The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes

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The American Society of Colon and Rectal Surgeons (ASCRS) is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines Committee is composed of society members who are chosen because they have demonstrated expertise in the specialty of colon and rectal surgery. This committee was created to lead international efforts in defining quality care for conditions related to the colon, rectum, and anus, in addition to the development of Clinical Practice Guidelines based on the best available evidence. These guidelines are inclusive and not prescriptive. Their purpose is to provide information on which decisions can be made, rather than to dictate a specific form of treatment. These guidelines are intended for the use of all practitioners, health care workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines.

It should be recognized that these guidelines should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of all the circumstances presented by the individual patient.

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METHODOLOGY

These guidelines are built on the last set of the ASCRS Practice Parameters for the Identification and Testing of Patients at Risk for Dominantly Inherited Colorectal Cancer published in 2003.[1] An organized search of MEDLINE (1946 to December week 1, 2016) was performed from 1946 through week 4 of September 2016 (Fig. 1). Subject headings for "adenomatous polyposis coli" (4203 results) and "intestinal polyposis" (445 results) were included, using focused search. The results were combined (4629 results) and limited to English language (3981 results), then further limited by study type for potential inclusion in the evidence-based review, using the publication type limits of case reports, clinical trial, comparative study, controlled clinical trial, guideline, meta-analysis, multicenter study, observational study, practice guideline, randomized controlled trial, or systematic reviews (1311 results). A second keyword search was done (not mapped to subject heading) for "familial polyposis" (1143 results), "*MYH* or *MUTYH*" (408 results), and "desmoid" (2303 results). These were limited in the same manner as the subject heading search, leaving 1249 results. They were merged with the 1311 prior results, leaving a total of 2343 titles for review. After title review, 361 abstracts were reviewed and selections made for full-text review, with directed search of imbedded references and article citation as needed. A total of 121 full-text articles were reviewed. Existing guidelines on this topic, their associated references, and cited articles were reviewed for any additional studies that may not have been included.[1–5] The final source material used was evaluated for the methodological quality, the evidence base was examined, and a treatment guideline was formulated by the subcommittee for this guideline. A final grade of recommendation was assigned using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (Table 1).[6] When agreement was incomplete regarding the evidence base or treatment guideline, consensus from the committee chair, vice chair, and 2 as-

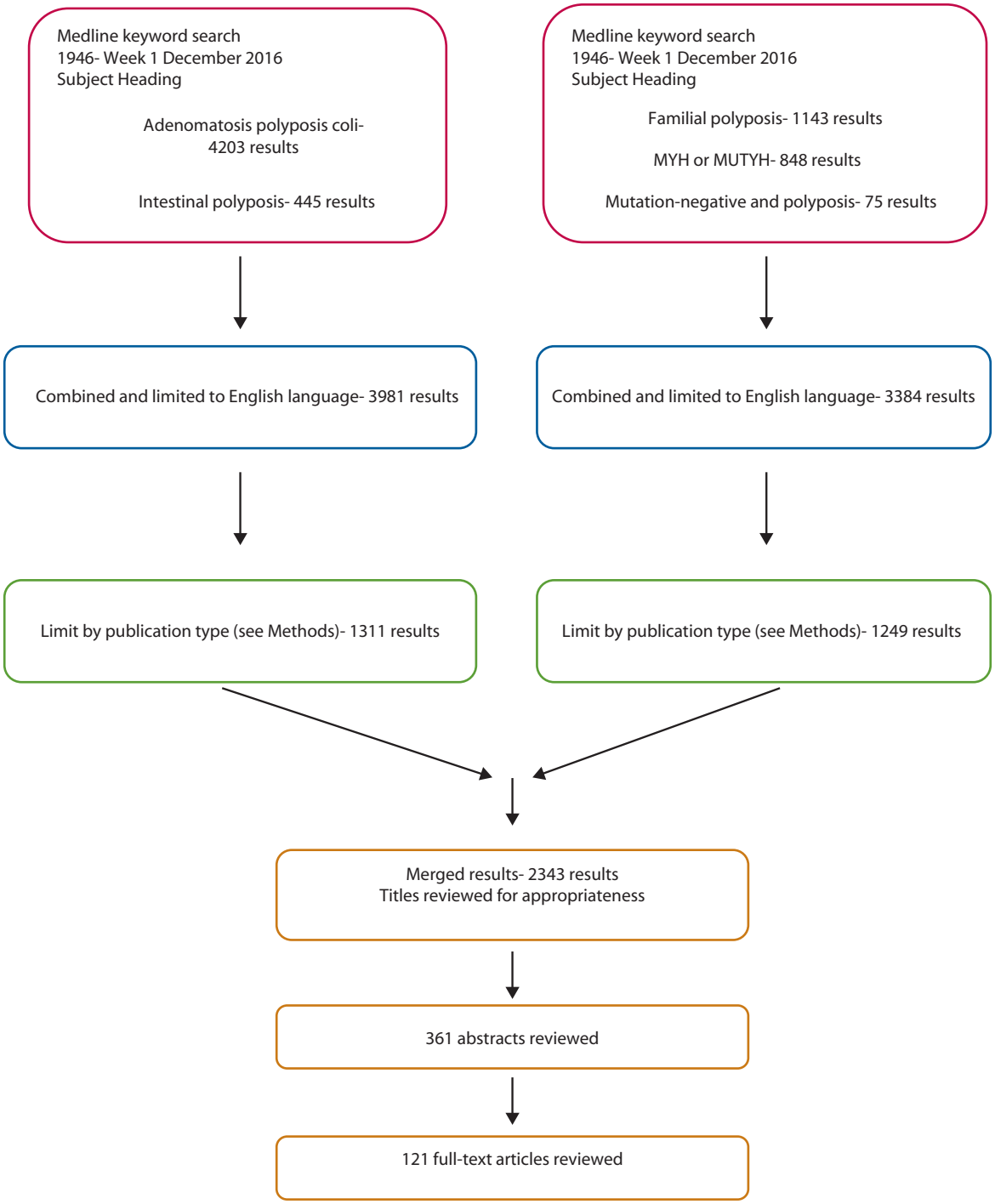

FIGURE 1. Literature search strategy.

signed reviewers determined the outcome. Members of the ASCRS practice guidelines committee worked in joint production of these guidelines from inception to final publication. Recommendations formulated by the subcommittee were reviewed by the entire Clinical Practice Guidelines Committee. Final recommendations were approved by the ASCRS Clinical Guidelines Committee and ASCRS Executive Committee.

STATEMENT OF THE PROBLEM

Colorectal cancer is the third most common cancer in men and women in the United States, and the second leading cause of cancer deaths. Approximately 20% to 30% of colorectal cancer cases are associated with a family history of colorectal polyps or cancer, and approximately 3% to 5% of cases are associated with an identifiable inherited colorectal cancer syn-

TABLE 1. The GRADE system: grading recommendations

	Description	*Benefit vs Risk and Burdens*	*Methodological Quality of Supporting Evidence*	*Implications*
1A	Strong recommendation, High-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, Moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, Low- or very-low-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, High-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendations, Moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, Low- or very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations, other alternatives may be equally reasonable

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; RCT = randomized controlled trial.
Adapted from Guyatt G, Gutermen D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129:174–181.[6] Used with permission.

drome. Of these inherited syndromes, polyposis syndromes and Lynch syndrome are the most common. Polyposis syndromes have been recognized for many years, because of a strong phenotype that includes the presence of multiple, even thousands of polyps of different histologic types.[7]

