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APC-Associated Polyposis Conditions

[*Includes: Familial Adenomatous Polyposis (Familial Polyposis Coli), Gardner Syndrome, Turcot Syndrome, Attenuated FAP*]

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Summary

Disease characteristics. *APC*-associated polyposis conditions include: familial adenomatous polyposis (FAP), attenuated FAP, Gardner syndrome, and Turcot syndrome. **FAP** is a colon cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps develop, beginning, on average, at age 16 years (range 7-36 years). By age 35 years, 95% of individuals with FAP have polyps; without colectomy, colon cancer is inevitable. The mean age of colon cancer diagnosis in untreated individuals is 39 years (range 34-43 years). Extracolonic manifestations are variably present and include: polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumors, desmoid tumors, and associated cancers. **Attenuated FAP** is characterized by a significant risk for colon cancer but fewer colonic polyps (average of 30), more proximally located polyps, and diagnosis of colon cancer at a later age; management may be substantially different. **Gardner syndrome** is characterized by colonic polyposis typical of FAP together with osteomas and soft tissue tumors. **Turcot syndrome** is the association of colonic polyposis and central nervous system (CNS) tumors. Differences in phenotype may relate to the location of the mutation within the *APC* gene.

Diagnosis/testing. *APC*-associated polyposis conditions are caused by mutations in the *APC* gene. The diagnosis relies primarily on clinical findings. Clinically available molecular genetic testing of *APC* detects disease-causing mutations in up to 90% of probands with typical FAP. Molecular genetic testing is most often used in the early diagnosis of at-risk family members, as well as in confirming the diagnosis of FAP or attenuated FAP in individuals with equivocal findings (e.g., <100 adenomatous polyps).

Management. *Treatment of manifestations:* Colectomy is advised when more than 20 or 30 adenomas or multiple adenomas with advanced histology have occurred. Nonsteroidal anti-inflammatory drugs (NSAIDs), especially sulindac, have caused regression of adenomas in FAP and decreased the number of polyps requiring ablation in the remaining rectum of persons with a subtotal colectomy. Endoscopic or surgical removal of duodenal adenomas is considered if polyps exhibit villous change or severe dysplasia, exceed one centimeter in diameter, or cause symptoms. Osteomas may be removed for cosmetic reasons. Desmoid tumors may be surgically excised or treated with NSAIDs, anti-estrogens, cytotoxic chemotherapy, or radiation. *Surveillance:* screening for hepatoblastoma by liver ultrasound and measurement of

serum alpha-fetoprotein concentration (until age five years); sigmoidoscopy or colonoscopy beginning at age ten to 12 years; annual colonoscopy once polyps are detected until colectomy; esophagogastroduodenoscopy by age 25 years or prior to colon surgery; small bowel x-ray or CT when duodenal adenomas are detected; and regular physical examinations including thyroid palpation. *Testing of relatives at risk:* Molecular genetic testing for early identification of at-risk family members improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation.

Genetic counseling. *APC*-associated polyposis conditions are inherited in an autosomal dominant manner. Approximately 75%-80% of individuals with *APC*-associated polyposis conditions have an affected parent. Offspring of an affected individual have a 50% risk of inheriting the altered *APC* gene. Prenatal testing and preimplantation genetic diagnosis are possible if a disease-causing mutation is identified in an affected family member.

Diagnosis

Clinical Diagnosis

The *APC*-associated polyposis conditions include: (1) the overlapping, often indistinguishable phenotypes of familial adenomatous polyposis (FAP), Gardner syndrome, and Turcot syndrome and (2) attenuated FAP, which has a lower colonic polyp burden and lower cancer risk:

Familial adenomatous polyposis (FAP) is diagnosed clinically in an individual with one of the following:

- One hundred or more colorectal adenomatous polyps

  Note: The diagnosis of FAP is generally considered in individuals with polyposis occurring before age 40 years.

- Fewer than 100 adenomatous polyps and a relative with FAP

Gardner syndrome is the association of colonic adenomatous polyposis, osteomas, and soft tissue tumors (epidermoid cysts, fibromas, desmoid tumors) [Gardner & Richards 1953].

Turcot syndrome is the association of colonic adenomatous polyposis and CNS tumors, usually medulloblastoma.

Attenuated FAP (AFAP) is considered in an individual with one of the following:

- Ten to 99 colonic adenomatous polyps.

  Note: Individuals with 100 or more polyps occurring at “advanced” ages (35 to 40 years or older) may be found to have attenuated FAP.

- A personal history of colorectal cancer before age 60 years and a family history of multiple adenomatous polyps

Currently, there is a lack of consensus regarding the exact diagnostic criteria that should be used for attenuated FAP. Nielsen et al [2007b] propose the following diagnostic criteria for attenuated FAP:

- No family member with more than 100 polyps before age 30 years

  AND

- At least two individuals with 10 to 99 adenomas diagnosed after age 30 years

OR

- One individual with 10 to 99 adenomas diagnosed after age 30 years and a first-degree relative with colorectal cancer with a few adenomas

Note: (1) This proposed definition takes into account the variability in colonic phenotype seen in attenuated FAP (i.e., some individuals may have ≥100 polyps at a later age, although most have <100 polyps) [Burt et al 2004]. (2) One limitation in the proposed criteria is that they do not take into account *APC* mutation status. A significant proportion of persons with polyposis who do not have an identified *APC* mutation have biallelic *MYH* mutations and therefore should be classified as having *MYH*-associated polyposis (see Differential Diagnosis).

Variable features not included in the diagnostic criteria of an *APC*-associated polyposis condition but potentially helpful in establishing the clinical diagnosis include: gastric polyps, duodenal adenomatous polyps, osteomas, dental abnormalities (especially supernumerary teeth and/or odontomas), congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumors (specifically epidermoid cysts and fibromas), desmoid tumors, and associated cancers.

Histology of adenomatous polyps

Dysplasia. Adenomatous polyps (often referred to as adenomas) are precancerous growths in which the surface epithelium of the gastrointestinal tract exhibits features of dysplasia. Dysplasia is characterized by branching of the microscopic glands, loss of goblet cells, and the following cellular features: loss of basilar polarity of the nucleus, increased nuclear/cytoplasmic ratio, increased basophilia of the cytoplasm, and loss of cytoplasmic glycogen. Dysplasia is graded as mild, moderate, or severe. Severe dysplasia is more likely to have cancer found somewhere within it and is more likely to progress to cancer.

Villous changes. In addition to the dysplastic features of an adenomatous polyp, villous changes, characterized by elongated villi at the surface of the polyp, may develop:

- **Villous adenomas** exhibit villous changes on the majority of the polyp surface. A greater risk of cancer is associated with villous features within an adenomatous polyp than with adenomatous changes alone.
- **Tubular adenomas** have no villous features.
- **Tubulovillous adenomas** have some villous features.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *APC* is the gene associated with *APC*-associated polyposis conditions.

Clinical testing

- **Full gene sequencing** of all *APC* exons and intron-exon boundaries appears to be the most accurate clinical test available to detect *APC* mutations [Giardiello et al 2001]. Most mutations in *APC* are nonsense or frameshift mutations that cause premature truncation of the APC protein.

The likelihood of detecting an *APC* mutation is highly dependent on the severity of colonic polyposis:

- Individuals with classic FAP are significantly more likely to have an *APC* mutation than individuals with a less severe colonic phenotype (i.e., <100 polyps) [Sieber et al 2002, Aretz et al 2005, Michils et al 2005, Aretz et al 2006].
- Fewer than 30% of individuals with attenuated phenotypes are expected to have an identifiable *APC* mutation [Lefevre et al 2006].
- Approximately 20% of individuals with an apparent *de novo APC* mutation have somatic mosaicism [Hes et al 2007].

