Familial adenomatous polyposis: Screening and management of patients and families

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INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal dominant disease caused by mutations in the *Adenomatous Polyposis Coli* gene. Classic FAP is characterized by the presence of 100 or more adenomatous colorectal polyps. When fully developed, patients can have up to thousands of colorectal adenomas and a 100 percent risk of colorectal cancer (CRC). An attenuated form of FAP is characterized by few colorectal adenomas with a later age of onset and an 80 percent lifetime risk of CRC. Patients with FAP are also at risk for several extracolonic malignancies. This chapter will review the management of FAP. The clinical manifestations and diagnosis of FAP and other hereditary CRC syndromes are discussed separately. (See "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management" and "*MUTYH*-associated polyposis" and "Juvenile polyposis syndrome" and "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

CANDIDATES FOR CANCER SCREENING

Screening for tumors associated with familial adenomatous polyposis (FAP) should be performed in individuals with a pathogenic *Adenomatous Polyposis Coli* mutation. Screening for FAP-associated cancers should also be performed in individuals at-risk for FAP who have either

not undergone genetic evaluation or have indeterminate genetic test results. Screening for colorectal cancer and other FAP-associated cancers in these patients must be individualized based on their personal and family history of adenomas and cancer.

Individuals at-risk for FAP include:

- First-degree relatives of those with FAP.
- Individuals with >10 cumulative colorectal adenomas or colorectal adenomas in combination with extracolonic features associated with FAP (eg, duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, or osteomas).

COLORECTAL CANCER

Guidelines for cancer screening in patients with familial adenomatous polyposis (FAP) have been proposed by several groups and are largely based on expert opinion and limited observational data [1,2]. Our recommendations are largely consistent with the National Comprehensive Cancer Network clinic practice guidelines in oncology.

Screening and surveillance

Classic FAP — In individuals at risk for classic FAP, we begin CRC screening around age 10 to 15 years with colonoscopy. The number, size, and distribution of polyps should be noted during the colonoscopy to define the extent of the polyposis and the plan for colectomy. Several polyps should also be sampled to confirm histology. Patients should continue to undergo annual CRC surveillance with colonoscopy while awaiting colectomy. (See 'Colectomy' below.)

Even in the absence of colorectal adenomas, CRC screening should be repeated annually. Screening should be continued lifelong in *Adenomatous Polyposis Coli (APC)* mutation carriers. However, in first-degree relatives of affected individuals from families without an identified pathogenic *APC* mutation, annual CRC screening should continue until age 24 years. If no adenomas have been detected on prior examinations, screening frequency may be extended to every two years for patients age 24 through 34 years, every three years for patients age 34 through 44 years, and every three to five years for patients older than 44 years.

AFAP — In contrast to classic FAP, attenuated FAP (AFAP) presents at a later age and with more proximal lesions. Colonoscopy should be performed every one to two years in at-risk individuals starting in the late teenage years [1]. Patients with colorectal polyps should undergo endoscopic resection of all detectable polyps when feasible, followed by annual colonoscopy for

surveillance. Patients with adenomas too numerous to clear endoscopically, or in whom endoscopic surveillance is not technically feasible, should undergo colectomy. (See 'Colectomy' below.)

Colectomy — Colectomy is recommended for patients with classic FAP, since the risk for developing CRC is considered to be 100 percent, and the high polyp number makes endoscopic control unrealistic. In patients with AFAP in whom endoscopic control is feasible, surveillance can obviate or delay the need for colectomy.

Indications for colectomy — Indications for a timely colectomy in patients with FAP include:

- Documented or suspected colorectal cancer
- Severe symptoms related to colonic neoplasia (eg, gastrointestinal bleeding)
- Adenomas with high-grade dysplasia or multiple adenomas larger than 6 mm
- Marked increases in polyp number on consecutive exams
- Inability to adequately survey the colon because of multiple diminutive polyps

Extent of colon resection — Surgical options for FAP patients include total proctocolectomy with end-ileostomy, total proctocolectomy with ileal pouch anal anastomosis (IPAA), or total colectomy with ileo-rectal anastomosis (IRA). When choosing the extent of colon resection, the preventive effect is weighed against the impact on postoperative quality of life and takes into account the patient's age and rectal polyp burden. A discussion regarding treatment options, risks, and need for ongoing surveillance should be performed with the patient.