Familial adenomatosis polyposis (FAP) is an autosomal dominant syndrome characterized by tens to thousands of colonic adenomas, one or more of which will progress to cancer unless they are diagnosed or treated. There are also higher lifetime risks of several other malignancies (eg, duodenum, pancreas, thyroid, brain). A germline mutation of the adenomatous polyposis coli (*APC*) tumor suppressor gene, located on chromosome 5q21, is found in most patients with classical adenomatous polyposis (>100 synchronous adenomas).[8,9] Affected individuals can have a range of disease severity, sometimes predicted by the location of the *APC* mutation, leading to the designation of "attenuated FAP" (AFAP) in more mildly affected individuals (<100 synchronous adenomas).[10,11] A distinct subset of patients with AFAP has now been recognized to arise from biallelic germline mutations of the base excision-repair gene *MutY* homologue (*MYH*), in a autosomal recessive syndrome termed *MYH*-associated polyposis, or MAP.[12,13] Despite recent advances, there are also individuals with clinically evident polyposis, either attenuated adenomatous polyposis or serrated polyposis, in whom a mutation is not found. This clinical practice guideline will cover the identification and management of FAP, AFAP, MAP, and polyposis without an identified genotype, and the extraintestinal manifestations included in the adenomatous polyposis syndromes. Hamartomatous polyposis syndromes, such as Peutz-Jeghers syndrome, juvenile polyposis syndrome, and *PTEN* Hamartoma tumor syndrome have little high-grade evidence to guide treatment and are not reviewed here.

RECOMMENDATIONS

Screening and Genetic Testing for Adenomatous Polyposis Syndromes

1. **Polyposis syndromes should typically be considered in patients with greater than 20 lifetime adenomas, patients with a personal history of desmoid tumor or other extracolonic manifestations of FAP, or family members of individuals with known FAP, AFAP, or MAP. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

A clinical diagnosis of FAP is generally agreed upon when >100 adenomas are found, and germline testing of the *APC* gene is recommended for these individuals, because this facilitates screening for the mutation in family members and may have predictive value for extracolonic manifestations. Although most probands with >100 adenomas will have a detectable mutation or deletion in *APC*, there is a small proportion of cases where no mutation can be found. Recently, deletions in *APC* promoter 1B have been found in such families, and this needs to be requested specifically. In a family with classical FAP but no identifiable mutation in *APC*, screening and treatment should follow the same principles as those with proven mutations.

For patients with fewer than 100 adenomas, clarifying the diagnosis can be difficult. The recent development of next-generation DNA sequencing and multigene panel testing allows these patients to be tested for all the known colorectal cancer genes with a single blood test. This is helpful because many syndromes have been associated with attenuated adenomatous polyposis (AFAP, MAP, polymerase proofreading associated polyposis, Lynch syndrome). The clinical question to answer is the threshold of cumulative adenoma numbers at which genetic testing should be sought. Although multiple criteria have been proposed, there is no consensus for the diagnosis of AFAP.[14–16] The diagnosis of AFAP often requires combining clinical findings, adenoma number (more than 10 or 20, but less than 100), family history, and genetic testing to distinguish the syndrome from MAP, polyposis of unknown etiology, or simply multiple sporadic adenomas.

There are few data to define the cumulative number of polyps that should prompt testing. A cross-sectional study of 8903 individuals who had samples submitted for *APC* and *MYH* mutations to Myriad Genetics Laboratories was published in 2012.[13] Mutations were found in 82% of individuals with >1000 polyps, 63% of individuals with 100 to 999 polyps, 17% of individuals with 20 to 99 polyps, and 9% of individuals with 10 to 19 polyps. These data show that reliance on genetic testing alone to define these syndromes is not adequate; clinical criteria for the diagnosis of polyposis are required for those in whom no known mutation is detected. Because the risk of finding a genetic abnormality does not rise above 10% until 20 or more adenomas are found, it is reasonable to use a cutoff of 20 cumulative adenomas to prompt genetic counseling and testing. We agree with multiple other existing guidelines that genetic testing should be preceded by genetic counseling, ideally by a certified genetic counselor when available.[17–19] Patients in whom no known mutation is found should be treated as having classic or attenuated polyposis, based on their observed phenotype.

A family history of polyposis is helpful, but not required for making decisions regarding genetic testing. A systematic evidence-based review of the accuracy of a family cancer history was reported by Murff et al[20] and established that patient-reported history is accurate and valuable in the evaluation of colon cancer and breast cancer patients. The absence of a family history of polyposis or colorectal cancer does not exclude the diagnosis of a polyposis syndrome, because de novo mutations in the *APC* gene may occur in up to 15% of FAP patients and MAP is recessively inherited.[21]

Treatment for FAP

1. **Treatment should include thorough counseling about the nature of the syndrome, its natural history, its extracolonic manifestations, and the need for compliance with recommendations for management and surveillance. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

In untreated patients with classic FAP, colorectal cancer is nearly universal by age 40. There are no randomized or prospective trials of different surveillance strategies. Multiple single-center observational studies and a single systematic review have demonstrated a reduction in colorectal cancer incidence and mortality for patients within registry screening programs.[22] Affected individuals have a risk of extracolonic manifestations, including gastric, duodenal, and small-bowel polyps and cancer, adrenal adenomas, thyroid cancer, desmoid tumors, hepatoblastoma, and congenital hypertrophy of the retinal pigment epithelium. A recent review of an institutional registry reported a sharp increase in gastric cancer in long-term follow-up of patients with FAP. Additional research in this area may influence future screening recommendations for gastric cancer.[23] Duodenal cancer and desmoid tumors are the most common causes of death in patients with FAP after colorectal cancer, and recent data suggest that the incidence of gastric cancer is increasing. Surveillance of these organs and management of the postsurgical lower GI tract is important. The risk of some of these can be estimated by the position of the codon mutation along the *APC* gene.[24] Based on low-quality evidence, we recommend that clinicians caring for patients with polyposis should have specialized expertise in the field and, ideally, work within a multidisciplinary team. A recent survey of the membership of the Association of Coloproctology of Great Britain and Ireland showed that even among specialist surgeons, awareness of the nature of polyposis syndromes is low.[23] Evidence supporting appropriate diagnosis and treatment, especially for AFAP and MAP, is evolving, and new findings may alter treatment recommendations.

Familial Screening for At-Risk Members

1. **At-risk family members of a patient with an identified mutation are screened for the mutation. For children and those who decline genetic testing, endoscopic**

surveillance is recommended until either genetic testing is performed or a diagnosis is clear based on phenotype. At-risk family members who do not carry the mutation should have the same screening as the average-risk population. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

When a patient is the first in a family to be diagnosed with FAP (proband), genetic testing is indicated. If a mutation is found, then all the at-risk relatives of the proband can be screened for this mutation. This process is much cheaper and quicker than multigene panel sequencing. Most authorities recommend testing children at puberty because cancer is rare before that age. Observational data support the finding that colorectal cancer has not been reported before age 9 in individuals with FAP. Combining data from 5 European registries of patients with polyposis, 0.2% developed cancer before age 15 and 1.3% developed cancer before age 20.[6] A survey of 26 registries found only 1 case of invasive cancer reported before age 17.[25] Two features of FAP help to develop rational screening strategies: 1) the rectum is almost always affected in classic FAP; and 2) although polyps form at a much younger age than in the general population, there is no clear evidence that progression from polyp to invasive cancer is accelerated.[26] Screening for polyps in children of patients with classic FAP can, therefore, begin at age 10 and can be accomplished with flexible sigmoidoscopy. Polyps should be sampled because lymphoid follicles are particularly prominent in children and can be mistaken endoscopically for adenomas. Those without evidence of polyposis should have the examination every 2 years. There are few data to guide decision making for children of affected individuals who reach adulthood without a phenotype of polyposis and without a positive genetic diagnosis. It is, however, reasonable for colonoscopy to replace flexible sigmoidoscopy in the later teenage years (16) and to be done every 2 years until age 20. If there are still no adenomas, surveillance intervals can be gradually extended. Children who are found to have adenomas on flexible sigmoidoscopy should have a colonoscopy to document the severity of the polyposis. They can generally defer surgical management until they have reached adulthood, based on moderate-quality evidence as noted above. Postoperative screening should follow guidance outlined later in this report.