  Note: In individuals with somatic mosaicism, sequencing of the *APC* gene may fail to detect disease-causing mutations because of weak mutation signals in peripheral blood lymphocytes [Aretz et al 2007, Hes et al 2007]. This, in part, may explain the lower mutation detection rate in simplex cases (i.e., a single occurrence in a family) than in persons with an affected parent.

- **Protein truncation testing**, which is positive in approximately 80% of individuals with classic FAP [Powell et al 1993], has largely been replaced by more sensitive full gene sequencing techniques.
- **Duplication/deletion analysis.** Methods commonly used to detect partial and whole-gene deletions or other large rearrangements include Southern blot analysis, multiplex ligation-dependent probe amplification (MLPA), and quantitative PCR. Approximately 8%-12% of individuals with an *APC*-associated polyposis condition and 100 or more polyps have a partial or whole *APC* gene deletion [Sieber et al 2002, Bunyan et al 2004, Aretz et al 2005, Michils et al 2005]. In one study, 19 of 296 (6%) individuals with ten or more adenomatous polyps who had no mutations in *MYH* (see Differential Diagnosis) or *APC* using sequencing, protein truncation testing, and denaturing gradient gel electrophoresis had a large *APC* deletion detected by MLPA [Nielsen et al 2007b].

  Interstitial deletions of chromosome 5q that include the *APC* gene have been identified on routine chromosome analysis in several individuals with colonic polyposis and mental retardation [Heald et al 2007]. In at least one individual, array comparative genomic hybridization (array CGH) detected a deletion that was not visible on routine cytogenetic studies [Heald et al 2007].

  Note: Cytogenetic analysis and/or array CGH are generally pursued only when adenomatous polyposis is accompanied by developmental delays.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *APC*-Associated Polyposis Conditions

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
APC	Sequence analysis	Sequence variants	≤90% [2]	Clinical Testing
	Duplication/ deletion analysis	Duplication/deletion of one or more exons	~8-12% [3]	

1. Detection rates are higher in classic polyposis than in attenuated colonic phenotypes [Sieber et al 2002, Aretz et al 2005, Michils et al 2005, Aretz et al 2006] and in individuals with a family history of polyposis than in those without affected family members in the previous generation [Truta et al 2005, Aretz et al 2007, Hes et al 2007].

3. [Sieber et al 2002, Bunyan et al 2004, Aretz et al 2005, Michils et al 2005]

2. [Giardiello et al 2001]

- **Linkage analysis.** When no disease-causing mutation is identified in an affected individual, linkage analysis can be considered in families with more than one affected family member belonging to different generations. Linkage studies are based on an accurate clinical diagnosis of an *APC*-associated polyposis condition in the affected family members and accurate understanding of genetic relationships in the family. Linkage analysis is dependent on the availability and willingness of family members to be tested. The markers used for linkage analysis of *APC*-associated polyposis conditions are highly informative and very tightly linked to the *APC* locus; thus, they can be used with greater than 98% accuracy in more than 95% of families with an *APC*-associated polyposis condition [Petersen et al 1991, Burt et al 1992]. Linkage testing is not available to families with a single affected individual, a situation that often occurs when an individual has a *de novo* gene mutation and no affected offspring.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband

- In individuals meeting the diagnostic criteria for FAP or individuals suspected of having an *APC*-associated polyposis condition, sequence analysis and duplication/deletion analysis of *APC* are performed.
- If no disease causing *APC* mutation is found, molecular genetic testing of the *MYH* gene (see Differential Diagnosis) should be considered.

Predictive testing for at-risk asymptomatic family members requires prior identification of the disease-causing mutation in the family.

Note: If no alteration in the *APC* gene is identified in a family with more than one affected relative belonging to different generations, linkage analysis can be considered.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Colon cancer and/or polyps

- **p.Ile1307Lys(I1307K),** a missense variant in the *APC* gene that appears to create a hypermutable tract in the gene, is found in approximately 6% of all individuals of Ashkenazi Jewish ancestry [Laken et al 1997]. Although studies have suggested that the p.Ile1307Lys mutation is associated with a moderately increased risk of colorectal polyps and cancer [Laken et al 1997, Rennert et al 2005], the utility of clinical testing for this variant is questionable [Strul et al 2003, Fidder et al 2005, Locker et al 2006].
- **p.Glu1317Gln(E1317Q),** another missense variant in the *APC* gene, may be associated with a predisposition to colon adenomas and/or colon cancer [Frayling et al 1998, Lamlum et al 2000, Popat et al 2000, Hahnloser et al 2003]; however, data are conflicting, and this mutation has not been found to track with polyposis in families [Frayling et al 1998, Michils et al 2002, Rozek et al 2006]. The role of the

p.Glu1317Gln variant in colon cancer is uncertain, and testing for this specific variant alone is not currently available on a clinical basis.

- **p.Val1822Asp(D1822V)** is a missense variant in the *APC* gene that occurs in approximately 10% of the population. Homozygosity for this variant may confer a greater colon cancer risk reduction from a low-fat, high-fiber diet than homozygosity for the wild type [Slattery et al 2001, Guerreiro et al 2007].

Deletion 5q22. Interstitial deletions of chromosome 5q22 that include the *APC* gene have been reported in individuals with attenuated adenomatous polyposis [Pilarski et al 1999] and classic adenomatous polyposis [Heald et al 2007]. In all reports, such individuals have had cognitive impairment, usually in the mild-to-moderate range; the majority have had dysmorphic features [Heald et al 2007].

Clinical Description

Natural History

APC-associated polyposis conditions include classic FAP, the two overlapping phenotypes Gardner syndrome and Turcot syndrome, and attenuated FAP.

Classic FAP—Colorectal adenomatous polyps begin to appear, on average, at age 16 years (range 7-36 years) [Petersen et al 1991]. By age 35 years, 95% of individuals with classic FAP have polyps. Once they appear, the polyps rapidly increase in number; when colonic expression is fully developed, hundreds to thousands of colonic adenomatous polyps are typically observed. Without colectomy, colon cancer is inevitable. The average age of colon cancer diagnosis in untreated individuals is 39 years (range 34-43 years). Seven percent of untreated individuals with FAP develop colon cancer by age 21 years, 87% by 45 years, and 93% by 50 years [Bussey 1975]. Although rare, asymptomatic individuals in their 50s have been reported [Evans et al 1993]. Inter- and intrafamilial phenotypic variability are common [Giardiello et al 1994, Rozen et al 1999].

Other features variably present in FAP

Gastric polyps. Gastric polyps can be either fundic gland or adenomatous [Bülow et al 1995]:

- Gastric fundic gland polyps, hamartomatous tumors located in the fundus and body of the stomach, occur in approximately half of individuals with FAP [Offerhaus et al 1999]. For a complete review of gastric fundic gland polyps and their relationship to FAP and attenuated FAP, see Burt [2003].
- Adenomatous polyps, the second most prevalent gastric lesion in individuals with FAP [Bülow et al 1995, Wallace & Phillips 1998], are usually confined to the gastric antrum [Offerhaus et al 1999].

The risk for gastric cancer in individuals with FAP living in Western cultures is low, although it has been reported [Offerhaus et al 1999, Garrean et al 2008]. The rates of gastric cancer in persons of Japanese and Korean heritage with FAP may be tenfold higher than the general population [Garrean et al 2008]. Gastric adenocarcinoma is believed to arise most often from adenomas but may also develop from fundic gland polyps [Zwick et al 1997, Hofgartner et al 1999, Attard et al 2001].

