HEREDITARY COLORECTAL CANCER AND POLYPOSIS SYNDROMES

Jose G. Guillem, MD, MPH, FACS, and John B. Ammori, MD*

The majority of cases of inherited colorectal cancer (CRC) are accounted for by two syndromes: Lynch syndrome and familial adenomatous polyposis (FAP). In both, the predisposition to disease is a germline mutation transmitted in an autosomal dominant fashion. Although the two syndromes are similar in some respects, differences in their phenotypic expression and in the certainty of disease development mandate distinctly different surgical approaches, including the timing and extent of prophylactic procedures in carefully selected patients. In the management of FAP, the role of prophylactic surgery is clearly defined, although the optimal procedure for an individual patient depends on a number of factors. In the management of Lynch syndrome, the indications for prophylactic procedures are emerging.

In addition to classic FAP, attenuated familial adenomatous polyposis (AAFP) and MUTYH-associated polyposis (MAP) are two other adenomatous polyposis syndromes being seen with increasing frequency because of increasing genetic testing. AAFP retains autosomal dominant inheritance, whereas MAP is autosomal recessive with increased risk, also described in heterozygote carriers. Given the variability in phenotypes with these syndromes, the role of prophylactic colectomy has to be carefully determined on a case-by-case basis.

Familial Adenomatous Polyposis

FAP is caused by a mutation in the tumor suppressor gene APC, located at 5q21. Nearly 80% of FAP patients belong to known FAP kindreds; 10 to 30% have new mutations. More than 300 distinct mutations have been identified within the APC gene locus in persons manifesting the FAP phenotype. More than half of the known germline mutations associated with classic FAP phenotype are concentrated in the 5’ region of exon 15. Genotype-phenotype correlative studies have revealed a wide range of phenotypic heterogeneity, ranging from the relatively mild presentation associated with attenuated FAP (discussed below) to the severe presentation associated with mutations downstream of codon 1250, particularly those in codon 1309.

CLINICAL EVALUATION

FAP, which accounts for less than 1% of the annual CRC burden, is characterized by the presence of more than 100 adenomatous polyps of the colorectum, virtually 100% penetrance, and a nearly 100% risk of CRC by the age of 40 if prophylactic colectomy is not performed.

Recently, hyperplastic polyposis syndrome (HPPS) has been suspected to have a familial basis. There is active ongoing investigation into determining the exact genetic profile, screening, and treatment for this syndrome.

Finally, there are other, less common, inherited hamartomatous polyposis syndromes, such as Cowden disease and Ruvalcaba-Myhre-Smith syndrome. At present, these syndromes appear to be associated with a low risk of CRC, which may not be different from that of the general population; accordingly, the role for prophylactic surgery remains uncertain.

INVESTIGATIVE FINDINGS

Pathologic Findings

Polyps develop by the age of 20 years in 75% of cases and are typically less than 1 cm in size. In severe FAP, they may carpet the entire surface of the colorectal epithelium. Adenomas may be either pedunculated or sessile and may have tubular, villous, or tubulovillous histology. Microscopic evaluation may reveal innumerable microadenomas within grossly normal-appearing colorectal mucosa. Foci of carcinoma in situ and invasive carcinoma may be found within larger polyps, and the incidence of invasive cancer is proportional to the extent of polyposis. Unlike CRC in the setting of Lynch syndrome, CRC in the setting of FAP is more commonly located on the left side.

Screening and Surveillance

Screening (genetic testing or annual or biennial flexible sigmoidoscopy) for at-risk family members should begin at 10 to 12 years of age [see Table 1]. In families with a demonstrated APC mutation, informative genetic testing can be carried out with the protein truncation test [see Table 2]. This test, which detects foreshortened proteins resulting from truncated APC mutations, is approximately 80% sensitive; however, the test results are commonly misinterpreted, even by physicians. Patients with the FAP phenotype and a negative protein truncation test should undergo APC gene sequencing. It is essential to first determine if the test is informative for that particular family. This is done by confirming that the test is abnormal in a family member.

Financial disclosure information is located at the end of this chapter before the references.

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<th>Genetic Basis</th>
<th>Diagnosis</th>
<th>GI Manifestations</th>
<th>Extracolonic Manifestations</th>
<th>Pathologic Features</th>
<th>CRC Screening and Surveillance</th>
<th>Surgical Management</th>
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</thead>
<tbody>
<tr>
<td>FAP</td>
<td>APC, 5q21 (&gt; 90%)</td>
<td>≥ 100 adenomatous polyps of colorectum or APC mutation</td>
<td>Adenomatous polyps of colon and rectum 100% risk of colorectal cancer by age 40 without colectomy</td>
<td>Desmoids Osteomas Odontomas Sebaceous and epidermoid cysts CHRPE Periapillary neoplasms</td>
<td>Tubular, villous, or tubulovillous histology</td>
<td>Consider genetic counseling/testing</td>
<td>If polyposis is confirmed, colectomy is indicated Options include the following: TAC with ileostomy, TAC/IRA, TPC with IPAA</td>
</tr>
<tr>
<td>Attenuated FAP</td>
<td>APC, 5' or 3' end</td>
<td>10–99 adenomatous polyps of colorectum and APC mutation</td>
<td>Adenomatous polyps of colon and rectum</td>
<td>Desmoids Osteomas Periapillary neoplasms</td>
<td>Tubular, villous, or tubulovillous histology</td>
<td>Consider genetic counseling/testing</td>
<td>Options include the following: TAC with ileostomy, TAC/IRA, TPC with IPAA</td>
</tr>
<tr>
<td>MYH-associated polyposis</td>
<td>Biallelic MYH mutation</td>
<td>MYH</td>
<td>Adenomatous polyps of colon and rectum 80% risk of CRC by age 70 without colectomy</td>
<td>Desmoids Osteomas Odontomas Sebaceous and epidermoid cysts CHRPE Periapillary neoplasms</td>
<td>Tubular, villous, tubulovillous, or sessile serrated adenomas or hyperplastic polyps</td>
<td>Consider genetic counseling/testing Biennial colonoscopy beginning at age 18–20 yr</td>
<td>Options include the following: TAC with ileostomy, TAC/IRA, TPC with IPAA</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MMR genes: MLH1 and MSH2 (80–90%), MSH6 (10%), PMS2</td>
<td>Associating tumors of endometrium, small bowel, ureter, or renal pelvis</td>
<td></td>
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<tr>
<td></td>
<td>mutation demonstrated or Family meets Amsterdam II criteria</td>
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<tr>
<td></td>
<td>Possibly few or no colorectal polyps Right-sided tumor (60–70%) MSI-high tumor (80–90%) Synchronous/metachronous tumors 80% lifetime risk of CRC</td>
<td>Associated tumors of endometrium, small bowel, ureter, or renal pelvis</td>
<td>Adenocarcinoma, frequently mucinous or signet-ring cell histology Solid or cribriform growth pattern Tumor infiltrating or peritumoral lymphocytes</td>
<td>Consider genetic counseling/testing</td>
<td>Affected patient with identified mutation or meeting Amsterdam criteria: colon cancer or advanced adenoma: perform TAC/IRA with annual rectal surveillance or segmental colectomy with annual colonoscopy Unaffected patient with identified mutation or meeting Amsterdam criteria: colonoscopy every 1–2 yr</td>
<td></td>
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<tr>
<td>Syndrome</td>
<td>Genetic Basis</td>
<td>Diagnosis</td>
<td>GI Manifestations</td>
<td>Extracolonic Manifestations</td>
<td>Pathologic Features</td>
<td>CRC Screening and Surveillance</td>
<td>Surgical Management</td>
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<tr>
<td>PJS</td>
<td>LTKB1/STK11, 19p13.3 (18–63%), MSI, SMAD4</td>
<td>Hamartomas of GI tract and At least 2 of the following: small bowel disease, mucocutaneous melanin, family history of PJS</td>
<td>Hamartomatous polyps throughout entire GI tract (small intestine, 90%; colon, 50%) Relative risk of CRC = 84</td>
<td>Mucocutaneous pigmentation (perioral and buccal areas, 95%)</td>
<td>Hyperplasia of smooth muscle of muscularis mucosa Arborization Pseudoinvasion</td>
<td>Consider genetic counseling/ testing</td>
<td>Perform operative or laparoscopically assisted polypectomy or segmental colectomy for polyps &gt; 1.5 cm that are not amenable to endoscopic removal. Perform segmental bowel resection for invasive cancers In the setting of laparotomy, perform intraoperative endoscopy (peroral or via enterotomy). Prophylactic colectomy has no role.</td>
</tr>
<tr>
<td>JPS</td>
<td>SMAD4/DPC4, 18q21.1 (50%), BM-PR1A, 10q22.3</td>
<td>≥ 3 juvenile polyps of colon and juvenile polyps throughout GI tract or Any number of polyps with family history of JPS</td>
<td>Multiple hamartomatous polyps throughout gastroduodenum 15% risk of CRC by age 35, 68% risk by age 65</td>
<td>Tumors of stomach, pancreas, duodenum</td>
<td>50–200 polyps Cystic, mucus-filled spaces with epithelial lining Attenuated smooth muscle layer Focal epithelial hyperplasia and dysplasia</td>
<td>Consider genetic counseling/ testing</td>
<td>Disease is local and no significant symptoms are present: manage endoscopically, with colonoscopic surveillance every 1–3 yr. Disease is diffuse or significant symptoms are present: perform TAC/IRA with rectal surveilliance every 1–3 yr</td>
</tr>
<tr>
<td>HPS</td>
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<td></td>
<td></td>
<td></td>
<td>Consider genetic counseling/ testing</td>
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</tbody>
</table>