In general, the preferred operation depends on the severity and distribution of colorectal adenomas. Other important factors to consider include the risk of desmoid tumors and the patient's age and comorbidities. The specific *APC* genotype may be useful in predicting which patients would be better suited for ileorectal anastomosis (IRA) versus total proctocolectomy with IPAA by predicting the severity of colorectal polyposis and the risk of desmoid development [3]. IPAA is more extensive surgery as compared with IRA and is associated with an increased risk of bleeding and reduction in fertility in women. Patients with an IRA who subsequently develop severe rectal polyposis will require a secondary proctectomy.

Guidelines suggest that a polyp number over 1000 is an indicator for a more extensive resection (proctocolectomy with IPAA versus total colectomy with IRA). Another critical variable is the extent of rectal involvement.

- In patients with <10 rectal adenomas, we suggest total colectomy with IRA, provided the rectal polyps can be managed endoscopically.

- In patients with profuse polyposis and >10 rectal adenomas, we suggest proctocolectomy with IPAA.

- In patients at risk for desmoids, we suggest primary proctocolectomy with IPAA as future conversion of IRA to IPAA might be difficult due to mesenteric desmoid tumors and shortening of the mesentery [4].

Timing of colectomy — The presence of symptoms, number and size of adenomas, and the presence of high-grade dysplasia or cancer influence the timing of colectomy.

Urgent (semi-elective) colectomy should be performed in patients with:

- Documented or suspected colorectal cancer
- Adenoma with high-grade dysplasia

Early (near the time of diagnosis) colectomy should be performed in patients with:

- Symptoms (eg, gastrointestinal bleeding)
- Multiple 6 to 10 mm polyps that cannot be cleared endoscopically
- Marked increase in polyp number in consecutive exams

Elective colectomy can be deferred to the late teens or early twenties in patients with classic FAP who are in the second decade of life with only sparse (<10) or small (<5 mm) adenomas.

Surveillance following colectomy — Colectomy does not completely eliminate the risk for cancer, as tumors may arise in the rectum if an IRA was performed or from the anal transition zone ("rectal cuff") or within the ileal pouch in those who have had an IPAA. Ongoing surveillance is therefore recommended after colectomy. Endoscopic evaluation of the rectum or ileal pouch should be performed every 6 to 12 months (or every year for end-ileostomies) [1,5]. Patients who have undergone total proctocolectomy remain at risk for the development of adenomas and adenocarcinoma in the ileal pouch [6-8]. In one study that included 212 FAP patients who underwent IPAA at a mean follow-up of 7.9 years, 25 (12 percent) developed an adenoma with advanced pathology and four (2 percent) developed a cancer in the pouch [9]. The cumulative risks of developing an adenoma and adenocarcinoma in the pouch at 10-year follow-up were 45 and 1 percent, respectively. The median interval between a prior endoscopy and the detection of cancer was 25 months. Pouchitis may develop in a subset of patients but is usually less severe than that found in patients with inflammatory bowel disease [10].

UPPER GASTROINTESTINAL TUMORS

Screening of the upper gastrointestinal (GI) tract is recommended in patients with classic and attenuated Familial Adenomatous Polyposis (FAP) given the high prevalence of gastric and duodenal polyps and risk of cancer; however, upper GI tract screening has not been demonstrated to decrease mortality [1,4,11,12]. The development of symptoms or signs referable to the upper digestive tract, including pancreatitis or biliary obstruction, should prompt evaluation of the stomach and duodenum, with particular attention to the ampulla of Vater.

Screening — Upper endoscopic screening using a forward-viewing endoscope for gastric polyps and a side-viewing duodenoscope for duodenal polyps should be initiated in patients with FAP (classic or attenuated) at the onset of colonic polyposis or around age 20 to 25 years (whichever comes first). Screening should be performed earlier if there is a history of early onset gastroduodenal cancer in the family. The papilla can also be visualized using a cap-assisted forward-viewing endoscope, although this technique needs to be further validated [10].

In patients without evidence of duodenal adenomas, we perform a repeat upper endoscopy with duodenoscopy every four years [1]. However, other expert groups have suggested repeat examinations every five years [13]. (See 'Surveillance' below.)

