American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy

Familial adenomatous polyposis (FAP) syndrome is a complex entity, which includes FAP, attenuated FAP, and MUTYH-associated polyposis. These patients are at significant risk for colorectal cancer and carry additional risks for extracolonic malignancies. In this guideline, we reviewed the most recent literature to formulate recommendations on the role of endoscopy in this patient population. Relevant clinical questions were how to identify high-risk individuals warranting genetic testing, when to start screening examinations, what are appropriate surveillance intervals, how to identify endoscopically high-risk features, and what is the role of chemoprevention. A systematic literature search from 2005 to 2018 was performed, in addition to the inclusion of seminal historical studies. Most studies were from worldwide registries, which have compiled years of data regarding the natural history and cancer risks in this cohort. Given that most studies were retrospective, recommendations were based on epidemiologic data and expert opinion. Management of colorectal polyps in FAP has not changed much in recent years, as colectomy in FAP is the standard of care. What is new, however, is the developing body of literature on the role of endoscopy in managing upper GI and small-bowel polyposis, as patients are living longer and improved endoscopic technologies have emerged. (Gastrointest Endosc 2020;91:963-82.)

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of death in both men and women in the United States.[1] Hereditary CRC because of mutations and defects in certain genes comprises roughly 5% of all CRC. Familial adenomatous polyposis (FAP) is a classic example of hereditary CRC, accounting for 1% to 2% of all CRCs. The risk of CRC is nearly 100% in classic FAP and nearly 70% in attenuated forms of FAP (AFAP), in addition to an increased risk for extraintestinal malignancies.[2] MUTYH-associated polyposis (MAP) is a related autosomal recessive condition with slightly lower risks of CRC and upper GI cancers. Given the substantial cancer risk, patients with these conditions are advised to receive intensive endoscopic surveillance and/or prophylactic surgery as part of their clinical management. The role of genetic counseling also becomes important in managing these patients and their family members.

The aim of this document is to provide evidence-based recommendations and clinical guidance in regard to the management of hereditary colorectal polyposis syndromes including FAP, AFAP, and MAP. We highlight the evidence supporting the use of endoscopy and potential chemoprevention strategies for the reduction of CRC and associated extracolonic malignancies. An insight into the best use of genetic counseling is discussed to provide busy clinicians tools to optimally manage this high-risk population.

METHODS

Overview

This document was prepared by a working group of the Standards of Practice committee of the American Society for Gastrointestinal Endoscopy (ASGE). It includes a systematic review of available literature along with guidelines

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2020.01.028

for the role of endoscopy in the management of FAP syndromes. After evidence synthesis, recommendations were drafted by the full panel during a face-to-face meeting on March 18, 2018 and approved by the Standards of Practice committee members and the ASGE Governing Board.

Panel composition and conflict of interest management

The panel was composed of 2 principal authors (J.Y., S.R.G.), a content expert (N.J.S.), a genetic counselor (C.K.), the committee chair (S.B.W.), and the members of the Standards of Practice committee. All panel members disclosed possible intellectual and financial conflicts of interest in concordance with ASGE policies (https://www.asge.org/docs/default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf).

Formulation of clinical questions

For all clinical topics, potentially relevant patient-important outcomes were identified a priori and rated from "not important" to "critical" through a consensus process. Relevant clinical topics were to identify high-risk individuals warranting genetic testing, when to start screening examinations, appropriate surveillance intervals, endoscopic identification of high-risk features and role of chemoprevention.

Literature search and study selection criteria

A systematic review of the literature was performed through the databases PubMed, EMBASE, Scopus, and Cochrane from January 2005 to May 2018 based on an update of the literature from the most recent European guideline addressing FAP.[3] A medical librarian (L.M.) conducted a comprehensive search using the following terms that were developed by the principal authors and content experts (J.Y., S.R.G., N.J.S.): familial adenomatous polyposis, adenomatous polyposis coli, colonoscopy, sigmoidoscopy, endoscopy, enteroscopy, capsule endoscopy, diagnosis, and therapy. Inclusion criteria were articles in the English language with the exclusion of animal studies, reviews, letters, editorials, and comments. Given the rarity of the disease, case reports were included. Seminal papers before 2005 were also included. Details of the search strategy are reported in Appendix 1 (available online at www.giejournal.org). Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa, USA), and duplicates were removed. The EndNote library was then uploaded into Covidence (www.covidence.org). The eligibility of each study was reviewed by 2 independent authors with resolution of any conflicts from the third author. One hundred seventy-two studies were identified. Most studies lacked a prospective design, and randomized controlled trials were limited to the use of chemoprevention, with none found in the endoscopic management of these conditions. The overall quality of evidence was low.

Certainty in evidence (quality of evidence)

The certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounders.

Considerations in the development of recommendations

During an in-person meeting, the panel developed recommendations based on certainty in the evidence, balance of benefits and harms of the compared management options, assumptions about the values and preferences associated with the decision along with available data on resource utilization, and cost-effectiveness. The final wording of the recommendations (including direction and strength), remarks, and qualifications were decided by consensus using criteria highlighted in Table 1[4] and were approved by all members of the panel. The strength of individual recommendations is based on the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as "we suggest…", whereas stronger recommendations are typically stated as "we recommend…".

FAP AND AFAP

Overview

FAP is an autosomal dominant disease characterized by the development of hundreds of colorectal adenomatous polyps that progress to CRC in nearly 100% of persons if left untreated (Fig. 1A-D). FAP is very rare, with a global prevalence of 1 in 10,000 live births.[5-7] FAP is the second most common hereditary monogenic CRC syndrome and accounts for approximately 1% of all CRCs. FAP classically presents in early adolescence with rectal bleeding or other nonspecific GI symptoms, and without intervention nearly 100% will develop CRC. In addition, there is a lower risk for extracolonic cancers including that of stomach, duodenum, thyroid, hepatoblastoma, osteomas, pancreas, and desmoid tumors (Table 2).[8]

AFAP is a less severe form of the disease. It is characterized by later onset of adenomas, fewer adenomas (0-100 colon adenomatous polyps with an average of 30), a lower lifetime risk of CRC (70%), and a predilection for proximal colon polyps and cancer.[9-11]

Genetics and diagnosis

Both FAP and AFAP are caused by germline mutations in the adenomatous polyposis coli (*APC*) gene, which encodes a tumor suppressor.[8,12] Mutations throughout the

TABLE 1. System for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	We are very confident that the true effect lies close to that of the estimate of effect.	⊕⊕⊕⊕
Moderate quality	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.	⊕⊕⊕○
Low quality	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.	⊕⊕○○
Very low quality	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.	⊕○○○

Adapted from Guyatt et al.[4]

gene are associated with FAP, with a predilection for AFAP when the mutation is located in the 5' or 3' region of the gene. Although patients usually have a family history of FAP, up to 30% of FAP and AFAP cases are because of new ("de novo") germline mutations in the *APC* gene.[6,13-17] Therefore, family history may not always be present, and genetic testing is recommended to make a molecular confirmatory diagnosis of FAP before proceeding with morbid surgery or invasive endoscopic screening. Genetic testing is also recommended in the following circumstances: (1) when 10 or more cumulative adenomatous polyps are noted on a single colonoscopy, (2) if an individual has 10 or more adenomas and a personal history of CRC, or (3) if an individual has 20 or more adenomatous polyps in his or her lifetime.[18] Even after genetic testing, up to 30% of individuals with a clinical diagnosis of FAP will not have an identifiable pathogenic mutation in the *APC* gene. Numerous reasons for this observation are reviewed elsewhere.[19] There are also several newly discovered genes with polyposis phenotypes similar to FAP and AFAP, including *POLE*, *POLD1*, and *GREM1*.[20,21]

Role of genetic counseling

Genetic counseling is recommended for all patients with or suspected to have an adenomatous polyposis syndrome.[22] Patients with hereditary adenomatous polyposis desire to receive care from healthcare providers who understand their condition and can provide guidance and support for this complex disease.[23] Genetic counselors play a key role in the patient's diagnosis as well as clinical care for patients' ongoing needs. This includes education regarding the implications for both affected individuals and their family members, inheritance of the condition, and the meaning of their genetic test results. At-risk family members are identified for testing, family communication is facilitated, and multidisciplinary care is coordinated for screening patients and children based on polyposis phenotype and the parents' decision. Patients and their children are also assessed for psychological support.[24] Because patients are often tested in adolescence and childhood, their needs for resources change as they approach various life stages, especially during college and family planning. Continued involvement of genetic counselors in the care of polyposis patients creates an opportunity to share up-to-date information regarding cancer risks, current recommendations, improvements in genetic testing technology (for those without previously detectable mutations), affordability, screening modalities, reproductive services, and research opportunities. If a facility does not have its own genetic counselor, providers can search www.NSGC.org (National Society of Genetic Counselors) or www.ABGC.net (American Board of Genetic Counseling) to find an available counselor in the area.