There are incomplete data to strongly support a screening strategy for attenuated FAP. Colorectal cancers occur significantly later with these mutations, and the rectum may be spared. A strategy that focuses on frequent flexible sigmoidoscopy in younger individuals may therefore be inadequate. Two observational studies in AFAP have shown no cancer before the age of 20, and the youngest reported has been at age 24.[15,27] Observational data and expert opinion support colonoscopy every 2 years, starting at age 20 until 1) preventive surgery is performed, or 2) genetic testing proves the absence of a known familial mutation. Because screening begins at an older age than with classic FAP, and because rectal sparing is seen with AFAP, colonoscopy instead of flexible sigmoidoscopy is recommended to properly identify affected individuals. Furthermore, besides establishing the clinical diagnosis of polyposis in AFAP, endoscopic clearance of polyps may delay or eliminate the need for preventative surgery. The interval between examinations has not been clearly established by available evidence. Existing general postpolypectomy surveillance guidelines may be modified to more frequent examinations if endoscopic clearance is the treatment plan, because polyp numbers may increase quickly, and subtle adenomas may be missed.[28]

Surgical Treatment of FAP and AFAP

1. **Proctocolectomy with ileostomy or IPAA is the treatment of choice for patients with a large number of rectal adenomas, but the optimal timing should be individualized. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

The aims of treatment of the lower GI tract in patients with FAP are to prevent death from cancer and to maximize quality of life. In general, colonoscopic clearance of adenomas in patients with classical FAP cannot guarantee that cancer will be prevented, so removal of the at-risk epithelium is required. The 2 decisions that need to be made in affected patients to fulfill those aims center around the timing of surgery and the type of operation to be performed.

Multiple factors need to be considered when determining the proper operation and timing of surgery. In addition to more traditional metrics such as medical comorbidities and nutritional status, the timing and choice of surgical procedure must also take into account the educational, intellectual, and emotional development of the patient and his or her reliability for follow-up evaluations. The 4 surgical options are: total colectomy with ileorectal anastomosis (IRA); proctocolectomy with stapled IPAA; proctocolectomy with mucosectomy and handsewn IPAA; and total proctocolectomy with end ileostomy. There is no randomized trial comparing IRA to proctocolectomy with IPAA. A meta-analysis of 12 nonrandomized studies demonstrated individual merits of each approach.[29] Factors that favor total abdominal colectomy and leaving the rectum in place include relative rectal sparing, and the desire to avoid pelvic dissection and possible infertility or sexual dysfunction. Factors that support a proctocolectomy with IPAA include the presence of rectal cancer, large rectal polyp burden (>20 synchronous adenomas, adenoma with high-grade dysplasia, large (>30 mm) adenomas), or a severe familial phenotype (>1000 synchronous adenomas).

There is a very small risk of adenocarcinoma after an IPAA, with only about 2 dozen reported cases in the literature

to date.[30–32] Most of these cases are cancer in the residual rectal or anal transitional zone (ATZ) mucosa. Whether IPAA should be performed with removal of the ATZ by mucosectomy and handsewn anastomosis or retaining some ATZ with a stapled anastomosis has been debated. The benefits of a stapled anastomosis include better function and fewer operative complications. The stapled IPAA is also easier to survey, and ATZ adenomas may possibly be treated endoscopically or transanally. The benefit of a handsewn IPAA is a reduced incidence of postoperative ATZ adenomas, but this is achieved at the potential cost of worse function and more complications.[33] The largest series analyzing ATZ neoplasia includes 206 patients with a median follow-up of 10.3 years. The risk of adenoma at the IPAA at 10 years was 22% in the mucosectomy group and 51% after stapled IPAA. One patient developed cancer after mucosectomy, and no patient developed cancer after stapled IPAA.[34] Pooled data from 5 registries of 97 patients with at least 1 year of endoscopic follow-up compared 35 patients with stapled IPAA to 62 patients with mucosectomy.[35] The risk of developing a polyp at the IPAA after 7 years was 31% after stapled IPAA vs 10% after mucosectomy. No patient developed an ATZ cancer. A protocol for a Cochrane review on this topic was published in 2014, but the analysis has not been published to date.[36] Additional low-quality evidence from multiple studies provides conflicting conclusions about the role of mucosectomy in cancer prevention and functional implications. The evidence available, however, does not support routine mucosectomy if the residual rectal cuff is free of polyps and can be surveyed. Annual endoscopic surveillance of the remaining rectal and ATZ mucosa and ileal pouch must be performed. Total proctocolectomy with end ileostomy can be considered for patients with poor sphincter function, incontinence, distal rectal cancer, cancers requiring radiation, or the desire to avoid the functional limitations of an ileoanal pouch.

Although laparoscopic proctocolectomy has some potential advantages over conventional open technique, only 1 randomized trial has been reported (comparing hand-assisted to open, and including patients with ulcerative colitis and FAP), which showed comparable outcomes.[37] Multiple nonrandomized studies demonstrating the safety and feasibility of the laparoscopic approach suffer from selection bias and are not adequate to conclude that 1 technique is superior. A Cochrane review on this topic demonstrated no significant differences in morbidity, recovery, or complications, but reported that cosmesis was better with the laparoscopic approach.[38]

2. **Total colectomy with ileorectal anastomosis (TAC-IRA) can be offered to patients with relative rectal sparing if all rectal adenomas >5 mm can be endoscopically removed. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

Before restorative proctocolectomy was available, patients typically underwent total colectomy with ileorectal anastomosis and accepted a risk of rectal cancer to avoid an ileostomy. Since restorative proctocolectomy has become widely available, the decision whether or not to retain the rectum is made based on functional considerations and on polyposis phenotype that includes rectal sparing.[1,39,40] Studies of rectal cancer risk in FAP after TAC-IRA should be viewed with caution if they include patients who had their operation before the availability of restorative proctocolectomy. Population-based data from 4 European centers evaluated 776 patients who had IRA, including 576 before the ileoanal pouch era, and 200 after the ileoanal pouch became available in these centers.[41] The cumulative risk of rectal cancer by Kaplan-Meier analysis was 10% in the prepouch era vs 2% in the pouch era. The most frequently used criteria to offer an ileorectal anastomosis is rectal polyp burden. A cohort study from Church et al[42] of 213 patients with FAP included 165 patients who had rectal-sparing surgery, with 128 of these having fewer than 20 polyps and 37 having greater than 20 polyps. The rectal cancer incidence was 1.6% in the patients with <20 polyps, compared with 10.8% in the patients with >20 polyps. A cohort study from the Singapore Polyposis Registry reported that recurrence- and disease-free survival was not different with selective use of ileorectal anastomosis after 98 months of follow-up. It is unlikely that a study will be done comparing functional and oncologic outcomes of IRA vs IPAA, because most individuals who are eligible for IRA would prefer a rectal-sparing procedure. Nevertheless, observational data support clear potential functional benefits of sparing the rectum, including decreased bowel frequency, decreased incontinence, decreased risk of urinary and sexual dysfunction, and the high chance of a single-stage operation and avoidance of an ileostomy. Using the current clinical criteria of rectal sparing, most frequently defined as fewer than 20 adenomas, ileorectal anastomosis has support from observational data. Annual surveillance of the rectum is required. Chemoprevention using celecoxib or sulindac can be considered, based on studies showing benefit in management of duodenal adenomas in this population (see below).

