The Genetics of Hereditary Colon and Rectal Cancer

THE ALPHABET SOUP
of Genetics and Diagnosis Explained

Part 4: Familial Adenomatous Polyposis: One Gene, Many Manifestations

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In Part 3 of this series, we looked at the inherited polyposis syndromes including familial adenomatous polyposis (FAP) and the underlying genetics. In Part 4, we will examine the ways in which this knowledge can be used to diagnose and treat patients and family members affected by these disorders.

Genotype to Diagnosis: From Appearance to Discovery

As 96% of adenomatous polyposis coli *(APC)* gene mutations in FAP result in a truncated protein product, the protein truncation test (PTT) has been developed to identify the area of the mutant *APC* gene that produces the abnormal protein. The *APC* gene mutation causes a premature termination of translation. Translation is the process whereby the nucleic code is translated into amino acids and then proteins. The PTT also is known as in vitro synthesized protein assay (IVSP). The DNA to be tested is extracted from lymphocytes in whole blood. The PTT has been found to be successful in confirming a diagnosis in 85% of cases.

Failure to diagnose FAP by PTT does not exclude the diagnosis, and the clinician should not rely on a negative test result and falsely reassure the patient at this point.[1] In those 15% of mutations missed by PTT, electrophoretic migration is used to find the undiscovered mutation. This sequential testing using two techniques has become commonplace and has a high sensitivity and high specificity.[2] If testing is successful in identifying a mutant APC protein, the mutated nucleotides causing the truncation can be precisely identified with gene sequence analysis. This may provide valuable information as to both diagnosis and phenotypic expression of the disease. The mutational information also can be used for comparison with family members being tested for the same mutation.

Predictive gene testing of unaffected family members has become an important tool in the screening of families with members at risk for FAP. PTT, electrophoretic migration testing or direct gene sequencing tests of DNA from whole blood samples can identify and confirm the diagnosis in both symptomatic and asymptomatic patients with a family history of the disease. This is especially useful in young patients or in those who do not wish to undergo an intensive clinical screening process.

Genetic Testing for Individuals and Family Members With Clinically Proven FAP

Before embarking on genetic testing, genetic counseling and informed consent should be given to patients and appropriate family members. In individuals affected with the clinical stigmata of FAP, the PTT is the first laboratory step toward making a definitive diagnosis (Figure 1, page 20).[2] Electrophoretic migration testing may be used to further study the *APC* gene if the PTT does not uncover a mutation. If either test is *APC* mutation–positive, surveillance is started as outlined below. If possible, genetic sequencing should be performed to further elucidate the phenotype risk. The mutant codon location information is used in genetic testing of family members to determine if they have the identical mutation. First-degree family members are at a 50% risk for carrying the mutation and should be counseled.

If no mutation is identified in a patient with the phenotypic appearance of FAP, the patient is *APC* mutation–negative. As the PTT and electrophoretic migration tests are highly sensitive for an *APC* mutation, patients with polyposis or related manifestations of the disease should be evaluated for a mutation in a different gene on a chromosome other than chromosome 5. An *MYH* mutation should be suspected, and gene analysis using DNA sequencing techniques can be performed to evaluate for this. Regardless of the result, continued intensive surveillance of the patient is performed because malignant degeneration of the polyps may occur.

Because there may be a mutation on a different chromosome, first-degree relatives should undergo colorectal surveillance every year between the ages of 12 and 25, every other year between the ages of 25 and 35, and every third year between the ages of 35 and 50. After age 50, healthy family members are considered to be unaffected.[3]

Genetic Testing for Clinically Normal Family Members Under Age 50, With Clinically Proven FAP in a Relative

With regard to family members under the age of 50 without observable disease, and who belong to an FAP kindred, a genetic evaluation should be performed (Figure 2).[2] Genetic counseling should be recommended, with informed consent obtained before any genetic testing.

In individuals with a known mutation previously identified in a family member, a PTT is performed. Electrophoretic migration testing can be performed if the PTT is negative. If either test is positive, the patient is an FAP mutation carrier and is at high risk for developing colorectal cancer. FAP surveillance is instituted. All first-degree relatives have a 50% risk for carrying the mutation, and they should be evaluated.

