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Genetics in Gastroenterology Practice (BW Katona, Section Editor)

Management of Familial Adenomatous Polyposis

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Abstract

Purpose of review This paper reviews important aspects in the management of individuals with familial adenomatous polyposis (FAP).
Recent findings Newly discovered germline pathogenic variants (PVs) beyond *APC* are a rare cause of adenomatous polyposis. The decreasing cost of multi-gene panel testing (MGPT) has broadened the use of commercial panels to enhance the genetic diagnosis of adenomatous polyposis in families where the causative germline PV in *APC* is not known. We elucidate emerging risks of cancer in FAP particularly gastric cancer and provide best practices to surveillance and cancer prevention in FAP, including dual therapy chemoprevention and trials utilizing novel mechanisms.
Summary Genetic testing is indicated in individuals with ≥ 10 lifetime adenomas. FAP and *MutYH*-associated polyposis (MAP) will be the most common germline causes of colorectal adenomatous polyposis. In FAP, upper endoscopy is indicated for surveillance of gastric polyposis and gastric cancer in addition to duodenal polyposis. Novel agents for chemoprevention have been shown to be effective and considered for selective use in patients with FAP.

Introduction

Familial adenomatous polyposis (FAP) is an autosomal-dominant hereditary cancer syndrome due to a germline pathogenic variant (PV) in the *APC* gene. FAP is characterized by colorectal polyposis and gastric and duodenal

polyposis, with an increased risk of colorectal, gastric, duodenal, and thyroid cancer, to name the most common. Approaches to chemoprevention and endoscopic management of polyps have been studied in the last 3 years. New guidelines provide management recommendation for patients with FAP.

Approach to determining the genetic cause of adenomatous polyposis

When faced with an individual with ≥ 10 cumulative lifetime colorectal adenomas, it is important to understand if there is a hereditary cause of the phenotype. If a germline PV causing the polyposis is detected, other organs at risk of cancer require specific surveillance, and genetic testing of at-risk family members needs to be incorporated into the family management plan.

The most widely understood germline cause of colorectal adenomatous polyposis is due to a PV in the tumor suppressor gene *APC* which causes FAP. There are over 1000 germline PVs in *APC*, and variability in colorectal polyposis phenotype in FAP has been correlated to certain genotypes [1]. PVs in exon 9 and the 5′ and 3′ of the *APC* gene have been associated with an attenuated colorectal polyposis phenotype, known as attenuated FAP (AFAP), defined as < 100 colorectal adenomas. Deletions in the *APC* promoter 1B can cause classic FAP while point mutations in *APC* promoter 1B cause the rare, gastric polyposis, and gastric cancer syndrome called gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), which is not associated with colorectal polyposis [2, 3]. Bi-allelic PV in *MutYH*, a gene that codes a DNA glycosylase involved in base excision repair, is another cause of adenomatous polyposis, called *MutYH*-associated polyposis (MAP) which usually has an attenuated phenotype [4]. Both FAP and MAP are associated with colorectal, duodenal, and thyroid cancer. Additional extracolonic cancers in MAP have been reported and include urothelial and ovarian cancer [5, 6]. One study of 8676 individuals who underwent full gene sequencing and large rearrangement analysis of *APC* and targeted sequence analysis of the 2 most common *MutYH* mutations (Y179C and G396D) found that the prevalence of PV in *APC* and *MutYH* were similar for oligopolyposis, though a PV in *APC* was far more likely for individuals with 100 or more adenomas [7].

Germline testing for a genetic cause of adenomatous polyposis should be considered in individuals with 10–19 lifetime cumulative adenomas, and performed in those with ≥ 20 adenomas or in a family with a known PV in a polyposis gene [8]. The clinical approach to germline genetic testing for patients and families with adenomatous polyposis has significantly changed since the implementation of next-generation sequencing (NGS) technology and the use of multi-gene panel testing (MGPT) [9]. MGPT can, at an affordable cost, efficiently analyze a set of genes associated with a specific syndrome or multiple cancer syndromes. Patients with a known family germline PV causing adenomatous polyposis should undergo testing for that PV. If the PV is not known in the family, MGPT should be offered. MGPT includes assessment of PVs in *APC* and *MutYH* but also includes the newly discovered polyposis genes which are responsible for novel, yet rare adenomatous polyposis syndromes (Table 1). The prevalence of these novel polyposis syndromes in the population has not

