Clinical manifestations and diagnosis of familial adenomatous polyposis

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INTRODUCTION

Familial adenomatous polyposis (FAP) is typically characterized by the presence of multiple colorectal adenomatous polyps (typically more than 100). Multiple colorectal adenomas may also be seen in individuals with *MUTYH*-associated polyposis (MAP). Other rare causes include the polymerase proofreading-associated polyposis (PPAP) syndrome or hereditary mixed polyposis [1].

This topic will review the genetics, clinical manifestations, and diagnosis of FAP and its variants (attenuated FAP [AFAP], and gastric adenocarcinoma and proximal polyposis of the stomach [GAPPS]), all of which are due to a germline mutation in the *Adenomatous Polyposis Coli (APC)* gene. Surveillance strategies for FAP and the clinical features and diagnosis of *MUTYH*-associated polyposis and the hamartomatous polyposis syndromes are discussed separately. (See "Familial adenomatous polyposis: Screening and management of patients and families" and "*MUTYH*-associated polyposis" and "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management" and "Juvenile polyposis syndrome" and "PTEN hamartoma tumor syndromes, including Cowden syndrome".)

EPIDEMIOLOGY

Familial adenomatous polyposis (FAP) has an estimated prevalence of 1 in 8000 to 1 in 18,000 and accounts for less than 1 percent of all colorectal cancers in the United States [2-5]. It affects both sexes equally and has a worldwide distribution [6].

GENETICS

Familial adenomatous polyposis (FAP) and its variants are caused by germline pathogenic variants in the tumor suppressor gene, *Adenomatous Polyposis Coli* (*APC*), located on chromosome 5q21-q22 [7,8].

FAP follows an autosomal dominant pattern of inheritance with nearly complete penetrance of colonic polyposis but variable penetrance of the extracolonic manifestations of the disease. Up to 25 percent of FAP cases are due to new or *de novo APC* mutations [3]. Such patients do not have a family history of FAP but are at risk of passing the mutation on to offspring. (See "Genetics: Glossary of terms" and "Inheritance patterns of monogenic disorders (Mendelian and non-Mendelian)" and 'Clinical manifestations' below and "Inheritance patterns of monogenic disorders (Mendelian and non-Mendelian)", section on 'Incomplete or variable penetrance'.)

More than 1000 different mutations of the *APC* gene associated with FAP have been described, most of which lead to frame shifts and premature stop codons [9,10]. However, large deletions may account for up to 15 percent of cases [11-13].

Inactivating mutations of both *APC* alleles are thought to be necessary for the development of adenomas in FAP [14]. This typically results from an inherited mutation of one *APC* allele and a somatic mutation or deletion of the other allele [15]. Mutations of both alleles in a single cell result in the absence of functional APC protein and aberrant accumulation of beta-catenin, leading to transcriptional activation of the *Wnt* (Wingless-type) signaling pathway and its target genes that control cell growth. (See "Molecular genetics of colorectal cancer", section on 'APC gene'.)

Somatic mutations of the *APC* gene also play a role in the development of sporadic colorectal cancer. Somatic *APC* mutations are found in as many as 80 percent of sporadic colorectal adenomas and cancers. (See "Molecular genetics of colorectal cancer".)

The location of the mutation within the *APC* gene has been associated with the severity of colonic polyposis, the degree of cancer risk, the age of cancer onset, survival, and the presence and frequency of extracolonic manifestations [16,17]. As a general rule, mutations between codons 169 to 1393 are associated with classic FAP (see 'Classic FAP' below). Attenuated FAP

(AFAP) is associated with mutations that are typically in the 5' (5' to codon 158) and 3' (3' to codon 1596) ends of the *APC* gene (see 'Attenuated FAP' below).