If all testing is *APC* mutation–negative in family members whose relative(s) has a known mutation, the patient and all other mutation–negative family members are not at risk for FAP and surveillance is the same as for the general population.

In patients of an FAP kindred whose family mutational status is unavailable, PTT and, if necessary, electrophoretic migration testing is performed. In those testing positive, germline analysis is performed and surveillance is the same as for patients with FAP. Family members of this newly diagnosed patient should be evaluated. It should be noted that 30% of FAP patients have a new, spontaneous mutation, and the parents of this patient will not be carriers of the mutation; they will test *APC* mutation–negative. However, descendants of the patient are at a 50% risk for carrying the mutant gene and should be tested even though their grandparents may have tested negative.

As protein testing is highly sensitive, if a mutation is not detected, the patient in question most likely does not have an *APC* mutation. However, another as yet undefined mutation may exist, and the patient must not be falsely reassured that he is mutation- or disease-free.[2] Colorectal surveillance should be continued. The patient should consider having the originally

FAP

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affected relative tested to evaluate for an *APC* mutation or other mutation.

From Diagnosis to Screening and Surveillance

The Physician on the Frontlines

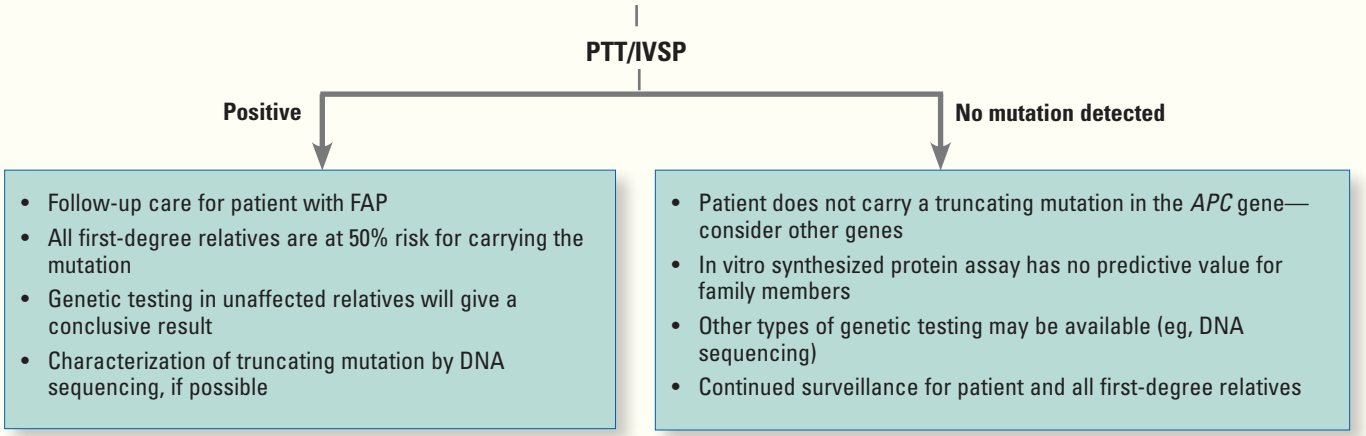
Genetic testing can guide screening and surveillance recommendations. The risk for developing colorectal cancer can be evaluated with genetic testing and shown to be either that of the general population at 3% or that of patients with untreated FAP at 100%.