CHRPE = congenital hypertrophy of retinal pigment epithelium; CRC = colorectal cancer; EGD = esophagogastroduodenoscopy; FAP = familial adenomatous polyposis; FS = familial adenomatous polyposis; GI = gastrointestinal; IPAA = ileal-pouch-anal anastomosis; JPS = juvenile polyposis syndrome; MMR = mismatch repair; MSI = microsatellite instability; PJS = Peutz-Jeghers syndrome; SBS = small bowel series; TAC/IRA = total abdominal colectomy with ileorectal anastomosis; TPC = total proctocolectomy.

Demonstrating the FAP phenotype. Subsequent family members who have a normal genetic analysis may then be discharged from further screening with a nearly 100% certainty that the mutation is absent. However, they should still undergo CRC screening starting at the age of 50 years, as is recommended for average-risk persons. When an APC mutation has not previously been identified in the family of an affected person, the patient should be tested first to identify the causative mutation. In families in which the protein truncation test and APC gene sequencing fail to provide conclusive information on carrier status, at-risk individuals should continue with the recommended endoscopic surveillance program. Other options for detecting APC mutations include linkage analysis and single-stranded confirmation polymorphism. Genetic counseling is an essential component of the evaluation of patients for FAP. Patients who have a positive genotype or who have adenomatous polyps on sigmoidoscopy should undergo full colonoscopy to establish the extent of polyposis.
**Table 2** Availability of Commercial Genetic Testing for Inherited CRC Syndromes

<table>
<thead>
<tr>
<th>Test</th>
<th>Approximate Time Frame</th>
<th>Approximate Cost</th>
<th>Clinical Availability (in United States)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein truncation test (APC)</td>
<td>4–6 wk</td>
<td>$1,100; if mutation known, $600</td>
<td>Mayo Clinic, Rochester, MN; (800) 533-1710</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Washington University, St. Louis, MO; (314) 454-7601</td>
</tr>
<tr>
<td>DNA sequencing, germline APC</td>
<td>3 wk</td>
<td>$1,500; if mutation known, $400</td>
<td>Baylor College of Medicine, Houston, TX; (800) 411-GENE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Huntington Medical Research Institute, Pasadena, CA; (626) 795-4343</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Myriad Inc., Salt Lake City, UT; (800) 469-7423</td>
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<tr>
<td></td>
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<td></td>
<td>University of Pennsylvania, Philadelphia, PA; (215) 573-9161</td>
</tr>
<tr>
<td>MSI analysis</td>
<td>2–4 wk</td>
<td>$1,150</td>
<td>ARUP Laboratories, Salt Lake City, UT; (800) 583-2787</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baylor College of Medicine, Houston, TX; (800) 411-GENE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mayo Clinic, Rochester, MN; (800) 533-1710</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Memorial Sloan-Kettering Cancer Center, New York, NY; (212) 639-5170</td>
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<td></td>
<td></td>
<td></td>
<td>Ohio State University, Columbus, OH; (614) 293-7774</td>
</tr>
<tr>
<td>IHC MMR (MLH1, MSH2, PMS2, MSH6)</td>
<td>2–3 wk</td>
<td>$1,100</td>
<td>Memorial Sloan-Kettering Cancer Center, New York, NY; (212) 639-5170</td>
</tr>
<tr>
<td>DNA sequencing, germline MMR mutation (MLH1, MSH2, MSH6)</td>
<td>3 wk</td>
<td>$2,950</td>
<td>Baylor College of Medicine, Houston, TX; (800) 411-GENE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Huntington Medical Research Institute, Pasadena, CA; (626) 795-4343</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myriad Inc., Salt Lake City, UT; (800) 469-7423</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Quest Diagnostics, Inc., San Juan Capistrano, CA; (949) 728-4279</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>University of Pennsylvania, Philadelphia, PA; (215) 573-9161</td>
</tr>
<tr>
<td>MSH6 rearrangement</td>
<td>3 wk</td>
<td>$1,800</td>
<td>Quest Diagnostics, Inc., San Juan Capistrano, CA; (949) 728-4279</td>
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<tr>
<td>PMS2 sequencing and deletion/duplication</td>
<td>4–5 wk</td>
<td>$1,400</td>
<td>ARUP Laboratories, Salt Lake City, UT; (800) 583-2787</td>
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<tr>
<td>MYH</td>
<td>4 wk</td>
<td>$325</td>
<td>Myriad Inc., Salt Lake City, UT; (800) 469-7423</td>
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<tr>
<td>MLH1 hypermethylation/BRaf</td>
<td>4–6 wk</td>
<td>$660</td>
<td>Mayo Clinic, Rochester, MN; (800) 533-1710</td>
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<tr>
<td>LKB1/STK11 testing</td>
<td>6–12 wk</td>
<td>$1,176–1,400; if mutation known, $200–350</td>
<td>Ohio State University, Columbus, OH; (614) 293-7774</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GenesDx Inc., Gaithersburg, MD; (301) 519-2100</td>
</tr>
<tr>
<td>SMAD4/BMPRIA testing</td>
<td>2 mo</td>
<td>$1,234–1,260; if mutation known, $200</td>
<td>Ohio State University, Columbus, OH; (614) 293-7774</td>
</tr>
</tbody>
</table>

CRC = colorectal cancer; IHC = immunohistochemical; MMR = mismatch repair; MSI = microsatellite instability.

**MANAGEMENT**

**Medical Therapy**

A number of nonsteroidal antiinflammatory drugs, including sulindac and its metabolite exisulind, have been shown to reduce the number and size of polyps in FAP patients. However, long-term use of chemopreventive agents for primary treatment of FAP is not recommended. In a randomized, placebo-controlled, double-blind study of genotype-positive, phenotype-negative patients, the use of sulindac had no effect on the subsequent development of colorectal polyposis. A randomized, placebo-controlled, double-blind study studying a selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, found a 28% reduction in polypl load at 6 months using a relatively high dose of 800 mg/day. There is no clear advantage in the long term. Furthermore, the development of rectal cancer has been reported in patients whose rectal polyps were effectively controlled with sulindac. Finally, these medications necessitate continued compliance and may be associated with significant side effects. Chemopreventive agents may be useful for reducing polypl load and facilitating endoscopic management of polyps in patients who have an ileorectal anastomosis, are at high risk for polypl development, and refuse proctectomy. In such cases, however, it is still necessary to perform careful surveillance of the residual rectum or the ileoanal pouch every 6 to 12 months.