Adenomatous polyps of the small bowel. Adenomatous polyps of the duodenum, observed in 50%-90% of individuals with FAP, are commonly found in the second and third portions of the duodenum [Kadmon et al 2001] and rarely in the distal small bowel [Wallace & Phillips

1998]. A classification system for duodenal polyps, based on number and size of polyps, histology, and degree of dysplasia, has been developed [Spigelman et al 1989]. No clear association between the number of colonic polyps and the number of upper gastrointestinal polyps has been identified [Kadmon et al 2001]. The lifetime risk of small bowel malignancy is 4%-12%; the majority occurs in the duodenum.

Adenomatous polyps of the periampullary region (including the duodenal papilla and ampulla of Vater) are seen in at least 50% of individuals with classic FAP. Polyps in this area can cause obstruction of the pancreatic duct resulting in pancreatitis or biliary obstruction, both of which occur at increased frequency in FAP. These polyps are often small and require a side-viewing endoscope for visualization. Some theorize that pancreaticobiliary secretions (e.g., bile) affect the development of adenomas [Wallace & Phillips 1998], and may account for the observed increased risk of malignancy of polyps in the periampullary region [Kadmon et al 2001].

Extraintestinal manifestations

Osteomas are bony growths found most commonly on the skull and mandible; however, they may occur in any bone of the body. Osteomas do not usually cause clinical problems and do not become malignant; they may appear in children prior to the development of colonic polyps.

Dental abnormalities. Unerupted teeth, congenital absence of one or more teeth, supernumerary teeth, dentigerous cysts (an odontogenic cyst associated with the crown of an unerupted tooth), and odontomas have been reported in approximately 17% of individuals with FAP compared to 1%-2% of the general population [Brett et al 1994].

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) refers to discrete, flat, pigmented lesions of the retina that are not age dependent and do not cause clinical problems. Visualization of CHRPE may require examination of the ocular fundus with an indirect ophthalmoscope through a dilated pupil. Observation of multiple or bilateral CHRPE may be an indication that an at-risk family member has inherited FAP, whereas isolated lesions may be seen in the general population [Chen et al 2006].

Benign cutaneous lesions include epidermoid cysts and fibromas that may be found on any part of the body, including the face, and are mainly of cosmetic concern. Multiple pilomatricomas, although rare, have also been reported [Pujol et al 1995].

Desmoid tumors develop in approximately 10% of children and adults with FAP [Gurbuz et al 1994, Clark & Phillips 1996]. The risk of desmoid tumors in individuals with FAP is 852 times the risk in the general population [Gurbuz et al 1994]. These poorly understood, benign fibrous tumors are clonal proliferations of myofibroblasts that are locally invasive but do not metastasize [Clark et al 1999]. A pathologically distinct fibromatous lesion called a Gardner-associated fibroma (GAF) is hypothesized to be a precursor lesion [Wehrli et al 2001].

Desmoid tumors form predominantly within the abdomen or in the abdominal wall but may also occur extra-abdominally. Desmoid tumors may compress abdominal organs or complicate abdominal surgery. About 5% of individuals with FAP experience morbidity and/or mortality from desmoid tumors. Abdominal desmoid tumors may occur spontaneously or following abdominal surgery [Bertario et al 2001]. Hyper-estrogen states such as pregnancy or oral contraceptive use may also increase risk. Independent predictors for desmoid tumor development include: an *APC* mutation 3' of codon 1444, family history of desmoids, female gender, and the presence of osteomas [Bertario et al 2001].

Desmoid tumors are best evaluated by CT scan [Clark & Phillips 1996] or MRI. A CT scoring system for desmoid tumors in FAP has been developed [Middleton et al 2003].

Adrenal masses. Although not thoroughly studied, a statistically significant association between adrenal masses and FAP has been reported. Adrenal masses are found in 1%-3% of the general population; a retrospective analysis identified adrenal masses in 7.4% of individuals with FAP [Marchesa et al 1997], and a prospective study of 107 individuals with FAP found 13% with an adrenal mass greater than or equal to 1.0 cm on abdominal CT scan [Smith et al 2000b]. Most of these masses appeared to be adrenocortical adenomas without endocrinopathy or hypertension.

Extracolonic cancers. Several extracolonic cancers occur with a higher incidence in individuals with FAP than in the general population (Table 2) [Burt 2000].

Table 2. Lifetime Risk of Extracolonic Cancer in FAP

Site	Type of Cancer	Lifetime Risk of Cancer
Small bowel: duodenum or periampulla	Carcinoma	4%-12%
Small bowel: distal to the duodenum		Rare
Pancreas	Adenocarcinoma	~2%
Thyroid	Papillary thyroid carcinoma	1%-2%
CNS	Usually medulloblastoma	<1%
Liver	Hepatoblastoma	1.6%
Bile ducts	Adenocarcinoma	Low, but increased

Duodenal adenocarcinoma has been reported between ages 17 and 81 years, with the mean age of diagnosis between 45 and 52 years [Wallace & Phillips 1998, Kadmon et al 2001]. It occurs most commonly in the periampullary area. Small bowel cancer distal to the duodenum occurs but is rare.

Thyroid cancers affect approximately 1%-2% of individuals with FAP [Cetta et al 2000, Truta et al 2003]. Familial occurrence and a female preponderance have been observed. In one small series of females with FAP, the prevalence was 12% [Herraiz et al 2007]. Papillary histology predominates and may commonly have a cribriform pattern.

The risk of hepatoblastoma in FAP is 750 to 7500 times higher than in the general population, although the absolute risk is estimated at less than 2% [Aretz et al 2007]. The majority of hepatoblastomas occur prior to age three years [Aretz et al 2007].

Pregnancy/hormone use. Limited information is available on the effect of pregnancy on females with FAP. In one study of 58 Danish women with FAP, the same frequency of fertility, pregnancy, and delivery was observed as in a control population [Johansen et al 1990]. A larger study of 162 women with FAP compared fertility rates before and after two types of colorectal surgery with a control population. Women with FAP who had not yet undergone surgery had the same fertility as a control population of normal women. Additionally, those women with FAP who had a colectomy with ileorectal anastomosis (IRA) had the same fertility as the control population. Fertility was significantly reduced in women with FAP who had a proctocolectomy with ileal pouch-anal anastomosis (IPAA) compared to the control population [Olsen et al 2003].

Women who have undergone colectomy are considered to have the same risk of obstetrical complications as any other woman who has had major abdominal surgery.

As anti-estrogen medications have been successfully used in the treatment of desmoid tumors, the development of desmoid tumors is thought to be affected by hormones important in

pregnancy. However, one study has shown that women who had a previous pregnancy and developed a desmoid tumor had significantly fewer complications from the desmoid tumor than those who had never had a pregnancy [Church & McGannon 2000].

In a study of women with FAP at the time of their colectomy, no association was found between pregnancy history and colonic polyp severity; however, the proportion of parous women with severe duodenal disease was significantly higher than the proportion of nulliparous women [Suraweera et al 2007].

Some studies have suggested that female hormones protect against colorectal cancer development in the general population. In one woman, reduction in polyps after use of oral contraceptives was observed [Giardiello et al 2005].

Gardner Syndrome—Gardner syndrome (GS) is the association of colonic adenomatous polyposis of classic FAP with osteomas and soft tissue tumors (epidermoid cysts, fibromas, desmoid tumors) [Gardner & Richards 1953]. These benign, extraintestinal growths occur in about 20% of individuals and families with FAP. When these findings are prominent, many clinicians continue to use the term Gardner syndrome.

Osteomas are most commonly found on the mandible and skull, although any bone of the body may be involved. Epidermoid cysts occur on any cutaneous surface and are mainly of cosmetic concern, as they do not appear to have malignant potential. Supernumerary teeth, odontomas, and desmoid tumors were originally described as a part of Gardner syndrome; however, like osteomas and epidermoid cysts, they can occur in any individual with FAP, whether or not other extraintestinal findings are present.