In patients with known FAP, routine endoscopic surveillance should begin at age 11 with a flexible sigmoidoscopy. The rationale for this limited exam is that polyps usually do not appear until puberty and are most commonly left-sided in 84% of patients. Colonoscopic surveillance should be started at age 14 and continued yearly for life. Patients should be counseled and prepared for a prophylactic colectomy. Genetic counseling should be offered regarding the risks to future offspring. In first-degree relatives without an identified mutation, screening should be performed at the time of initial genetic testing but no later than age 15. As the genetic testing is highly sensitive, an *APC* mutation–negative patient should undergo future surveillance in the same manner as in colorectal cancer surveillance in the general population. The traditional approach to prophylactic colectomy for FAP has been that it should be performed by age 25 in patients with polyps, although the choice of this age is arbitrary, and many affected individuals have undergone operative prophylaxis by the age of 20 years.[4,5] It is now recommended that operative intervention be undertaken as soon as polyposis is discovered. Without treatment, there is close to a 100% risk for the development of colorectal cancer by age 40. In patients undergoing an early prophylactic procedure, long-term survival rates are between 87% and 94%. In patients presenting with an established malignancy, the 10-year survival rate is 40%.[6,7] The pendulum seems to be swinging toward earlier prophylactic colectomy, possibly within two years of the discovery of the disease.

In attenuated FAP (AFAP), full colonoscopic screening should begin at age 20 as this entity has a later age of onset, with polyps found more commonly in the proximal colon. The screening interval is similar to those in patients with FAP.

Upper gastrointestinal surveillance should begin at age 20 and continue for the lifetime of the patient at intervals between one and five years, depending on the findings. Alternatively, surveillance can begin at the same time as a diagnosis of FAP is secured. Strict attention must be paid to performing a thorough duodenal inspection using both straight-viewing and side-viewing endoscopes. The lifetime risk for forming duodenal adenomas approaches 100%. If surgical intervention is to be undertaken, the entire gastrointestinal tract must be evaluated prior to the intervention.[8,9]

FIGURE 1. INDIVIDUALS AFFECTED WITH FAP



APC, adenomatosis polyposis coli; **FAP**, familial adenomatous polyposis; **PTT/IVSP**, protein truncation test/in vitro synthesized protein assay. *Adapted from Reference 2.*

From Screening and Surveillance to Therapy

The Surgeon on the Frontlines: Surgical Prophylaxis and Treatment

Before any operative intervention, histopathologic confirmation of FAP is mandatory so as to not confuse FAP with other polyposis syndromes that resemble FAP, but may not require radical operative treatment.

With operative intervention, the goal is to remove as much of the colorectal mucosa as possible. Currently, four operations are available to treat FAP. None of them cure the underlying disease. The aim of each is to remove as much susceptible tissue as possible, while retaining normal colorectal functioning.

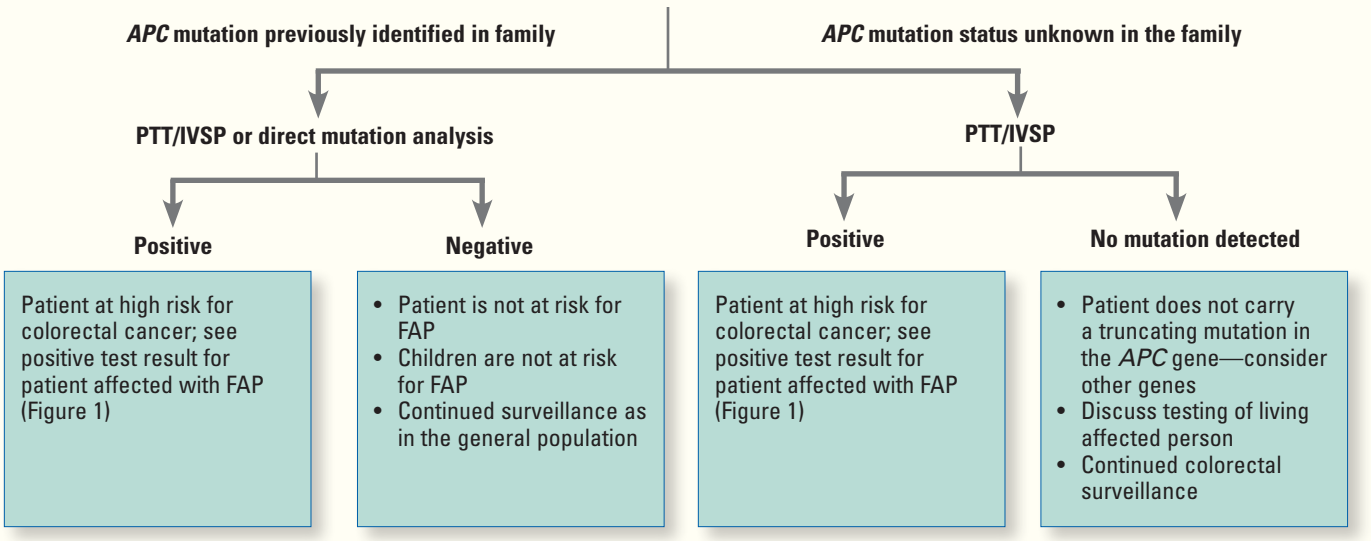
Laparoscopic or Open Proctocolectomy With an End Ileostomy