Table 1. Novel hereditary adenomatous polyposis syndromes

Syndromes	Mode of transmission	Genetic mutation	Clinical features	Recommendations according to the 2020 NCCN guidelines [8]
NTHL-1-associated polyposis (NAP) [10]	Autosomal recessive	Mutation in *NTLH1*, a glycoslase involved in base excision repair	Adenomatous polyposis Multi-tumor syndrome due to multiple extracolonic cancers reported meningioma, bladder, basal cell carcinoma breast, and endometrial cancers.	Screening colonoscopy at age 25–30 and every 2–3 years in patients without polyps. If polyps present, recommend colonoscopy every 1–2 years. Consider surgical evaluation in patients with high polyp burden that is not endoscopically manageable.
POLE and *POLD1*: polymerase proofreading-associated polyposis (PPAP) [11]	Autosomal-dominant	Mutation in the exonuclease domains of the DNA polymerase epsilon (*POLE*) and delta (*POLD1*)	Oligopolyposis Extracolonic tumors: Endometrial (female *POLD1* carriers), and gastroduodenal adenomas	
MSH3 polyposis [12]	Autosomal recessive	Germline bi-allelic mutation of *MSH3*	Adenomatous polyposis; Benign and malignant tumors	
Axin2-associated polyposis [13]	Autosomal-dominant	*Axin 2*, a negative regulator of the WNT pathway, contributes to the assembly of the B-catenin degradation complex.	Adenomatous polyposis; Severe permanent tooth agenesis (oligodontia); Mild ectodermal dysplasia (sparse hair and eyebrows)	
GREM1-associated mixed polyposis [14]	Autosomal-dominant	40-kb duplication upstream of *GREM1* in Ashkenazi Jewish ancestry 16-kb duplication upstream of *GREM*1 in non-Ashkenazi Jewish descent	Colorectal polyps containing a mixture of histologies including adenomatous, serrated, and inflammatory features	
Colonic polyposis of unknown etiology (CPUE)		No known pathogenic mutation found	Variable number of adenomatous polyps	Patients with ≥ 100 adenomas should be managed as FAP; patients with > 20 to < 100 should have colonoscopy every 1–2 years.

Table 2. Randomized control trials in FAP enrolling > 20 individuals

Drug	Organ	Dose	Comparator	Study Length	Findings	Other
Sulindac (29)	Colon	150mg BID 75/150mg BID	Placebo Placebo	9 mos 48 mos	n=22 (18 pre colectomy).: 44% ⬇ number, 35% ⬇ diameter n=41 (no polyps at BL) – TAs developed in 43% vs 55% placebo (NS)	Recurrence after 3 mos
Sulindac (30, 31)	Duodenum	200mg BID 200mg BID	Placebo Placebo	6 mos 6 mos	N=24 Stage III/IV SS: N=24. No difference between groups in proportion of "better", "same", or "worse" Video re-review of above – ≤2mm: 9/11 vs 4/12 placebo regressed. 2/11 vs 5/12 with new polyps. >2mm – no change.	Effective for small polyps on re-review
Celecoxib (32-34)	Post-colectomy Duodenum Colon	400mg BID 100mg BID 400mg BID 16mg/kg/day	Placebo Placebo Placebo	6mos 6 mos 60 mos	N=77 (post colectomy, min 5 rectal polyps): 28% ⬇ number vs 4.5% placebo Secondary analysis of above. Qualitative and quantitative improvement. No improvement with 100mg. N=106 pediatrics. Med tx duration 23.3 mos treatment vs 25.5 placebo. Endpoint – disease progression (≥20polyps >2mm). 12.7 tx vs 25.5% pl) in 2 vs 1.1 years.	 Terminated early for low disease progression
Aspirin ± Starch (35, 38)	Rectosigmoid pre-colectomy	ASA -/600mg 30mg 100mg	Placebo ,±starch (30mg) Placebo	17mos 6 mos	N=133, 10-21yo. No reduction in number with trend toward diameter reduction. Subgroup >1 year had significant decrease in diameter N=34	 Terminated for complications (underpowered)
Eicosopantoneic acid (37)	Post-colectomy		Placebo	6mos	N=58. 22.4% ⬇ count & 29.8% ⬇ size vs placebo	
Curcumin (39)	Pre-colectomy	3g daily	Placebo	12 mos	No change in polyp number or size	
Vit. C (40)	Post-colectomy	3g daily	Placebo	18 mos	N=49. No change in polyp number or surface area	
Vit.C/E Fiber (41)	Post-colectomy	Vit C 4g, Fiber 22.5g, Vit E 400mg daily		48 mos	N=62. No difference in polyp numbers at 48 mos. High fiber ⬇ number at 27 and 33 mos	Limited by various group combinations
DMFO/Celecoxib (42)	Colon	0.5g/m2/day 400mg BID	Celecoxib	6 mos	N = 375. No significant difference in reduction of number (11 vs 1%), burden (32 vs 22%), and video burden rating (49vs 26%) in specific colon areas. Secondary analysis – video ratings of those with complete polyps counts of whole colon resulted in qualitative significant reduction.	
Eflorniithin	Duodenum	750mg	3 arms	48 mos	N=100, 33-34/arm. Disease progression – 39% (arm	Substantia