Several other genotype-phenotype correlations have also been reported, although there is considerable variability within families and among individuals with identical mutations [18]. Mutations between codons 463 to 1444 have been associated with benign retinal lesions (congenital hypertrophy of the retinal pigment epithelium [CHRPE]) [19-22], mutations between codons 1445 and 1578 have been associated with desmoid tumors [21-23], mutations between codons 279 to 1309 have been associated with duodenal polyposis [24], and mutations between codons 686 and 1217 have been associated with medulloblastoma [25]. (See "Genetics: Glossary of terms" and 'Clinical manifestations' below.)

Rare mutations in the promoter region of *APC* (promoter 1B) have been linked to a related polyposis syndrome: gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [8,26].

CLINICAL MANIFESTATIONS

Familial adenomatous polyposis (FAP) is characterized by the presence of numerous colorectal adenomas (usually hundreds). A number of extracolonic manifestations have also been associated with FAP.

The majority of patients are asymptomatic until they present with symptoms of colorectal cancer. In such cases, patients with FAP may present with gastrointestinal bleeding, abdominal pain, and diarrhea. Most patients are diagnosed between 20 to 40 years of age, and 75 percent of them are symptomatic. These rates may change with increased awareness and availability of genetic testing [27]. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Clinical presentation'.)

Colonic manifestations

Classic FAP — Classic FAP is characterized by the presence of 100s to 1000s of adenomatous colorectal polyps (picture 1 and picture 2). Patients with profuse polyposis often exhibit an earlier age of onset and mutations are often located between codons 1250 to 1464 [28].

Diffuse polyposis typically develops in the second or third decade of life. The mean age of polyp emergence is 16 years, but the onset of polyps has been noted in patients as young as eight years [29].

Colorectal cancer occurs in nearly 100 percent of individuals with FAP if untreated, with an average age of 39 years at cancer diagnosis. Approximately 40 percent of individuals with colorectal cancer have synchronous malignancies, and over 80 percent of tumors are left sided [30,31]. Adenomas in patients with FAP behave in a similar manner to sporadic adenomas and do not intrinsically have a higher malignant potential. The increased risk of colorectal cancer in FAP is attributable to the vast number of adenomas that occur at an early age (figure 1); over time, one or more of these adenomas invariably progresses to colorectal cancer.

Attenuated FAP — A milder or attenuated form of FAP has been recognized [32-36]. Although there is no consensus regarding the precise definition of attenuated FAP (AFAP), it is typically characterized by oligopolyposis (10 to 99 adenomas). Adenomas and cancer in AFAP are diagnosed at a later age than in classic FAP (mean ages of 44 and 58 years, respectively) and are characterized by a more proximal distribution in the colon [34,37]. The overall risk of colorectal cancer in AFAP remains high, but is somewhat lower (approximately 80 percent) compared to classic FAP.

Extracolonic manifestations — Polyps occur in the upper gastrointestinal tract in 30 to 100 percent of patients with FAP [38,39].

- Gardner syndrome — Gardner syndrome was a term used originally to describe families with colonic polyposis and extracolonic manifestations [40]. These extraintestinal manifestations include desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas (especially of the mandible), fibromas, supernumerary teeth, gastric fundic gland polyps, juvenile nasopharyngeal angiofibromas, and CHRPE. As Gardner syndrome is also caused by an underlying *APC* mutation, and most individuals with FAP invariably exhibit some extracolonic features, the distinction between FAP and Gardner syndrome is semantic, and the terms are essentially interchangeable [41]. (See "Gardner syndrome".)

- Turcot syndrome — Turcot syndrome also known as brain tumor-polyposis syndrome is a historical term that originally described the association of familial colon cancer with brain tumors (primarily medulloblastomas and gliomas). [42]. These terms have also been applied to patients with Lynch syndrome who develop brain tumors (astrocytoma or glioblastoma), despite the clear difference in the underlying genetics. [43]. (See "Histopathology, genetics, and molecular groups of medulloblastoma", section on 'Familial adenomatous polyposis (APC)' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Extracolonic manifestations'.)