**Surgical Therapy**

The timing of surgical treatment depends to some degree on the extent of polyplosis in that the risk of CRC is partially dependent on the number of polyps present. Practically speaking, the best time is usually the summer between high school and college. However, in carefully selected cases of mild polyposis, it may be beneficial to delay surgery until after college, particularly to reduce the rate of development of desmoids. Patients with severe polyposis, dysplasia, adenomas larger than 5 mm, and significant symptoms should undergo surgery as soon after diagnosis as is practical. One may consider delaying prophylactic colectomy in very carefully selected asymptomatic patients with small adenomas who have a strong family history of aggressive
abdominal desmoids because the risk of desmoid-related complications may outweigh the risk of developing CRC.

There are three basic surgical options for treating FAP: (1) total proctocolectomy (TPC) with permanent ileostomy, (2) total abdominal colectomy with ileorectal anastomosis (TAC/IRA), and (3) proctocolectomy with ileal-pouch-anal anastomosis (IPAA). The optimal procedure for a given patient is determined on a number of factors, including endoscopic and APC mutation status, differences in postoperative functional outcome, preoperative anal sphincter status, and patient preference.

TPC  TPC with permanent ileostomy is rarely chosen as a primary procedure. More commonly, it is considered an option for patients in whom a proctectomy is required but an IPAA is contraindicated (e.g., those with rectal tumors involving the anal sphincters or those with poor baseline sphincter function) or for patients in whom an IPAA is not technically feasible (e.g., those with desmoid disease and foreshortening of the small bowel mesentery). Occasionally, however, TPC is chosen as a primary procedure in patients whose lifestyle would be compromised by frequent bowel movements.

IPAA versus IRA  The choice between IPAA and TAC/IRA is generally more challenging. The main considerations to be taken into account are the risk of rectal cancer development if the rectum is left in site and the differences in functional outcome (and associated quality of life) between procedures.

It has been estimated that the risk of rectal cancer after a TAC/IRA may be as high as 4 to 8% at 10 years and 26 to 32% at 25 years. The true risk, however, may be somewhat lower. Most of the studies from which these figures were derived were completed before IPAA became available; thus, patients and physicians may have been more likely to choose IRA even in the setting of more extensive rectal disease, given that TPC with permanent ileostomy was the only other option at the time. The magnitude of risk in an individual patient is related to the overall extent of colorectal polyposis. TAC/IRA may be an option for patients with fewer than 1,000 colorectal polyps and fewer than 20 rectal adenomas because these patients appear to be at relatively low risk for rectal cancer. Ideally, patients with severe rectal adenomas (> 20 adenomas) or colonic (> 1,000 adenomas) polyposis, an adenoma larger than 3 cm, or an adenoma with severe dysplasia should be treated with IPAA.

The risk of secondary rectal excision as a consequence of uncontrollable rectal polyposis or rectal cancer may be estimated on the basis of the specific location of the causative APC mutation. In a study of 87 FAP patients with an identified APC mutation who underwent TAC/IRA, those with a mutation located downstream from codon 1250 had an approximately threefold higher incidence of secondary rectal resection than those with a mutation located upstream of codon 1250. Furthermore, patients with a mutation located between codons 1250 and 1464 had a 6.2-fold higher risk of rectal cancer than those with a mutation before codon 1250 or after codon 1464.

A more recent study examined genotype-phenotype correlations as a potential guide to select patients with FAP for either TAC/IRA or IPAA. A total of 475 patients who underwent TAC/IRA from four national European polyposis registries were examined. Attenuated phenotypes (discussed later in this chapter) were at codons 1 to 157, 312 to 412, and 1596 to 2843; intermediate phenotypes at 158 to 311, 413 to 1249, and 1465 to 1595; and severe phenotype at codon 1250 to 1464. Cumulative risk of secondary proctectomy in the 20 years following TAC/IRA were 10%, 39%, and 61% in the attenuated, intermediate, and severe genotype groups, respectively. Cumulative risks of rectal cancer after TAC/IRA were 3.7%, 9.3%, and 8.3%. These data should be considered when counseling patients regarding surgical options; however, given the phenotypic variability that occurs even among family members, at this time, the choice of surgical procedure should be made based on the clinical phenotype of the patient’s disease rather than the patient’s genotype.

The risk of polyp and cancer development after index surgery is not limited to patients undergoing TAC/IRA. In patients undergoing IPAA, the pouch-anal anastomosis may be either handsaw after complete anal mucosectomy or stapled to a 1 to 2 cm anal transition zone. Neoplasia may occur at the site of the anastomosis, and the incidence appears to be higher after stapled anastomosis (28 to 31%) than after mucosectomy and handsewn anastomosis (10 to 14%). Function, however, may be better after stapled anastomosis. In the case of anal transition zone neoplasia after stapled anastomosis, transanal mucosectomy can sometimes be performed, followed by advancement of the pouch to the dentate line. Of additional concern is the development of adenomatous polyps in the ileal pouch itself, which occurs in 35 to 42% of patients at 7 to 10 years.

With respect to postoperative bowel function and associated quality of life, IPAA has been associated with a higher frequency of both daytime and nocturnal bowel movements, a higher incidence of passive incontinence and incidental stooling, and higher postoperative morbidity than TAC/IRA. Accordingly, some authors recommend TAC/IRA for patients with mild rectal polyposis. Other authors, however, have found the two approaches to be equivalent in terms of functional results and quality of life and therefore recommend IPAA for most patients because of the risk of rectal cancer associated with TAC/IRA.

Regardless of which procedure is performed, however, lifetime surveillance of the rectal remnant (after TAC/IRA) or the ileal pouch (after IPAA) is required. Endoscopic surveillance of the bowel at intervals of 6 months to 1 year after index surgery is recommended. After TAC/IRA, small (< 5 mm) adenomas may be safely observed, with biopsy performed to rule out severe dysplasia. If adenomas increase in number, the frequency of surveillance should be increased, and polyps larger than 5 mm should be removed. When fulguration and polypectomy are repeated over a period of many years, subsequent polypectomy may become difficult, rectal compliance may be reduced, and flat cancers may be hard to identify against a background of scar tissue. The development of severe dysplasia or a villous adenoma larger than 1 cm is considered an indication for proctectomy.
**Extracolonic Disease**

After TAC/IRA and regular surveillance, the risk of death appears to be three times higher for FAP patients than for age- and sex-matched control populations. The main causes of death after IRA are desmoid disease and upper gastrointestinal (GI) malignancy.

**Desmoid disease** Desmoids are histologically benign tumors that arise from fibroaponeurotic tissue and occur in 12 to 17% of FAP patients. Unlike those in the general population, desmoids in FAP patients tend to be intra-abdominal (up to 80% of cases) and mainly occur after abdominal surgical procedures. Females who undergo colectomy younger than age 18 are twice as likely to develop intra-abdominal desmoids compared with females operated on after age 18. Patients with APC mutations located between codons 1310 and 2011 are at increased risk for these tumors. To avoid the occurrence of desmoids and the possibility of fertility issues, some authors suggest that selected young nulliparous women may benefit from delaying surgery, undergoing laparoscopic surgery, or undergoing TAC/IRA instead of TPC with IPAA. Desmoids often involve the small bowel mesentery (> 50% of cases), making complete resection difficult or impossible. Not uncommonly, patients present with small bowel obstruction. Morbidity after attempted resection, which often involves the removal of a significant length of small bowel, is substantial. The recurrence rate after attempted resection is also high, and the recurrent disease is often more aggressive than the initial desmoid.

Intra-abdominal desmoid formation may be more common after TAC/IRA than after IPAA, and the disease may be more severe after TAC/IRA as well. When desmoid tumors involve the small bowel mesentery, the mesentery may become foreshortened and thereby render IPAA impracticable, especially in patients undergoing a subsequent completion proctectomy after an initial TAC/IRA. This possibility should be considered when making the choice between TAC/IRA and IPAA as the initial procedure for FAP.