Table 2. (continued)

e/Sulindac (43)	Pre-colectomy Post-colectomy	Eflornithine (arm1), 150mg sulindac (arm 2), or both daily (arm 3)			1), 41% (arm 2), 46% (arm3) N=37, 12-13/arm. Disease progression – 42% (arm 1), 46% (arm 2), 17% (arm3) N=34, 11-12/arm. Disease progression – 42% (arm 1), 18% (arm 2), 36% (arm3) No difference between arms for disease progression (composite of surgery, endoscopic excision of advanced adenoma, HGD in rectum or pouch, duodenal disease progression).	l improvement in global polyp burden Pts in the combo arm did not require advanced adenoma resection or lower-GI surgery
Erlotinib/Sulindac (44, 45)	Duodenum Colon, IPAA, IRA	75mg daily 150mg BID	Placebo	6 mos	N=92. Significant change in median duodenal polyp burden (-19) and count (-8). Secondary analysis of above trial. 69.4% difference in number change.	More profound effect in those with high duodenal polyp burden N=82.

yet been determined. In cohort studies of patients with unexplained polyposis or early-onset colorectal cancer, the prevalence of a common germline mutation in *POLE*: polymerase proofreading-associated polyposis, encoding the pathogenic p.Lys424Val, was reported in 1:67 to 1:858 individuals. Compared to MAP, the prevalence of *NTHL1*-associated polyposis in the European population is estimated to be at least five times lower (1: 114770) [11, 15]. Despite their rarity, these newly discovered adenomatous polyposis syndromes are presumed to carry a higher risk of colorectal and other cancers compared to average risk individuals based on limited series and case reports.

The utility of MGPT has been made obvious in a recent study in 450 colorectal cancer patients younger than 50 years old. PVs were identified by MGPT in more than 30% of patients who did not meet the National Comprehensive Cancer Network (NCCN) guideline testing criteria for the PV [15]. The increased diagnostic yield of pan-cancer MGPT must be balanced against the identification of a PV in poorly described cancer risk genes, and the high detection of variants of unknown significance.

Despite high throughput DNA sequencing, up to 30% of patients with more than 100 adenomas and up to 90% of patients with 10–90 adenomas have no PV identified on genetic testing. The term often used to describe the phenotype of patients with genotype-negative adenomatous polyposis is colonic polyposis of unknown etiology (CPUE). CPUE patients with more than ≥ 20 lifetime cumulative adenomas should be managed as if they have FAP, and those with 10–19 adenomas should be surveilled based on their personal (adenoma burden) and family history.