Gastric polyps — Fundic gland polyps are found in most patients with FAP. These are small (<1 cm), sessile polyps located in the fundus or body of the stomach, and some patients may have

hundreds of these lesions [44]. Fundic gland polyps are composed of normal gastric corpus-type epithelium arranged in a disorderly and/or microcystic configuration. Low-grade dysplasia occurs in nearly one-half of fundic gland polyps, although they rarely progress to cancer [45,46]. Gastric adenomas are much less common than fundic gland polyps in patients with FAP; they are typically isolated, located in the antrum, and are associated with a relatively low but definite risk of progression to cancer. (See "Gastric polyps", section on 'Fundic gland polyps'.)

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) — This rare variant has been linked to mutations in a noncoding region of the *APC* gene (promoter 1B). GAPPS is characterized by >100 polyps in the gastric body and fundus with antral sparing. Although fundic gland polyps are the most common type of gastric polyp identified, other histologic types including hyperplastic polyps and adenomatous polyps can be observed. Patients with GAPPS have a high risk of gastric cancer. Polyposis generally does not develop in the colon, differentiating the phenotype from classic FAP [8,26]. (See 'Genetics' above.)

Duodenal adenomas — Duodenal adenomas occur in 34 to 90 percent of patients with FAP, and there is a predilection for the ampullary and periampullary regions. The lifetime risk for duodenal cancer is 3.1 to 5 percent, constituting the second most common cause of death in FAP patients [28,38,39,47]. Adenomas can occur rarely in the gallbladder, bile duct, and the small bowel, particularly the distal ileum [38,48-50].

Desmoid tumors — Desmoid tumors are mesenchymal tumors that occur in 10 to 15 percent of FAP patients. Although these tumors are slow growing and do not metastasize, they may nevertheless cause significant morbidity and mortality. Desmoids are most commonly located in the abdomen, and while some may resolve spontaneously or remain stable, approximately 10 percent of cases will have a rapidly progressive course, compressing and encasing adjacent structures. This may result in pain, bowel obstruction, ureteral obstruction, and vascular compromise [51].

Other manifestations — Up to one-half of patients with FAP have benign thyroid nodules. The prevalence of thyroid cancer in patients with FAP is 2.6 percent with a female-to-male ratio of 19:1 [52]. The average age of thyroid cancer diagnosis is 31 years [52]. Thyroid cancer in FAP is typically the papillary subtype and can be multifocal. The cribriform-morular variant accounts for up to one-third of cases [53-55]. (See "Papillary thyroid cancer: Clinical features and prognosis".)

Hepatoblastomas are embryonal tumors that diagnosed at a mean age of 6 to 36 months and occur in 1.6 percent of FAP patients. Unlike desmoid and thyroid tumors, hepatoblastoma has a male predilection [30].

Approximately 1 to 2 percent of FAP patients develop brain tumors. These include medulloblastoma (80 percent of cases), ependymomas and high-grade astrocytoma, and this combination has been historically designated Turcot syndrome (see discussion above) [43]. (See 'Extracolonic manifestations' above and "Clinical presentation, diagnosis, and risk stratification of medulloblastoma".)

Sebaceous or epidermoid cysts, lipomas, osteomas, fibromas, dental abnormalities (eg, impacted teeth, tooth ankyloses, hypodontia, or supernumerary teeth), juvenile nasopharyngeal angiofibromas, and adrenal adenomas have also been associated with FAP. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is also a feature of the disease in some families [56]. On slit lamp examination, CHRPE can be seen as discrete, darkly pigmented, round, oval, or kidney-shaped lesions. The presence of bilateral or multiple (more than four) lesions is specific (94 to 100 percent) but only moderately sensitive (58 to 84 percent) for FAP [57-59]. CHRPE, as the name suggests, appears to be congenital and can be detected in children as young as three months.

Laboratory features — Most patients with FAP have no abnormal laboratory findings, but some patients may present with iron deficiency anemia due to unrecognized bleeding from adenomas [27].

DIAGNOSIS

The diagnosis of familial adenomatous polyposis (FAP) should be suspected in any patient found to have 10 or more cumulative colorectal adenomas. It should also be suspected if an individual has a history of adenomas in combination with extracolonic features of FAP such as duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, CHRPE, epidermal cysts, or osteomas, even if the absolute number of adenomas is lower.

