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How many is too many? Polyposis syndromes and what to do next

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Abstract

Purpose: This goal of this review is to help providers recognize, diagnose and manage gastrointestinal (GI) polyposis syndromes.

Recent findings: Intestinal polyps include a number of histological sub-types such as adenomas, serrated, hamartomas among others. Over a quarter of individuals undergoing screening colonoscopy are expected to have colonic adenomas. While it is not uncommon for adults to have a few GI polyps in their lifetime, some individuals are found to have multiple polyps of varying histology throughout the GI tract. In these individuals, depending on polyp histology, number, location and size as well as extra-intestinal features and/or family history, a polyposis syndrome should be considered with appropriate testing and management.

Summary: Diagnosis and management of polyposis syndromes has evolved with advent of multi-gene panel testing and new data on optimal surveillance strategies. Evidence-based recommendations and current practice guidelines for polyposis syndromes are reviewed here. Areas of uncertainty and future research are also highlighted.

Keywords

polyposis; genetics; adenomas; serrated polyps; hamartomas

Introduction

Performing risk assessment for polyposis syndromes can be complicated, as there are many genes that, when mutated, can increase the risk of polyps. Polyp histology, in particular, as well as polyp number, size and anatomic location of polyps can help narrow down the differential diagnosis (Figure 1). Testing for an adenomatous polyposis syndrome should be performed in an individual with 10 or more cumulative adenomas (1)(2). Adenomatous polyposis syndromes include familial adenomatous polyposis (FAP), *MUTYH*-associated

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polyposis (MAP) as well as a number of rare genetic or other non-genetic causes. Serrated polyposis syndrome (SPS) is defined by World Health Organization (WHO) criteria based on number, size and location of colonic serrated polyps(3); no definitive genetic basis for SPS has been identified. Hamartomatous polyposis syndromes include juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS) and PTEN hamartoma tumor syndromes (PHTS). Depending on the syndrome, hamartomas are found in the stomach, small intestine and/or colon with a number of extra-intestinal manifestations.

Currently, multi-gene panels are the preferred method of genetic testing (2)(4). Panel testing is cost effective, has a reasonable turnaround time, allows testing of many genes that may have overlapping phenotypes and is not dependent on family history knowledge. Identification of a pathogenic/likely pathogenic (P/LP) variant allows for appropriate management. A study of multigene panel testing in individuals with 10 or more polyps (5) showed that the likelihood of detecting a P/LP variant increases with the number of adenomatous polyps present, but not with the number of hamartomatous polyps. In total, 10.4% of patients with 10 or more polyps had a P/LP variant identified in a polyposis gene, while an additional 3.6% had a P/LP variant in a non-polyposis colorectal cancer gene for which surveillance guidelines exist. Once a P/LP variant has been identified, the patient should be counseled to inform family members so they can be tested (termed cascade testing).

Adenomatous polyposis syndromes

Familial adenomatous polyposis.

FAP results from P/LP variants in the *APC* gene and is inherited in an autosomal dominant fashion with nearly complete penetrance (6). The estimated live birth incidence of FAP is 1 in 8,000 to 1 to 10,000 (7). Nearly one third of FAP cases occur in individuals without a family history of the disease (6) due to *de novo* mutations or, as more recently reported, mosaicism (8)(9).

In classic FAP, 100s-1000s of synchronous adenomas carpet the colon. Attenuated FAP (AFAP) is characterized by oligopolyposis with polyp burden of 10s-100 adenomatous polyps (10). Gastric fundic gland polyps and duodenal adenomas are common in FAP, occurring in about 50% of cases (11), while adenomatous gastric polyps are less common. Other extracolonic manifestations of both FAP and AFAP can include papillary thyroid cancer, epidermal cysts, bone osteomas, desmoid tumors, adrenal gland adenomas, supernumerary teeth, and congenital hypertrophy of the retinal pigment epithelium (CHRPE) (12).

The lifetime risk of colon cancer in classic FAP approaches 100% with average age of onset 40 years, whereas in AFAP the lifetime risk is lower at 70% with average onset age closer to age 55 (13). Risk of duodenal cancer is increased and associated with duodenal polyposis burden. There is also a rising incidence of gastric cancer (14). For patients with the classic FAP phenotype, colonoscopy is recommended starting at age 10–12 and should be repeated every 1–2 years rated as having moderate level of evidence by the American Society of Gastrointestinal Endoscopy (ASGE) (15). In AFAP, colonoscopy should begin

at age 18 unless symptoms warrant earlier screening (6) for which quality of evidence was deemed low (15). Upper endoscopy with a clear cap or side viewing endoscope is recommended starting at around age 20–25 for the detection of dysplastic gastric polyps (with special attention to carpeted or polyp mounds (16)), duodenal adenomas, or ampullary adenomas due to risk of gastric and duodenal cancers. These recommendations are based on low quality of evidence per ASGE (15). Additionally, due the papillary thyroid cancer risk, thyroid ultrasound is recommended for FAP patients starting in the late teenage years, with repeat every 2–5 years if negative (6).