Gardner syndrome was once thought to be a distinct clinical entity; however, it is now known that mutations in the *APC* gene give rise to both classic FAP and Gardner syndrome. Other manifestations of FAP, such as upper gastrointestinal polyposis, are also found in Gardner syndrome. Some correlation exists between extraintestinal growths and mutation location in *APC*. See Genotype-Phenotype Correlations.

Turcot Syndrome—Turcot syndrome is the association of colonic polyposis or colorectal cancer and CNS tumors. The molecular basis of most Turcot syndrome is either a mutation in the *APC* gene associated with FAP or a mutation in one of the mismatch repair genes associated with hereditary non-polyposis colon cancer (HNPCC) [Hamilton et al 1995]. The CNS tumors in individuals with *APC* mutations are typically medulloblastoma, whereas those with mismatch repair mutations are usually glioblastoma multiforme. The risk of CNS tumors is substantially increased in persons with FAP generally, although the absolute risk is only approximately 1%. Families with *APC*-associated polyposis conditions in which multiple individuals have CNS tumors raise the possibility of mutation specificity or modifying genes.

Attenuated FAP—Attenuated FAP is characterized by fewer colonic polyps (average of 30) than classic FAP but a significant risk for colorectal cancer. Polyps tend to be found more proximally in the colon than in classic FAP.

The exact lifetime risk of colorectal cancer in attenuated FAP is unclear; the cumulative risk by age 80 years is estimated to be approximately 70% [Neklason et al 2008]. The average age of colon cancer diagnosis in individuals with attenuated FAP is 50 to 55 years — ten to 15 years later than in those with classic FAP, but earlier than in those with sporadically occurring colon cancer [Spirio et al 1993, Giardiello et al 1997].

In two large kindreds with attenuated FAP and an identical *APC* germline mutation [Burt et al 2004, Neklason et al 2008]:

- The median number of adenomatous polyps in 120 mutation-positive individuals was 25 (range 0-470).
- Forty-four of 120 (~37%) mutation-positive individuals with detailed colonoscopy records available had fewer than ten adenomatous polyps.
- Three of the 44 mutation-positive individuals with fewer than ten polyps had colorectal cancer; one of the three was diagnosed before age 30 years.

Additional findings in attenuated FAP can include:

- Upper gastrointestinal polyps and cancers
- Extraintestinal manifestations of FAP; however, CHRPE and desmoid tumors are rare [Burt 2003, Knudsen et al 2003, Burt et al 2004].
- Thyroid cancer [Truta et al 2003, Burt et al 2004]

Genotype-Phenotype Correlations

Although variation occurs among and within individuals and among and within families with identical *APC* mutations [Giardiello et al 1994, Friedl et al 2001], much effort has gone into making genotype-phenotype correlations. Some have suggested basing management strategies on these associations [Vasen et al 1996], whereas others feel that therapeutic decisions should not be based on genotype [Friedl et al 2001].

While not in routine use at present, the following correlations may become important in management decisions in the future (see Table 3 for reference sequences for mutations discussed in this section):

- The most frequent *APC* mutation is located at codon 1309 (c.3927_3931delAAAGA) [Friedl & Aretz 2005]. Mutations at this codon lead to a high number of colonic adenomas at an early age [Friedl et al 2001, Bertario et al 2003].
- The average age of onset in individuals with colonic symptoms [Friedl et al 2001] varied by mutation location:
  - At codon 1309: age 20 years
  - Between codon 168 and 1580 (excluding 1309): age 30 years
  - 5' of codon 168 and 3' of codon 1580: age 52 years
- Profuse polyposis (an average of 5000 polyps) has been reported with mutations in codons 1250-1464 [Nagase et al 1992].
- Attenuated FAP is associated with the following:
  - Mutations (usually truncating mutations) in the 5' part of the gene (codons 1-177) [Sieber et al 2006], exon 9 [van der Luijt et al 1995, Soravia et al 1998, Sieber et al 2006], and the distal 3' end of the gene [Friedl et al 1996, van der Luijt et al 1996, Walon et al 1997, Sieber et al 2006].
  - Interstitial deletions of chromosome 5q22 that include the *APC* gene [Pilarski et al 1999]
  - Partial and whole-gene deletions [Nielsen et al 2007a]

  - Somatic mosaicism for *APC* mutations that are generally associated with classic FAP [Friedl & Aretz 2005, Aretz et al 2007, Hes et al 2007]

- A fourfold increased risk for duodenal adenomas was found in individuals with mutations between codons 976 and 1067 in one study of Italian individuals with FAP [Bertario et al 2003].
- Prominent extracolonic manifestations often correlate (though not completely) with more distal *APC* mutations. A retrospective study of 190 individuals with FAP that evaluated nine extracolonic manifestations (desmoid tumors, osteomas, epidermoid cysts, duodenal adenomas, gastric polyps, hepatoblastoma, dental anomalies, periampullary cancers, and brain tumors) [Wallis et al 1999] revealed that:
  - Individuals with mutations in codons 1395-1493 have significantly higher rates of desmoid tumors, osteomas, and epidermoid cysts than those with mutations in codons 177-452.
  - Individuals with mutations in codons 1395-1493 have significantly higher rates of desmoid tumors and osteomas than those with mutations in codons 457-1309.
  - No individuals with mutations in codons 177-452 developed osteomas or periampullary cancers.
  - Only individuals with mutations in codons 457-1309 developed hepatoblastoma and/or brain tumors.
- Desmoid tumors show the following correlations:
  - *APC* mutations between codons 1444 and 1580 are associated with a higher incidence of desmoid tumors than mutations in other codons [Caspari et al 1995, Davies et al 1995].
  - A study of 269 individuals with identifiable *APC* mutations found desmoid tumors in 20% of individuals with mutations 5' to codon 1444, 49% of individuals with mutations 3' to codon 1444, and 61% of individuals with mutations in codons 1445-1580 [Friedl et al 2001].
  - Several families with severe desmoid tumors with mutations at the extreme 3' end of the gene have been reported [Eccles et al 1996, Scott et al 1996, Couture et al 2000].
  - A study of Italian individuals with FAP found that mutations between codons 1310 and 2011 are associated with a sixfold risk of desmoid tumors compared to mutations between codons 159 and 495 [Bertario et al 2003].
  - A review of the literature by Nieuwenhuis & Vasen [2007] revealed a consistent association of desmoid tumors with mutations distal to codon 1444.
- CHRPE is associated with:
  - Mutations between codons 311 and 1444 [Nieuwenhuis & Vasen 2007]
  - Whole A*PC* gene deletions [Aretz et al 2005]
- In individuals with thyroid cancer and FAP:
  - In 24 individuals, the majority of mutations identified were 5' to codon 1220 [Cetta et al 2000].

  - Nine of 12 individuals had *APC* mutations identified proximal to the mutation cluster region (codons 1286-1513) [Truta et al 2003].

- A review of the literature up to August 2006 and a report of additional cases by Nielsen et al [2007a] revealed 89 submicroscopic *APC* gene deletions (42 partial and 47 whole-gene deletions). Most partial and whole *APC* gene deletions are associated with 100-2000 colonic adenomas, although attenuated FAP has been seen [Nielsen et al 2007a]. Extracolonic findings were seen in 36% of cases, with no significant differences between those with partial and whole-gene deletions [Nielsen et al 2007a].

Penetrance

In FAP, the penetrance of colonic adenomatous polyposis and colon cancer is virtually 100% in untreated individuals.