**Medical therapy** When desmoid tumors are clinically inert, they may be treated with sulindac. Tamoxifen or other antiestrogens may be added for slow-growing or mildly symptomatic tumors. More aggressive desmoid tumors may be treated with chemotherapy. Vinblastine and methotrexate achieve some degree of response in 40 to 50% of patients. For more rapidly growing desmoids, an anti-sarcoma agent, such as doxorubicin and dacarbazine, may be administered. Radiation therapy may also be effective but can result in substantial small bowel morbidity.

**Surgical therapy** Surgical treatment of intra-abdominal desmoid tumors is challenging because the natural history is variable and uncertain. Therefore, although surgery should be considered in all cases, it should be reserved for small, well-defined lesions with clear margins. When intra-abdominal desmoids involve the bowel mesentery, they should be treated according to their initial presentation and rate of growth. In patients with desmoid lesions that are refractory to all medical treatments and call for surgical treatment with extensive small bowel resection, small bowel transplantation may be feasible in selected cases.

Contradistinction, abdominal wall desmoids that are symptomatic and appear amenable to a complete removal with negative margins should be resected.

**Periampullary neoplasms** In approximately 80 to 90% of persons with FAP, duodenal adenomas, periampullary adenomas, or both will develop. Of these patients, 14 to 50% will eventually exhibit advanced polyposis, and as many as 6% will eventually have invasive cancer. Although the risk of periampullary or duodenal cancer in FAP patients is relatively low, it is still several hundred times higher than that in the general population. Among FAP patients, those with APC mutations between codons 976 and 1067 appear to have the highest incidence of duodenal adenoma.

Surveillance should begin with side-viewing esophagogastroduodenoscopy (EGD) and biopsy of suspicious polyps either at the age of 20 years or at the time of prophylactic colectomy, whichever is earlier. The purpose of screening is not to remove all disease but to watch for the development of high-grade dysplasia. Duodenal polyposis can be staged using the Spigelman classification [see Table 3]. The surveillance interval is determined by Spigelman stage: stage 0 or 1, every 3 years; stage 2, every 2 years; stage 3, every 1 to 2 years; stage 4, surgery is recommended. Small tubular adenomas without high-grade dysplasia may be biopsied and observed; adenomas that are larger than 1 cm or that exhibit high-grade dysplasia, villous changes, or ulceration should be removed. Surgical options include endoscopic removal and transduodenal excision, but both approaches have drawbacks: endoscopic ablation generally requires multiple settings, and recurrence is high after either procedure. Endoscopic ablation is a reasonable initial approach for most patients without invasive cancer and is an attractive alternative for patients who are unfit for duodenal resection. For patients with persistent or recurrent high-grade dysplasia in the papilla or duodenal adenomas and for patients with Spigelman stage IV disease, pancreas-preserving duodenectomy or pancreaticoduodenectomy is recommended, depending on local expertise. The results reported for duodenal resection in patients with malignant lesions are encouraging, with good local control and low morbidity.

**Attenuated Familial Adenomatous Polyposis**

An attenuated form of FAP (AFAP) has been described that is associated with fewer adenomas and later development of CRC compared with classic FAP. It is associated with autosomal dominant transmission and with germline APC mutations.

**Table 3 Spigelman Classification for Staging Duodenal Polyposis**

<table>
<thead>
<tr>
<th>Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Polyph number</td>
<td>1–4</td>
<td>5–20</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Polyph size (mm)</td>
<td>1–4</td>
<td>5–10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Histology</td>
<td>Tubular</td>
<td>Tubulovillous</td>
<td>Villous</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

No polyph, stage 0; 1 to 4 points, stage 1; 5 to 6 points, stage 2; 7 to 8 points, stage 3; 9 to 12 points, stage 4

(Continued...)

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with germline mutations at the 5’ and 3’ ends of the APC gene, usually codons 78 to 167 and codons 1581 to 2843.58

**CLINICAL EVALUATION**

The AFAP phenotype occurs in less than 10% of FAP patients. The clinical criteria for AFAP are no family members with more than 100 adenomas before the age of 30 years and (1) at least two patients with 10 to 99 adenomas at age over 30 years or (2) one patient with 10 to 99 adenomas at age over 30 years and a first-degree relative with CRC with few adenomas.59

**INVESTIGATIVE STUDIES**

**Pathologic Findings**

Polyps are typically diagnosed at a mean age of 44 years, with cancers diagnosed at a mean age of 54 to 58 years.62–64 The youngest reported case of CRC in the setting of AFAP is 24 years.65 As in classic FAP, adenomas may be either pedunculated or sessile and may have tubular, villous, or tubulovillous histology. However, there is a higher propensity for sessile polyps in AFAP compared with classic FAP. Some authors have reported a predominance of right-sided CRC in the setting of AFAP, whereas others report a more uniform distribution.54,55 Extracolonic manifestation, such as desmoids, osteomas, and periumbilical tumors, occurs in AFAP.66,67 CHRPE, however, has not been reported in AFAP.

**Screening and Surveillance**

The cumulative risk of CRC by age 80 has been estimated to be 69%.64 Given that CRC tends to be right-sided and appears approximately 10 years later than in classic FAP, screening (genetic testing or annual or biennial colonoscopy) for at-risk family members should begin at 18 to 20 years of age. Like classic FAP, AFAP is associated with duodenal polyposis. As such, the duodenum should be surveyed in the same manner as in classic FAP. As in all genetic syndromes, genetic counseling is an essential component of the evaluation of the AFAP patient.

**MANAGEMENT**

**Surgical Therapy**

Given that polyposis has a later onset and the risk of CRC is less well established in AFAP, some authors question whether prophylactic colectomy is necessary in all AFAP patients.55,58–60 In patients with few adenomas, repeated colonoscopic polypectomies may be preferable to surgery.55,59,60 Colectomy should be considered for those patients whose colon polyps cannot be controlled endoscopically.50,58 However, because there is clearly an increased risk of CRC, some authors support prophylactic colectomy.13,27,14,61,62 One author recommends colectomy at age 20 to 25 as the gold standard.13 Most recommend TAC/IRA, as opposed to IPAA, in AFAP patients due to the tendency for rectal sparing.63 One study that examined four national polyposis registries reported a 10% cumulative risk of secondary protectomy and 3.7% cumulative risk of rectal cancer in 58 AFAP patients following TAC/IRA.20

**MYH-Associated Polyposis**

In 2002, mutY human homologue (MYH)-associated polyposis (MAP) was documented in three siblings with multiple colorectal adenomas and carcinomas.64 MAP is an autosomal recessive disorder caused by biallelic mutation in the MYH gene. MYH is a base excision repair gene that, when absent, leads to a high proportion of somatic G:C to T:A transversions.64 Over 80 germline MYH mutations have been identified.65 The most common MYH mutations are Y165C and G396D, which are found in 1 to 2% of North Americans and northern Europeans.66–70 These transversions are found in the APC and KRAS genes in adenomas of MAP patients.41,71,72

**CLINICAL EVALUATION**

The number of polyps in MAP is highly variable, ranging from a few adenomas to hundreds of adenomas, making it sometimes difficult to distinguish between AFAP and classic FAP. MAP has been diagnosed in over 7% of patients with polyposis (greater than 100 adenomas) and lack of an APC mutation.71 Polyps may be found throughout the colon, but, as in AFAP, there is a slight propensity to CRC proximal to the splenic flexure.74 It has been suggested that approximately 30% of MAP patients with CRC do not develop polyposis.73,74 The mean age at CRC diagnosis is between the late forties and early fifties, which is later than classic FAP but similar to AFAP. Synchronous cancers occur in up to 24% of patients.72 The estimated cumulative risk of CRC in biallelic MYH mutation carriers is 80% by age 70.78 Additionally, there is a twofold increased risk of CRC for heterozygous carriers of MYH mutations compared with the general population.79