Novel findings impacting patient management

While upper endoscopy has been a standard of care for surveillance of duodenal polyposis and ampullary adenomas in FAP, a newly emerging finding which should alter the upper endoscopic surveillance of patients with FAP is the occurrence of gastric cancer. Nearly all patients with FAP will develop gastric fundic gland polyposis but gastric cancer in non-Asian patients with FAP was considered rare. Two recent studies from Europe and the USA have reported an increasing incidence of gastric cancer [16••, 17]. One report from the USA observed it in 1.3% of 767 patients with FAP undergoing EGD surveillance with a standardized incidence ratio of 140 compared to the general population [16••]. We suspect that the rising incidence of gastric cancer is due to a combination of better survival and environmental exposure. The average age of diagnosis is 57, and many have a trend toward advanced duodenal disease as well [18]. The gastric cancers are solitary, often advanced when detected, and located in the proximal stomach. Endoscopic features associated with gastric cancer include a carpeting of proximal gastric polyposis, which may make detection of the precursor lesion difficult, solitary proximal gastric polyps > 20 mm, polypoid mounds of proximal polyps, and white mucosal patches in the proximal stomach [19]. While the precursor lesion of FAP-associated gastric cancer is not confirmed, it is likely due to adenomatous polyps in the proximal stomach which have been found to be more prevalent than in patients with FAP who did not develop gastric cancer. These presumed high-risk lesions include polypoid intestinal metaplasia, gastric adenomas, fundic gland polyps with high-grade dysplasia, and pyloric gland adenomas [18]. Fundic gland polyps are observed in nearly 90% of individuals with FAP. Nearly half of fundic gland polyps in the setting of FAP harbor low-grade foveolar dysplasia. In contrast, the finding of low-grade dysplasia is rare in individuals with sporadic fundic gland polyps. The finding of fundic gland polyp low-grade dysplasia is of no known clinical consequence and does not in and of itself warrant intervention. Endoscopic imaging criteria to help endoscopists identify high-risk polyps include a surface color on high-definition white light that was lighter or darker than the background mucosa, an open pit pattern, unsmooth surface, and other than color, appear similar under HDWL and NBI [20••]. Experts have recommended EGD surveillance include evaluation of the duodenum and stomach and be done at the shorter interval based upon the organ with most severe disease. In the proximal stomach, random biopsy of numerous polyps, snare resection of unusually appearing polyps, polyps ≥ 10 mm, and antral lesions is encouraged. Proximal mucosal white patches and polypoid mounds should also be resected. We suggest an EGD interval of 3 months to 3 years based upon the severity of

proximal gastric polyposis and cross-sectional imaging to survey for local and deep invasion of polypoid mounds due to the frequent finding of metastatic disease. Patients with high-grade dysplasia or cancer should be recommended to undergo gastrectomy.

Estimates for duodenal cancer risk come from the Spigelman stage of duodenal polypsis, which incorporates polyp number, size, grade of dysplasia, and villosity. In a case-control study on FAP patients with duodenal cancer, 53% of cases did not progress through the highest Spigelman stage and that the Spigelman components of size and high-grade dysplasia but not number nor villous pathology were associated with cancer. Furthermore, villous pathology of the papilla was strongly associated (80% vs 22%) with duodenal, including non-ampullary, cancer [21]. A review of 273 papilla biopsies performed over 792 EGDs and found that the results increased the Spigelman stage in 13.2% with only 2 cases of pancreatitis [22]. Taken together, these studies provide evidence for biopsy of the papilla during EGD surveillance and increased awareness of duodenal cancer risk in those with pathologically advanced adenoma of the papilla. Finally, once individuals do have duodenectomy for advanced duodenal polyposis, endoscopic surveillance should continue as duodenal bulb and jejunal polyposis are frequently diagnosed post-operatively. Out of 64 duodenectomy cases, 59% had jejunal polyposis at a median 55 months post-operatively with advanced lesions in a fifth [23]. Once individuals with advanced duodenal neoplasia have been downstaged or undergone duodenectomy, standard forward viewing upper endoscopic surveillance should continue no less frequently than on an annual basis or more frequently pending findings in the duodenal bulb or jejunum. While no data exists on the routine utility of deeper small bowel surveillance by either enteroscopy or capsule endoscopy in FAP, we suggest a baseline capsule assessment in patients with stage III or stage IV duodenal polyposis and repeat it every 3 years in those who have undergone duodenectomy for advanced duodenal polyposis. We do attempt endoscopic resection when polyps do occur, though it is technically difficult, particularly due to difficulty in lifting the lesion. Despite this, no cancers have been noted in 10 years of follow-up.