The penetrance of other intestinal and extraintestinal manifestations is less well understood and may depend in part on the mutation location in the *APC* gene.

Anticipation

Although a recent observation has suggested the possibility of anticipation in *APC*-associated polyposis conditions [Heald et al 2007], true genetic anticipation (in which subsequent generations have an increased risk of more severe disease manifestations because of the underlying mutational mechanism) has not been observed in *APC*-associated polyposis conditions. Rather, milder disease manifestations in the first person to have the disorder in a family are most often the result of somatic mosaicism for the disease-causing mutation in that individual.

Nomenclature

Another term used historically for FAP is adenomatous polyposis coli (i.e., APC), which is now used for the relevant gene.

The term Gardner syndrome is mainly of historical interest as it is now known to arise from mutations of the *APC* gene like FAP. Furthermore, with sufficient investigation, subtle extraintestinal manifestations can be found in almost all individuals with FAP. Nonetheless, individuals and families with particularly prominent extracolonic manifestations will undoubtedly continue to be referred to as having Gardner syndrome.

In some families with FAP, multiple individuals have CNS tumors, making Turcot syndrome a historical term of uncertain significance as it relates to FAP.

Attenuated FAP appears to be the same as the “hereditary flat adenoma syndrome” [Lynch et al 1992].

Prevalence

The prevalence data reported from national registries include all of the *APC*-associated polyposis conditions (except possibly some cases of attenuated FAP); reported prevalence is 2.29 to 3.2 per 100,000 individuals [Burn et al 1991, Jarvinen 1992, Bülow et al 1996].

Attenuated FAP is likely underdiagnosed, given the lower number of colonic polyps and lower risk of colorectal cancer compared to classic FAP [Neklason et al 2008].

APC-associated polyposis conditions historically accounted for about 0.5% of all colorectal cancers; this figure is declining as more at-risk family members undergo successful treatment following early polyp detection and prophylactic colectomy.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

APC-associated polyposis conditions may be distinguished from other inherited colon cancer conditions and other gastrointestinal polyposis syndromes by molecular genetic testing, histopathologic findings, and phenotypic characteristics. Conditions to consider in the differential diagnosis include the following hereditary disorders:

- ***MYH*-associated polyposis.** The colonic phenotype of *MYH*-associated polyposis is similar to attenuated FAP but is inherited in an autosomal recessive manner. Germline mutations in *MYH* predispose individuals to multiple adenoma or polyposis coli. If an *APC* mutation is not identified in an individual with colonic polyposis, molecular genetic testing of *MYH* should be considered [Sieber et al 2003].

  Biallelic *MYH* mutations have been found in a few individuals diagnosed with colorectal cancer at age 50 years or younger who have had few or no polyps [Wang et al 2004]. The frequency of duodenal polyposis is between 4% and 25% of individuals with biallelic *MYH* mutations; extraintestinal findings are also noted on occasion [Aretz et al 2006].

  In one study of individuals with polyposis without an identified *APC* mutation, the detection rate of *MYH* mutations varied by the colonic severity [Aretz et al 2006]; biallelic *MYH* mutations were found in:

  - Forty of 227 (18%) individuals diagnosed with ten to 100 polyps after age 25 years or more than 100 polyps after age 45 years;
  - Seven of 26 (27%) individuals with more than 100 polyps diagnosed between ages 35 and 45 years;
  - None of 41 individuals with more than 100 polyps diagnosed before 35 years of age;
  - One individual with approximately 1000 polyps diagnosed at age 68 years.
- **Hereditary non-polyposis colon cancer(HNPCC),** caused by a germline mutation in one of four mismatch repair genes, is characterized by an increased risk of colorectal cancer and other cancers (e.g., of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, skin). It may be difficult to distinguish between HNPCC and attenuated FAP in individuals and families who have few adenomatous colonic polyps [Cao et al 2002]. In this situation, family history of extracolonic cancers and manifestations as well as microsatellite instability (MSI) testing and/or immunohistochemistry (IHC) testing on a tumor block from a colorectal cancer may be helpful in deciding which condition to pursue further.

  Biallelic mutations in the mismatch repair genes, although rare, have been reported. Affected individuals frequently have brain tumors, hematologic malignancies, and colorectal cancer in childhood [De Vos et al 2005, Felton et al 2007]. Café-au-lait spots are seen in most individuals, and multiple adenomas may also be present [Felton et al 2007].

- **Turcot syndrome** is the association of colonic polyposis or colorectal cancer and CNS tumors, usually medulloblastoma. Two-thirds of individuals with Turcot syndrome have a mutation in the *APC* gene, and one-third have mutations in one of the mismatch repair genes that cause hereditary non-polyposis colon cancer (HNPCC) [Hamilton et al 1995, Paraf et al 1997]. The CNS tumors in individuals with HNPCC are usually glioblastoma multiforme.
- **Peutz-Jeghers syndrome(PJS).** Inherited in an autosomal dominant manner, PJS is characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. Peutz-Jeghers type hamartomatous polyps are most prevalent in the small intestine (jejunum, ileum, and duodenum, respectively) but can occur elsewhere in the gastrointestinal (GI) tract. Mucocutaneous hyperpigmentation appears in children under age five years as dark blue to dark brown mucocutaneous macules around the mouth, eyes, and nostrils, in the perianal area, on the buccal mucosa, and on the fingers. Females are at risk for sex cord tumors with annular tubules (SCTAT), a benign neoplasm of the ovaries. Males occasionally develop calcifying Sertoli cell tumors of the testes, which secrete estrogen and can lead to gynecomastia. Individuals with Peutz-Jeghers syndrome are at increased risk for intestinal and extraintestinal malignancies, including colorectal, gastric, breast, gynecologic, lung, and pancreatic cancers [Giardiello et al 2000]. Molecular genetic testing of the *STK11* gene reveals disease-causing mutations in most cases.
- **PTEN hamartoma tumor syndrome(PHTS)** includes: Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome. CS is a multiple hamartoma syndrome with a high risk of benign and malignant tumors of the thyroid, breast, and endometrium. BRRS is a congenital disorder characterized by macrocephaly, intestinal polyposis, lipomas, and pigmented macules of the glans penis. PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses. Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS. Approximately 80% of individuals who meet the diagnostic criteria for CS and 60% of individuals with a clinical diagnosis of BRRS have a detectable *PTEN* gene mutation.
- **Juvenile polyposis syndrome(JPS)** is characterized by predisposition for hamartomatous polyps in the GI tract, specifically in the stomach, small intestine, colon, and rectum. JPS is diagnosed if any one of the following is present: more than five juvenile polyps of the colorectum OR multiple juvenile polyps throughout the GI tract OR any number of juvenile polyps and a family history of juvenile polyps [Jass et al 1988]. The term "juvenile" refers to the type of polyp, not the age of onset of polyps. Most individuals with JPS have some polyps by age 20 years. Some individuals may have only four or five polyps over their lifetimes, whereas others in the same family may have more than 100. Most juvenile polyps are benign; however, malignant transformation can occur. Estimates of developing GI cancers in families with JPS range from 9% to 50%. Three genes are known to be associated with JPS: *MADH4* (previously *SMAD4)*, *BMPR1A*, and *ENG*. JPS is inherited in an autosomal dominant manner.
- **Hereditary mixed polyposis syndrome (HMPS)** is associated with an increased risk of colorectal tumors including juvenile polyps, adenomatous polyps, hyperplastic polyps, polyps containing mixed histology, and carcinomas. A locus associated with HMPS has been mapped to 15q13-q14 [Jaeger et al 2003]. HMPS appears to be inherited in an autosomal dominant manner.