The extracolonic manifestations typical in FAP are also seen in MAP. Duodenal polyps occur in nearly one third of MAP patients, and an increased risk of duodenal adenocarcinoma has been reported.74 Interestingly, a Dutch registry study reported an increased risk of breast cancer, which occurred in 18% of female patients.74

**INVESTIGATIVE STUDIES**

**Pathologic Findings**

As in classic FAP, adenomas may be either pedunculated or sessile and may have tubular, villous, or tubulovillous histology. Unlike FAP, patients with MAP may also have hyperplastic polyps (HPs) and sessile serrated adenomas (SSAs), whereas others may have no polyps.75,76,80 Adenomas are microsatellite stable. Deficiency in MYH leads to G:C to T:A transversions in the APC and KRAS genes. In one study of 17 MAP patients with multiple adenomas, eight were also found to have HPs and SSAs. Three of eight patients with HPs met the criteria for HPPS. KRAS mutations were detected in 70% of the HPs and SSAs of MAP patients compared with 17% of controls. KRAS mutations were also identified in 23% of adenomas. APC mutations with G:C to T:A transversions were observed in 41% of adenomas in MAP patients and not in controls. No APC mutations were identified in HPs and SSAs.80

The genotype of MYH mutations can predict phenotype. Patients with a homozygous G396D mutation are diagnosed.
with CRC at a mean age of 46 years. Patients with a compound heterozygous mutation (G396D/Y179C) are diagnosed with CRC at a mean age of 52 years, whereas those with a homozygous Y179C mutation have a mean age of 58 years at CRC diagnosis. This information is important when counseling patients with known mutations.

Screening and Surveillance

Given that CRC tends to be right-sided, the European guidelines from the Mallorca group recommend biennial colonoscopy beginning between ages 18 and 20 years. Upper GI endoscopy is advised starting from between 25 and 30 years of age. The recommended screening interval is determined by the Spigelman classification.86

Management

Surgical Therapy

Most MAP patients present with an attenuated phenotype and relative sparing of the rectum.79,85 It is sometimes possible to control these patients with endoscopic polypectomies. If surgery is necessary and the rectum is spared, TAC/IRA is recommended. If rectal polyposis is severe, total proctocolectomy with IPAA is advised.86 The rectal stump should be examined by yearly surveillance endoscopy.

Lynch syndrome

Lynch syndrome was initially described as an inherited form of CRC. The name hereditary nonpolyposis colorectal cancer (HNPPC) syndrome was used to clarify to physicians the nature of the disease. However, over time, there has been recognition that Lynch syndrome is associated with an increased risk of other cancers in addition to CRC. Therefore, the name Lynch syndrome was reintroduced at an international meeting in Bethesda, Maryland, in 2004.82 Currently, the Lynch syndrome diagnosis is reserved purely for those with a documented mutation in one of the DNA mismatch repair (MMR) genes (MLH1, MLH2, MSH6, PMS2).93,94 A heterodimer of MSH2/MSH6 recognizes DNA mismatches and招募s other components of the mismatch machinery, such as the MLH1/PMS2 heterodimer. Two genes (MLH1, MSH2) are responsible for as many as 80 to 90% of causative germline MMR mutations. A significant percentage of cases may be attributable to large germline deletions that are difficult to detect by means of direct sequencing. It appears that genomic deletions may account for as many as 7% of Lynch syndrome cases defined on the basis of clinical criteria.95

Clinical Evaluation

Lynch syndrome is characterized by early-onset CRC, a predominance of lesions proximal to the splenic flexure (60 to 70% of cases), benign and malignant extracolonic tumors, and a predisposition for synchronous and metachronous colorectal tumors.9 Microsatellite instability (MSI), reflecting an accumulation of mutations within regions of repetitive nucleotides called microsatellites, occurs due to a deficiency in the DNA repair secondary to a mutation in the MMR genes. MSI is noted in approximately 80 to 90% of Lynch syndrome–related tumors.96 The lifetime risk of CRC in Lynch syndrome is approximately 80%.1,16,66 Endometrial cancer occurs in 43%, gastric cancer in 19%, urinary tract cancer in 18%, and ovarian cancer in 9%.87

Deciding who to test for a diagnosis of Lynch syndrome is much more challenging than establishing a clinical diagnosis of FAP in that it requires a careful and detailed family history. The Amsterdam II criteria [see Table 4] require that there be three relatives (of which one must be a first-degree relative of the other two) with a Lynch syndrome–related cancer (of the colorectum, endometrium, small bowel, ureter, or renal pelvis), that two or more successive generations be involved, and that at least one relative have a CRC diagnosed before the age of 50.90,92 Finally, FAP should be excluded.

The Muir-Torre variant of Lynch syndrome is associated with dermatologic manifestations in addition to the other common tumors. This rare variant is most often associated with MSH2 mutations.90 Typical skin tumors include sebaceous adenomas and carcinomas, keratoacanthomas, and basal cell carcinomas with sebaceous differentiation.93

Investigative Studies

Pathologic Findings

Adenomas in Lynch syndrome patients show high-grade dysplasia and villous changes more frequently than adenomas in sporadic CRC patients.1 Adenomas may also appear at an earlier age and are often larger than those found in the general population. Other pathologic features reported to be more common in Lynch syndrome–related cancers include a mucinous or poorly differentiated histology, a solid or cribriform growth pattern, signet-ring cell tumors, and the presence of tumor-infiltrating and peritumoral lymphocytes. Lynch syndrome–related CRCs have also been shown to have a lower rate of lymph node involvement.92

Given that antibodies for MMR proteins are available, immunohistochemical (IHC) testing is becoming more routinely reported as part of the pathology report. Studies assessing the addition of MMR IHC staining have found that approximately 20% of specimens will detect loss of MMR proteins.93,94 Loss of MMR proteins in tissue can be followed by germline mutation testing. Some tumors show loss of MSH2 and MSH6 staining without evidence of germline MSH2 or MSH6 mutation. This can be explained by mutations in genes upstream to MSH2, such as the epithelial cell adhesion molecule gene (EpCAM), also known as TACSTD1. Deletions in the last exons of the EpCAM gene can lead to EpCAM/MSH2 fusion transcripts causing the Lynch phenotype in 6.3 to 19% of families without MMR gene mutation.95,96 Thus, patients who show loss of MSH2 and/or MSH6 on IHC without germline mutation should undergo EpCAM testing.

<table>
<thead>
<tr>
<th>Amsterdam II Criteria</th>
<th>Clinical Criteria for Diagnosis of Lynch Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three or more relatives with a Lynch syndrome–associated cancer (in colorectum, endometrium, small bowel, ureter, or renal pelvis). One first-degree relative of the other two. Two or more successive generations. One CRC diagnosed at age &lt; 50 yr. FAP excluded.</td>
<td>CRC = colorectal cancer; FAP = familial adenomatous polyposis.</td>
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</table>

Table 4  Clinical Criteria for Diagnosis of Lynch Syndrome

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Approximately 15 to 20% of sporadic CRC will have MSI. This may occur by epigenetic silencing of the MLH1 gene by hypermethylation of its promoter region.\(^{98-100}\) Loss of MLH1 protein by IHC may be seen. MLH1 hypermethylation is exceedingly rare in sporadic microsatellite stable (MSS) CRC and in Lynch syndrome, in which there is a germline mutation.\(^{98,99}\) Furthermore, sporadic MSI CRC with MLH1 hypermethylation also shows a high level of a characteristic BRAF \(^{V600E}\) mutation, in contrast to Lynch syndrome CRC and sporadic MSS CRC.\(^{98,100}\) Therefore, in selected cases, where there is a loss of MLH1 on IHC testing but a low clinical suspicion for Lynch syndrome, upfront BRAF mutation testing can be performed to rule out Lynch syndrome.\(^{101,102}\)

A founder mutation has been recognized in the Ashkenazi Jewish population. The mutation is a mutation in a single amplicon, A636P, of the MSH2 gene.\(^{103}\) Testing for this single amplicon is rapid, relatively inexpensive, and suggested for Ashkenazi Jewish patients meeting the revised Bethesda criteria because the test result can be obtained in a timely fashion to help decide between segmental versus a TAC.\(^{104}\)