In some circumstances, the clinical diagnosis of FAP is readily apparent by the autosomal dominant inheritance of diffuse colonic polyposis and classic extracolonic features. A germline mutation in the *APC* gene establishes a diagnosis of FAP [60-62]. We perform genetic testing for FAP and *MUTYH*-associated polyposis (MAP) in individuals with 10 adenomas because of overlapping clinical features between FAP and MAP (algorithm 1) [62-66]. Broader multigene panel testing is now an option, and these panels typically include other polyposis associated genes (*DNA polymerase* ε [*POLE*] and δ [*POLD1*], and *Gremlin 1 homolog* [*GREM1*]).

Genetic counseling should be offered prior to genetic testing [67]. A meticulous review of personal and family medical history, including verification of adenomatous histology is critical.

(See "Genetic testing" and "Familial adenomatous polyposis: Screening and management of patients and families", section on 'Colorectal cancer'.)

If an *APC* mutation is identified, mutation-specific genetic testing should be offered to at-risk relatives of the index case. This includes all first-degree relatives of the index case and also first-degree relatives of those subsequently found to have an *APC* mutation. In addition, second-degree relatives can be offered genetic evaluation and testing when a family member declines genetic testing or has died. The reasonable age at which to begin genetic evaluation for *APC* mutation in minors is 10 to 12 years, prior to the initiation of screening colonoscopy. Earlier testing can be considered in families of patients with early onset tumors, including childhood hepatoblastoma [62]. Prenatal genetic testing and preimplantation genetic diagnosis (PGD) specifically should be discussed as options in FAP patients of childbearing age [68]. (See "Preimplantation genetic testing".)

DIFFERENTIAL DIAGNOSIS

In patients with multiple colorectal polyps, it is essential to define the histology of the polyps. Multiple adenomatous polyps may also be found in cases with autosomal recessive *MUTYH*-associated polyposis (MAP) or Polymerase proofreading-associated polyposis (PPAP) that results from mutations in *DNA polymerase* ε (*POLE*) and δ (*POLD1*). Multiple colonic adenomas as well as duodenal adenomas and desmoid tumors were reported in the setting of *Gremlin 1 homolog* (*GREM1)* duplication [69]. (See "*MUTYH*-associated polyposis".)

Individuals with attenuated familial adenomatous polyposis (AFAP) and who present with relatively few colorectal adenomas may be difficult to distinguish clinically from Lynch syndrome or sporadic adenomas. Only genetic testing can definitively distinguish between familial adenomatous polyposis (FAP), MAP, and Lynch syndrome, although an autosomal dominant pattern of colorectal cancer in a family would make MAP unlikely. (See 'Genetics' above and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Genetics'.)

A significant number of individuals with multiple colorectal adenomas have no mutation in the *APC* or *MUTYH* genes [70]. Rare families with polyposis due to germline mutations in *POLE*, *POLD1*, and *GREM1* have been described [1], and there may well be other, as yet unidentified, polyposis genes. A cross-sectional study examined the prevalence of *APC* and *MUTYH* mutations in 8676 individuals with a personal or family history suggestive of a polyposis syndrome who underwent clinical genetic testing [70]. The prevalence of *APC* and *MUTYH* mutations was 80 and 2 percent, respectively, among individuals with >1000 adenomas (classic polyposis), 56 and 8

percent, respectively, among individuals with 100 to 999 adenomas (classic polyposis), 10 and 7 percent, respectively, among individuals with 20 to 99 adenomas (attenuated polyposis), and 5 and 4 percent, respectively, among individuals with 10 to 19 adenomas. In this study, 34 percent of individuals with extensive polyposis (>100 adenomas) and 81 percent of individuals with an attenuated polyposis phenotype (20 to 99 adenomas) had no mutation in either the *APC* or *MUTYH* gene. In another study of 3197 individuals with at least 10 adenomatous colon polyps, the prevalence of *APC* mutations increased with polyp burden. The *APC* mutation prevalence was 1.5, 4.3, and 36.5 percent in those with 10 to 19 colon polyps, 20 to 99 colon polyps, and >100 colon polyps, respectively [71].