Individuals with FAP and AFAP are usually managed with a prophylactic colectomy with ileorectal anastomosis or total proctocolectomy with ileal pouch creation or as intervention for CRC treatment. The timing of and type of prophylactic surgery is determined by the polyp burden, degree of dysplasia, symptoms, presence of desmoids, and age, with consideration of other psychosocial issues. Sarvepalli assessed the need and timing for colon surgery in 168 patients with FAP with intact colons undergoing colonoscopy surveillance in a single FAP center who were a median 13.5 years of age. Forty-five percent underwent surgery after an average of 3.8 years of surveillance. A variety of factors enhanced the likelihood of surgery, while others mitigated it [24]. The clinical factors were used to develop an internally validated web-based model to predict the need for surgery within 2 and 5 years of first diagnosis, providing a tool for clinicians and families to plan for surgery [25]. The tool can be found at http://app.calculoid.com/#/calculator/29638. Once colectomy is performed, surveillance of the intact rectum or ileal pouch is recommended no less frequently than annually and more frequently pending findings. We suggest clearance of all adenomas when feasible or all adenomas ≥ 3 mm if the adenoma burden is profuse.

The third most common cause of cancer in FAP is that of the thyroid, for which annual thyroid ultrasounds are recommended. Monachese reviewed 264 patients who had at least 2 thyroid ultrasounds over a 10-year period, and found that individuals with a normal baseline exam did not develop cancer for the 5.1 year entirety of follow-up. This suggests that a baseline normal ultrasound may obviate the need for annual exams [26]. Supported by this data, the NCCN guidelines have extended the interval of thyroid ultrasound surveillance from annually in individuals whose baseline ultrasound is normal to every 2–5 years. Individuals with an abnormal ultrasound or family history of thyroid cancer should be managed by a thyroid specialist, and shorter ultrasound intervals may warrant pending findings [8].

Chemoprophylaxis of polyposis

FAP is a systemic disease which is not curable by surgery. The aim of management is to prevent cancer or detect it early and prevent death from cancer. In roads have been made in identifying targets for chemoprevention agents to control polyposis. They should be used in select individuals, not as the sole preventative modality, but always as an adjunct to endoscopic, and when needed, surgical management [27]

There are two overarching principles that guide chemoprophylaxis in FAP. First is the understanding that the duodenum and the colorectum are unique organs with different tissues, functions, and microenvironments. The downstream effects of a mutant APC protein and the response to therapy will differ between the two organs. Second, optimal chemoprophylaxis should decrease cancer-related mortality at a low cost and with minimal toxicity. To date, no drug has achieved this Holy Grail. They are used to delay surgery or decrease polyp burden in order to aid the endoscopist during surveillance. In a precolectomy population, individuals exposed to at least 3 months of NSAIDs had an annual rate of polyposis at a tenth of those not exposed (2.5 vs 25 polyps/year) [24]. Nevertheless, briefly reviewing the past highlights how we have arrived to the current state. Over the decades, drug development has focused on the inflammatory cascade and activated molecular pathways involved in colorectal cancer development in FAP, with initial efforts targeting single pathways. One function of *APC* is to regulate cyclooxygenase expression, the overexpression of which drives adenoma growth. Sulindac, a non-specific cyclooxygenase inhibitor (non-steroidal anti-inflammatory drug), was shown to reduce polyp number and size in the colorectum but not in the duodenum [28–31]. Celecoxib and rofecoxib, cyclooxygenase-2 inhibitors, have been shown to decrease polyp burden in both the duodenum and rectum [32–34]. Interestingly, 100- or 600-mg doses of aspirin do not have an effect on polyp size. NSAIDs have been associated with gastrointestinal and cardiovascular toxicity, and do not have a durable effect with a rapid recurrence of polyps when discontinued, and may mask cancers by shrinking or flattening polyps that make endoscopic detection difficult [28, 35]. For example, polyps reoccur within 3 months of sulindac discontinuation [36]. Free fatty acids reduce COX-2 expression, and eicosopentanoic free fatty acid has been shown to reduce rectal polyp burden [37]. Other single agents with anti-inflammatory properties include curcumin, vitamin E, vitamin C, lyophilized black berries,

and fiber (Table 2) [37, 39–41, 46].