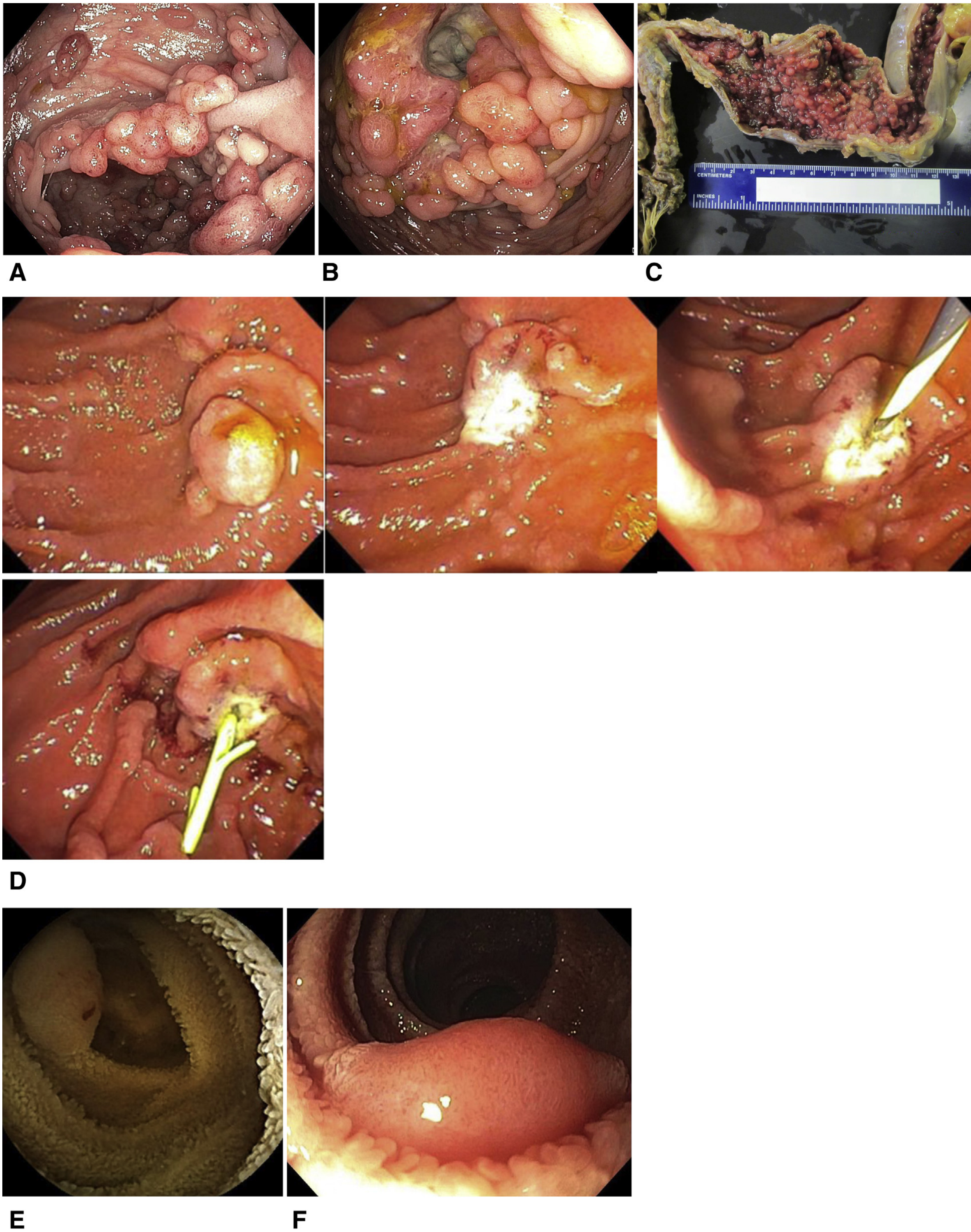
ROLE OF ENDOSCOPY IN THE COLORECTUM

Role of endoscopy in FAP

The primary goal of screening and surveillance endoscopy in FAP patients is early detection of cancer, prevention of cancer through polypectomy, and thereby reduction in cancer incidence and mortality. The risk of CRC is nearly 100% in FAP patients who do not undergo endoscopic or surgical treatment.

Impact of screening programs. Although there are no randomized or prospective studies regarding different screening strategies, multiple observational studies and a systematic review have demonstrated a reduction in CRC incidence and mortality in patients participating in screening programs.[5,25-29] Barrow et al[25] reviewed results from 27 studies comparing CRC incidence between symptomatic and screened patients. All but 1 study showed a statistically significant reduction in CRC incidence in the screening population with an odds ratio of less than 1.00 in all studies. Eight studies compared CRC-related mortality between screened and symptomatic groups in FAP. All studies showed a significant reduction in CRC-related mortality with screening. Bülow et al[30] reported improved 10- year survival in patients with FAP who were participants of the centralized registration, prophylactic examination, and treatment. Several other registry studies have also shown an improved survival in patients who were undergoing surveillance colonoscopies or received prophylactic colectomy.[31-36]

Screening strategy. Based on data from multiple registries, experts recommend *APC* gene testing and screening examinations in children at ages 10 to 12 years



Figures 1. Familial adenomatous polyposis (FAP) is characterized by the presence of hundreds to thousands of adenomatous colorectal polyps, which often start in adolescence. **A,** Polyposis in the colon. **B,** Colon adenocarcinoma in FAP. **C,** Gross pathology specimen from total colectomy of a FAP patient. **D,** Ampullary adenoma in a FAP patient and subsequent endoscopic ampullectomy with placement of a prophylactic pancreatic duct stent. **E** and **F,** Capsule endoscopy and double-balloon enteroscopy images of a jejunal adenoma.

TABLE 2. Cancer risks and genes associated with hereditary polyposis syndromes

Syndrome	Gene	Inheritance pattern	Lifetime cancer risks	Percentage
Familial adenomatous polyposis	*APC*	Autosomal dominant	Colorectum	Nearly 100
			Duodenum/ampulla	4-12
			Stomach	1
			Pancreas	2
			Thyroid	1-2
			Liver (hepatoblastoma)	1-2
			Central nervous system (medulloblastoma)	<1
Attenuated FAP	*APC*	Autosomal dominant	Colorectum	70
			Duodenum/ampulla	4-12
			Thyroid	1-2
MUTYH-associated polyposis	*MUTYH*	Autosomal recessive	Colorectum	80
			Duodenum	4
			Stomach	1

because CRC development is rare before this age.[3] Younger children (6 months to 5 years) can undergo confirmatory *APC* genetic testing if parents are agreeable to screen for hepatoblastoma with α-fetoprotein and liver US every 6 months. Otherwise, testing is deferred until ages 10 to 12 years. Children who do not carry an *APC* gene mutation are recommended to follow average-risk screening guidelines.

Combined data from European registries of FAP revealed no CRC before age 10 years, .2% developed cancer before age 15 years, and 1.3% developed cancer before age 20 years.[3] A survey by Church et al[37] included data from 26 registries and found only 1 case of invasive cancer reported before age 17 years.

In general, the risk of CRC in patients with FAP starts in the second decade and increases with age. Because the rectum is almost always involved in patients with classic FAP, sigmoidoscopy is adequate for screening purposes (Table 3).[27] Patients who do not have polyps on initial sigmoidoscopy should be offered screening at 2-year intervals. Children found to harbor polyps in the rectosigmoid colon should undergo a complete colonoscopy to assess the severity of polyposis and to resect large polyps. It is also reasonable to initially screen children with colonoscopy, given the specific challenges with bowel preparation and need for sedation even when performing a sigmoidoscopy. Polyps in FAP follow the adenoma–carcinoma sequence and take approximately 15 to 20 years for the development of malignancy.[27] In patients with FAP and a manageable polyp burden, surveillance colonoscopy has been shown to reduce the risk of CRC.[5,7,34,38] Once the polyp burden becomes difficult to manage endoscopically, surgical colectomy is recommended. In high-risk patients with a genetic mutation and no polyps on initial sigmoidoscopy or colonoscopy, a follow-up screening colonoscopy should be offered in late teenage years and continued every 2 years until 40 years of age.[39,40] If there are no adenomas, screening intervals can be gradually extended.

The use of chromoendoscopy in FAP has also been studied. In a small case series, chromoendoscopy detected a significantly higher number of colon polyps (43.3 ± 38.5) when compared with white-light endoscopy (12.2 ± 13.9, $P = .005$).[41] However, unlike in hereditary nonpolyposis colon cancer syndrome, polyps are not subtle in FAP; hence, additional detection of small adenomas is unlikely to change overall management and referral for eventual colectomy. Further studies are warranted to determine the role, if any, of chromoendoscopy and other advanced imaging techniques in this patient population. Currently, it is not recommended for routine use.