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: Familial adenomatous polyposis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome caused by germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21-

q22. (See 'Genetics' above.)

- FAP occurs in approximately 1 in 8000 to 1 in 18,000 individuals, and accounts for less than 1 percent of all colorectal cancers in the United States. (See 'Epidemiology' above.)

- FAP is characterized by the presence of multiple colorectal adenomas. In classic FAP, there are >100 adenomatous colorectal polyps. Polyposis typically develops in the second or third decade of life and colorectal cancer occurs in essentially 100 percent of untreated individuals.

  Attenuated FAP (AFAP) is characterized by more than 10 to 20 adenomas but fewer than 100. Individuals with AFAP have up to an 80 percent risk of developing colorectal cancer at an average age of 56 years. (See 'Colonic manifestations' above.)

- Fundic gland polyps are found in most patients with FAP but rarely progress to cancer. Duodenal adenomas occur in 45 to 90 percent of patients with FAP, most commonly at or adjacent to the ampulla. Patients with FAP have a 5 percent lifetime risk of duodenal cancer. Individuals with FAP are also at risk for follicular or papillary thyroid cancer, childhood hepatoblastoma, and central nervous system tumors, but these are much less common than colon and duodenal cancer. (See 'Extracolonic manifestations' above.)

- The diagnosis of FAP should be suspected in individuals with >10 cumulative colorectal adenomas or a history of 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). Germline mutations in the *APC* gene establish the diagnosis of FAP or attenuated FAP. (See 'Diagnosis' above.)

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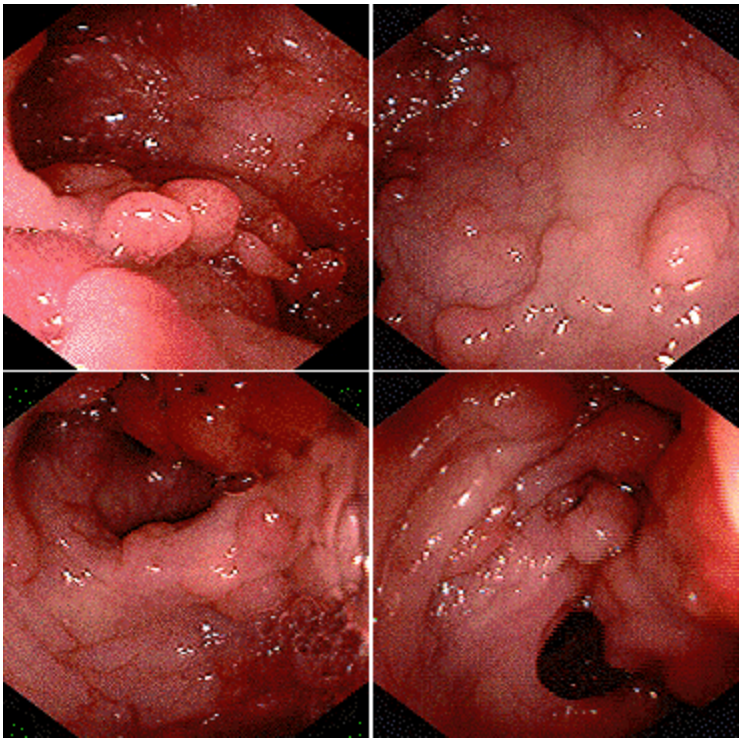
Topic 2593 Version 39.0

GRAPHICS

Endoscopic appearance of multiple polyps in familial adenomatous polyposis

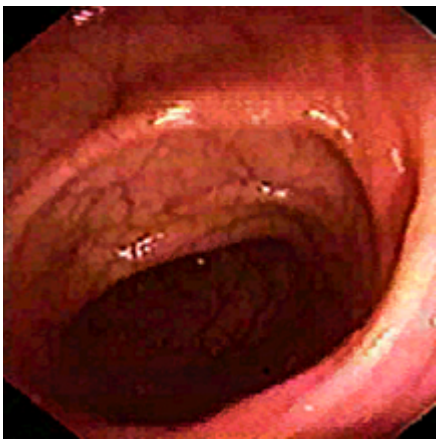


Endoscopic findings at multiple levels in a 50-year-old man with familial adenomatous polyposis. Multiple polyps of various sizes are seen. At colectomy, some of these polyps had areas of high-grade dysplasia and early malignant transformation.