- **Neurofibromatosis type 1(NF1).** Individuals with NF1 may exhibit multiple intestinal polypoid neurofibromas or ganglioneuromas in the small bowel, stomach, and colon.

Conditions to be considered in the differential diagnosis include the following acquired disorders:

- **Cronkite-Canada syndrome**, characterized by generalized gastrointestinal hamartomatous polyposis, cutaneous hyperpigmentation, hair loss, and nail atrophy
- **Nodular lymphoid hyperplasia**, a lymphoproliferative disorder resulting in hyperplastic lymphoid nodules in small bowel, stomach, and colon; may be associated with common variable immunodeficiency syndrome
- **Lymphomatous polyposis**, characterized by occurrence of primary extranodal lymphomas in the gastrointestinal tract; two types include multiple lymphomatous polyposis and Mediterranean-type lymphoma.
- **Inflammatory polyposis**, characterized by acquired, non-neoplastic polyps associated with inflammatory bowel disease, most commonly ulcerative colitis
- **Sporadic colorectal tumors.** The majority of colorectal tumors not known to be familial have been shown to have a somatic mutation in the *APC* gene [Miyoshi et al 1992, Powell et al 1992, Smith et al 1993] that is believed to occur early in colorectal tumorigenesis [Fearon & Vogelstein 1990].
- **Hyperplastic polyposis (or metaplastic polyposis),** comprising multiple, non-neoplastic hyperplastic polyps of the gastrointestinal tract; whether it is inherited or acquired is unknown.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with an *APC*-associated polyposis condition, the following evaluations are recommended:

- Personal medical history with particular attention to features of *APC*-associated polyposis (colon cancer, colon polyps, rectal bleeding, diarrhea, abdominal pain)
- Family history with particular attention to features of *APC*-associated polyposis
- Physical examination with particular attention to extraintestinal manifestations of *APC*-associated polyposis
- Ophthalmologic evaluation for presence of congenital hypertrophy of the retinal pigment epithelium (CHRPE) (optional)
- Colonoscopy with review of pathology
- Consideration of upper GI tract evaluation, including endoscopy with a side-viewing scope; if symptomatic, small-bowel imaging such as small-bowel enteroclysis (an x-ray that looks at how contrast moves through the area) or abdominal and pelvic CT with contrast

Note: Smith et al [2000b] and Ferrández et al [2006] found no evidence to warrant screening for adrenal masses in FAP.

Treatment of Manifestations

Colonic polyps. Practice parameters, including information on surgery, have been outlined by the American Society of Colon and Rectal Surgeons [Church et al 2003b], in addition to the American Society of Clinical Oncology and the Society of Surgical Oncology [Guillem et al 2006].

For individuals with classic FAP, colectomy is recommended after adenomas emerge; colectomy may be delayed depending on the size and number of adenomatous polyps. Colectomy is usually advised when more than 20 or 30 adenomas or multiple adenomas with advanced histology have developed.

For individuals with attenuated FAP, colectomy may be necessary, but in approximately one-third of individuals the colonic polyps are limited enough in number that surveillance with periodic colonoscopic polypectomy is sufficient (See Surveillance).

The types of colectomy include the following:

- Restorative proctocolectomy
- Proctocolectomy with ileal pouch anal anastomosis
- Total colectomy with ileorectal anastomosis; often used for individuals with attenuated FAP or in instances in which the rectum is spared of polyps
- Total proctocolectomy with permanent ileostomy.

  Note: This procedure is rarely needed.

A study of individuals with FAP and ileal pouches found that 57% had adenomatous polyps in the ileal pouch. No apparent relationship between the development of pouch adenomas and the severity of polyps in the colon or duodenum was found [Groves et al 2005].

The risk of cancer in the surgical transition zone is very low but has been reported [Ooi et al 2003].

Small bowel polyps. Endoscopic or surgical removal of duodenal and/or ampullary adenomas should be considered if polyps exhibit villous change or severe dysplasia, exceed one centimeter in diameter, or cause symptoms [Wallace & Phillips 1998, Saurin et al 1999, Kadmon et al 2001].

Pancreaticoduodenectomy (Whipple procedure) may occasionally be necessary to treat severe duodenal adenomas.

Osteomas may be removed for cosmetic reasons.

Desmoid tumors. Available treatments include surgical excision (associated with high rates of recurrence), nonsteroidal anti-inflammatory drugs (NSAIDs), anti-estrogens, cytotoxic chemotherapy, and radiation [Griffioen et al 1998, Clark et al 1999, Smith et al 2000a, Tonelli et al 2003, Gega et al 2006]. A review of desmoid treatments can be found in Guillem et al [2006].

Nonsteroidal anti-inflammatory drugs (NSAIDs), especially sulindac, [Steinbach et al 2000, Higuchi et al 2003, Keller & Giardiello 2003], have been shown to cause regression of adenomas in FAP and to decrease the number of polyps requiring ablation in the remaining rectum of individuals who have had a colectomy with ileorectal anastomosis.

Note: NSAID use before colectomy remains experimental.

Sulindac appears to be the only option. Withdrawal from the market of rofecoxib in 2005 because of untoward cardiovascular and cerebrovascular events and the observation that similar events occur with the doses of celecoxib needed for adenoma regression has brought into question the long-term use of these agents for treatment of FAP.

Surveillance

Recommended surveillance of individuals known to have FAP or an *APC* disease-causing mutation and individuals at risk for FAP who have not undergone molecular genetic testing or who are members of families in which molecular genetic testing did not identify a disease-causing mutation [Giardiello et al 2001]:

- Sigmoidoscopy or colonoscopy every one to two years, beginning at age ten to 12 years
- Colonoscopy, once polyps are detected
- Annual colonoscopy, if colectomy is delayed more than a year after polyps emerge. In individuals age ten to 20 years in whom adenomas are smaller than 6.0 mm and without villous component, delay in colectomy may be considered.
- Esophagogastroduodenoscopy (EGD) beginning by age 25 years or prior to colectomy and repeated every one to three years

  Note: (1) The frequency of EGD depends on the severity of duodenal adenomas; Spigelman staging criteria can help determine the frequency of EGD.

  (2) A side-viewing instrument should be used to visualize the duodenal papilla.

  (3) As adenomatous tissue is commonly found at the papilla, biopsy may be justified if no polyps are visualized but the papilla seems enlarged.

  (4) In some cases, endoscopic retrograde cholangiopancreatography (ERCP) may be necessary to evaluate for adenomas of the common bile duct.

  (5) The utility of video capsule endoscopy (VCE) in screening for small-bowel lesions in FAP is unclear. Inaccurate identification of large polyps in the proximal small bowel and the inability to view the ampulla call into question the use of VCE in *APC*-associated polyposis conditions [Wong et al 2006].
- Small-bowel imaging (small-bowel enteroclysis or abdominal and pelvic CT with orally administered contrast) when duodenal adenomas are detected or prior to colectomy, repeated every one to three years depending on findings and presence of symptoms
- Screening for hepatoblastoma: efficacy in individuals with FAP is unclear. Screening protocols in Beckwith-Wiedemann syndrome, in which the risk of hepatoblastoma is also increased, often include frequent (every 2-3 months) abdominal ultrasound examinations and measurement of serum alpha-fetoprotein concentrations and have resulted in early detection of hepatoblastomas [Tan & Amor 2006]. Screening for hepatoblastoma in FAP using the same protocol may be considered from infancy to age five years. However, the optimal interval for hepatoblastoma screening in FAP is not known, although it has been recommended that screening should occur at least every three months [Hirschman et al 2004, Aretz et al 2007].
- Annual physical examination, including evaluation for extraintestinal manifestations, usually for cosmetic concerns, and palpation of the thyroid with consideration of follow-up ultrasound examination and fine-needle aspiration if thyroid nodules are present [Herraiz et al 2007]

Recommended surveillance for individuals who have undergone colectomy

- If total colectomy with ileo-anal pull-through was performed, routine endoscopic surveillance of the ileal pouch every two years
- If subtotal colectomy was performed, surveillance of the remaining rectum every six to 12 months, depending on the number of polyps that develop. Cancer may still occur in the remaining rectum, but the risk is low with the current management [Church et al 2003a].