Focus has shifted from single-drug strategies to combination therapy in the last 3–4 years. The many mutations and activated pathways that *APC*-deficient cells accumulate lead to cell proliferation by maneuvering around single-drug agents. Targeting multiple pathways may theoretically allow for synergistic growth suppression while minimizing drug toxicity by utilizing lower doses of individual drugs. Lynch et al. evaluated the synergistic effect of celecoxib and difluoromethylornithine (DMFO) on rectal adenoma count and burden. DMFO irreversibly inhibits ornithine decarboxylase, which limits the formation of polyamines, increased levels of which have been implicated in CRC. Experiments that demonstrated prostaglandin-dependent promotion of ornithine decarboxylase production, CRC reduction in $APC^{Min/+}$ mice that received combination therapy vs either agent alone, and human reduction in sporadic adenoma recurrence provided the biologic plausibility for the trial [46–48]. One hundred twelve adults with intact colons or rectums were randomized to receive 400 mg celecoxib and either 0.5 mg/kg DMFO or placebo for 6 months, with polyp count and burden estimated from still images that included landmarks such as the ileocecal valve, appendiceal orifice, rectum, and tattoos placed adjacent to polyp clusters. There was no difference between the groups for reduction in total polyp number (the primary outcome), but the combination therapy arm had a significant reduction in polyp burden on secondary analysis based on global assessment by video review. The underwhelming results were attributed to the low baseline polyp numbers, difficulty in assessing the primary endpoint on endoscopy in a mobile organ, and efficacy of celecoxib. In addition, GI toxicity and ototoxicity were worrisome side effects [42]. A phase III trial in 171 adults with FAP randomized to eflornithine (750 mg), sulindac (150 mg), or both once daily for up to 48 months assessed the time to progression to first FAP-related event including in the duodenum or lower gastrointestinal tract defined as a need for surgery, endoscopic excision of advanced adenomas, or duodenal stage progression. Overall, no significant difference was noted between the trial arms. However, a compelling finding showed no patients in the combination arm had a need for lower gastrointestinal surgery or advance adenoma resection which was not the case in the monotherapy arms. Importantly, no difference in toxicity was noted between arms [43].

In the duodenum, the combination of the epidermal growth factor receptor (EGFR) erlotinib and sulindac has shown to reduce polyp burden. A randomized control trial comparing the combination to placebo revealed a significant decrease in polyp burden, number, and size at 6 months, as well as lack of phosphorylation of EGFR (inactive). EGFR promotes COX-2 expression when active and phosphorylated. There was a significant reduction in polyp burden, count, and size even after accounting for presence or absence of *APC* mutation, baseline polyp burden, and attenuated versus classic FAP. Mechanistically, all EFGR isolates from 7 polyps in the treatment arm were unphosphorylated, while 6/7 from the placebo arm were phosphorylated. The most common adverse event was an erlotinib acneiform rash in 87% of participants [44••]. In our experience, the rash can be managed topically with steroids or antibiotics, but it can be widespread and resembles bad "teenage" acne. This may deter younger patients. A 6-month phase 2 study on the efficacy of once weekly dosing of erlotinib to reduce duodenal polyp burden in individuals with stage II

and III Spigelman stage polyposis just closed in May of 2020. The results will add perspective on the effects of sole EGFR pathway inhibition on individuals with earlier stage disease. A subgroup analysis of the study evaluating 22 intact colons, 44 pouches, and 16 individuals with an ileorectal anastomosis, which were distributed evenly between the treatment and placebo groups, resulted in a significant polyp reduction when stratified by amount of intact colon. Of note, the baseline median polyp count in individuals with intact colons was 39 (range 19–81), with a median decrease of 27 compared to 2 in the placebo group [45]. Though impressive, the clinical significance is unclear.