Courtesy of James B McGee, MD.

Graphic 59413 Version 2.0

Normal sigmoid colon

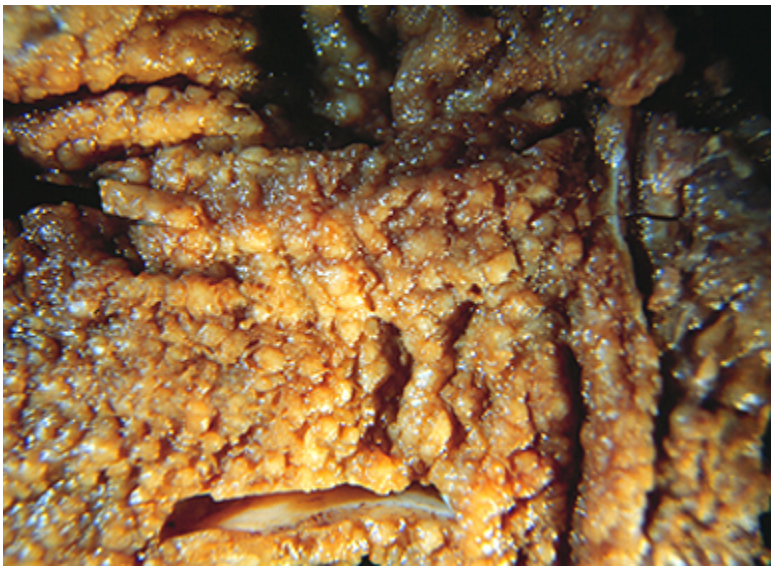


Endoscopic appearance of the normal sigmoid colonic mucosa. The fine vasculature is easily visible, and the surface is shiny and smooth. The folds are of normal thickness.

Courtesy of James B McGee, MD.

Graphic 55563 Version 1.0

Multiple colorectal polyps in patients with familial adenomatous polyposis

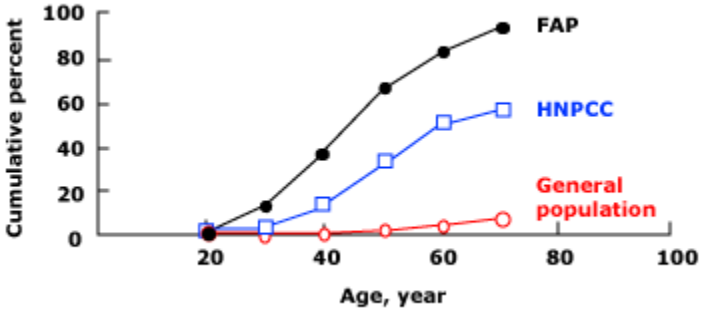


Gross specimen of the colon from a patient with familial adenomatous polyposis shows innumerable small polyps.

Courtesy of Robert Odze, MD.

Graphic 73267 Version 3.0

Cumulative incidence of colorectal cancer by age in subjects with genetic syndromes compared with the general public