Evaluation and management of detected lesions

Gastric polyps — Fundic gland polyps are found in most patients with FAP. They are usually located in the fundus or body of the stomach and are associated with a low risk of progression to cancer. Small proximal gastric polyps should be biopsied in patients with FAP to confirm their histology. Large or irregular appearing polyps should be biopsied or resected completely to assess for dysplasia. Low-grade dysplasia is common in fundic gland polyps, but surgery should be reserved for high-grade dysplasia or cancer [1]. Antral polyps are usually adenomas and should be completely resected endoscopically if possible. (See "Gastric polyps", section on 'Fundic gland polyps' and "Gastric polyps", section on 'Gastric adenomas' and "Clinical manifestations and diagnosis of familial adenomatous polyposis", section on 'Extracolonic manifestations' and "Gastric polyps", section on 'Management'.)

Gastric screening in GAPPS — Although consensus surveillance guidelines for patients with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) syndrome have not yet been established, we suggest upper endoscopy every 6 to 12 months. While the specific indications for prophylactic total gastrectomy have not yet been defined, it should be strongly considered in GAPPS patients with fundic gland polyposis and dysplasia [14].

Duodenal polyps — Endoscopically visible duodenal adenomas are identified in more than half of FAP patients. Approximately half of duodenal cancers are ampullary or periampullary [4].

Complete polypectomy or sampling of duodenal polyps should be performed at the time of initial discovery and on each subsequent examination [15]. An abnormal-appearing papilla should be biopsied. Adenomas identified at the ampulla of Vater should be removed endoscopically if possible [16,17]. Management of high-grade dysplasia in the periampullary region (surgery/ablative therapy versus more frequent surveillance) is controversial and should be individualized based on the patient's age and the number of duodenal adenomas. The resection margins should be free of neoplastic tissue. A study that included 26 FAP patients who underwent endoscopic ampullectomy demonstrated the procedure can be performed safely, but ongoing surveillance is required because recurrences were common [18]. (See "Ampullary adenomas: Management", section on 'Management'.)

The severity of duodenal polyposis, as determined by the Spigelman stage (0 to IV), is used to guide subsequent surveillance (table 1) [19,20]. Surgery (duodenectomy) is reserved for patients with stage IV polyposis. (See 'Surveillance' below.)

Surveillance — The frequency of upper endoscopic surveillance varies based on the severity of duodenal polyposis. The presence of non-dysplastic fundic gland polyps should not alter the recommended screening intervals [21,22]. (See 'Gastric polyps' above and 'Duodenal polyps' above.)

The optimal surveillance strategy has not been established. We suggest the following surveillance intervals for a repeat upper endoscopy and duodenoscopy based on the Spigelman stage of duodenal polyposis (table 1):

- Stage 0: Every three to five years
- Stage I: Every two to three years
- Stage II: Every one to two years
- Stage III: Every 6 to 12 months
- Stage IV: In the absence of surgery (duodenectomy), surveillance every three to six months

Evidence to support routine screening of the distal small bowel is lacking. However, small bowel imaging with a capsule colonoscopy may be performed in individuals with advanced duodenal polyposis.

THYROID CANCER

We perform thyroid ultrasound in patients with familial adenomatous polyposis (FAP) starting in the late teenage years and repeat the ultrasound every two to five years if normal [1]. Physical examination alone is insufficient to detect malignancy. In a study of 192 FAP patients screened

for thyroid cancer, none of the five patients diagnosed with thyroid cancer was diagnosed through clinical history and neck examination [23]. In a prospective screening program that included 205 patients with FAP, approximately one half of patients had at least one thyroid nodule and approximately one third required fine-needle aspiration biopsy [24].

HEPATOBLASTOMA

Screening for hepatoblastoma is controversial due to the low risk and uncertain effectiveness of screening [25]. If there is a family history of hepatoblastoma, we suggest genetic testing for familial adenomatous polyposis during infancy and screening of affected children with serum alpha-fetoprotein, palpation of the liver, and abdominal ultrasounds every three to six months from infancy until 5 years of age [1,26]. Serum alpha-fetoprotein is elevated in approximately two-thirds of patients with a hepatoblastoma.

OTHER ISSUES

Patients with familial adenomatous polyposis (FAP) are at risk for other extraintestinal tumors (eg, pancreatic cancer, central nervous system cancers) and benign extraintestinal lesions (eg, osteomas, epidermoid cysts, fibromas). Other than an annual physical examination, screening for central nervous system cancers is not recommended. Screening for pancreatic cancer is also not routinely recommended. However, the decision to undergo pancreatic cancer screening must be individualized based on a family history of pancreatic cancer [5].