A novel mechanism with a trial currently under design is inhibition of mammalian target of rapamycin (mTOR), which plays an integral role in cellular growth and division. At high doses, mTOR inhibitors are utilized for immunosuppression in organ transplant recipients with a documented anti-neoplastic activity in these recipients. Interestingly, COX inhibition results in decreased mTOR signaling activity, $APC^{Min/+}$ treated with rapamycin have decreased polyp growth, and transgenic *APC* mice lacking functional APC protein survive over 3× longer than untreated mice with a < 5% polyp burden. Furthermore, two case studies have demonstrated a subjective decrease in colon polyp burden [49]. Another novel study took advantage of erythromycin's ability to "turn on" ribosomal translation of nonsense FAP gene mutations, which usually do not lead to any protein production. The colonic polyp number and burden significantly decreased in ten patients treated with 250–500 mg twice daily erythromycin for 4 months. Though small, this highlights that production of a faulty protein may be better than no protein and delay cancer onset [50].

Other trials currently enrolling or completed trials with results pended include a 6-month double-blind RCT on an anti-helminth niclosamide drug (inhibits Wnt pathway) for colorectal and duodenal polyps; a 2-year, double-blind phase III RCT on EPA-FFA capsules; a double-blind RCT with metformin (mTOR inhibition) on polyps in the duodenum and colorectum in non-diabetic FAP patients; a 6-month double-blind phase 1b RCT on the IL-23 inhibitor guselkumab on colorectal polyp burden; a 2-year, double-blind RCT on the combination of DMFO and sulindac in delaying time to the first occurrence of an FAP-related event compared to DMFO and sulindac alone; and an RCT evaluating berberine (Chinese herb with anti-tumorigenic activity) on colorectal adenomas [44••].

We recommend chemoprevention with sulindac 150 mg BID for colorectal polyposis patients (FAP or MAP) that have a progressive polyp burden and need to delay or refuse colorectal surgery after meeting with a colorectal surgeon and understanding the colorectal cancer risk. We generally use it when the polyp burden is over 100 with primarily small < 10-mm polyps. Larger polyps are less likely to respond. If they progress on therapy in size, morphology (flat and difficult to detect), or dysplasia (high-grade dysplasia), we recommend against endoscopic surveillance with chemoprophylaxis. Once they have had surgery, we recommend sulindac 150 mg BID in individuals with a rapid increase in burden or InSiGHT polyposis staging system (IPSS) stage III.

For the duodenum, we offer Celebrex 400 mg BID for advanced duodenal stage III or IV disease with the goal of preventing recurrent polyps. Celebrex is dually effective for the rectal polyp burden in these patients, and sulindac is not needed.

Conclusions

FAP is the best studied for hereditary adenomatous polyposis syndromes. Individuals with more than 10 cumulative lifetime adenomas should be evaluated for a germline PV in one of the adenomatous polyposis genes. MGPT has revolutionized the approach to germline genetic testing, and novel genes have been discovered to be associated with adenomatous polyposis. Patients with more than 20 adenomas and negative genetic testing should be managed as if they have FAP. Surveillance colonoscopy and lifelong upper endoscopy and thyroid ultrasound are standard of care. Once colectomy is performed, lower endoscopy must continue. Gastric cancer is a rising concern in FAP, and clinicians need to be familiar with the associated endoscopy and pathologic features of the presumed precursor lesions. Upper endoscopic management of gastric polyposis is necessary as is control of duodenal polyposis. Novel targets for chemoprevention are being studied. These agents when safe and effective should be used in select patients as an adjunct to endoscopy.

Compliance with Ethical Standards

Conflict of interest

GM is a co-investigator with trials that utilize guselkumab and erlotinib. CAB has been a co-investigator or lead investigator for multiple trials, active ones which include guselkumab, erlotinib, and sulindac/DMFO. CM declares that she has no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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