Surveillance compliance. Compliance with screening and surveillance guidelines is essential to prevent colorectal and extracolonic cancers in patients with FAP. Data from the Dutch FAP registry reported lower level of compliance with screening recommendations in 20% of at-risk individuals and 25% of patients with ileorectal anastomosis (IRA).[42] Factors attributed to this lower level of compliance included psychosocial measures, such as patients' low levels of confidence to follow screening advice ($P = .02$) and lower perceived risk of developing CRC ($P = .02$). This group also received more unsedated procedures and reported more pain after the procedure compared with those who were compliant. Therefore, patient education about the natural history and cancer risks associated with FAP, as well as improved procedure experience, are paramount to the management of this patient population.

Role of endoscopy in AFAP

Screening recommendations in AFAP are based on limited available literature.[10,43,44] Compared with FAP, AFAP patients often develop polyps and CRC at a later age. In a European registry–based study of 9 families with AFAP (n = 40), the mean age at diagnosis of CRC

TABLE 3. Colorectal screening/surveillance recommendations in patients and family members at risk for FAP, attenuated FAP, and MUTYH polyposis

Condition	Screening examination	Starting age at screening	Surveillance interval	Quality of evidence
FAP	Sigmoidoscopy or colonoscopy Colonoscopy when polyps are found	10-12 y	1-2 y	⊕⊕⊕○
Attenuated FAP	Colonoscopy	18-20 y	1-2 y	⊕⊕○○
MUTYH- associated polyposis	Colonoscopy	18-20 y	1-2 y	⊕⊕○○
MUTYH heterozygote + first-degree relative with CRC	Colonoscopy	40 y, or before 10 y age of first-degree relative's age of CRC diagnosis	5 y	⊕○○○
MUTYH heterozygote without family history of CRC	Unknown	Unknown	Unknown	_
After total colectomy with IPAA	Pouch endoscopy	1 y after surgery	1-2 y 6 mo if advanced adenoma including HGD	⊕○○○
After subtotal colectomy and ileorectal anastomosis	Sigmoidoscopy	6 mo after surgery	6 mo to 1 y	⊕○○○

FAP, Familial adenomatous polyposis; *CRC*, colorectal cancer; *IPAA*, ileal pouch anal anastomosis; *HGD*, high-grade dysplasia.

was 54 years (range, 24-83), which is 10 to 15 years delayed compared with patients with classic FAP.[13] In an American study, Burt et al[9] reported adenoma development in 111 of 120 gene carriers who were undergoing screening colonoscopy at an average age of 41 years. The median number of adenomas was 25 (range, 0-470), with a wide variability of polyp formation in patients with a disease-causing mutation. CRC developed in 27 gene carriers, and the average age at diagnosis was 58 years (range, 29-81).[9] Proximal colonic predominance was seen both for polyps and cancers in these patients. Based on these observations, screening colonoscopy should be offered to patients with AFAP starting at age 18 to 20 years (ie, later than classic FAP). Colonoscopy is recommended as the screening tool to assess for proximal lesions. Flexible sigmoidoscopy is an inadequate examination, because these patients may not develop any rectal polyps. Surveillance colonoscopy with polypectomy is recommended at 1- to 2-year intervals, which may delay or eliminate the need for preventive surgery in patients with low polyp burden.

MUTYH-associated polyposis

Overview. The *MUTYH* gene is a DNA base excision repair gene that repairs DNA injury from oxidative stress. MAP, first described in 2002, is an autosomal recessive condition associated with an increased risk of CRC development. Biallelic MUTYH pathogenic mutations lead to the development of multiple colorectal adenomas, usually <100 in a patient's lifetime.[45] The colonic polyposis phenotype is similar to AFAP with possible rectal sparing and a right-sided colon predominance.[46] A higher prevalence of serrated adenomas has also been observed in patients with MAP.[47]

Genetics and diagnosis. The most common deleterious alleles in the European population in the *MUTYH* gene are Y179C and G396D.[48,49] Full sequencing is now offered for this gene as mutations apart from these 2 cause MAP in non-European populations. It is important to obtain a complete family history because the recessive nature of this disease can be difficult to discern. This includes discussion about consanguinity in the family because this increases the risk of being homozygous for the mutations in *MUTYH*.

The lifetime risk of CRC in those with biallelic mutations in MAP approaches 80%.[50] The CRC risk in monoallelic *MUTYH* mutation carriers is shown to impart minimal or no additional risk compared with biallelic patients. However, a study by Win et al[51] observed an increased CRC risk in monoallelic carriers who also had a history of a first-degree relative with CRC. Once an individual is found to be affected with MAP, his or her relatives should also be screened for mutations in *MUTYH*. Genetic testing of children, however, should be postponed until adulthood when individuals can make their own informed decision about pursuing testing, because disease onset is later than FAP and screening begins in adulthood. Similar to FAP, genetic testing for mutations in *MUTYH* should be considered in those with (1) 20 or more colorectal adenomas over multiple colonoscopies, (2) a known family history of MAP, (3) 10 or more adenomas found on a single colonoscopy, or (4) criteria for serrated polyposis syndrome with at least some adenomas noted on examination.[40] Serrated polyposis syndrome is defined by the World Health

Organization as any 1 of the following conditions: (1) at least 5 serrated polyps proximal to the sigmoid colon with 2 or more >10 mm in size, (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis syndrome, or (3) >20 serrated polyps of any size distributed throughout the colon.[52]

Role of endoscopy in MAP. The risk of CRC in MAP is estimated to be 28-fold higher when compared with the general population.[53] Similar to AFAP, CRC onset is later than in individuals with classic FAP. Nielsen et al[54] reported CRC in 26 of 40 Dutch patients with *MUTYH* gene mutations within the age range of 21 to 67 years (median, 45). This study also revealed a right-sided preponderance for colon polyps and cancer. Several other studies support these findings as well.[55-58] Nieuwenhuis et al[56] reviewed the natural history and outcomes of colorectal surveillance in 254 European biallelic *MUTYH* patients. CRC was diagnosed in 58% of patients at a mean age of 48.5 years (range, 21-77). Moreover, 13% of those CRC patients who were under surveillance developed a metachronous CRC. The risk of CRC was not associated with the number of adenomas. Two patients who presented with CRC had no colorectal polyps. The estimated cumulative lifetime risk of CRC was 63% at age 60 years.

Because the youngest age of CRC in biallelic MAP patients has been reported to be 21 years, it is recommended that colonoscopy screening start at age 18 to 20 years with close surveillance at 1- to 2-year intervals.[56] Rectal involvement is uncommon in MAP; hence, a sigmoidoscopy is not adequate as a screening examination. Patients with low colonic polyp burden can be managed with polypectomy. However, once polyp burden is unmanageable or CRC diagnosed, subtotal colectomy rather than hemicolectomy is recommended given the risk for metachronous cancers.

Surgical management of FAP and MAP

The type of colorectal surgery offered to patients depends on several factors, including patient age, severity of polyposis including rectal involvement, risk of developing desmoids, and location of mutations.[59-63] Colectomy with ileal pouch anal anastomosis (IPAA) is generally considered most appropriate in patients with a large number of rectal polyps (rectal polyp burden >20), polyps >1 cm in size, or with advanced histology. Colectomy with IRA is less commonly offered because of increased risk of subsequent rectal cancer and cancer-related mortality in FAP patients. In a retrospective follow-up study, Campos et al[64] reported rectal cuff cancer in 6 of 36 patients who had IRA (16.6%) over a period of 91.1 months (range, 3-557) of follow-up, but only 1 of 26 patients with IPAA (3.8%) developed ileal pouch cancer over a period of 50.8 months (range, 5-228) of follow-up. However, colectomy with IRA can be an option in patients with either rectal-sparing or preoperative endoscopic clearance of the rectum to avoid pelvic dissection and possible infertility or sexual dysfunction.[60]

A registry study from Finland compared short- and long-term outcomes of patients who underwent colectomy with IPAA versus IRA. This study found improved long-term survival in patients who pursued IPAA with no difference in short-term outcomes including postoperative adverse events when compared with patients undergoing colectomy with IRA, which is likely related to the long-term risk of rectal cancer.[63]

Role of endoscopy in patients with IPAA or IRA after colectomy

There is an increased risk of adenomas in the ileum, rectal cuff, and anal transition zone after colectomy and IPAA and IRA; therefore, surveillance after surgery is necessary.[64-72] Friedrich et al[69] showed a 45% cumulative risk of developing an adenoma in the pouch 10 years after proctocolectomy with IPAA. Twelve percent of these patients had an adenoma with advanced pathology. However, the cumulative risk of cancer was low at 1% in 10 years. A subgroup of patients who underwent chromoendoscopy of the pouch had a high prevalence of adenomas (75.7%), suggesting a role of advanced imaging technologies in detecting small polyps. However, data are inadequate to support the routine use of chromoendoscopy at this time. Groves et al[70] reported pouch adenomas associated with increasing patient age and length of follow-up since surgery but not associated with the severity of colonic or duodenal polyposis. In contrast, Pommaret et al[68] reported increased risk of pouch adenomas in the setting of advanced duodenal adenomas. Overall, however, the risk of advanced neoplasia is infrequent in patients who undergo surveillance endoscopy and ablative therapies.[73,74]