MYH-*Associated Polyposis*

1. **The diagnosis of MAP should be considered in patients presenting with colorectal polyposis (>20 lifetime adenomas). Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

MAP is an autosomal recessively inherited colorectal polyposis syndrome caused by biallelic germline mutations in the base-excision repair gene *MYH*, located on chromosome 1.[13] Because the autosomal recessive inheritance pattern requires that affected individuals have a biallelic mutation, both parents of affected individuals must be at least monoallelic carriers. If so, siblings of affected individuals have a 25% chance of biallelic mutations, and chil-

dren of affected individuals will be at least heterozygous carriers. It is not clear whether individuals with monoallelic mutations have a higher risk of colorectal neoplasia.[43,44] A multicenter European case-control study of cases matched with population controls identified a standardized incidence rate of colorectal cancer at 2.12.[45] Because the reported increases are around the same or lower than the increased risk reported for first-degree relatives of sporadic colorectal cancer, these individuals should be screened in the same way as people with one affected first-degree relative.

Population-based cohort studies provide the best estimate for the prevalence of monoallelic *MYH* mutations, thought to occur in 0.7% to 1% of the population.[44,46–49] The number of polyps may not correlate with the prevalence of biallelic *MYH* mutations as well as it does with *APC* mutations, making it difficult to recommend screening for MAP based on a specific number of polyps. Although many reports cite a threshold of 10 polyps as an indication for genetic testing, the National Comprehensive Cancer Network guidelines have moved to a threshold of 20 polyps.[2–6,13,47,50] While acknowledging the limited evidence supporting a specific polyp number cutoff, consideration for genetic testing for MAP should be given in most patients with >20 lifetime adenomas. Because most genetic testing today is done with multigene panels, patients who are screened for genetic causes of colonic polyposis syndromes will likely have *APC* and *MYH* evaluated at the initial genetic evaluation.

2. **Patients with biallelic *MYH* mutations need yearly colonoscopy and polypectomy, as long as the adenomas can be controlled endoscopically. Siblings or children of an affected individual need to be screened for the family mutations in *MYH*. Those who have not been tested should undergo colonoscopy every 2 years, starting at age 20. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.**

In general, the colorectal MAP phenotype resembles that of attenuated FAP, but individuals with biallelic mutations may present with an apparently sporadic cancer, as a cancer at a young age, or even mimicking Lynch syndrome. The average age of colorectal cancer in patients with MAP is 47 years (age range, 29–72 years).[51–55] Colorectal cancer due to biallelic *MYH* mutations before the age of 30 is rare, and, because of lower polyp numbers, maintaining endoscopic clearance of polyps is possible in some patients. Rectal cancer is uncommon in MAP; a population-based study of 9268 patients with colorectal cancer identified 27 patients with biallelic *MYH* mutations who had a lower-than-expected rate of rectal cancer when compared with sporadic cases.[56] A registry-based cohort study from the Netherlands demonstrated that 62% of MAP-associated cancers occurred proximal to the splenic flexure.[52] Because of an accelerated adenoma-to-carcinoma progression in patients with MAP, patients with proven biallelic *MYH* mutations and siblings who have not been tested should have colonoscopy every year starting at age 20.[52] Flexible sigmoidoscopy is not acceptable for screening because of the frequency of proximal colon cancer.

3. **Timing and type of surgery in patients with a biallelic *MYH* mutation depend on the ability to maintain clearance of polyps, the rectal polyp count, and the presence of malignancy. Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.**

The lifetime risk of developing colorectal cancer in the setting of biallelic *MYH* mutation is poorly defined, but a population-based study estimated a 28-fold increased risk of colorectal cancer over the general population with an estimated penetrance (occurrence of colorectal cancer) of 19% by age 50, 43% by age 60, and 80% by age 80.[56] There are inadequate data to recommend a specific operation for all patients, and the MAP phenotype varies so much that defining a standard operation is inappropriate. A retrospective review combining 2 familial cancer registries identified 14 patients. One had a proctocolectomy for severe polyposis, 2 had proctocolectomies for rectal cancer and polyposis, and 11 had a total colectomy with ileorectal anastomosis. All patients were followed with annual proctoscopy with no loss to follow-up over a median surveillance of 5 years (range, 2–23 years), and no patient developed rectal cancer. Although polyps were frequently found, with an average of 1.52 adenomas per year per patient, they were all successfully managed with endoscopic resection. Colorectal cancer should be treated in accordance with oncologic principles, with more extensive resections for the purpose of prophylaxis made on a case-by-case basis. Patients with MAP and rectal sparing can be offered colectomy with ileorectal anastomosis.[57,58] Given the typically high polyp burden, long-term endoscopic management of the whole colon, in general, is not successful, but may be considered in selected cases with a low polyp burden.[59]

Extraintestinal Manifestations

Screening for Duodenal Neoplasia

1. **Screening for duodenal adenomas in individuals with FAP and AFAP should begin with a baseline esophagogastroduodenoscopy beginning at age 20 to 25, with subsequent examinations at intervals based on the endoscopic findings. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.**

Three prospective and multiple retrospective studies support screening of the duodenum to detect duodenal polyposis.[60–62] A prospective multinational European study of 368 patients with FAP screened with biannual upper endoscopy showed that the cumulative incidence of duodenal adenoma by age 70 was 90%, and the cumulative incidence of duodenal cancer was 4.5%.[60] Although this is 100 to 300 times higher than in the general population, the low absolute incidence and the prolonged time from adenoma to carcinoma make it hard to design a study that would show a reduction in cancer incidence based on endoscopic screening. Duodenal cancer is rare before the age of 30 and, in the absence of symptoms, screening can begin at age 20 to 25. The Spigelman classification stratifies the risk of developing cancer based on the polyp number, polyp size, histology, and degree of dysplasia (Tables 2 and 3).[63] While surveillance with selective polypectomy/ampullectomy has been shown to decrease the Spigelman score, the ability of endoscopic polypectomy to prevent cancer has been questioned. A cohort of 114 patients who were prospectively managed and followed for 10 years demonstrated that 6 of 114 (5.2%) developed cancer, but in patients with the most advanced polyps (Spigelman IV), 4 of 11 (38%) of patients developed cancer This suggests that endoscopic management may only be appropriate for Spigelman I to III disease, and that duodenectomy should be considered for patients with Spigelman IV disease.[64] A cohort of patients with FAP in an endoscopic surveillance program in Toronto showed that, with a prospectively defined endoscopic management strategy, progression to cancer was slow, averaging 15 years after the initial endoscopy, and only occurred in 5 of 167 (3%) of patients.[65] Although screening is therefore appropriate for early diagnosis and to slow the progression of disease, it remains unclear if endoscopic prevention of all duodenal cancers is possible. The optimal age to start screening is based on consensus opinion, and the appropriate interval for endoscopy should be based on findings at the initial upper GI esophagogastroduodenoscopy (EGD). The strategy reported by Soravia et al[66] does not use the Spigelman classification but has been evaluated with subsequent reported follow-up. Available evidence supports EGD every 5 years after a normal examination, every 2 to 3 years for Spigelman I, every 1 to 2 years for Spigelman stage II, and every 6 to 12 months for Spigelman stage III. Spigelman stage IV patients should be managed by a multidisciplinary team with individualized decision making regarding ongoing endoscopic surveillance or surgical resection.

