

The majority of individuals with FAP will also develop polyps in the small intestine and about half in the stomach and periampullary region. The lifetime risk of duodenal or periampullary cancer is 4-12%. Several additional cancers appear more often in families with FAP than in the general population, including stomach, thyroid, bile duct, medulloblastoma, and hepatoblastoma. However, the absolute lifetime risk of developing any one of these cancers is low, likely less than 2%.

Other features present in a smaller proportion of individuals with FAP are dental abnormalities (including supernumerary teeth), soft tissue tumours on the face, scalp, or abdomen (desmoids) and bony growths on the skull or jaw (osteomas). Some individuals may have a benign freckle of the retina that does not affect vision (called congenital hypertrophy of the retinal pigment epithelium, CHRPE).

Historically, individuals with colorectal polyps and extracolonic features were described as having *Gardner syndrome*, and those with colorectal cancer and brain tumours as having *Turcot syndrome*. These terms have been retired in favour of recognizing these clinical presentations to be within the broader APC-associated polyposis spectrum.

Pre-surgical Colorectal Screening

- Colonoscopy (preferred) or flexible sigmoidoscopy every 1-2 years, beginning at age 10-12 years
- Once adenomas are detected, proctocolectomy (TPC) or colectomy is recommended. Delay of colectomy can be considered in individuals ages 10-20 years in whom adenomas are smaller than 6.0 mm and without villous component. Annual colonoscopy should be continued until colectomy done

Post-surgical Colorectal Screening (depending on patient's procedure)

- Ileorectal anastomosis (IRA): endoscopic evaluation of the rectum every 6-12 months, depending on the polyp burden
- TPC with ileal-pouch anastomosis (IPAA): annual endoscopic evaluation of ileal pouch and rectal cuff, shortened to every 6 months if large, flat polyps with villous histology and/or high-grade dysplasia (HGD)
- Ileostomy: consider annual visualization and stoma inspection with ileoscopy to evaluate for polyps or malignancy every 1- 3 years
- If retained rectosigmoid, completion proctocolectomy is recommended for dense polyposis or HGD that cannot be managed endoscopically
- Chemoprevention may be considered

Duodenum/Peri-Ampulla Screening

- Esophagogastroduodenoscopy (EGD) beginning at age 20-25 years. Endoscopic surveillance should include side-viewing endoscopy to ensure medial wall and papilla are assessed.
- Frequency depends on the severity of duodenal adenomas (Spigelman criteria), ranging from every 3 months to 5 years.
- Consider duodenectomy for Spigelman Stage IV disease and adenomas larger than 10 mm

Thyroid Screening:

- Baseline thyroid ultrasound from age 18
- Consider repeating every 2-5 years (or shorter if family history of thyroid cancer)
- Patients with abnormal thyroid ultrasound should be referred to a thyroid specialist

Gastric Screening:

- Fundic gland polyps are common in FAP patients, and low-grade dysplasia is typically non-progressive. In the absence of high-risk features, patients typically do not require specialized surveillance
- If high-risk features are present, consider need for specialized surveillance or surgery at a centre of expertise. Patients with high-risk lesions that cannot be removed endoscopically should be referred to a specialized centre for consideration of gastrectomy.

Other Screening:

- There are no established guidelines for surveillance of desmoid tumours. Suggestive abdominal symptoms for desmoids, such as new, unexplained and persistent abdominal, should prompt immediate abdominal imaging. Recommend annual (or more frequent) abdominal MRI with and without contrast if family history of symptomatic disease.
- Evidence to support routine screening is lacking for hepatoblastoma. Consider liver palpation, abdominal ultrasound, and measurement of AFP q3-6 months during first five years of life.
- No routine surveillance imaging for CNS. Prompt reporting of abnormal neurologic symptoms to physicians.
- Evidence to support routine small bowel screening is lacking. Consider small bowel visualization (e.g. capsule endoscopy), especially if advanced duodenal polyposis.

Pancreatic Cancer Screening:

- Evidence to support routine screening is lacking and screening should be based on family history of pancreatic cancer
- There is no clear data to recommend surveillance with ***'s family history
- Avoid or quit smoking, this will help lower the risk
- Investigate any new onset evidence of diabetes carefully
- Begin screening for type 2 diabetes at age 40, repeat every 3 years

Attenuated Familial Adenomatous Polyposis (aFAP)

Individuals with AFAP develop tens of cumulative adenomas (range 10-99, average 30), usually at older ages compared to those with classic FAP. The majority of polyps develop on the right side.

A small proportion of individuals with AFAP develop extraintestinal features, including desmoid tumours, upper GI polyps, thyroid cancer, and duodenal cancer.

Colorectal Cancer Screening and Prevention

For small polyp burden that can be managed endoscopically:

- Colonoscopy and polypectomy every 1-2 years beginning at age 18-20

For polyp burden that cannot be managed endoscopically:

- Colectomy with ileorectal anastomosis. Post surgery, endoscopic evaluation of the rectum every 6-12 months, depending on polyp burden.
- Consider proctocolectomy with ileal-pouch anastomosis if dense rectal polyposis not manageable with polypectomy
- Chemoprevention may be considered

Extraintestinal Screening:

- **Annual physical examination**
- **Thyroid ultrasound** starting in late teenage years, repeat every 2-5 years if normal and no family history. If abnormal, refer to thyroid specialist for investigation
- **Upper endoscopy** starting at age 20-25 years, repeat every 3-5 years if no polyps are identified. If polyps are present, use Spigelman criteria to guide screening interval.

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)

The GAPPS phenotype is characterized by polyposis of the stomach, typically with the index case having more than 100 polyps carpeting the proximal stomach. The polyps are predominantly fundic gland polyps of which some may contain regions of dysplasia. Point mutations in promoter 1B of the APC gene are associated with GAPPS and have rarely been associated with colonic polyposis. However, deletions that include all or some of promoter 1B and portions of the APC gene have been associated with colonic polyposis. **The lifetime risk of stomach cancer is 12-25%.**

Colorectal Screening:

- Baseline colonoscopy at age 25

Gastric Cancer Screening and Risk Reduction:

- Annual esophagogastroduodenoscopy (EGD) beginning at age 15 years.
- Consider risk-reducing total gastrectomy from age 30-35 years, or five years earlier than youngest diagnosis of gastric cancer in the family

Family and Reproductive Considerations

Inheritance

APC-associated polyposis follows an autosomal dominant pattern. Each child of someone with a *PMS2* pathogenic variant has a 50% chance of inheriting the variant.

Family members are encouraged to contact their local genetics clinic to learn more about whether genetic testing or cancer screening may be helpful for them. Family members who live in British Columbia or the Yukon can contact our program directly at

hereditarycancer@bccancer.bc.ca.

Note: In the information above, male/female refers to sex assigned at birth.

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