Desmoid tumors — We perform an abdominal computed tomography scan to assess for desmoids in the following patients:

- Prior to colectomy in patients at increased risk for desmoids (personal or family history of desmoids or an *Adenomatous Polyposis Coli* mutation beyond codon 1444).
- Palpable abdominal mass on physical examination.
- Symptoms suggestive of abdominal organ obstruction.

The management of desmoids is discussed in detail separately. (See "Desmoid tumors: Epidemiology, molecular pathogenesis, clinical presentation, diagnosis, and local therapy", section on 'Treatment' and "Desmoid tumors: Systemic therapy".)

Adrenal tumors — The lifetime prevalence of adrenal tumors is 7 to 13 percent in individuals with FAP [27]. The tumors are rarely malignant and routine surveillance is not recommended. Adrenal masses are often detected incidentally on imaging studies conducted for other reasons.

The clinical presentation, diagnosis, and management of adrenal tumors is discussed in detail separately. (See "Clinical presentation and evaluation of adrenocortical tumors" and "Evaluation and management of the adrenal incidentaloma".)

CHEMOPREVENTION

The role of chemopreventive agents in patients with familial adenomatous polyposis (FAP) is uncertain given their undefined efficacy in cancer prevention [28-35].

- Aspirin **and nonsteroidal anti-inflammatory drugs** – Sulindac has been used in some centers to reduce the rectal polyp burden following surgery and as an adjunct to endoscopic surveillance. Although sulindac can cause regression of colorectal adenomas in FAP, regression is incomplete and the degree of protection from the development of colorectal cancer is unknown [28-31]. Sulindac is ineffective in delaying the time of initial development of adenomas [36]. Aspirin has not been demonstrated to prevent adenoma progression. In a randomized trial in which 206 patients with FAP were assigned to aspirin (600 mg) and/or resistant starch, neither intervention significantly reduce polyp number or size [35].

- Erlotinib – Erlotinib, an epidermal growth factor inhibitor, has been evaluated to determine its effect on duodenal adenoma regression in patients with FAP. In a randomized trial, 92 patients with FAP were assigned to sulindac and erlotinib for six months [37,38]. The use of sulindac and erlotinib resulted in a significantly lower duodenal and colorectal polyp burden as compared with placebo. However, the side effect profile was significant and the long-term benefit is undefined. Additional studies are needed to evaluate the efficacy of erlotinib alone and to determine the role of erlotinib in the primary prevention and management of polyps.

- **COX-2 inhibitors** – Celecoxib has also been shown to modestly reduce the number of colonic and duodenal adenomas in patients with FAP [32-34]. However, its use has been limited by the increased risk of cardiovascular disease. (See "Overview of COX-2 selective NSAIDs", section on 'Toxicities and possible toxicities'.)

- Eflornithine – In a randomized trial in which 171 patients were assigned eflornithine, an irreversible inhibitor of ornithine decarboxylase, sulindac, or both for two years, rates of progression of polyposis (major surgery, endoscopic excision of advanced adenomas, diagnosis of high grade dysplasia in the rectum or pouch, or progression of duodenal disease) were not significantly lower with combination therapy as compared with sulindac

or eflornithine alone [39]. In subgroup analysis, precolectomy patients who received combination therapy had a low incidence of disease progression suggesting a potential role in patients with an intact colon. However, further studies are needed to validate these results.

- **Curcumin** – Evidence to support the use of curcumin, a polyphenol extracted from turmeric, in patients with FAP is lacking [40]. Curcumin in combination with quercetin has been demonstrated to reduce the number and size of intestinal adenomas in one small series of patients with FAP [41]. However, these findings were not replicated in a randomized trial that evaluated curcumin alone. In this trial, 44 patients with FAP who had at least five intestinal adenomas, were assigned to treatment with curcumin (1,500 mg orally, twice per day) or placebo capsules for 12 months [40]. The incidence of adverse events did not differ significantly between the curcumin and placebo groups but the average rates of compliance were 83 and 91 percent, respectively. At one year, there was no significant difference in the mean number or size of polyps between the two groups even after adjusting for differences in compliance.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary colorectal cancer syndromes".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (See "Patient education: Colon and rectal cancer screening (The Basics)" and "Patient education: Colonoscopy (The Basics)" and "Patient education: Familial adenomatous polyposis (The Basics)".)

- Beyond the Basics topics (See "Patient education: Screening for colorectal cancer (Beyond the Basics)" and "Patient education: Colonoscopy (Beyond the Basics)" and "Patient education: Flexible sigmoidoscopy (Beyond the Basics)".)