ROLE OF ENDOSCOPY IN THE UPPER GI TRACT

Stomach

Fundic gland polyps. Fundic gland polyps (FGPs) are commonly found in FAP patients with a prevalence of up to 88%.[75] They arise in the pediatric population where they can be seen in 25% to 51% of children undergoing index screening EGD at a mean age of 13 years.[76-78] Endoscopically, they appear similar to sporadic FGPs but pathologically are distinct in that they harbor germline *APC* alterations.[79,80]

Unlike sporadic FGPs, dysplasia can develop in FGPs associated with FAP. In a study of 75 consecutive patients undergoing upper endoscopic surveillance for FAP, dysplasia was found in 42% of FGP, of which 38% were low grade and 3% high grade.[75] Similarly, in an Italian study, dysplasia within FGPs has been reported in up to 44% of FAP patients.[81] Even in the pediatric FAP population, FGPs harboring low-grade dysplasia were seen in up to 42% of cases on index screening EGD.[77,78] FGP dysplasia is associated with larger polyp size (>1 cm) and increased severity of duodenal polyposis.[75] Although it may be common to find dysplasia, FGPs rarely develop into adenocarcinoma. In the rare cases of malignant transformation, the primary tumor was large (>3 cm) in the background of diffuse gastric polyposis in patients old than 37 years.[82-86]

Adenomas. Gastric adenomas are less common than FGPs in patients with FAP, with variation in prevalence between the West and the East. The prevalence in the United States and Europe is approximately 10%, whereas the prevalence is higher in Asia (36%-50%), possibly because of an overall higher incidence of gastric cancer in this region of the world.[75,87,88] In a Korean FAP cohort, gastric adenomas were found in 14.2% of 148 FAP patients on index EGD.[89]

Adenomas can occur anywhere within the stomach but occur more commonly in the antrum. Antral adenomas are usually flat, sessile, and subtle with a villiform red appearance, whereas those in the gastric body and fundus are more polypoid with a pale yellow surface and are difficult to differentiate from FGPs.[87] Therefore, endoscopists should have a high degree of suspicion for gastric adenomas with a low threshold to biopsy sample and resect polyps, particularly in the antrum where they may be difficult to identify. Gastric adenomas have also been reported to be associated with a significant degree of duodenal polyposis (Spigelman stages III and IV),[88] although other case series have not confirmed this finding.[87]

Gastric cancer. The development of adenocarcinoma follows the adenoma to carcinoma sequence. Case reports demonstrate gastric cancer in FAP patients as young as 16 years old.[90] Adenocarcinoma can occur anywhere in the stomach and can be multicentric and metachronous.[91] Discrepancy in worldwide prevalence exists similar to gastric adenoma. In the Western population, there is no overall increased risk compared with the general population: .1% (2/1391)[92] and .6% (7/1255),[93] respectively. However, a recent increase in gastric adenocarcinoma in FAP patients in the United States has been reported with an overall incidence of 1.3% (10/767).[94] The interval from initial colectomy to diagnosis of gastric cancer was an average of 23 years. Nearly all patients were under surveillance. Endoscopic risk factors associated with malignancy included carpeted FGPs and the development of large, densely concentrated mounds of gastric polyps in the fundus and body within 1 to 2 years before cancer diagnosis.[95] These mounds of polyps can occur either alone or in the background of carpeted polyps. The authors recommended 3- to 6-month interval surveillance EGD with aggressive polyp sampling and endoscopic debulking of these large gastric polyposis mounds, because more stage I cancers were found with this protocol. Moreover, mucosal biopsy sampling may not be adequate to assess for malignancy within these thick layers of carpeted polyposis or mounds of gastric polyps; therefore, EUS may be helpful to evaluate for an underlying malignancy (Fig. 2).

In the Eastern population, the incidence is noted to be higher: 2.6% (27/1050),[96] 2.7% (4/148),[89] 7.1% (3/42),[91] and 7% (9/130).[97] Iida et al[98] described the natural history of gastric adenomas in Japanese patients with FAP. Fifty percent of their patients were found to have adenomas on index EGD with 1 of 13 patients developing gastric cancer after an average follow-up of 6.8 years.

Data regarding gastric findings and risk for gastric cancer in MAP are still being collected from registries around the world. In a multicenter European cohort, the incidence of gastric lesions in MAP was 11%, of which most were FGPs and adenomas.[99] Gastric adenocarcinoma was found in 3 of 150 patients who underwent EGDs with ages ranging from 17 to 48 years. The incidence was not significantly increased from the general population (Standardized incidence ratio, 4.2; 95% confidence interval, .9-12), although the study sample size was too small to accurately estimate the incidence of gastric cancer.

Recommendations. The optimal strategies for surveillance and endoscopic management of patients with FAP (including AFAP and MAP) are unknown, with various recommendations issued by polyposis registries around the world.[73,99,100] During screening and surveillance endoscopy, we recommend careful evaluation of polyps including FGPs with random biopsy sampling and complete resection of polyps >1 cm for the evaluation of indolent dysplasia and malignant transformation, particularly in the setting of diffuse gastric polyposis and large gastric mounds. All antral polyps should be endoscopically removed, given the high probability of adenoma. Surgery should be reserved for patients with FGP and adenomas harboring advanced histologic features who fail endoscopic management.

Duodenum

Epidemiology. Duodenal adenomas occur in nearly all FAP patients, with an incidence of >90% and a mean age at presentation of 52 years. Duodenal involvement starts early and can be seen in up to 52% of children (mean age, 12 years) undergoing their first screening endoscopy.[77] Duodenal lesions at this age are usually few in number (up to 4 polyps), under 5 mm in size, involve the second portion of the duodenum and around the ampulla, and rarely involve the papilla.[76,77] However, ampullary involvement in the pediatric population usually involves concomitant duodenal polyposis.[77] Although adenomas are commonly found in FAP children, it is rare for these lesions to progress to high-grade dysplasia (HGD) at this age.[101,102] In the literature, there is only 1 case report of HGD in a duodenal adenoma in a 12-year-old child presenting with CRC.[103]

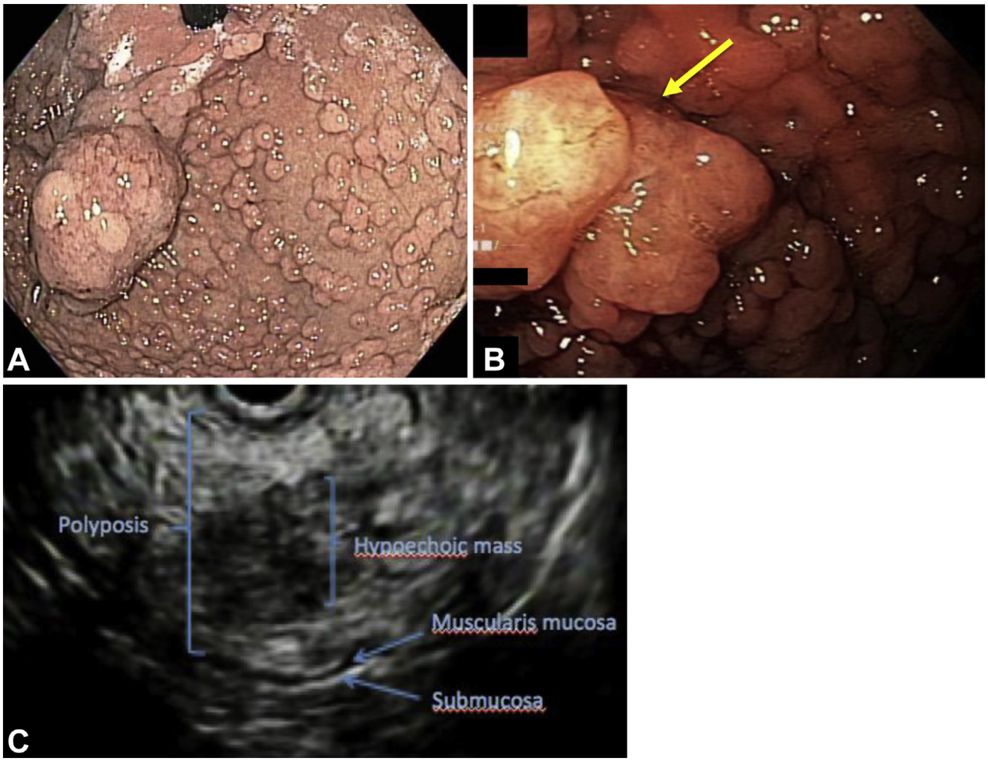


Figure 2. High-risk gastric endoscopic features in familial adenomatous polyposis (FAP). **A,** Large isolated gastric polyp and carpeted polyposis. **B,** Gastric body mound of polyps (*arrow*) within the background of carpeting. Biopsy specimens revealed fundic gland polyp–high-grade dysplasia and multifocal tubular adenoma–high-grade dysplasia. Gastrectomy demonstrated intramucosal adenocarcinoma.[94] **C,** EUS demonstrating underlying hypoechoic mass within a mound of gastric polyps. Prior EGD with biopsy samples throughout the polyposis were negative for HGD and cancer. Gastrectomy confirmed underlying adenocarcinoma.[95]

TABLE 4. Modified Spigelman staging system for duodenal polyposis in familial adenomatous polyposis

Polyps	1 point	2 points	3 points
Number	<4	5-20	>20
Size, mm	0-4	5-10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Low-grade dysplasia	—	High-grade dysplasia

Overall score of 0 points = stage 0; 1-4 points = stage I; 5-6 points = stage II; 7-8 points = stage III; and 9-12 points = stage IV. —, not applicable.
Adapted from Spigelman et al[88] according to current dysplasia classifications.