A proctocolectomy with an end ileostomy provides the most complete colorectal cancer risk reduction but requires the creation of a permanent stoma, making it an unpopular option for many patients. Young patients are unlikely to choose this approach. However, total abdominal colectomy with a proctectomy is the procedure of choice in patients with a distal rectal carcinoma. It also is an option for patients who cannot undergo a rectal or anal anastomosis because of intraoperative technical difficulties (the planned reconstruction will not reach the anastomotic site due to anatomic considerations or infiltrative mesenteric desmoid disease) or poor sphincter function. A variation on this operation involves creating a continent ileostomy, or Kock pouch. In this procedure, a reservoir is created using the terminal ileum. A nipple valve is constructed and brought out through the abdominal wall. Ideally, there is no need to wear an ostomy appliance as the reservoir holds the intestinal contents until the patient performs a self-catheterization, usually four to six times per day. When not in use, the ostomy is covered with a bandage. The esthetic and cosmetic advantages are obvious. However, the procedure is associated with prolapse of the nipple. The Kock pouch is rarely used.

Laparoscopic or Open Total Abdominal Colectomy With an Ileorectal Anastomosis

A total abdominal colectomy with an ileorectal anastomosis may be used in patients with few rectal adenomas or in patients with AFAP, as AFAP usually spares the rectum. A total abdominal colectomy with an ileorectal anastomosis is relatively easy to perform, usually does not require a temporary protective ileostomy, restores intestinal continuity and achieves good functional results. The risk

FIGURE 2. UNAFFACTED INDIVIDUALS YOUNGER THAN 50 WHO ARE MEMBERS OF AN FAP KINDRED (WITH OR WITHOUT A PREVIOUS ENDOSCOPIC EXAMINATION)



APC, adenomatosis polyposis coli; **FAP**, familial adenomatous polyposis; **PTT/IVSP**, protein truncation test/in vitro synthesized protein assay. *Adapted from Reference 2.*

for erectile and ejaculatory dysfunction that may occur in a more extensive operation secondary to operative nerve trauma during the pelvic dissection is largely avoided. Female fertility is preserved as well. Patients must submit to regular, lifelong endoscopic surveillance with removal of any new rectal polyps. However, repeated endoscopic polyp removal may lead to rectal scarring, stenosis and poor rectal functioning.

The risk for developing a malignancy in the remaining rectal mucosa is estimated to be between 0%[10] and 32%.[11] This development would require a completion proctectomy. Factors that seem to be associated with this risk are having more than 20 polyps in the rectum or colon cancer resected before or during the colectomy. In a St. Mark's series, the cumulative risk for developing a malignancy in the retained rectum was 10% at 20 years, increasing to greater than 35% at 35 years. The report concluded that the means of surveillance must be improved or that the patients must undergo a complete proctocolectomy at a younger age.[12] Even with increased surveillance, other studies have echoed these results, thus calling into question the use of the total abdominal colectomy with ileorectal anastomosis for the treatment of FAP.