Screening for Thyroid Disease

1. **Screening for thyroid disease should be considered in patients with FAP with an annual ultrasound preferred over physical examination alone, especially for women. Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.**

TABLE 2. Spiegelman stage: duodenal adenomatosis staging system

Polyps	*1 Point*	*2 Points*	*3 Points*
Number	<4	5–20	>20
Size	0–4 mm	5–10 mm	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Thyroid cancer occurs in 1% to 2% of the FAP population, compared with 0.2% in the general population, with the majority of cases occurring in women.[67–73] There are no prospective studies comparing the screening strategies of physical examination or ultrasound. Results of universal screening of 192 patients with FAP included in a registry showed that 72 (38%) had a thyroid nodule and 5 (2.6%) had thyroid cancer.[74] A subsequent study comparing patients with screen-detected cancers with those with incident cancers showed that screening led to detection of smaller tumors with fewer positive lymph nodes.[75] In another report, universal screening of 50 patients who underwent ultrasound led to 7 (14%) patients having an fine-needle aspiration and 2 (4%) being diagnosed with papillary thyroid cancer.[76] Based on the increased risk of thyroid cancer, screening should be considered and discussed with patients, especially women. Additional data are needed to define the age screening should start and the optimal interval for screening.

Extracolonic Manifestations of MAP

1. **Upper GI endoscopy is recommended for patients beginning at age 30, with subsequent examinations at intervals based on the endoscopic findings. Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.**

Extracolonic manifestations of MAP include the risk of duodenal and other intestinal cancers as well as extraintestinal neoplasia. A multicenter registry-based cohort of European centers, including 276 patients from 181 fami-

TABLE 3. Spigelman stage: recommended duodenal surveillance frequency

Spigelman stage	*Total points*	*Frequency of surveillance*
0	0	Every 4 y
I	≤4	Every 2–3 y
II	5–6	Every 1–3 y
III	7–8	Every 6–12 y
IV	9–12	Expert surveillance every 3–6 mo Surgical evaluation Complete mucosectomy or duodenectomy or Whipple procedure if duodenal papilla is involved

lies, identified the prevalence of duodenal polyps at 17% and a lifetime risk of duodenal cancer of 4%. The observed frequency of duodenal adenomas is much lower than that observed in FAP, but greater than the general population. Upper GI endoscopy including visualization of the duodenum and ampulla (with visualization improved by using a side-viewing endoscope) is recommended starting at age 30.[2,3] The interval between surveillance examinations depends on the number of duodenal adenomas as well as adenoma characteristics including size, histology, and the degree of dysplasia (Spigelman classification) (Tables 2 and 3).[63] The use of the Spigelman criteria is extrapolated from FAP; it was not developed from MAP patients. Although there may be an increased incidence of ovarian, bladder, and skin cancer, insufficient data are available to support specific screening for these malignancies.

Surgery for Intra-abdominal Desmoid Tumors

1. **Surgery for intra-abdominal desmoid tumors, in general, is not recommended and should typically be reserved for small, well-defined tumors when a clear margin can be obtained. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.**

Desmoid tumors are histologically benign but potentially locally aggressive growths that affect about 15% of patients with FAP. Abdominal wall desmoids need to be considered separately from mesenteric and intra-abdominal desmoids.

In contrast to desmoids found in other populations, FAP-associated desmoids tend to be intra-abdominal, involve the small-bowel mesentery, and occur after surgery. The relationship of colectomy and desmoids is a key part of the decision regarding the timing and type of colonic operation to be done.

Church et al[77,78] proposed a desmoid-staging system based on symptoms with a subsequent report noting that the staging was predictive of the need for treatment and mortality (Table 4). Multiple single-center retrospective reports have attempted to define the role of surgery, but the lack of standardization and treatment bias limit the generalizability of the results. Even in selected patients, however, recurrence rates are high, and the overall benefit of resection is not clear.[79] Nearly all studies are retrospective and many include both FAP-related desmoid disease and non-FAP-related desmoids. A prospective cohort study of 64 patients with FAP who have intra-abdominal desmoids treated with high-dose selective estrogen receptor modulators and sulindac demonstrated regression in 85% of patients with no progression or treatment failures requiring surgery.[80] At this time, insufficient data exist to recommend a specific treatment modality for desmoids, but surgical therapy has a very limited role that should typically be confined to small, well-defined tumors where a clear margin can be obtained.

Chemoprevention of Adenomas

1. **Individuals with FAP, AFAP, or MAP with any retained rectum or established duodenal adenomas should be considered for chemoprevention with either sulindac or celecoxib after an individualized risk/benefit assessment. Grade of Recommendation: Weak recommendation based on high-quality evidence, 2A.**

Most patients are eligible for chemoprevention because proctocolectomy with IPAA or a colectomy with ileorectal anastomosis can retain at-risk rectal mucosa, and the duodenal mucosa remains at risk in all these patients. It should be noted that although no drug, including those described here, is approved by the Food and Drug Administration for the indication of chemoprevention, several drugs have been studied in over a dozen randomized controlled trials and in many observational studies (Table 5).[81–96] Of 4 trials examining the use of sulindac, 3 reported positive findings.[81–84] The negative trial was a primary prevention trial in patients who were phenotypically unaffected but had *APC* mutations. These findings may not be applicable to the postoperative population of patients with a highly penetrant polyposis phenotype.[84] One trial evaluating dual treatment with sulindac and erlotinib for duodenal polyp suppression was stopped early because of the superiority of the chemoprevention over placebo, although there was a high rate of grade 1 and 2 adverse events, including an acne-like rash in 87% of treated patients.[85] Of 7 trials examining the role of selective cyclooxygenase-2 inhibition, 6 reported positive results.[86–92] An international randomized controlled trial of celecoxib and difluoromethylornithine showed that the addition of difluoromethylornithine was required to achieve a benefit in reduction of adenoma

TABLE 4. Desmoid tumor staging system

Stage	*Symptoms*	*Size*	*Growth rate*
I	Asymptomatic	<10 cm maximum diameter	None
II	Mild	<10 cm maximum diameter	None
III	Moderate, or with bowel/ureteric obstruction	10 or 20 cm	Slow
IV	Severe	>20 cm	Rapid

Quality of symptoms are defined as: mild, no restrictions, pain, and a sensation of mass; moderate, restrictions, but no hospitalization, pain, and a sensation of mass; and severe, restrictions and hospitalization, pain, and a sensation of mass.
Adapted from Church et al. Staging intra-abdominal desmoid tumors in familial adenomatous polyposis: a search for a uniform approach to a troubling disease. *Dis Colon Rectum*. 2005;48:1528–1534.[77]

TABLE 5. Randomized controlled trials examining the chemoprevention strategies for polyp suppression