Risk stratification. Spigelman classification. The severity of duodenal polyposis is characterized by the Spigelman classification (stages 0-IV) based on polyp number, size, histology, and severity of dysplasia (Table 4). This classification, however, does not take into account ampullary lesions and is not validated for the management of isolated ampullary disease. This classification has been widely used for risk stratification in duodenal polyposis, with stage IV having the greatest risk for malignant transformation. A 10-year follow-up study demonstrated the risks of developing duodenal cancer for each initial Spigelman stage: stages II, III, and IV were associated with a 2.3%, 2.4%, and 36% risk, respectively.[100] In contrast, early stage 0 and I patients rarely progressed over 10 years and never developed invasive cancer.

The severity of duodenal polyposis increases with age. The cumulative risk of developing stage IV duodenal polyposis is estimated to be up to 43% by age 60 years (95% confidence interval, 35.7%-50%) and 50% by age 70 years (95% confidence interval, 42.9%-57.1%).[104] Bülow et al[105] estimated cumulative lifetime risk of stage IV disease to be 35%. A French prospective series also demonstrated that an initial Spigelman score ≥7 is a risk factor for developing HGD (P = .032),[104] and a Spanish series showed a similar finding of a 50% increase in dysplasia in this high Spigelman group.[106] Duodenal polyp size is also

TABLE 5. Studies of endoscopic treatment and surveillance for upper GI polyposis in familial adenomatous polyposis

Study	No. of patients/age (y)	Study design	Intervention
Cordero-Fernandez 2009,[106] Spain	29/mean 29 (13-55)	Prospective cohort	EGD 1-3 yr in stage I-III, EGD 6 mo in stage IV Resection of all antral polyps, larger fundal, duodenal, and ampullary polyps. APC after piecemeal resection
Jaganmohan 2012,[127] USA	55/mean 45 (15-85)	Retrospective cohort	EGD yearly with biopsy sampling of polyps <1 cm, polypectomy/EMR polyps >1 cm, APC ablation for debulking and margins post-EMR, EUS before EMR if suspected invasion, ERCP + prophylactic pancreatic duct stent in ampullectomy
Moussata 2014,[112] France	35/mean 48 (21-65)	Retrospective cohort	Stage IV only patients: EMR >5 mm sessile, APC <10 mm flat or <5 mm polyps, ampullectomy >10 mm
Drini 2012,[137] Australia	67/32-67 surgical patients	Retrospective cohort	EMR of 10-30 mm polyps, APC <10 mm, ampullectomy >12 mm Referral for surgery based on individual polyp characteristics (>30mm size, >50% lumen, ulceration, and friability) rather than Spigelman stage
Serrano 2015,[101] Canada	218/10-72	Prospective cohort 30-y enrollment	EMR and ampullectomy of polyps >10 mm or <10 mm + HGD APC ablation of flat >20 mm polyps Surveillance EGD 6 mo Surgery for carpeted polyposis
Johnson 2010,[129] USA	168/mean 39.5 (13-84)	Retrospective cohort	45% stage III/IV at index EGD No standardized protocol: polypectomy, EMR, APC ablation, PDT, EUS Surveillance based on stage

APC, Adenomatous polyposis coli; *HGD*, high-grade dysplasia; *PDT*, photodynamic therapy.

a risk for developing dysplasia, with HGD occurring more commonly in larger polyps >1 cm.[104]

In patients with MAP, duodenal polyposis develops less frequently and at a later age than in patients with FAP. A retrospective European study of 92 patients undergoing surveillance found the prevalence of duodenal adenomas was 34% at a median age of 50 years.[107] Most polyps (84%) were found in early Spigelman stages I and II and did not harbor HGD. Increasing lesion size and villous change were associated with adenoma progression, but polyp number and dysplasia were not. To date, there are no reports of ampullary involvement in MAP. Therefore, it is unknown if the ampulla needs to be part of the screening examination. In a similar fashion, patients with clinical colorectal polyposis but absent *APC* or *MUTYH* mutations are less likely to have duodenal adenomas (9.6%) and lower-risk duodenal adenomas if present.[108] The risk of duodenal cancer in patients with clinical polyposis (mutation negative) is unknown.

Duodenal cancer. Duodenal cancer, along with desmoid tumors, is the most common cause of death after CRC in patients with FAP. The cumulative risk of duodenal cancer by age 60 years ranges from 4.0% to 10%.[3,109] The risk is highest in patients with Spigelman stage IV, with a 36% risk of duodenal cancer in this group.[100] Half of cancers are located at the ampulla and periampullary area, followed by the proximal and distal duodenum and the proximal jejunum. The risk of periampullary cancer is estimated to be between 3% and 8.5% with a cumulative incidence of cancer of 4.5% at age 57.

The development of malignancy follows the adenoma to carcinoma sequence similar to CRC with a slow progression to carcinoma, which is estimated to take approximately 15 to 20 years.[110] The Canadian registry of 218 FAP patients estimated a median time of 15 years from index EGD at age 25 to duodenal cancer development.[101] It is extremely rare for duodenal cancer to occur in patients younger than 30 years old.[111] Controversy exists over whether or not there is a relationship with the location of genetic mutations.[100,104,105]

Ampullary adenoma and cancer. Given the predilection for malignancy to occur at and near the ampulla in patients with FAP and AFAP, this area must be carefully evaluated. Adenomas are found at the ampulla in up to 72% of stage IV FAP patients.[112] Interestingly, adenomatous changes can also be found in a macroscopically normal-appearing ampulla in 29% to 54% of individuals undergoing random biopsy sampling.[106,113] There are also reports of developing ampullary cancer in patients with a normal ampulla on index screening.[100]

Use of a side-viewing duodenoscope is considered the criterion standard for examining the ampulla. The original Spigelman group detected twice the number of adenomas using a duodenoscope, compared with surveillance using a

TABLE 5. Continued

Follow-up (y)	Outcomes	Endoscopic adverse events
9.3 (mean)	Reduction in polyp number, size, and degree of dysplasia of 69.2%, 61.5%, and 61.5%, respectively No stage IV or duodenal cancer at end of study	1 hemorrhage (polypectomy)
4.5 (mean)	31% histologic progression 75% with persistent or recurrent adenoma after APC. No duodenal cancer	1 hemorrhage (ampullectomy)
9 ± 4.5 (mean)	>95% downstaged with mean Spigelman score decrease of 6 ± 2.2 No duodenal cancer	6%-delayed hemorrhage, pancreatitis, perforation requiring surgery
7 postoperative (mean)	16% (11/67) referred for surgery 2/11 duodenal cancer (17mm and 40mm, both friable/ulcerated and Stage IV)	10% hemorrhage, postpolypectomy Surgery group: 45% morbidity, 9% mortality
11 (median)	10% (21/218) referred for surgery 24% (5/21) duodenal cancers 2.3% overall incidence of duodenal cancer at median age 58 y	11% hemorrhage, 9% pancreatitis, 1% mortality from severe pancreatitis after ampullectomy Surgery group: 60% morbidity, 0% mortality
8.3 (mean)	23% underwent endoscopic resection 30% referred for surgery: all stage IV and III + HGD 3% duodenal cancer	7.5%,-1 mild pancreatitis, 2 perforations requiring surgery, 1 duodenal stricture post-PDT requiring dilation

standard gastroscope alone.[88] Alternatively, cap-assisted upper endoscopy can be performed to visualize the ampulla. A soft, transparent cap is fitted on the distal tip of an endoscope that helps to flatten duodenal folds and allow for more en face views of the ampulla. It also allows scope stabilization in the duodenum.[114-116] Because nearly half of patients may harbor ampullary adenomas, routine biopsy sampling may not be necessary, especially given the potential risk of pancreatitis.[100,117] Of note, asymptomatic increase in amylase (<2 times the upper limit of normal) has been reported in 30% of FAP patients undergoing systematic ampullary biopsy sampling.[104] Suspicious ampullary lesions, however, should undergo biopsy sampling to rule out underlying dysplasia and indolent malignancy. Endoscopic features suggestive of malignancy include ulceration, friability, firmness, and nonlifting of the periampullary component with submucosal injection. Such lesions should be considered for surgical resection rather than endoscopic papillectomy, even in the absence of malignancy on biopsy specimens. Endoscopic resection should be considered for patients with polyps >1 cm, advanced histology such as tubulovillous adenoma and HGD, or obstructive symptoms including abnormal liver function tests or pancreatitis. Given the risks of pancreatitis, papillectomy should be performed at high-volume centers. Readers are referred to the ASGE Standards of Practice guideline on the role of endoscopy in ampullary and duodenal adenomas for details and techniques of resection.[118]