SUMMARY AND RECOMMENDATIONS

- Familial Adenomatous Polyposis (FAP) is an autosomal dominant disease caused by mutations in the *Adenomatous Polyposis Coli* (*APC*) gene. Patients with FAP are at high risk for the development of colorectal cancer (CRC) as well as upper intestinal and extraintestinal tumors. Classic FAP is characterized by the presence of 100 or more colorectal adenomas. An attenuated form of FAP (AFAP) is characterized by fewer colorectal adenomas (>10 to 99) with a later age of onset. (See 'Introduction' above.)

- Screening for FAP-associated cancers should be performed in individuals with a known pathogenic *APC* mutation. Screening for FAP-related cancers should also be performed in individuals at risk for FAP who have either not undergone genetic evaluation or have indeterminate genetic test results. Individuals at risk for FAP include:

  - First-degree relatives of those with FAP.

  - Individuals with >10 cumulative colorectal adenomas or colorectal adenomas in combination with extracolonic features associated with FAP (eg, duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, or osteomas). (See 'Candidates for cancer screening' above.)

- Screening guidelines for CRC differ in patients with classic versus attenuated FAP because of differences in the age of onset, distribution, and extent of colorectal polyposis. (See "Clinical manifestations and diagnosis of familial adenomatous polyposis", section on 'Colonic manifestations'.)

  - In individuals at risk for classic FAP, we perform a colonoscopy annually starting around age 10 to 12 years. Patients should continue to undergo annual colonoscopy while awaiting colectomy. (See 'Classic FAP' above.)

- In individuals at risk for AFAP, we perform colonoscopy every one to two years starting in the late teenage years. Patients with colorectal polyps should undergo polypectomy when feasible, followed by annual colonoscopy for surveillance. (See 'AFAP' above.)

- Indications for colectomy in patients with FAP include:

  - Documented or suspected CRC
  - Adenoma with high-grade dysplasia
  - Significant symptoms related to colonic neoplasia (eg, gastrointestinal bleeding)
  - Marked increases in polyp number on consecutive exams
  - Inability to adequately survey the colon because of multiple diminutive polyps

  Colectomy is eventually necessary in all patients with classic FAP. Patients with AFAP can often be managed with colonoscopic polypectomy and may possibly never need colectomy. Surveillance following colectomy should include annual endoscopic examination of the rectum or ileal pouch, or examination of an ileostomy every two years. (See 'Surveillance following colectomy' above.)

- We perform the following tests to screen for extra-colonic malignancies in all patients with FAP (see 'Upper gastrointestinal tumors' above):

  - Upper endoscopy using a forward-viewing endoscope for gastric polyps and a side-viewing duodenoscope for duodenal polyps at the time of onset of colonic adenomas or around age 20 to 25 years, whichever comes first. Subsequent upper endoscopic surveillance and management is guided by the severity of duodenal polyposis (table 1).

  - Thyroid ultrasound starting in late teenage years, repeating every two to five years. (See 'Thyroid cancer' above.)

  - If there is a family history of hepatoblastoma, we perform genetic testing during infancy and screen affected children with serum alpha-fetoprotein and ultrasounds every three to six months from infancy until five years of age. (See 'Hepatoblastoma' above.)

- We do not routinely screen all patients with FAP for intra-abdominal desmoids, but perform an abdominal computed tomography scan to assess for desmoids in the following patients (see 'Desmoid tumors' above):

  - Prior to colectomy in patients at increased risk for desmoids
  - Palpable abdominal mass on physical examination

- Symptoms suggestive of abdominal organ obstruction

- The role of chemopreventive agents in patients with FAP is uncertain given their undefined efficacy in cancer prevention. (See 'Chemoprevention' above.)

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GRAPHICS

Modified Spigelman score and classification of duodenal polyposis

Factor	Score		
	1 point	2 points	3 points
Number of polyps	1-4	5-20	>20
Polyp size, mm	1-4	5-10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	--	High grade

Classification: no polyp: stage 0; 1 to 4 points: stage I; 5 to 6 points: stage II; 7 to 8 points: stage III; 9 to 12 points: stage IV.

Graphic 71691 Version 5.0

Contributor Disclosures

Daniel C Chung, MD Grant/Research/Clinical Trial Support: Janssen [Clinical trial support - FAP syndrome]. All of the relevant financial relationships listed have been mitigated. **Linda H Rodgers, MGC, CGC** No relevant financial relationship(s) with ineligible companies to disclose. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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