Group	*Design*	*N*	*Patients*	*Drug*	*Outcome*	*Polyp size*	*Polyp number*	*Side effects*
Sulindac								
Labayle et al 1991[82]	RPCDB	10	FAP	Sulindac (300 mg/day)	Rectal polyp number	–	Decrease (9/10 people)	None
Giardiello et al 1993[81]	RPCDB	22	FAP	Sulindac (300 mg/day)	Colorectal polyp number and size	Decrease (44%)	Decrease (35%)	None
Nugent et al 1993[83]	RCT	24	FAP	Sulindac (400 mg/day)	Duodenal and rectal polyp number and proliferation	–	Decrease	Indigestion
Giardiello et al 2002[84]	RPCDB	41	FAP (phenotypically negative)	Sulindac (150–300 mg/day)	Adenoma development, number, and size	No significant change ($p = 0.17$)	No significant change ($p = 0.69$)	None
Samadder et al 2016[85]	RPCDB	92	FAP	Sulindac (300 mg/day) + erlotinib (75 mg/day)	Duodenal polyp number and size	Decrease (by 8.5 mm)	Decrease (37.9%)	Rash
COX-2 selective inhibitors								
Steinbach et al 2000[86]	RDBPC	77	FAP	Celecoxib (200 or 800 mg/day)	Colorectal polyp number and size	Decrease (28%)	Decrease (30.7%)	Diarrhea, abdominal pain
Phillips et al 2002[92]	RPCDB	83	FAP	Celecoxib (200 mg/day) vs celecoxib (800 mg/day)	Duodenal polyp burden	-	Decrease with CXB 800 mg/day (14.5%)	None
Lynch et al 2010[87]	Phase I trial	18	FAP (children)	Celecoxib (4–16 mg/kg/day)	Colorectal polyp number	-	Decrease (44.2%)	None
Lynch et al 2016[91]	RCT	112	FAP	Celecoxib (800 mg/day) vs celecoxib + DFMO (0.5 g/m^2/day)	Colorectal polyp number and size	Decrease with CXB + DFMO (40%)	Decrease with CXB + DFMO (13%)	None
Hallak et al 2003[90]	Phase I trial	8	FAP	Rofecoxib (25 mg/day)	Colorectal polyp number	–	Decrease ($p = 0.008$)	None
Higuchi et al 2003[88]	RPCDB	21	FAP	Rofecoxib (25 mg/day)	Rectal polyp number and size	Decrease (16.2%)	Decrease (6.8%)	Stomatitis, abdominal pain
Iwama et al 2006[89]	RPCDB	61	FAP	Tiracoxib (150–200 mg/day)	Colorectal polyp number and size	No change (0%)	No change (0%)	None
Others								
Bussey et al 1982[94]	RDB	49	FAP	Ascorbic acid (3 g/day)	Rectal polyp number and size	Decrease (trend)	Decrease ($p < 0.03$)	None
DeCosse et al 1989[95]	RPCDB	58	FAP	Vit C (2 g/day) + Vit E (400 mg/day) ± wheat fiber (22.5 g/day)	Rectal polyp number and size	No change	No change	None
Thomas et al 1993[96]	RPCDB	25	FAP	Calcium (1500 mg/day)	Rectal polyp number and size	No change	No change	None
West et al 2010[93]	RPCDB	55	FAP	EPA (2 g/day)	Rectal polyp number and size	Decrease (29.8%)	Decrease (22.4%)	None

CXB = celecoxib; COX-2, cyclooxygenase-2; DFMO = difluoromethylornithine; EPA = eicosapentaenoic acid; FAP = familial adenomatosis polyposis; RCT = randomized controlled trial; RDB = randomized double blind; RPCDV = randomized prospective controlled double blind; Vit = vitamin.

count when compared with placebo.[91] Another trial examined eicosapentaenoic acid with positive results.[93] Three studies have examined vitamin C, vitamin E, calcium, or a combination, with mixed but overall negative results.[94–96]

Substantial evidence supports the use of chemoprevention in patients who have polyposis with duodenal adenomas or at-risk rectal mucosa. Sulindac has a higher rate of gastritis than celecoxib; in patients over age 65, or who have a history of a peptic ulcer, or who require concurrent use of aspirin, corticosteroids, or anticoagulants for other medical problems, sulindac should usually be given with a proton-pump inhibitor.[97,98] The risk of adverse events or GI bleeding, as well as issues with compliance, cost, or patient preference, however, may preclude the use of chemoprevention in all or even many cases. It is important to note that chemoprevention should not replace routine endoscopic surveillance, that the role of chemoprevention for the suppression of polyps in the retained rectum is extrapolated from the duodenal adenoma studies, and that compliance with long-term treatment has not been well studied.

Surveillance and Treatment of Polyposis Without an Identified Gene Mutation

1. Patients with clinical polyposis, but without an identified mutation, should be treated and followed based on their phenotype. Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.

Between 20% and 50% of patients with oligopolyposis will not have a mutation found in the *APC* or *MYH* genes.[13,99–101] Multiple case series have identified alterations that are not included in existing commercial testing that may play a role in polyposis, such as genomic rearrangements involving *APC*, *APC* mosaicism, and mutations in the *APC* promoter.[102–104] Other patients may harbor rare or as yet unknown causes of polyposis, such as the recently described polymerase proofreading-associated polyposis.[105]

Management of patients with mutation-negative polyposis has been described in observational studies. Tieu et al[100] described 27 patients with multiple colorectal adenomas with a phenotype similar to attenuated polyposis with an average of 51 polyps. Eighteen patients (67%) underwent colectomy after a mean of 3.1 years after diagnosis due to the concern for cancer or for an inability to provide endoscopic clearance. Extracolonic findings in these patients may mirror attenuated polyposis syndromes as EGD-identified polyps in 47% of patients. A second observational study of patients with *APC* mutation-negative polyposis, however, showed they were less likely to display extracolonic manifestations.[106] In the absence of a genetic defect, it is reasonable to treat patients according to their phenotype by maintaining endoscopic clearance in patients when possible and proceeding with colectomy or proctocolectomy if required according to the polyp number.

REFERENCES

1. Church J, Simmang C; Standards Task Force; American Society of Colon and Rectal Surgeons; Collaborative Group of the Americas on Inherited Colorectal Cancer and the Standards Committee of The American Society of Colon and Rectal Surgeons. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer). *Dis Colon Rectum*. 2003;46:1001–1012.
2. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110:223–263.
3. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. V2. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp- Fort Washington, PA, 2016. Accessed October, 14, 2016.
4. Balmaña J, Balaguer F, Cervantes A, Arnold D; ESMO Guidelines Working Group. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2013;24(suppl 6):vi73–vi80.
5. Stoffel EM, Mangu PB, Limburg PJ; American Society of Clinical Oncology; European Society for Medical Oncology. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. *J Oncol Pract*. 2015;11:e437–e441.
6. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129:174–181.
7. Bussey HJ, Veale AM, Morson BC. Genetics of gastrointestinal polyposis. *Gastroenterology*. 1978;74:1325–1330.
8. Kinzler KW, Nilbert MC, Su LK, et al. Identification of FAP locus genes from chromosome 5q21. *Science*. 1991;253:661–665.
9. Bisgaard ML, Fenger K, Bülow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat*. 1994;3:121–125.
10. Giardiello FM, Brensinger JD, Luce MC, et al. Phenotypic expression of disease in families that have mutations in the 5' region of the adenomatous polyposis coli gene. *Ann Intern Med*. 1997;126:514–519.
11. Lynch HT, Smyrk T, McGinn T, et al. Attenuated familial adenomatous polyposis (AFAP). A phenotypically and genotypically distinctive variant of FAP. *Cancer*. 1995;76:2427–2433.
12. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C–>T:A mutations in colorectal tumors. *Nat Genet*. 2002;30:227–232.
13. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. *JAMA*. 2012;308:485–492.
14. Knudsen AL, Bisgaard ML, Bülow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. *Fam Cancer*. 2003;2:43–55.
15. Nielsen M, Hes FJ, Nagengast FM, et al. Germline mutations in APC and MUTYH are responsible for the majority of families with attenuated familial adenomatous polyposis. *Clin Genet*. 2007;71:427–433.