Endoscopic evaluation and management. The endoscopic strategy in the management of duodenal polyposis consists of identifying and resecting high-risk polyps with the goal to downstage disease with strict surveillance of advanced duodenal polyposis because of the higher probabilities of malignancy transformation. Multiple series have demonstrated a more favorable prognosis of FAP patients undergoing surveillance, with endoscopic protocols varying worldwide (Table 5). Targeted endotherapy in the highest risk stage IV group resulted in a decrease in Spigelman scores in 95% of patients by 6 ± 2.2 points (P = .002) and no duodenal cancers found over a 10-year follow-up period.[112] Data suggest that prognosis is also improved in asymptomatic versus symptomatic duodenal cancers. In a series of 304 patients with a median follow-up of 14 years, overall survival was 8 years after a surveillance-detected duodenal cancer versus .8 years (95% confidence interval, .03-1.7) after a symptomatic cancer (P < .0001), although there was the potential of both lead-time and length-time bias in this study.[105]

Endoscopic therapies for duodenal adenomas include polypectomy, EMR, and ablation. Prospective controlled studies on the effectiveness of these endoscopic modalities in FAP are lacking. Additionally, techniques of endoscopic removal of duodenal adenomas, even in sporadic cases, are not standardized. Thin wall, retroperitoneal fixation, and risks of electrocautery in the duodenum present unique challenges of endoscopic resection of duodenal adenomas, which explains higher adverse events compared with endoscopic resection in the colon.[119-121] In studies of endoscopic resection of sporadic duodenal adenomas, complete endoscopic resection is achieved in >90% on initial procedure.[121-125] Adverse events include immediate and delayed hemorrhage after EMR, with rates varying from 7% to 43% and 5 to 15%, respectively, with higher risks of bleeding associated with larger duodenal adenomas (>20 mm, $P = .03$[123]; >3 cm, $P = .02$[121]; and >3 cm, $P = .003$[125]). Bleeding can be successfully managed either conservatively or with endoscopic intervention. Prophylactic clipping of EMR defects decreases delayed bleeding compared with no clipping (7% vs 32%, $P < .004$).[119,120] The risk of perforation in the duodenum with EMR ranges from 0% to 4%. In contrast, ESD of duodenal adenomas carries substantial risk of perforation with rates of >20% and is therefore not recommended.[126] Close follow-up surveillance endoscopy after sporadic duodenal adenoma resection is necessary, because recurrence can be up to 30% after 1 year in sporadic cases, and is also associated with increasing polyp size.[121-123] Recurrent adenoma can be successfully managed endoscopically on subsequent examinations.

APC ablation as a primary or adjunctive therapy to destroy residual adenoma after polypectomy is also associated with a high rate of adenoma recurrence in FAP. In 1 study, persistent or recurrent adenoma was seen in 75% of FAP patients (12/16) who had APC ablation as primary therapy, of whom 25% went on to histologic progression.[127] There was no regression of the primary lesion after APC ablation. A Canadian group also reported recurrent adenoma in all ablation cases.[101] Given the technical difficulty and higher incidence of adverse events, endoscopic resection of duodenal adenomas should be performed by skilled endoscopists at high-volume centers.

Similarly, regarding surgical options, duodenotomy for the resection of large polyps is not recommended because of inevitable adenoma recurrence at the surgical site. The Spigelman group observed adenoma recurrence at a mean of 13 months after duodenotomy with progression of polyposis stage.[128] The Cleveland Clinic series also found adenoma recurrence after all transduodenal polypectomy and ampullectomy cases.[129]

Few studies look specifically at the role of EUS in FAP or its role in staging with cross-sectional imaging. EUS, as used in nonpolyposis cases, is important to detect depth of invasion in advanced adenomas and malignancy, nodal status, and intraductal involvement. In a case series of 38 FAP patients with ampullary adenomas, EUS upstaged 9 additional patients to advanced adenoma and downstaged 1, altering treatment management in 36% of patients.[130] Refer to Table 6 for overall recommendations for duodenal screening and surveillance.

Chromoendoscopy has been shown to increase the detection of duodenal adenomas in FAP, mostly of small polyps <1 cm in size. Dekker et al[131] demonstrated the additional value of chromoendoscopy compared with high-resolution endoscopy alone, resulting in an increased Spigelman score in 8 of 43 patients (19%) with a corresponding upgrade in the Spigelman stage in 5 of 43 patients (12%, $P = .03$). Improved adenoma detection with chromoendoscopy was also seen in both FAP ($P = .002$) and MAP ($P = .013$) patients with a 3-fold increase in adenoma number but no impact on size of polyp.[132] Chromoendoscopy upstaged the Spigelman score based on polyp number but did not detect more dysplasia or polyps >1 cm in size. The clinical impact of enhanced adenoma detection on the course of malignancy potential is unknown. Larger prospective studies with long-term follow-up are needed. Therefore, at this time, routine chromoendoscopy is not recommended during upper endoscopy in individuals with FAP and MAP.

The role of endoscopic therapy is to delay major surgery, whether a pylorus or pancreas-preserving duodenectomy or traditional pancreaticoduodenectomy, given that morbidity and mortality can be greater than 50% and 5%, respectively, in FAP.[133-138] Morbidity factors unique to FAP are patients who have already had major abdominal surgery (colectomy) and the increased risk of developing and/or stimulating the growth of mesenteric desmoid tumors. Altered anatomy after pancreaticoduodenectomy will also present an additional challenge to survey and endoscopically reach lesions in the small bowel. Nevertheless, stage IV patients should optimally be referred for surgery before cancer develops, because resectable duodenal adenocarcinoma is rare if preoperative biopsy sampling identifies carcinoma.[100] It is also important to note that despite endoscopic surveillance, undetected malignancy can be found in 13% to 32% of stage III and IV patients referred for surgical resection.[127,139] A limitation of many of these prior studies was a reliance on standard-definition endoscopes, and it is unknown whether these rates would be lower in the current era of high-definition endoscopy.

Recommendations. In summary, duodenal polyposis occurs in almost all FAP patients, with most having early-stage disease. Progression to stage IV disease occurs in about 15 to 20 years with a median age at diagnosis of duodenal cancer in the fifth decade. Important aspects of management are to identify and closely follow patients with risk factors for developing malignancy, such as those with Spigelman stages III and IV at baseline EGD, as well as individual polyp characteristics of HGD, polyp size >1 cm, and flat, carpeted growth that may be difficult to completely resect. Particular attention to the periampullary area, where 50% of the cancers occurs, is recommended. Endoscopic treatment is used to downstage disease with the goal to delay the development of stage IV disease. Advanced duodenal disease should be followed more

TABLE 6. Upper GI and small-bowel screening/surveillance recommendations in hereditary polyposis syndromes

Condition	Examination	Screening	Surveillance	Quality of evidence
FAP and attenuated FAP	EGD with duodenoscope or cap-assisted gastroscope	20-25 y or before colectomy		⊕⊕○○
MUTYH-associated polyposis	EGD	30-35 y or before colectomy		⊕○○○
Spigelman stage 0-I			5 y	⊕○○○
Spigelman stage II			3 y	⊕○○○
Spigelman stage III			6-12 mo	⊕○○○
Spigelman stage IV			3-6 mo, surgical evaluation	⊕○○○
Gastric adenoma			1 y	⊕⊕○○
Gastric HGD			3-6 mo, surgical evaluation	⊕○○○
Gastric polyposis mounds	Baseline EUS		3-6 mo	⊕○○○
Gastric polyposis mounds + HGD			Surgery	⊕⊕○○
Index small-bowel screening	Capsule endoscopy or MRE	Spigelman stages III and IV or before duodenectomy	2-4 y	⊕○○○
Jejunal or ileal polyps >1 cm found on capsule endoscopy or MRE	Double-balloon enteroscopy or single-balloon enteroscopy for polypectomy			⊕○○○

FAP, Familial adenomatous polyposis; *HGD*, high-grade dysplasia; *MRE*, magnetic resonance enterography.

closely and treated more aggressively. Once Spigelman stage IV is present, multidisciplinary discussion is recommended to assess the appropriate time for surgical resection. Although endoscopic resection of duodenal and ampullary lesions is recommended, it is unknown if this truly changes the natural history of cancer risk based on the original Spigelman stage because there is an underlying field defect in the duodenum. Further long-term prospective studies are needed to evaluate this important question.