### Screening and Surveillance

CRC patients who have a pedigree suggestive of Lynch syndrome should be offered screening by MSI testing or four-marker IHC panel for loss of MMR protein expression. MSI testing will yield positive results (i.e., an MSI-high tumor) in 80 to 90% of patients belonging to families that meet the Amsterdam criteria.\(^{82}\) Patients with \(\text{MSH6}\) mutations can test falsely as MSS when using a panel of two mononucleotide and three dinucleotide repeats, but a pentaplex panel comprising five mononucleotide repeats for MSI detection more efficiently discriminates the MSI status of tumors with an \(\text{MSH6}\) defect.\(^{105}\) IHC for loss of MMR proteins and MSI testing are comparable in sensitivity, but IHC testing is less expensive and can help target a specific mutation for germline testing. Patients with MSI-high tumors or loss of MMR proteins on IHC should undergo testing for germline MMR mutations [see Table 2]. However, if there is absence of \(\text{MLH1}\) on IHC testing, BRAF mutation testing can be performed prior to germline testing. If there is absence of \(\text{MLH2}\) and \(\text{MSH6}\) on IHC testing but no germline mutation is identified, testing can be performed for deletion in the \(\text{EpCAM}\) gene. If tumor tissue is not available, initial germline testing may be considered. As in FAP, a mutation in an affected individual must first be established for testing in at-risk individuals to be informative.\(^4\)

Recommended surveillance in Lynch syndrome includes colonoscopy, initially every 1 to 2 years beginning at the age of 20 to 25 and then annually after age 40.\(^{106,107}\) Given the increasing evidence of an accelerated adenoma-carcinoma sequence in Lynch syndrome, annual colonoscopy should be strongly considered, especially in families with early-age onset of CRC.\(^5\) Some have recommended that female patients undergo annual transvaginal ultrasonography and measurement of CA 125 levels starting at 25 to 35 years of age, as well as annual endometrial aspiration.\(^{108}\) Annual EGD is recommended for patients belonging to kindreds with a history of gastric cancer. Finally, ultrasonography and urine cytology every 1 to 2 years may be considered to screen for urinary tract malignancy, although the yield appears to be limited.

### Management

#### Surgical Therapy

Although the development of CRC in persons with Lynch syndrome is not a certainty, the 80% lifetime risk, the 45% rate of metachronous tumors, and the possibility of an accelerated adenoma-carcinoma sequence mandate consideration of prophylactic surgical options.\(^{1,5}\) Patients who have Lynch syndrome and who have a colon cancer or more than one advanced adenoma should be offered either (1) prophylactic TAC/IRA and yearly flexible sigmoidoscopy or (2) segmental colectomy with yearly colonoscopy.\(^{1,108,109}\) The first option, however, is open only to patients with normal rectal and anal sphincter function. Although the risk of metachronous colon cancers may be higher after partial colectomy than after TAC/IRA, intensive colonoscopic surveillance and polypectomy may minimize the number of metachronous cancers in the remaining colon.\(^{98,112}\) Careful surveillance is also necessary after TAC/IRA, given that the risk of metachronous rectal cancer after total colectomy is approximately 12% at 10 to 12 years.\(^{113}\) However, because of increased risk of metachronous high-risk polyp/carcinoma development and subsequent laparotomy in patients with prior segmental resections, TAC/IRA is our preferred approach and has emerged as the treatment of choice for the index cancer.\(^{112,113}\)

Lynch syndrome patients with an index rectal cancer that is amenable to a sphincter-preserving resection should be offered either (1) total proctocolectomy with IPAA or (2) low anterior resection (LAR) with primary reconstruction.\(^{112,108}\) The rationale for total proctocolectomy is based on the 17 to 45% rate of metachronous cancer in the remaining colon associated with an index rectal cancer in Lynch syndrome patients.\(^{112}\) The decision between the two procedures depends in part on the patient’s willingness to undergo intensive surveillance of the retained proximal colon, as well as on the level of bowel function.

Mutation-positive patients with a normal colon and rectum may also be offered prophylactic colectomy in selected cases.\(^{106,115}\) This approach is supported by the similarity of lifetime cancer risk between patients with germline \(\text{APC}\) mutations and those with MMR mutations, as well as by the observation that TAC/IRA yields less functional disturbance than a prophylactic procedure often recommended for FAP (total proctocolectomy with IPAA).\(^{106,115}\) An alternative strategy in these patients is to carry out colonoscopic surveillance every 1 to 2 years. This strategy has proven to be cost-effective and to reduce both the rate of CRC development and overall mortality.\(^{88,116-118}\) There is a risk that CRC may develop in the intervals between colonoscopies. However, when the surveillance interval is shorter than 2 years, tumors generally tend to be found in the early stages, when they are curable.\(^{88,116,118}\)

A study using a decision analysis model suggested that prophylactic TAC at the age of 25 might offer a survival benefit of 1.8 years when compared with colonoscopic surveillance. The benefit of prophylactic colectomy decreased when surgery was delayed until later in life and became negligible when it was performed at the time of cancer development. However, surveillance provided a greater
benefit with respect to quality of life (measured in quality-adjusted life-years).\textsuperscript{117} On the basis of this evidence, some surgeons recommended that prophylactic colectomy be performed only in highly selected situations (e.g., when colonoscopic surveillance is not technically possible or when a patient refuses to undergo regular surveillance). Thus, the decision between prophylactic surgery and surveillance for gene-positive unaffected patients is based on many factors, including the penetrance of disease in a family, the age at cancer onset in family members, functional and quality of life considerations, and the likelihood of patient compliance with surveillance.

**Extracolonic Disease**

Management of extracolonic cancers in Lynch syndrome patients is less well defined. Female patients with a family history of uterine cancer should be offered prophylactic total abdominal hysterectomy (TAH) if their childbearing is complete or if they are undergoing abdominal surgery for other conditions.\textsuperscript{11} This recommendation is based on the high (43%) rate of endometrial cancer in mutation-positive persons and on the inefficacy of screening demonstrated in some studies.\textsuperscript{89,119} In addition to having a higher incidence of MSS CRC, patients with MSH6 mutations have a particularly high risk of developing endometrial cancer (71% by the age of 70, with a mean age at diagnosis of 54 years).\textsuperscript{120} Oophorectomy should be added to TAH because of the high (9%) incidence of ovarian cancer in Lynch syndrome patients and the frequent coexistence of endometrial cancer with ovarian cancer.\textsuperscript{99,121} The optimal timing for prophylactic TAH is unclear. However, given that endometrial cancer has been reported in Lynch syndrome patients before the age of 35, it seems reasonable to begin surveillance at the age of 25 and delay prophylactic surgery until childbearing is complete.\textsuperscript{11}

**Familial Colorectal Cancer Syndrome Type X**

The term familial colorectal cancer type X (FCCTX) was coined to describe families meeting the Amsterdam criteria or with an apparent autosomal dominant CRC predisposition who do not have a mutation in the MMR genes. As many as 45% of all families meeting Amsterdam criteria qualify for this syndrome.\textsuperscript{122} These families have an increased risk of CRC compared with the general population, but the risk is not as high as that for families with Lynch syndrome.\textsuperscript{122} In contrast to Lynch syndrome, CRC in patients with FCCTX is MSS, occurs more commonly on the left side, and presents about 10 years later (mid to late fifties).\textsuperscript{123–125} These families do not have other Lynch syndrome–associated tumors.

**Clinical Evaluation**

The clinical evaluation in a patient presenting with adenoma or nonpolyposis carcinoma and an apparent familial CRC syndrome should proceed as for Lynch syndrome, namely, tissue IHC testing for loss of MMR protein or MSI testing. Patients with loss of an MMR protein or with an MSI tumor should undergo confirmatory germline testing in blood. If these do not confirm a mutation, APC and MYH gene testing is performed.