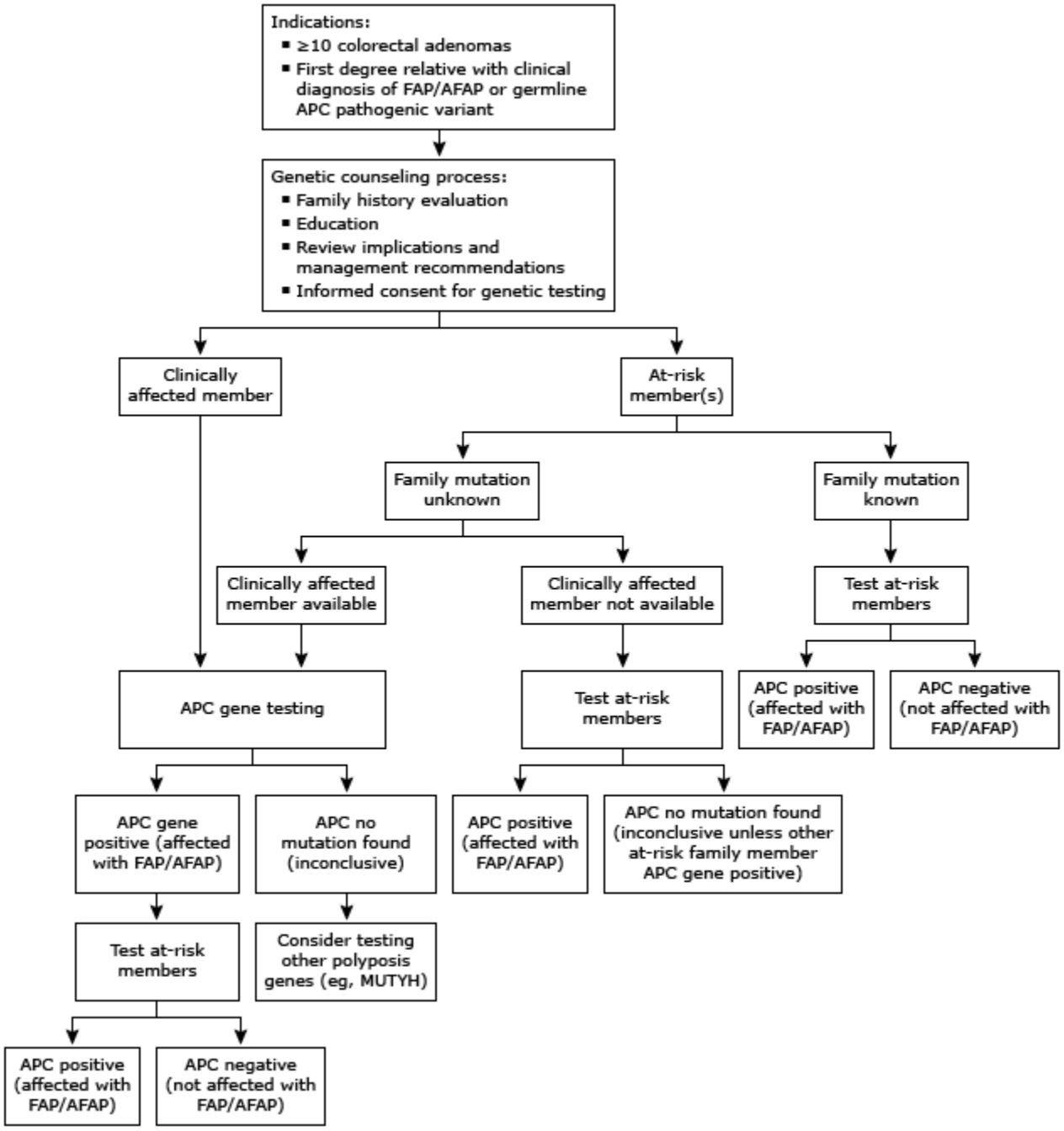


FAP: familial adenomatous polyposis; HNPCC: hereditary nonpolyposis colorectal cancer.

Data from: Winawer SW, Fletcher RH, Mille L, et al. AGA guidelines: Colorectal cancer screening: Clinical guidelines and rationale. Gastroenterology 1997; 112:594.

Graphic 58291 Version 2.0

APC gene testing algorithm



AFAP: attenuated familial adenomatous polyposis; FAP: familial adenomatous polyposis.

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Graphic 65992 Version 6.0

Contributor Disclosures

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Conflict of interest policy

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