Given that the more aggressive and complete proctocolectomy with a restorative ileal pouch–anal anastomosis (IPAA) is associated with greater morbidity, studies have examined features that might guide the surgeon in choosing a total abdominal colectomy with an ileorectal anastomosis rather than a proctocolectomy with an IPAA. (See below for description of IPAA.) The two factors that helped exclude patients from having an ileorectal anastomosis were the severity of colorectal polyposis[13] and the location of the mutation on the *APC* gene. The risk for the development of a second carcinoma was greater if the mutation was located between codons 1250 and 1500, especially at codon 1309, a known "hot spot." None of the patients with AFAP and mutations in codons 0 to 200, or in a codon greater than 1500, required a secondary proctectomy.[14] These studies conclude that it is reasonable to perform a total abdominal colectomy with ileorectal anastomosis in young patients with fewer than 200 rectal adenomas, fewer than 1,000 colonic adenomas (considered to be mild disease), and in FAP with mutations in codons 0 to 200 or greater than 1500. Lifetime surveillance is required with the understanding that a future proctectomy may be required.

Candidates for total abdominal colectomy with ileorectal anastomosis include:

- Young patients with fewer than 20 rectal adenomas;
- Patients with fewer than 1,000 adenomas and a small number of rectal adenomas; and
- FAP with mutations in codons 0 to 200 or in a codon greater than 1500.

Laparoscopic or Open Proctocolectomy With an Ileal Pouch–Anal Anastomosis or an Ileoanal Anastomosis

The third treatment option for FAP is a laparoscopic or open total abdominal proctocolectomy with an IPAA, with or without a rectal mucosectomy. This also is known as a J-pouch. Potential advantages of this approach include restored intestinal continuity with a new rectal reservoir, or neo-rectum, in those patients who do not want an end ileostomy, and an almost complete removal of the at-risk colorectal tissue. This approach is favored for situations in which there is extensive polyposis, more than 20 rectal polyps, polyps that cannot be controlled endoscopically, adenomatous dysplasia or carcinoma at any location in the large intestine, in patients with a history of desmoid tumors for whom the operative risk is higher due to the desmoid disease and for whom a second or completion operative procedure would potentially be fraught with technical problems, or in those patients with *APC* mutations associated with an increased risk for rectal cancer. However, patients must be carefully selected, because those with poor preoperative sphincter function, especially the elderly, may have poor functional results after IPAA. Additionally, anatomic considerations or infiltrative mesenteric desmoid disease may make the creation of an IPAA technically difficult or impossible, requiring a temporary or permanent ileostomy. Preoperatively, the patient must be prepared for this eventuality.

The operation itself is associated with a greater blood loss and an increased risk for immediate postoperative sepsis. Local sepsis is associated with pouch failure requiring excision of the pouch. A longer hospital stay is not uncommon. Longer-term complications include the possibility of postoperative anal stenosis with troublesome functional symptoms, and increased stool frequency during the day and nighttime. Stool frequency often is associated with perianal skin irritation. Urinary and sexual functioning may be compromised after this extensive dissection due to disruption of the autonomic pathways.

Other disadvantages include the unsuspected retention of rectal mucosa and the new, potentially occult development of rectal polyps. In patients undergoing an IPAA, continued endoscopic surveillance is mandatory as pouch adenomas can develop in the small intestinal pouch mucosa in 30% of patients. Additionally, 10% to 30% of patients may develop cancer in the pouch, at the site of the anastomosis or in the anal transition zone. The carcinomas can be locally advanced (T4) or not (T1, T2).[15] Continued lifetime surveillance is mandatory. A prospective study from the Cleveland Clinic found the risk for developing adenomas in the pouch and anal transition zone or at the anastomotic staple line to be twice as high in a stapled IPAA as in a hand-sewn anastomosis (28% vs. 14%). The study found that the postoperative development of adenomas was related to the severity of the colonic polyposis preceding operative intervention. However, the incidence of cancer development was minimal in both techniques, although the study stated that this may have been due to a short follow-up period. The article concluded that the risk for future neoplasia must be balanced against the relatively better functional outcome with an IPAA.[16]

Proctocolectomy With Straight Ileoanal Anastomosis

A proctocolectomy with a straight ileoanal anastomosis is also an option that may function as well as an IPAA and have the advantage of removing all at-risk colorectal tissue. This technique can be used by surgeons unfamiliar with the construction of an IPAA, or for those patients in whom an IPAA will not extend to the anorectal cuff. The procedure is associated with morbid complications similar to those of IPAA, although the incidence of fecal soiling and difficulty with control may be higher than with IPAA. A proctocolectomy with a straight ileoanal anastomosis is performed much less often in the era of IPAA.