Recommended surveillance of individuals known to have attenuated FAP

- Colonoscopy every two to three years, beginning at age 18 to 20 years
- Colectomy: usually advised when more than 20 or 30 adenomas or multiple adenomas with advanced histology have developed (See Recommended surveillance for individuals who have undergone colectomy.)
- Esophagogastroduodenoscopy (EGD) beginning by age 25 years or prior to colectomy and repeated every one to three years

  Note: (1) The frequency of EGD is dependent on the severity of duodenal adenomas; Spigelman staging criteria can help determine the frequency of exams.

  (2) A side-viewing instrument should be used to visualize the duodenal papilla.

  (3) Because adenomatous tissue is commonly found at the papilla, biopsy may be justified if no polyps are visualized but the papilla seems enlarged.

  (4) In some cases, endoscopic retrograde cholangiopancreatography (ERCP) may be necessary to evaluate for adenomas of the common bile duct.
- Annual physical examination with palpation of the thyroid with consideration of follow-up ultrasound examination and fine-needle aspiration if thyroid nodules are present [Herraiz et al 2007]

Recommended surveillance of at-risk family members who, on molecular genetic testing, have not inherited the disease-causing *APC* mutation previously identified in an affected family member:

- Colon cancer screening for individuals at average risk beginning at age 50 years

Testing of Relatives at Risk

Recommended genetic testing for at-risk family members. Early recognition of *APC*-associated polyposis conditions may allow for timely intervention and improved final outcome; thus, surveillance of asymptomatic, at-risk children for early manifestations is appropriate (see American Gastroenterological Association Medical Position Statement and American College of Medical Genetics/American Society of Human Genetics Joint Statement).

Use of molecular genetic testing for early identification of at-risk family members (see Genetic Counseling) improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation. A cost analysis comparing molecular genetic testing and sigmoidoscopy screening for individuals at risk for *APC*-associated polyposis conditions shows that genetic testing is more cost effective than sigmoidoscopy in determining who in the family is affected [Cromwell et al 1998]. Additionally, individuals diagnosed with *APC*-associated polyposis conditions as a result of having an affected relative have a significantly greater life expectancy than those individuals diagnosed on the basis of symptoms [Heiskanen et al 2000].

As colon screening for those at risk for classic FAP begins as early as age ten to12 years, molecular genetic testing is generally offered to children at risk for classic FAP by age ten years. Genetic testing at birth may also be warranted, as some parents and pediatricians may consider hepatoblastoma screening from infancy to age five years in affected offspring. Colon screening for those with attenuated FAP begins at age 18 to 20 years; thus, molecular genetic testing should be offered to those at risk for attenuated FAP at approximately age 18 years.

Note: No evidence points to an optimal age at which to begin screening; thus, the ages at which testing is performed and screening initiated may vary by center, family history, hepatoblastoma screening, and/or parents'/child's needs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

NSAIDs have been used unsuccessfully in an attempt to prevent the emergence of colonic adenomatous polyposis [Giardiello et al 2002].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

APC-associated polyposis conditions are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 20%-25% of individuals with an *APC*-associated polyposis condition have the altered gene as the result of a *de novo* gene mutation [Bisgaard et al 1994].
- Investigations to determine the parental origin of a *de novo APC* gene mutation suggest a slight preponderance of mutations of paternal origin (12/16 families; not statistically significant) [Aretz et al 2004] while another report shows equal maternal

and paternal origin [Ripa et al 2002]. Thus, *de novo APC* mutations do not appear to demonstrate an advanced paternal age effect [Ripa et al 2002, Aretz et al 2004].

- It is appropriate to evaluate the parents of an affected individual (a) with molecular genetic testing of the *APC* gene if the disease-causing mutation is known in the proband or (b) for clinical manifestations of *APC*-associated polyposis conditions.

Note: Although most individuals diagnosed with an *APC*-associated polyposis condition have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the parents.
- If a parent is affected or has the disease-causing mutation, the risk to the sibs of inheriting the mutation is 50%.
- If neither parent has the *APC* mutation identified in the proband, the risk to the sibs is low but greater than that of the general population because of the possibility of germline mosaicism. Thus, molecular genetic testing should be offered to the sibs of an individual with an apparent *de novo* mutation.
- Germline mosaicism has been documented in an asymptomatic 79 year old woman who had two sons with thousands of adenomatous colonic polyps and an *APC* mutation [Hes et al 2007]. Another unaffected woman was demonstrated to have germline mosaicism, as two of her children had colonic adenomatous polyposis and were subsequently found to have an *APC* mutation [Schwab et al 2007].

Offspring of a proband. Every child of an individual with an *APC*-associated polyposis condition has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent is found to be affected or to have an *APC* disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic individuals during adulthood and childhood. Consideration of molecular genetic testing of young, at-risk family members is appropriate for guiding medical management (see Management).

Molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members when a clinically diagnosed relative has undergone molecular genetic testing and is found to have a mutation in the *APC* gene.

The use of molecular genetic testing for determining the genetic status of at-risk relatives when a clinically diagnosed relative is not available for testing is problematic, and test results need to be interpreted with caution. A positive test result in the at-risk family member indicates the presence of an *APC* disease-causing mutation and also indicates that the same molecular genetic testing method can be used to assess the genetic status of other, at-risk family members. In contrast, when genetic testing is offered to an at-risk family member prior to testing a family member known to be affected, the failure to identify a disease-causing mutation in the at-risk family member does not eliminate the possibility that an *APC* disease-causing mutation is present. The genetic status of such individuals cannot be determined through molecular genetic

testing, and they need to follow the recommendations for clinical surveillance of at-risk family members.

Because colon screening for those at risk for classic FAP begins as early as age ten years, molecular genetic testing is generally offered to individuals by this age. Colon screening for those at risk for attenuated FAP begins at age 18 to 20 years; thus, molecular genetic testing should be offered at about age 18 years. Molecular genetic testing may be performed earlier if it alters medical management of the child, as is the case when parents are considering hepatoblastoma screening for their at-risk offspring. Predictive genetic testing may be considered within the first few months of life as a result of the increased risk of hepatoblastoma in FAP.

Parents often want to know the genetic status of their children prior to initiating screening in order to avoid unnecessary procedures in a child who has not inherited the altered gene. Special consideration should be given to education of the children and their parents prior to genetic testing. A plan should be established for the manner in which results are to be given to the parents and their children. Although most children do not show evidence of clinically significant psychological problems after presymptomatic testing, Codori et al [2003] recommend that long-term psychological support be available to these families.

Other issues to consider. It is recommended that physicians ordering *APC* molecular genetic testing and individuals considering undergoing testing understand the risks, benefits, and limitations of the testing prior to sending a sample to a laboratory. A study demonstrated that for almost one-third of individuals assessed for FAP, the physician misinterpreted the test results [Giardiello et al 1997]. In addition, Michie et al [2002] found that at-risk relatives who were found to be mutation-negative were more likely to request continued bowel surveillance when results were relayed to them by non-geneticist physicians than by genetics professionals. In a follow-up study evaluating why some at-risk individuals are not reassured by negative molecular genetic test results and request continued surveillance, Michie et al [2003] conclude that effective communication is key to facilitating adaptive behavior. Referral to a genetic counselor and/or a center in which testing is routinely offered is recommended.