In cases where colon polyp burden becomes unmanageable endoscopically (either due to number or morphology), colectomy should be considered. Additionally, development of multiple large adenomas (>6mm), dysplasia, or suspected carcinoma are indications for consideration of surgery (6,13). Patients with classic FAP should be counseled early on eventual need for colectomy, though elective colectomy can be deferred to the second decade of life in those with low and resectable polyp burden. For patients undergoing colectomy, shared decision making should be utilized in determining the optical surgical approach based on patient specific factors. Patients with a resultant ileoanal anastomosis or ileal pouch anal anastomosis (IPAA) should undergo yearly endoscopic surveillance due to the continued risk of cancer development in these areas. Those with an end ileostomy should have surveillance every 2 years (17). The role of chemoprevention in management of FAP is actively being studied (18) with promising results for sulindac and erlotinib (19),(20),(21).

MUTYH polyposis.

MUTYH-associated polyposis (MAP) is an oligopolyposis syndrome characterized by the development of 10s to 100 colon polyps. MAP results from germline P/LP variants in the DNA base excision repair gene *MUTYH*. In contrast to FAP, inheritance is autosomal recessive and requires a homozygous or compound heterozygous mutation phenotype for expression of the disease (22). Colon polyps in MAP are most commonly adenomas, however a mixed polyposis with sessile serrated lesions/polyps and hyperplastic polyps can also be seen. Duodenal polyposis also occurs in approximately 15–21% of MAP cases (6, 23) and, based on results from a recent international study of nearly 400 MAP patients, duodenal adenoma burden was lower than in FAP but the Spigelman staging system failed to identify high risk individuals and duodenal cancers (23).

The lifetime risk of colorectal cancer in MAP is estimated at 80% without surveillance (24). Management of MAP includes colonoscopy beginning at age 20–25, repeated every 1–2 years if negative based on low quality of evidence (6, 15). Similar to FAP and AFAP, colectomy is recommended if polyp burden cannot be managed with endoscopic surveillance. Due to the 4% lifetime risk of duodenal adenomas, EGD (with assessment of the ampulla) is recommended starting at age 30–35 (25) which is also based on low quality evidence (15).

Monoallelic P/LP variants in *MUTYH* are found in 1–2% of the population and do not present with a polyposis phenotype (26). This is especially important to recognize because monoallelic *MUTYH* variants are one of the most common findings on multigene panel tests. The colon cancer risk in these cases is estimated to be slightly higher than the

general population especially with family history of colorectal cancer, though the absolute risk level is not well established (24). ACG guidelines recommend colonoscopy starting at age 40 in these patients with repeat screening exam every 5 years (6), while NCCN and ASGE recommend earlier surveillance only in individuals with a first degree relative with colorectal cancer (1,15).

Other polyposis syndromes.

A summary of other genes that lead to adenomatous polyposis (*POLE, POLD1, NTHL1, MSH3, MLH3, AXIN2* and *GREM1*) is shown in Table 1. In addition to these, patients with P/LP variants in Lynch syndrome genes, especially *MSH2* and *MSH6* (27), can present with an attenuated polyposis phenotype. Individuals with biallelic MMR mutations have a condition called Constitutional Mismatch Repair Deficiency syndrome (CMMRD), characterized by young onset malignancies of the GI tract, gliomas and lymphomas/leukemias. A study of 24 individuals with CMMRD identified 9 individuals with adenomas (one with high-grade dysplasia), in addition to 7 with colorectal cancer at initial colonoscopy (28).

Survivors of childhood or young adult cancers are at risk for therapy-associated polyposis (TAP). Clinical manifestations include polyposis with adenomas, serrated polyps, inflammatory/hamartomatous polyps and mixed polyp types (29). A recent multi-center study of 34 patients with TAP reported diagnosis an average of 27 years after initial treatment (30). The average number of polyps was 32, 94% of TAP patients had more than one histologic type, and 74% of patients who had an EGD had polyps in the upper GI tract. In total, 41% of patients had at least some of their colon resected; 50% for cancer and 50% for management of polyps. The authors propose current oncology specific colorectal cancer guidelines be expanded to include individuals receiving chemotherapy (without abdominopelvic radiation); colonoscopy every 5 years, beginning at age 35 (with modifications for age at time of chemotherapy or radiation) (31). They also recommend baseline EGD when colon polyposis is found.