Putting It All Together

A clinician who is knowledgeable in mutational genetics and who cares for patients at the early part of the diagnostic algorithm is in an ideal position to do a tremendous service for those patients and family members presenting with signs and symptoms pointing to a diagnosis of FAP. With advances in early detection and with the concomitant improvement in survival rates and functional outcomes, operative intervention in patients with known or newly diagnosed FAP or AFAP is gratifying for the patient, the family, any newly diagnosed relatives, the astute physician who first considers and confirms the diagnosis and the surgeon who performs the preventive or curative operative procedure. Further improvements in early detection will enhance the ability to diagnose and treat this family of genetic disorders.

References

1. Giardello FM, Brensinger JD, Peterson GM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *N Engl J Med.* 1997;336: 823-827.

2. Wong N, Lasko D, Rabelo R, et al. Genetic counseling and interpretation of genetic tests in familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer. *Dis Colon Rectum.* 2001;44:271-279.

3. Rabelo R, Foulkes W, Gordon PH, et al. Role of molecular diagnostic testing in familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer. *Dis Colon Rectum.* 2001;44:437-446.

4. Peterson GM. Genetic counseling and predictive testing in familial adenomatous polyposis. *Semin Colon Rectal Surg.* 1995;6:55-60.

5. Karen P, Nugent MA. Total colectomy and ileorectal anastomosis. In: Phillips RK, Spigelman AD, Thompson JP, eds. *Familial Adenomatous Polyposis and Other Syndromes.* London: Edward Arnold; 1994:80-91.

6. Bertario LS, Presciuttini S, Sala P. Causes of death and postsurgical survival in familial adenomatous polyposis: results from the Italian Registry. *Semin Surg Oncol.* 1994;10:225-234.

7. Heiskanen I, Luostarinen T, Järvinen HJ. Impact of screening examinations on survival in familial adenomatous polyposis. *Scand J Gastroenterol.* 2000;35:1284-1287.

8. Burke CA, Beck GJ, Church JM, Van Stolk RW. The natural history of duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. *Gatrointest Endosc.* 1999;49:358-364.

9. Brosens LA, Keller JJ, Offerhaus GJ, et al. Prevention and management of duodenal polyps in familial adenomatous polyposis. *Gut.* 2005;54:1034-1043.

10. Gingold BS, Jagelman DJ, Turnbull RB. Surgical management of familial adenomatous polyposis and Gardner's syndrome. *Am J Surg.* 1979;137:54-56.

11. Bess MA, Adson MA, Elveback LR, Moertel CG. Rectal cancer following colectomy for polyposis. *Arch Surg.* 1980;115:460-467.

12. Bussey HJ, Eyers AA, Ritchie SM, Thompson JP. The rectum in adenomatous polyposis: the St. Mark's policy. *Br J Surg.* 1985;72(suppl):S29-S31.

13. Chruch J, Burke C, McGannon E, et al. Predicting polyposis severity by proctoscopy: how reliable is it? *Dis Colon Rectum.* 2001;44:1249-1254.

14. Bülow C, Vasen H, Järvinen H. Ileorectal anastomosis is appropriate for a subset of patients with familial adenomatous polyposis. *Gastroenterology.* 2000;119:1454-1460.

15. Gordon PH, Nivatvongs S. Part III: Colorectal disorders. *Principles and Practice of Surgery for the Colon, Rectum and Anus.* New York, NY: Informa Healthcare USA, Inc.; 2007:466-487.

16. Remzi FH, Church JM, Bast J. Mucosectomy vs. stapled ileal pouch-anal anastomosis in patients with familial adenomatous polyposis: functional outcome and neoplasia control. *Dis Colon Rectum.* 2001;44:1590-1596.

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