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see:

- Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors
- Elements of Cancer Genetics Risk Assessment and Counseling (part of PDQ®, National Cancer Institute)

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or are carriers, or are at risk of being affected or carriers.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at 50% risk for *APC*-associated polyposis conditions is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed. The criteria for use of molecular genetic testing discussed in Testing of at-risk asymptomatic individuals during adulthood and childhood apply to prenatal testing as well. It should be noted that detection of an *APC* mutation in a fetus at risk does not predict the time of onset or severity of the disease.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as the *APC*-associated polyposis that do not affect intellect and have treatment available are not common. A pilot study of 20 individuals with FAP revealed that 100% believed it was ethical to provide prenatal testing for FAP, and 95% (19/20) would consider it themselves [Kastrinos et al 2007]. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) has been successfully used in pregnancies at risk for several inherited cancer predisposition syndromes and may be an option for couples at risk of having offspring with an *APC*-associated polyposis condition [Rechitsky et al 2002, Davis et al 2006, Moutou et al 2007]. The parent's disease-causing allele must be identified before PGD can be performed. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of *APC*-Associated Polyposis Conditions

Gene Symbol	Chromosomal Locus	Protein Name
APC	5q21-q22	Adenomatous polyposis coli protein

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for *APC*-Associated Polyposis Conditions

175100	ADENOMATOUS POLYPOSIS OF THE COLON; APC
276300	MISMATCH REPAIR CANCER SYNDROME

Table C. Genomic Databases for *APC*-Associated Polyposis Conditions

Gene Symbol	Locus Specific	Entrez Gene	HGMD
APC	APC	324 (MIM No. 175100)	APC

For a description of the genomic databases listed, click here.

Note: HGMD requires registration

Normal allelic variants: The gene is alternatively spliced in multiple coding and noncoding regions; the main transcript has 15 exons with 8532 base pairs that code for 2843 amino acids and result in a 311.8-kd protein. Exon 15 is large and comprises over three-quarters of the coding region of the gene.

Pathologic allelic variants: Over 826 germline mutations have been found in families with an *APC*-associated polyposis condition [Beroud et al 2000]. Mutations almost always cause a premature truncation of the APC protein, usually through single amino-acid substitutions or frameshifts. While mutations have been found scattered throughout the gene, they are predominantly located in the 5' end of the gene. The most common germline *APC* mutation is c.3927_3931delAAAGA. (For more information, see Genomic Databases table.)

Table 3. *APC* Allelic Variants Discussed in This *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Alias[1])	Protein Amino Acid Change (Alias[1])	Reference Sequence
Normal [2]	c.5465T>A	p.Val1822Asp (D1822V)	NM_000038.3 NP_000029.2
Uncertain clinical significance [1]	c.3949G>C	p.Glu1317Gln	
Predisposition to colon cancer [1]	c.3920T>A	p.Ile1307Lys	
Pathologic	c.3927_3931delAAAGA	p.Glu1309AspfsX4	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Variant designation that does not conform to current naming conventions
2. See Genetically Related Disorders.

Normal gene product: The APC protein has been localized to the nucleus and membrane/cytoskeleton in human epithelial cells [Neufeld & White 1997]. It has also been shown to homodimerize [Joslyn et al 1993] and bind to other proteins including GSK3b [Rubinfeld et al 1996], b-catenin [Rubinfeld et al 1993, Su et al 1993], g-catenin [Hulsken et al 1994, Rubinfeld et al 1995], tubulin [Munemitsu et al 1994, Smith et al 1994], EB1 [Su et al 1995], and hDLG, a homolog of the *Drosophila* discs large tumor-suppressor protein [Matsumine et al 1996]. The APC protein product is a tumor suppressor. APC protein forms a complex with glycogen synthase kinase 3b (GSK-3b) [Rubinfeld et al 1996], which targets b-catenin, a protein involved in both cell adhesion and intracellular signal transduction [Korinek et al 1997, Morin et al 1997, Nakamura 1997, Peifer 1997, Rubinfeld et al 1997]. The presence of normal APC protein appears to maintain normal apoptosis and may also decrease cell proliferation, probably through its regulation of b-catenin. This pathway is normally involved with Wingless-Wnt signaling, which participates in several known cell growth functions.

The APC protein has been shown to accumulate at the kinetochore during mitosis, contribute to kinetochore-microtubule attachment, and play a role in chromosome segregation in mouse embryonic stem cells [Fodde et al 2001, Kaplan et al 2001]. The APC protein may play a role in chromosomal instability, the presence of which is often observed when APC function is lost.

Other possible roles for the APC protein include: regulation of cell migration up the colonic crypt and cell adhesion through association with E-cadherin, regulation of cell polarity through association with GSK3b and other functions related to association with microtubule bundles [Nathke et al 1996, Barth et al 1997, Etienne-Manneville & Hall 2003]. Goss & Groden [2000] provide an excellent review of the function of the APC protein.

Abnormal gene product: Disease-causing mutations in the *APC* gene most often result in truncated protein products. Experiments have localized normal full-length APC protein to the membrane/cytoskeleton and nuclear fractions of human epithelial cells but demonstrated that colon cancer cells containing only mutant *APC* genes revealed no truncated APC protein in nuclear fractions [Neufeld & White 1997].

When the *APC* gene is mutated and abnormal protein is present, high levels of free cytosolic b-catenin result. Free b-catenin migrates to the nucleus, binds to a transcription factor Tcf-4 or Lef-1 (T cell factor-lymphoid enhancer factor), and may activate expression of genes such as the oncogenes c-Myc and cyclin D1 [Chung 2000]. The specific genes targeted are not yet known but may include those increasing proliferation or decreasing apoptosis. Because *APC* may be important in cell migration, abnormal APC protein may disrupt normal cellular positioning in the colonic crypt. Additionally, mutations in the *APC* gene are thought to contribute to chromosomal instability in colorectal cancers [Fodde et al 2001].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Collaborative Group of the Americas on Inherited Colorectal Cancer
www.cgaicc.com

Genetics of Colorectal Cancer (PDQ)
A service of the National Cancer Institute
Genetics of colorectal cancer

IMPACC (Intestinal Multiple Polyposis and Colorectal Cancer)
PO Box 11
Conyngham, PA 18219
Phone: 570-788-3712
Fax: 717-788-1818
Email: impacc@epix.net

National Library of Medicine Genetics Home Reference
Familial adenomatous polyposis

American Cancer Society
Provides contact information for regional support
1599 Clifton Road NE
Atlanta, GA 30329
Phone: 800-227-2345
www.cancer.org

C3: Colorectal Cancer Coalition
1225 King Street 2nd Floor
Alexandria, VA 22314
Phone: 703-548-1225
Fax: 202-315-3871
Email: info@FightColorectalCancer.org
www.FightColorectalCancer.org

Colon Cancer Alliance
1200 G Street, NW Suite 800
Washington, DC 20005
Phone: 877-422-2030 (toll-free helpline)
Fax: 866-304-9075
Email: kelly@ccalliance.org
www.ccalliance.org

Colorectal Cancer Network
PO Box 182
Kensington, MD 20895-0182
Phone: 301-879-1500
Fax: 301-879-1901
Email: CCNetwork@colorectal-cancer.net
www.colorectal-cancer.net

United Ostomy Association, Inc
PO Box 66
Fairview, TN 37062-0066
Phone: 800-826-0826
Email: info@uoa.org
www.uoa.org

Teaching Case-Genetic Tools
Cases designed for teaching genetics in the primary care setting
Case 9. Colorectal Cancer in a 28-Year-Old Woman

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Chapter Notes

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