**Investigative Studies**

**Pathologic Findings**

Adenomas and CRC tend to be left-sided. Patients present with less synchronous or metachronous tumors compared with Lynch syndrome patients. A slower progression from adenoma to carcinoma is suggested because there are more adenomas and a greater adenoma/carcinoma ratio than in Lynch syndrome patients.

**Screening and Surveillance**

FCCTX patients should be screened with colonoscopy beginning 10 years prior to the age at the earliest CRC diagnosis in the family. The frequency of subsequent colonoscopy is determined by the initial findings but should be no longer than 5 years.

**Management**

Segmental colectomy should be offered for CRC diagnosis. Annual surveillance colonoscopy is performed. The time between colonoscopies can be lengthened if the examination is normal.

**Hyperplastic Polyposis Syndrome**

HPs are sessile polyps of the colon marked by lengthening and cystic dilation of mucosal glands. HPs are the most common benign colorectal polyp, most commonly located in the distal colon.\textsuperscript{122} They have long been thought to be clinically innocuous. More recent data suggest an association of hyperplastic polyposis and CRC.\textsuperscript{122} The World Health Organization definition of HPPS includes one of the following: (1) at least five HPs proximal to the sigmoid colon, two of which are greater than 1 cm in diameter, or (2) more than 30 HPs at any site in the colon, or (3) any number of HPs in a patient who has a first-degree relative with HPPS.\textsuperscript{122} There have been conflicting data regarding the development of CRC in HPPS by the serrated neoplasia pathway.\textsuperscript{129,130} Thus far, no germline mutation has been identified, but multiple factors suggest a hereditary etiology, including familial clustering.\textsuperscript{131}

**Clinical Evaluation**

The number of polyps is variable and may exceed 100 but typically ranges from 40 to 100 polyps.\textsuperscript{130,132} CRC develops at a median age between 48 and 55 years but has been diagnosed as early as 11 years of age.\textsuperscript{130,133,134} Polyps are distributed throughout the entire colon; however, there appears to be a predilection for right-sided colon cancers.\textsuperscript{126}

**Investigative Studies**

**Pathologic Findings**

No germline mutation has been identified for HPPS. Patients have acquired somatic mutations in either BRF or KRAS in HPs, but not in both.\textsuperscript{130} Unlike HPs with KRAS mutations, HPs with BRF mutations are associated with a high level of DNA methylation in CpG islands.\textsuperscript{135} MSI status is variable, but most HPs are microsatellite stable.\textsuperscript{130,136} The increased risk of CRC is proposed through the SSA
pathway. Dysplastic polyps that are larger than 1 cm are at highest risk for malignant transformation.\(^{138}\)

**Screening and Surveillance**

There is no identified germline mutation for testing. There are no specific screening guidelines, although yearly colonoscopy should be performed once the diagnosis is made.

**Management**

There are no consensus guidelines for the management of HPSS. A logical approach would be to manage these patients in a manner similar to that for Lynch syndrome. Patients who have a colon cancer or more than one advanced adenoma should be offered either (1) prophylactic TAC/IRA and yearly flexible sigmoidoscopy or (2) segmental colectomy with yearly colonoscopy.

**Conundrum of Oligopolyposis**

In practice, one may encounter a patient who has several adenomatous polyps but without a known genetic syndrome identified. In such a patient, a genetic syndrome should be suspected and a rational workup performed. Initial testing includes APC gene testing and MSI testing or IHC for loss of MMR proteins. Patients with loss of MMR protein or MSI tumors should undergo MMR gene testing. If these do not confirm a mutation, MYH gene testing is performed.

Treatment should be based on the genetic syndrome, if found. Often, however, no known genetic defect is identified. In these cases, management is determined by the disease phenotype. If there is oligopolyposis, as defined by 5 to 100 polyps without cancer, yearly surveillance colonoscopy with endoscopic treatment as required is an option that would need to be carefully considered on a case-by-case basis. If cancer is identified, segmental colectomy with yearly colonoscopy is recommended. Alternatively, total colectomy with IRA and yearly flexible sigmoidoscopy is an option to be considered, particularly for patients with a strong family history and non-identifiable gene mutation. Similarly for a diagnosis of rectal cancer, segmental resection with yearly colonoscopy is the preferred approach, whereas total proctocolectomy with IPAA is a less often required option. Surgical treatment should be tailored to best address the patient’s phenotype.

**Peutz-Jeghers Syndrome**

Like FAP and Lynch syndrome, PJS follows an autosomal dominant pattern of inheritance with variable penetrance. It is caused in part by mutations in the gene LKB1/STK11, which maps to the telomeric region of chromosome 19p13.3. This gene, which codes for a multifunctional serine-threonine kinase, is thought to function as a tumor suppressor gene.\(^{137-140}\) Germline mutations in LKB1/STK11 can be demonstrated in 18 to 63% of PJS patients, which suggests the existence of additional PJS loci.\(^{140-143}\) Genetic testing for PJS can be accomplished through direct sequencing of the LKB1/STK11 gene [see Table 2]; however, such testing is not widely available. In families with an established mutation, genetic testing of at-risk individuals is informative, with a reported accuracy of 95%.\(^{144}\)

**Clinical Evaluation**

PJS is a hereditary polyposis syndrome characterized by hamartomas of the GI tract, as well as by mucocutaneous melanin pigmentation. Hamartomatous polyps may occur throughout the GI tract but are most frequently found in the small intestine (90%). Other common sites of hamartomas in PJS are the large intestine (50%) and the stomach; less common sites are the renal pelvis, bile ducts, urinary bladder, lungs, and nasopharynx.\(^{145,146}\) Mucocutaneous pigmentation generally appears during infancy. The perioral and buccal areas are involved in 95% of cases. The periorbital and facial areas, genital region, and acral areas (including the hands and feet) may be involved.\(^1\) The average age at diagnosis of PJS is 22 years in men and 26 years in women.

In as many as 86% of cases, the initial presentation of PJS is small bowel obstruction secondary to intussusception of hamartomas. Other presentations include acute or chronic GI bleeding, biliary and gastric outlet obstruction, and anal protrusion of polyps. The diagnosis of PJS is established by the presence of histologically confirmed hamartomas of the GI tract plus two of the following three criteria: (1) small bowel polyposis, (2) mucocutaneous melanin pigmentation, and (3) a family history of PJS.\(^{147}\)

Patients with PJS are at significantly increased risk for both intestinal and extraintestinal malignancies. A meta-analysis found that in comparison with the general population, PJS patients were at a 15.2 relative risk for the development of any malignancy.\(^{148}\) The relative risks for the development of specific cancers were as follows: small bowel, 520; gastric, 213; pancreatic, 132; colorectal, 84; esophageal, 57; ovarian, 27; lung, 17; endometrial, 16; and breast, 15. The cumulative risk for the development of any cancer between the ages of 15 and 64 was 93%.\(^{149}\) Although the relative risk for the development of CRC was high in this study, the reported magnitude of risk in the individual studies included in the meta-analysis varied considerably.\(^{148}\) Given that other studies also report a wide range of CRC incidence in these patients, the true incidence of CRC in PJS patients remains unclear.\(^1\) Other cancers associated with PJS are cholangiocarcinomas, testicular neoplasms, and duodenal tumors.\(^1\)

**Investigative Studies**

**Pathologic Findings**

The polyps seen in PJS are hamartomas characterized by hypertrophy or hyperplasia of the smooth muscle of the muscularis mucosa. Smooth muscle extends into the superficial epithelial layer of the bowel wall in a treelike fashion (a process referred to as arborization). Epithelial cells may become entrapped within the muscle layer, and this “pseudo-invasion” can be mistaken for malignant transformation. Therefore, to diagnose a malignancy in a PJS polyp, cellular atypia or an elevated mitotic rate must be documented.\(^{149}\) Sporadic PJS polyps do occur, generally secondary to somatic LKB1/STK11 mutations in one or both alleles, and are histologically identical to their hereditary counterparts.

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These sporadic polyps appear not to be associated with an increased risk of GI cancer.150

Histologically, areas of cutaneous pigmentation reveal an increased number of melanocytes at the dermal-epidermal junction, with elevated melanin levels in the basal cells. These lesions do not appear to have any malignant potential.