16. Knudsen AL, Bülow S, Tomlinson I, Möslein G, Heinimann K, Christensen IJ; AFAP Study Group. Attenuated familial adenomatous polyposis: results from an international collaborative study. *Colorectal Dis*. 2010;12(10 online):e243–e249.
17. Geller G, Botkin JR, Green MJ, et al. Genetic testing for susceptibility to adult-onset cancer. The process and content of informed consent. *JAMA*. 1997;277:1467–1474.
18. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2012;21:151–161.
19. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. *J Clin Oncol*. 1996;14:1730–1740.
20. Murff HJ, Byrne D, Syngal S. Cancer risk assessment: quality and impact of the family history interview. *Am J Prev Med*. 2004;27:239–245.
21. Aretz S, Uhlhaas S, Caspari R, et al. Frequency and parental origin of de novo APC mutations in familial adenomatous polyposis. *Eur J Hum Genet*. 2004;12:52–58.
22. Barrow P, Khan M, Lalloo F, Evans DG, Hill J. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. *Br J Surg*. 2013;100:1719–1731.
23. Warrier SK, Kalady MF, Kiran RP, Church JM. Results from an American Society of Colon and Rectal Surgeons survey on the management of young-onset colorectal cancer. *Tech Coloproctol*. 2014;18:265–272.
24. Nieuwenhuis MH, Mathus-Vliegen LM, Slors FJ, et al. Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis. *Clin Gastroenterol Hepatol*. 2007;5:374–378.
25. Church JM, McGannon E, Burke C, Clark B. Teenagers with familial adenomatous polyposis: what is their risk for colorectal cancer? *Dis Colon Rectum*. 2002;45:887–889.
26. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer*. 1975;36:2251–2270.
27. Burt RW, Leppert MF, Slattery ML, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. *Gastroenterology*. 2004;127:444–451.
28. National Comprehensive Cancer Network. Colorectal Cancer Screening Version 2. 2016. https://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf - Fort Washington, PA, 2016. Accessed October 14, 2016.
29. Aziz O, Athanasiou T, Fazio VW, et al. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. *Br J Surg*. 2006;93:407–417.
30. Tajika M, Niwa Y, Bhatia V, Tanaka T, Ishihara M, Yamao K. Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis. *World J Gastroenterol*. 2013;19:6774–6783.
31. Smith JC, Schäffer MW, Ballard BR, et al. Adenocarcinomas after prophylactic surgery for familial adenomatous polyposis. *J Cancer Ther*. 2013;4:260–270.
32. Boostrom SY, Mathis KL, Pendlimari R, Cima RR, Larson DW, Dozois EJ. Risk of neoplastic change in ileal pouches in familial adenomatous polyposis. *J Gastrointest Surg*. 2013;17:1804–1808.
33. Remzi FH, Church JM, Bast J, et al. 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.
34. von Roon AC, Will OC, Man RF, et al. Mucosectomy with handsewn anastomosis reduces the risk of adenoma formation in the anorectal segment after restorative proctocolectomy for familial adenomatous polyposis. *Ann Surg*. 2011;253:314–317.
35. van Duijvendijk P, Vasen HF, Bertario L, et al. Cumulative risk of developing polyps or malignancy at the ileal pouch-anal anastomosis in patients with familial adenomatous polyposis. *J Gastrointest Surg*. 1999;3:325–330.
36. Cirocchi R, Morelli U, Arezzo A, et al. Double-stapled anastomosis versus mucosectomy and handsewn anastomosis in ileal pouch-anal anastomosis for ulcerative colitis or familial adenomatous polyposis.. *Cochrane Database Sys Rev*. 2004;CD011089.
37. Maartense S, Dunker MS, Slors JF, et al. Hand-assisted laparoscopic versus open restorative proctocolectomy with ileal pouch anal anastomosis: a randomized trial. *Ann Surg*. 2004;240:984–991.
38. Ahmed Ali U, Keus F, Heikens JT, et al. Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. *Cochrane Database Syst Rev*. 2009;CD006267.
39. Koskenvuo L, Mustonen H, Renkonen-Sinisalo L, Järvinen HJ, Lepistö A. Comparison of proctocolectomy and ileal pouch-anal anastomosis to colectomy and ileorectal anastomosis in familial adenomatous polyposis. *Fam Cancer*. 2015;14:221–227.
40. Church J, Burke C, McGannon E, Pastean O, Clark B. Risk of rectal cancer in patients after colectomy and ileorectal anastomosis for familial adenomatous polyposis: a function of available surgical options. *Dis Colon Rectum*. 2003;46:1175–1181.
41. Bülow S, Bülow C, Vasen H, Järvinen H, Björk J, Christensen IJ. Colectomy and ileorectal anastomosis is still an option for selected patients with familial adenomatous polyposis. *Dis Colon Rectum*. 2008;51:1318–1323.
42. Church J, Burke C, McGannon E, Pastean O, Clark B. Predicting polyposis severity by proctoscopy: how reliable is it? *Dis Colon Rectum*. 2001;44:1249–1254.
43. Win AK, Hopper JL, Jenkins MA. Association between monoallelic MUTYH mutation and colorectal cancer risk: a meta-regression analysis. *Fam Cancer*. 2011;10:1–9.
44. Croitoru ME, Cleary SP, Di Nicola N, et al. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. *J Natl Cancer Inst*. 2004;96:1631–1634.
45. Jones N, Vogt S, Nielsen M, et al. Increased colorectal cancer incidence in obligate carriers of heterozygous mutations in MUTYH. *Gastroenterology*. 2009;137:489–94, 494.e1.
46. Kastrinos F, Syngal S. Inherited colorectal cancer syndromes. *Cancer J*. 2011;17:405–415.
47. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. *N Engl J Med*. 2003;348:791–799.
48. Fleischmann C, Peto J, Cheadle J, Shah B, Sampson J, Houlston RS. Comprehensive analysis of the contribution of germline MYH variation to early-onset colorectal cancer. *Int J Cancer*. 2004;109:554–558.
49. Cleary SP, Cotterchio M, Jenkins MA, et al. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. *Gastroenterology*. 2009;136:1251–1260.

50. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL; Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015;17:70–87.
51. Leite JS, Isidro G, Martins M, et al. Is prophylactic colectomy indicated in patients with MYH-associated polyposis? *Colorectal Dis*. 2005;7:327–331.
52. Nielsen M, Franken PF, Reinards TH, et al. Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). *J Med Genet*. 2005;42:e54.
53. Nieuwenhuis MH, Vogt S, Jones N, et al. Evidence for accelerated colorectal adenoma–carcinoma progression in MUTYH-associated polyposis? *Gut*. 2012;61:734–738.
54. Lipton L, Halford SE, Johnson V, et al. Carcinogenesis in MYH-associated polyposis follows a distinct genetic pathway. *Cancer Res*. 2003;63:7595–7599.
55. Sampson JR, Dolwani S, Jones S, et al. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. *Lancet*. 2003;362:39–41.
56. Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. *J Clin Oncol*. 2009;27:3975–3980.
57. Valanzano R, Ficari F, Curia MC, et al. Balance between endoscopic and genetic information in the choice of ileorectal anastomosis for familial adenomatous polyposis. *J Surg Oncol*. 2007;95:28–33.
58. Nascimbeni R, Pucciarelli S, Di Lorenzo D, et al. Rectum-sparing surgery may be appropriate for biallelic MutYH-associated polyposis. *Dis Colon Rectum*. 2010;53:1670–1675.
59. Liang J, Church JM. Rectal cancers in patients with familial adenomatous polyposis. *Fam Cancer*. 2013;12:749–754.
60. Bülow S, Björk J, Christensen IJ, et al; DAF Study Group. Duodenal adenomatosis in familial adenomatous polyposis. *Gut*. 2004;53:381–386.
61. Cordero-Fernández C, Garzón-Benavides M, Pizarro-Moreno A, et al. Gastroduodenal involvement in patients with familial adenomatous polyposis. Prospective study of the nature and evolution of polyps: evaluation of the treatment and surveillance methods applied. *Eur J Gastroenterol Hepatol*. 2009;21:1161–1167.
62. Saurin JC, Gutknecht C, Napoleon B, et al. Surveillance of duodenal adenomas in familial adenomatous polyposis reveals high cumulative risk of advanced disease. *J Clin Oncol*. 2004;22:493–498.
63. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet*. 1989;2:783–785.
64. Groves CJ, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. *Gut*. 2002;50:636–641.
65. Serrano PE, Grant RC, Berk TC, et al. Progression and management of duodenal neoplasia in familial adenomatous polyposis: a cohort study. *Ann Surg*. 2015;261:1138–1144.
66. Soravia C, Berk T, Haber G, Cohen Z, Gallinger S. Management of advanced duodenal polyposis in familial adenomatous polyposis. *J Gastrointest Surg*. 1997;1:474–478.
67. Bülow C, Bülow S. Is screening for thyroid carcinoma indicated in familial adenomatous polyposis? The Leeds Castle Polyposis Group. *Int J Colorectal Dis*. 1997;12:240–242.
68. Bülow S, Holm NV, Mellemgaard A. Papillary thyroid carcinoma in Danish patients with familial adenomatous polyposis. *Int J Colorectal Dis*. 1988;3:29–31.
69. van der Linde K, Vasen HF, van Vliet AC. Occurrence of thyroid carcinoma in Dutch patients with familial adenomatous polyposis. An epidemiological study and report of new cases. *Eur J Gastroenterol Hepatol*. 1998;10:777–781.
70. Truta B, Allen BA, Conrad PG, et al. Genotype and phenotype of patients with both familial adenomatous polyposis and thyroid carcinoma. *Fam Cancer*. 2003;2:95–99.
71. Giardiello FM, Offerhaus GJ, Lee DH, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. *Gut*. 1993;34:1394–1396.
72. Plail RO, Bussey HJ, Glazer G, Thomson JP. Adenomatous polyposis: an association with carcinoma of the thyroid. *Br J Surg*. 1987;74:377–380.
73. Herraiz M, Barbesino G, Faquin W, et al. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. *Clin Gastroenterol Hepatol*. 2007;5:367–373.
74. Jarrar AM, Milas M, Mitchell J, et al. Screening for thyroid cancer in patients with familial adenomatous polyposis. *Ann Surg*. 2011;253:515–521.
75. Feng X, Milas M, O'Malley M, et al. Characteristics of benign and malignant thyroid disease in familial adenomatous polyposis patients and recommendations for disease surveillance. *Thyroid*. 2015;25:325–332.
76. Steinhagen E, Hui VW, Levy RA, et al. Results of a prospective thyroid ultrasound screening program in adenomatous polyposis patients. *Am J Surg*. 2014;208:764–769.
77. Church J, Berk T, Boman BM, et al; Collaborative Group of the Americas on Inherited Colorectal Cancer. Staging intra-abdominal desmoid tumors in familial adenomatous polyposis: a search for a uniform approach to a troubling disease. *Dis Colon Rectum*. 2005;48:1528–1534.
78. Church J, Lynch C, Neary P, LaGuardia L, Elayi E. A desmoid tumor-staging system separates patients with intra-abdominal, familial adenomatous polyposis-associated desmoid disease by behavior and prognosis. *Dis Colon Rectum*. 2008;51:897–901.
79. Berk T, Cohen Z, McLeod RS, Stern HS. Management of mesenteric desmoid tumours in familial adenomatous polyposis. *Can J Surg*. 1992;35:393–395.
80. Quast DR, Schneider R, Burdzik E, Hoppe S, Möslein G. Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: a single-center long-term observational study in 134 patients. *Fam Cancer*. 2016;15:31–40.
81. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med*. 1993;328:1313–1316.
82. Labayle D, Fischer D, Vielh P, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology*. 1991;101:635–639.
83. Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK. Randomized controlled trial of the effect of sulindac

on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg*. 1993;80:1618–1619.
84. Giardiello FM, Yang VW, Hylind LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med*. 2002;346:1054–1059.
85. Samadder NJ, Neklason DW, Boucher KM, et al. Effect of sulindac and erlotinib vs placebo on duodenal neoplasia in familial adenomatous polyposis: a randomized clinical trial. *JAMA*. 2016;315:1266–1275.
86. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med*. 2000;342:1946–1952.
87. Lynch PM, Ayers GD, Hawk E, et al. The safety and efficacy of celecoxib in children with familial adenomatous polyposis. *Am J Gastroenterol*. 2010;105:1437–1443.
88. Higuchi T, Iwama T, Yoshinaga K, Toyooka M, Taketo MM, Sugihara K. A randomized, double-blind, placebo-controlled trial of the effects of rofecoxib, a selective cyclooxygenase-2 inhibitor, on rectal polyps in familial adenomatous polyposis patients. *Clin Cancer Res*. 2003;9:4756–4760.
89. Iwama T, Akasu T, Utsunomiya J, Muto T. Does a selective cyclooxygenase-2 inhibitor (tiracoxib) induce clinically sufficient suppression of adenomas in patients with familial adenomatous polyposis? A randomized double-blind placebo-controlled clinical trial. *Int J Clin Oncol*. 2006;11:133–139.
90. Hallak A, Alon-Baron L, Shamir R, et al. Rofecoxib reduces polyp recurrence in familial polyposis. *Dig Dis Sci*. 2003;48:1998–2002.
91. Lynch PM, Burke CA, Phillips R, et al. An international randomised trial of celecoxib versus celecoxib plus difluoromethylornithine in patients with familial adenomatous polyposis. *Gut*. 2016;65:286–295.
92. Phillips RK, Wallace MH, Lynch PM, et al; FAP Study Group. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut*. 2002;50:857–860.
93. West NJ, Clark SK, Phillips RK, et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut*. 2010;59:918–925.
94. Bussey HJ, DeCosse JJ, Deschner EE, et al. A randomized trial of ascorbic acid in polyposis coli. *Cancer*. 1982;50:1434–1439.
95. DeCosse JJ, Miller HH, Lesser ML. Effect of wheat fiber and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. *J Natl Cancer Inst*. 1989;81:1290–1297.
96. Thomas MG, Thomson JP, Williamson RC. Oral calcium inhibits rectal epithelial proliferation in familial adenomatous polyposis. *Br J Surg*. 1993;80:499–501.
97. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104:728–738.
98. Rostom A, Muir K, Dubé C, et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. *Clin Gastroenterol Hepatol*. 2007;5:818–28, 828.e1.
99. Filipe B, Baltazar C, Albuquerque C, et al. APC or MUTYH mutations account for the majority of clinically well-characterized families with FAP and AFAP phenotype and patients with more than 30 adenomas. *Clin Genet*. 2009;76:242–255.
100. Tieu AH, Edelstein D, Axilbund J, et al. Clinical characteristics of multiple colorectal adenoma patients without germline APC or MYH Mutations. *J Clin Gastroenterol*. 2016;50:584–588.
101. Castellsagué E, González S, Guinó E, et al. Allele-specific expression of APC in adenomatous polyposis families. *Gastroenterology*. 2010;139:439–47, 447.e1.
102. Heinimann K, Thompson A, Locher A, et al. Nontruncating APC germ-line mutations and mismatch repair deficiency play a minor role in APC mutation-negative polyposis. *Cancer Res*. 2001;61:7616–7622.
103. Yamaguchi K, Komura M, Yamaguchi R, et al. Detection of APC mosaicism by next-generation sequencing in an FAP patient. *J Hum Genet*. 2015;60:227–231.
104. Spier I, Drichel D, Kerick M, et al. Low-level APC mutational mosaicism is the underlying cause in a substantial fraction of unexplained colorectal adenomatous polyposis cases. *J Med Genet*. 2016;53:172–179.
105. Bellido F, Pineda M, Aiza G, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. *Genet Med*. 2016;18:325–332.
106. Giarola M, Stagi L, Presciuttini S, et al. Screening for mutations of the APC gene in 66 Italian familial adenomatous polyposis patients: evidence for phenotypic differences in cases with and without identified mutation. *Hum Mutat*. 1999;13:116–123.