Small bowel: beyond the ligament of Treitz

Epidemiology and diagnostic imaging. Adenomas beyond the ligament of Treitz are less frequent than duodenal adenomas, with the prevalence of jejunal and ileal adenomas ranging from 45% to 75% and 10% to 20%, respectively.[140-142] The incidence varies depending on the modality used for detection. Initially, contrast studies (small-bowel follow-through, enteroclysis) were the examinations of choice. With the advent of capsule endoscopy (CE), this diagnostic test has become the preferred imaging modality, because false-negative rates in contrast studies are up to 42% for polyps >10 mm in FAP patients.[143,144] When compared with magnetic resonance enterography (MRE), CE is also more sensitive for detecting smaller polyps. The 2 tests performed equally for detecting polyps >15 mm, although MRE was more reliable for determining the location and size of polyps. MRE also has the advantage of imaging outside the GI tract, including detecting desmoid tumors.[145]

In a study where both push enteroscopy and CE were performed, 24% of FAP patients had polyps in the distal jejunum and ileum that could only be detected by CE.[146] This was also confirmed in a German study where more than 50% of adenomas found on CE were not accessible to push enteroscopy.[143] However, there are some limitations of CE in FAP. It underestimates duodenal polyps and cannot reliably visualize the ampulla.[142,146-148] Therefore, CE does not replace direct endoscopic evaluation of the duodenum and ampulla. In regard to adverse events, CE in FAP patients can be successfully performed even in patients with prior bowel surgery.[149,150] However, there are some case reports of capsule retention in the pouch.[146,151,152]

Most jejunal and ileal adenomas are small (<1 cm), harbor no dysplasia, and mainly occur in patients with advanced stages of duodenal polyposis. Multiple case series demonstrate that the severity of duodenal polyposis is a predictor for detecting deeper small-bowel adenomas.[140,141,146,150,153,154] On the other hand, jejunal or ileal adenomas are rare in patients without duodenal adenomas.[146,148,153,154] Moreover, advanced lesions also predominate proximally in the jejunum rather than the ileum. In a review of the literature of 319 FAP patients (mean age, 39 years) who underwent small-bowel evaluations, 8.8% were found to have advanced lesions, defined as polyps >1 cm or with HGD, located solely in the jejunum.[140]

Natural history and risk for small-bowel cancer. Although CE can detect small-bowel adenomas, the clinical significance of this is unknown. There are very limited data on the natural history of jejunal and ileal adenomas. Most are case series with small numbers of FAP patients and with limited follow-up between 2 and 7 years. Günther et al[155] described evidence of progression in the number and size of proximal jejunal adenomas in 3 of 5 FAP patients undergoing repeated video CE with a 2- to 7-year interval, whereas Matsumoto et al[141] observed no change in the burden of small-bowel adenomas during follow-up double-balloon enteroscopy after 2 to 4 years in 5 FAP patients. Japanese data suggest that jejunal adenomas have a slow rate of progression to cancer, although the numbers are small.

There is also no significant increased risk of nonduodenal small-bowel cancers in FAP patients compared with the general population, with a prevalence of .4% jejunal cancer and .1% ileal cancer.[93] However, when patients present with symptoms (GI bleeding, intussusception, bowel obstruction), small-bowel cancer is usually late stage with a poor prognosis, as seen in symptomatic duodenal disease. There are a total of 20 reported cases of jejunal and ileal cancers in FAP with a mean patient age of 47 years.[156,157] Overall, conclusions cannot be determined regarding the characterization and frequency of small-bowel adenoma surveillance because of the lack of data regarding the natural history of adenomas and low incidence of jejunal and ileal cancers.

Role of deep enteroscopy. Because small-bowel adenomas are more frequent and harbor more advanced lesions proximally, it is feasible to follow up with a deep enteroscopy for polyp resection. There are 5 case series of successful deep enteroscopy with either single-balloon enteroscopy or double-balloon enteroscopy in FAP patients.[140,141,153,158,159] Most study patients underwent diagnostic small-bowel examinations, because only a few cases were described as harboring advanced small-bowel lesions requiring endoscopic resection[149,153,155,159] Because noninvasive CE and MRE are available, deep enteroscopy is not recommended for routine small-bowel screening. However, deep enteroscopy with polypectomy should be considered in patients with a positive CE or MRE for a suspected advanced jejunal or ileal polyp or in patients who are symptomatic.

Recommendations. In summary, the optimal strategy is to screen patients with the highest risk for having jejunal and ileal adenomas (patients with advanced Spigelman stage IV duodenal polyposis). CE and MRE are the most sensitive diagnostic tests to evaluate small-bowel polyps. The overall risk for small-bowel cancer is rare; therefore, routine enteroscopy is not recommended. However, enteroscopy, whichever modality is available, can be considered for therapeutic intent in patients with a positive CE or MRE, who are symptomatic, and in the context of preoperative screening in patients awaiting duodenal surgery to possibly identify advanced deeper small-bowel lesions and to avoid reconstruction with a small-bowel segment with a high density of adenomas.

CHEMOPREVENTION

Although the management of FAP has relied on endoscopic and surgical treatments, most notably colectomy, which has reduced the risk of cancer death, both are associated with adverse events and neither can prevent the development of new adenomas. Medication to reduce polyp burden and negate or delay the need for surgery therefore is a very attractive concept. Nonsteroidal anti-inflammatory drugs, particularly sulindac, is the most extensively studied and clinically used chemoprevention agent.

Chemoprevention in the colon

Sulindac. The seminal study that supports the use of sulindac is a randomized controlled trial of 22 FAP patients (18 of whom had not yet undergone colectomy) who were treated for 9 months with sulindac (150 mg twice a day) and assessed with endoscopy every 3 months.[160] There was a 56% reduction in adenoma count and 65% reduction in average adenoma size. However, no patient had complete adenoma regression, and regrowth of polyps was observed soon after discontinuation of therapy, suggesting the need for continuous treatment. Similar results have been reported by others with various doses, routes of administration, and length of follow-up.[161-163] There has been growing concern of a risk of interval cancer during therapy with sulindac because of a transformation of polyp morphology into a sessile nature, making them more difficult to visualize and resect with colonoscopy.[164,165] Sulindac (150 mg twice daily) can be used for the control of polyposis in the retained rectum of FAP patients with a colectomy and IRA or IPAA with rectal cuff. Because of the risk of interval cancer, patients must continue annual surveillance while on therapy.

Other chemopreventive agents. A cyclooxygenase-2 selective inhibitor, such as celecoxib, has the theoretical advantage of reduced GI adverse effects and was found to have an effect on adenoma regression at doses of 400 mg twice a day.[166,167] However, the U.S. Food and Drug Administration indication for celecoxib in FAP was recently withdrawn because of a failure by the pharmaceutical company to perform a postmarketing study intended to verify clinical benefit. Most recently, a chemoprevention trial involving dual inhibition of cyclooxygenase and epidermal growth factor receptor signaling (using a combination of sulindac and erlotinib) found a nearly 70% regression in colorectal adenomas after only 6 months of therapy.[168]

Chemoprevention in the duodenum

Chemoprevention has also been applied to the unmet need of decreasing duodenal neoplasia in FAP, particularly given the morbidity associated with pancreaticoduodenectomy and ampullectomy. Unfortunately, sole therapy with nonsteroidal anti-inflammatory drugs has minimal efficacy in the prevention of duodenal adenomas.[169,170] A randomized controlled trial of 92 FAP patients treated with dual cyclooxygenase and epidermal growth factor receptor inhibition (sulindac 150 mg twice daily and erlotinib 75 mg daily) reported a 71% decrease in duodenal polyp burden after 6 months of therapy.[171] However, the use of erlotinib at the doses used in the trial may be limited by the frequency of side effects, primarily an acne-like rash. A follow-up multicenter clinical trial with erlotinib is now underway to explore alternative dosing options to mitigate side effects while retaining chemopreventive efficacy.[172]

CONCLUSION

Hereditary adenomatous polyposis syndromes encompass groups of individuals at high risk for CRC and extracolonic malignancies. Colonic phenotypes may differ in FAP, AFAP, and MAP, and therefore genetic testing and counseling are warranted. In AFAP, there is proximal colon predominance with a later onset than FAP. MAP is autosomal recessive, is also later in onset, and is associated with more serrated adenomas. We await further natural history and surveillance outcome data regarding monoallelic and biallelic mutations in *MUTYH* to further clarify the role of endoscopic management, including upper GI risks.

Surveillance in FAP has decreased the incidence of CRC and CRC-related deaths. Patients are living longer and are at risk of developing extracolonic malignancies seen later in their life, with gastric and duodenal cancers occurring approximately 20 years after colectomy. Clinicians should be aware of high-risk endoscopic features, such as thick gastric polyposis mounds and Spigelman stage IV disease, with particular attention to the periampullary region, given the predilection for malignancy in these locations. Endoscopic polypectomy and ampullectomy, performed by expert endoscopists, can be successfully and safely performed. Because it is not possible to remove all adenomas, a targeted approach to resect high-risk lesions such as villous and dysplastic polyps and polyps >1 cm is advised. Future studies with standardized therapeutic endoscopic protocols are needed. The goal of endoscopic management is to downstage disease with close surveillance, thus avoiding symptomatic presentation of malignancy, which portends a poorer prognosis. However, it is not known if decreasing polyp burden, whether endoscopically or through chemoprevention agents, reduces overall risk for cancer. Once the polyposis burden is difficult to manage endoscopically, surgical consultation is needed. A multidisciplinary team approach to the care of this patient population is essential.