**Screening and Surveillance**

Clinical screening of asymptomatic persons is facilitated by the appearance of perioral hyperpigmentation during early childhood. Once the diagnosis of PJS is made, patients generally enter a surveillance program. Recommended surveillance for GI disease includes annual serum hemoglobin measurement and EGD and small bowel series every 2 to 3 years, beginning at the age of 6. Colonoscopy is added at age 18. Sigmoidoscopy is usually not employed for surveillance, because the rectum may be spared in patients with more proximal disease. Upper endoscopic ultrasonography is recommended every 1 to 2 years, whereas computed tomography and/or CTA 19-9 may be offered as options. Boys may be offered ultrasonography of the testicles every 2 years until age 12. Women should undergo annual pelvic examinations and Papanicolaou smears beginning at age 21. Starting at age 25, annual transvaginal ultrasonography and serum CA 125, as well as semiannual clinical breast examinations with annual mammography (magnetic resonance imaging may be offered as an alternative), are recommended.151 The frequency of surveillance examinations may be modified in individual circumstances.

**MANAGEMENT**

**Medical Therapy**

COX-2 is known to be overexpressed in the hamartomatous tissue of PJS patients, and there is a correlation between the expression of the COX-2 protein and expression of the LKB1/STK11 protein in PJS polyps and cancers.152,153 These findings suggest that COX-2 may be a potential target for chemoprevention of PJS.

**Surgical Therapy**

Indications for surgical management of PJS include the presence of polyps larger than 1.5 cm that cannot be removed endoscopically, incomplete removal of polyps with adenomatous changes, the development of polyp-associated complications (e.g., obstruction, intussusception, and bleeding), and the management of malignant disease.154

Endoscopic polypectomy is generally employed as initial therapy when it is technically feasible. For some polyps, however, operative polypectomy performed through an enterotomy is required. Segmental resection should be avoided. In the context of a laparotomy, intraoperative endoscopy (either peroral or via an enterotomy) allows direct visualization of the remainder of the small bowel and endoscopic clearance of any synchronous polyps. This procedure significantly reduces the need for subsequent laparotomy. The St. Mark’s Hospital group in London found that none of 25 patients who underwent enteroscopy during laparotomy required subsequent laparotomy within a 4-year period, whereas 17% of historical control patients who did not undergo intraoperative enteroscopy required repeat laparotomy within a 1-year period.155

Laparoscopy-assisted polypectomy and laparoscopic management of small bowel intussusception are additional surgical options.

Given the risk of CRC development in PJS patients, careful colonoscopic surveillance is clearly warranted. However, the role of prophylactic colectomy in patients who are at risk or are mutation positive is unclear. Because the true risk of CRC in these patients is unknown and genetic testing for PJS is not widely available, no recommendations can be made at present regarding the role of prophylactic colectomy in the PJS population.154

**Juvenile Polyposis Syndrome**

Initial evidence suggested that mutations in the PTEN gene were responsible for JPS; however, subsequent evidence implicated SMAD4/DPC4 at 18q21.1 as a more common case, accounting for as many as 50% of familial cases.156–159 Mutations in BMPR1A at 10q22-q23 have also been reported to cause JPS but display variable penetrance [see Table 2].160,161 Clonal genetic alterations are detected in stromal rather than epithelial cells, which suggests that the genetic changes in juvenile polyps originate in the nonepithelial component of the polyps.

**CLINICAL EVALUATION**

Like PJS, JPS is characterized by the development of multiple hamartomas throughout the GI tract. Isolated juvenile polyps are common in children and are found in approximately 1% of persons younger than 21 years. Juvenile polyposis, however, is much less common. A family history of juvenile polyposis is present in 20 to 50% of JPS patients.1 Although JPS is an autosomal dominant disorder, its variable penetrance results in a less obvious pattern of inheritance than is seen with FAP or Lynch syndrome. JPS affects both sexes equally and generally manifests itself during the first or second decade of life (mean age at diagnosis 18.5 years).1 Common presenting symptoms include chronic anemia, acute GI bleeding, prolapse of rectal polyps, protein-losing enteropathy, and intussusception with or without obstruction.1

Extracolonic manifestations of JPS include gastroduodenal and small bowel polyps, malrotation of the midgut, and mesenteric lymphangiomas. Extraintestinal manifestations include clubbing, hypertrophic pulmonary osteoarthropathy, hydrocephalus and macrocephaly, alopecia, cleft lip and palate abnormalities, supernumerary teeth, porphyria, congenital cardiac and arteriovenous malformations, psorias, vitellointestinal duct abnormalities, renal structural abnormalities, and bifid uterus and vagina. JPS is also part of the phenotype for Ruvalcaba-Myhre-Smith syndrome and Gorlin syndrome. Cowden disease, which is characterized by hamartomatous polyposis and is associated with breast and thyroid cancer, may be a phenotypic variant of JPS.1,161

The diagnostic criteria for JPS are as follows: (1) the presence of three or more juvenile polyps of the colon; (2) the presence of three or more juvenile polyps throughout the entire GI tract; or (3) the presence of any number of polyps in a patient with a known family history of JPS [see

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Table 1. The clinical presentation of JPS can be divided into three main clinical variants: (1) JPS of infancy, which is a non–sex-linked recessive condition characterized by failure to thrive, susceptibility to infections, protein-losing enteropathy, bleeding, diarrhea, rectal prolapse, intussusception, and death by the age of 2 years in severe cases; (2) generalized JPS, which occurs in the first decade of life and is characterized by juvenile polyps throughout the GI tract; and (3) JPS of the colon, the most common presentation, which is characterized by colonic polyposis only.1

Patients with JPS appear to be at increased risk for GI malignancies, especially CRC. One study estimated the risk of CRC to be 15% by age 35 and 68% by age 65.163 In another study, GI malignancies (mostly CRC) were diagnosed in 17% of JPS patients at a mean age of 33 years.164 Associated gastric, pancreatic, duodenal cancers have also been reported. CRCs are thought to arise from malignant transformation of dysplastic polyps.1 Adenocarcinomas occur, on average, 15 years after diagnosis of JPS and generally are poorly differentiated or mucinous tumors with a poor prognosis.1

INVESTIGATIVE STUDIES

Pathologic Findings

The number of polyps seen in JPS patients varies but typically ranges from 50 to 200. The polyps are usually smaller than 1.5 cm but can be as large as 3 cm. Grossly, they appear as red-brown, smooth, pedunculated lesions with lobulated or spherical heads and superficial ulceration; the cut surface demonstrates cystic spaces corresponding to mucus-filled glands. Histologically, polyps are characterized by an inflammatory infiltration of the lamina propria, an attenuated smooth muscle layer, and cystically dilated mucus-filled glands lined by columnar epithelium. Focal epithelial hyperplasia and dysplasia may be present.

Screening and Surveillance

Initial evaluation of the proband and the first-degree relatives, which ideally would be done in the middle to late teenage years, should include colonoscopy, EGD, and a small bowel series. If the initial evaluation yields negative results, a repeat evaluation should be performed in 3 years and then every 3 years thereafter as long as the results remain negative. If disease is encountered, random biopsies of polyps and intervening mucosa should be performed to detect adenomatous and dysplastic changes. Management depends on the presence of symptoms and on the extent and severity of polyposis. When polyposis is mild, endoscopic management may be feasible. Continued annual surveillance after endoscopic management is required; the surveillance interval may be lengthened to 3 years if subsequent evaluations reveal no disease.1,162

MANAGEMENT

When polyposis is severe or significant symptoms are apparent, prophylactic colectomy with IRA may be considered for suitable surgical candidates. Although rectal polyposis can generally be managed with rigid or flexible proctoscopy, IPAA may be considered if the polyposis is extensive. Continued annual surveillance of the rectal remnant (after IRA) or the ileal pouch (after IPAA) is required. Surveillance intervals may be increased to 3 years if subsequent evaluations find no evidence of disease.1,162

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References