Recommendations

1. We recommend genetic counseling and testing in patients with clinical polyposis defined as 10 or more adenomas found on a single endoscopy and 20 or more adenomas during their lifetime. ⊕⊕○○
2. We recommend genetic counseling and testing in all first-degree relatives of confirmed polyposis syndrome patients. Suspected FAP individuals should be tested at ages 10 to 12 years, whereas suspected AFAP and MAP should be tested at ages 18 to 20 years. ⊕⊕○○
3. We recommend screening sigmoidoscopy or colonoscopy in children with or suspected to have FAP starting at ages 10 to 12 years. We recommend follow-up colonoscopy for patients found to have rectosigmoid polyps if sigmoidoscopy was the initial screening test. In patients with negative sigmoidoscopy findings, colonoscopy screening should be offered starting in late teen years. ⊕⊕⊕○
4. We recommend surveillance colonoscopy at 1- to 2-year intervals in FAP. ⊕⊕⊕○
5. We recommend screening colonoscopy in patients with or suspected to have AFAP starting at ages 18 to 20 years. ⊕⊕○○
6. We recommend surveillance colonoscopy at 1- to 2-year intervals in AFAP. ⊕⊕○○
7. We recommend screening colonoscopy at ages 18 to 20 years in patients with or suspected to have MAP. ⊕⊕○○
8. We recommend surveillance colonoscopy at 1- to 2-year intervals in MAP. ⊕⊕○○
9. We recommend a pouch endoscopy or ileoscopy in patients with IPAA or ileostomy surgery at 1- to 2-year intervals. ⊕○○○
10. We recommend a sigmoidoscopy in patients with IRA surgery at 6-month to 1-year intervals indefinitely. ⊕○○○
11. We recommend upper GI surveillance based on the interval advised for the most severely affected organ, whether stomach or duodenum. ⊕⊕○○
12. Surveillance examinations should include random biopsy sampling as well as targeted biopsy sampling of any suspicious lesions to assess for dysplasia and accurate duodenal Spigelman stage. Baseline Spigelman score $\geq$7 is associated with the development of duodenal HGD. ⊕⊕○○
13. We recommend endoscopic resection of gastric and duodenal polyps >1 cm, given the risk of developing dysplasia. ⊕⊕○○
14. We recommend endoscopic resection of all antral polyps, given the predominance of gastric adenomas in this location. ⊕⊕○○
15. We recommend careful examination of the ampulla and periampullary region using a duodenoscope or cap-assisted gastroscope, given the predilection for cancer in this area. ⊕⊕○○
16. We recommend biopsy sampling of the ampulla to assess for villous histology or dysplasia for only those with an identifiable mucosal abnormality, with care taken to avoid the pancreatic orifice because of the risk for pancreatitis. ⊕⊕○○
17. We recommend the use of chemopreventive agents within the confines of a tertiary hereditary cancer center and/or as part of clinical trials, because data are still emerging regarding its clinical application in hereditary polyposis syndromes. ⊕○○○

ACKNOWLEDGMENT

We thank Lisa A. Marks, MLS, AHIP, and Swati Patel, MD, for their contributions to the guideline.

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Abbreviations: AFAP, attenuated familial adenomatous polyposis; APC, adenomatous polyposis coli; ASGE, American Society for Gastrointestinal Endoscopy; CE, capsule endoscopy; CRC, colorectal cancer; FAP, familial adenomatous polyposis; FGP, fundic gland polyp; HGD, high-grade dysplasia; IPAA, ileal pouch anal anastomosis; IRA, ileorectal anastomosis; MAP, MUTYH-associated polyposis; MRE, magnetic resonance enterography.

DISCLOSURE: *J. Yang is a consultant for Olympus. S. Gurudu has received a research grant from Gilead Pharmaceuticals. C. Koptiuch disclosed no financial relationships. D. Agrawal disclosed no financial relationships. J. Buxbaum is a consultant for Olympus and Boston Scientific; and has received research support from Covidien. S. Fehmi disclosed no financial relationships. D. Fishman disclosed no financial relationships. M. Khashab is a consultant for BSCI, Olympus, and Medtronic. L. Jamil is a consultant and speaker for Aries Pharmaceutical. T. Jue disclosed no financial relationships. J. Law disclosed no financial relationships. J. Lee disclosed no financial relationships. M. Naveed disclosed no financial relationships. B. Qumseya disclosed no financial relationships. M. Sawhney is a stockholder with Allurion Technology, Inc. N. Thosani is a consultant for Boston Scientific, Medtronic, Endogastric Solutions, and Pentax of America; a speaker for Abbvie, and receives royalties from UpToDate. S. Wani is a consultant for Boston Scientific, Medtronic, and Interpace, and is on the advisory board for Cernostics. N. Samadder is a consultant for Jansen Research and Development and Cancer Prevention Pharmaceuticals.*

Received January 17, 2020. Accepted January 18, 2020.

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APPENDIX 1

OVID

Database(s): Embase 1988 to 2018 Week 20, EBM Reviews – Cochrane Database of Systematic Reviews 2005 to May 9, 2018. Search strategy was as follows for DIAGNOSIS:

Number	Searches
1	exp familial colon polyposis/di [Diagnosis]
2	enteroscopy.mp
3	exp capsule endoscopy/
4	exp sigmoidoscopy
5	exp colonoscopy
6	exp endoscopy
7	2 OR 3 OR 4 OR 5 OR 6
8	1 AND 7
9	limit 8 to (editorial OR letter OR report)
10	8 NOT 9
10	2005 to Current

Database: PubMed 2005 to Current. Search strategy was as follows for DIAGNOSIS:

Number	Searches
1	Adenomatous polyposis coli/diagnosis [Mesh]
2	"sigmoidoscopy"[Mesh] OR "capsule endoscopy"[Mesh] OR enteroscopy OR "colonoscopy"[Mesh] OR "endoscopy"[Mesh]
3	("2005/01/01"[PDat] : "2018/05/31"[PDat]
4	1 AND 2 AND 3
5	(case reports[ptyp] OR editorial[ptyp] OR letter[ptyp]
6	4 NOT 5

Database: Scopus 2005 to Current. Search strategy was as follows for DIAGNOSIS:

1. TITLE-ABS-KEY (familial AND adenomatous AND polyposis)
2. TITLE-ABS-KEY (enteroscopy OR capsule AND endoscopy OR sigmoidoscopy OR colonoscopy OR endoscopy)
3. #1 AND #2
4. DOCTYPE(le) OR DOCTYPE(ed)
5. #3 NOT #4
6. DATE RANGE: 2005 to Present

OVID

Database(s): Embase 1988 to 2018 Week 20, EBM Reviews–Cochrane Database of Systematic Reviews 2005 to May 9, 2018. Search strategy was as follows for THERAPY:

Number	Searches
1	exp familial colon polyposis OR familial adenomatous polyposis.mp
2	enteroscopy.mp
3	capsule endoscopy.mp OR exp capsule endoscopy/
4	sigmoidoscopy.mp OR exp sigmoidoscopy
5	colonoscopy.mp OR exp colonoscopy
6	Endoscopy.mp OR exp endoscopy
7	2 OR 3 OR 4 OR 5 OR 6
8	1 AND 7
9	(treatment OR therap*).mp [mp.=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
10	8 AND 9
11	limit 10 to (editorial OR letter OR report)
12	10 NOT 11
13	2005 to Current

Database: PubMed 2005 to Current. Search strategy was as follows for THERAPY:

Number	Searches
1	Adenomatous polyposis coli/therapy [Mesh] OR familial adenomatous polyposis
2	"sigmoidoscopy/therapeutic use"[Mesh] OR "capsule endoscopy/therapeutic use"[Mesh] OR "colonoscopy/ therapeutic use" [Mesh] OR "endoscopy/therapeutic use"[Mesh] OR enteroscopy
3	("2005/01/01"[PDat] : "2018/05/31"[PDat]
4	1 AND 2 AND 3
5	(case reports[ptyp] OR editorial[ptyp] OR letter[ptyp]
6	4 NOT 5

Database: Scopus 2005 to Current. Search strategy was as follows for THERAPY:

1. TITLE-ABS-KEY (familial AND adenomatous AND polyposis)
2. TITLE-ABS-KEY (enteroscopy OR capsule AND endoscopy OR sigmoidoscopy OR colonoscopy OR endoscopy)
3. #1 AND #2
4. TITLE-ABS-KEY (treatment OR therap*)
5. #3 AND #4
6. DOCTYPE(le) OR DOCTYPE(ed)
7. #5 NOT #6
8. DATE RANGE: 2005 to Present