Only 13.5% individuals with >10 adenomas had a P/LP variant on multigene panel testing, meaning that the cause of polyposis is not identified in most cases (5). An individual with a personal history of ≥10 polyps in the absence of an identifiable P/LP variant has a diagnosis of colonic polyposis of uncertain etiology (CPUE). It is likely that CPUE is due to low penetrance genetic and/or environmental factors (e.g., tobacco, alcohol, obesity, diet). NCCN recommends managing CPUE patients based on their personal and family history. Individuals with >100 adenomas should be followed as if they have FAP, while those with 20–99 polyps should have colonoscopy every 1–2 years. Patients with CPUE might also benefit of baseline EGD, with follow up based on findings. Patients with 11–20 adenomas should be managed based on clinical judgment and consider size, number, and type of polyp and family history.

Serrated Polyposis Syndrome

Serrated polyposis syndrome (SPS) is a clinical syndrome characterized by numerous cumulative colonic serrated lesions including traditional serrated adenomas, sessile serrated

polyps, and hyperplastic polyps. SPS is the most common colonic polyposis syndrome with primary screening cohort studies finding 1:239 (0.42%) of patients meet criteria for SPS (32), though it is likely underdiagnosed (33). Updated WHO criteria for SPS (34) are listed in Table 2. A definitive genetic cause for SPS has not been established, though P/LP variants in *RNF43* have been reported (35) but appear to be rare and not found in other cohorts (35, 36).

In SPS, colorectal cancer incidence is reported at 15–30% (32, 37). Once a diagnosis of SPS has been established, colonoscopy with polypectomy should be performed at short intervals to clear the initial polyp burden. Following this, surveillance colonoscopy is recommended every 1–3 years for polyp management (39–41) due to ongoing risk (42). Like other polyposis syndromes, surgical management should be considered when endoscopic management is no longer feasible.

Hamartomatous polyposis syndromes (Table 3)

Juvenile polyposis syndrome.

JPS has an estimated incidence of 1:16,000–1:100,000 live births. A clinical diagnosis is made when any one of the following is met: 5 or more juvenile polyps in the colon, multiple juvenile polyps in the GI tract or any number of juvenile polyps with family history of JPS (1). It should be noted that about 1% of children will develop a single juvenile polyp in their lifetime but should not be tested for JPS unless other clinical criteria are met. About 50% of individuals who meet clinical criteria are found to have P/LP variants in one of two genes involved in TGFß-signaling, *SMAD4* and *BMPR1A,* and is inherited in an autosomal dominant pattern. The primary clinical manifestations are juvenile polyps and cancers in the colon and stomach. Carriers of *SMAD4* P/LP variants are also at risk for hereditary hemorrhagic telangiectasia (HHT). A recent European multi-center study (43) characterized a large cohort of JPS patients (n=221 patients from 126 kindreds; 57% with P/LP variants in *SMAD4* or *BMPR1A*) (43). Compared to *BMPR1A* carriers, *SMAD4* carriers had higher prevalence of anemia (58% vs. 26%), HHT (32% vs. 0%) and gastric polyps (39% vs. 13%). Colonic polyps were found in both *BMPR1A* and *SMAD4* index carriers (91% and 86%) with more proximal distribution and numbering between 5–100. Overall cancer rate was 15% with 78% being identified before or at the time of JPS diagnosis. Colorectal cancer was found in 12% and 7% of *SMAD4* and *BMPR1A* carriers, respectively. Current US management guidelines recommend colonoscopy and upper endoscopy every 2–3 years (or more frequently based on polyps or symptoms) beginning at age 15; carriers of *SMAD4* P/LP variants should also be screened for HHT (1).

Peutz-Jeghers syndrome.

PJS has an estimated incidence of 1:50,000–1:200,000 live births. A clinical diagnosis is based on 2 or more of the following: 2 or more PJ hamartomas in the GI tract, characteristic mucocutaneous pigmentation and/or family history of PJS (1). The primary clinical manifestations vary by age. In children, complications related to small bowel hamartomas such as bleeding or intussusception are most common, while, in adults, cancer risks predominate. Given the rarity of PJS, accurate cancer risk estimates are challenging

due to small numbers and ascertainment bias. Within these limitations, lifetime estimates of GI cancer risks are: colorectal (36–39%), gastric (24–29%), small bowel (10–14%), and pancreatic (11–36%) (1, 43). Non-GI cancer risks include: breast (19–54%), sex cord/Sertoli cell ovarian (10–21%), cervical (10%), uterine (9%), testicular (9%) and lung (7–17%) (1, 43). About 80–94% of individuals with PJS are found to have a P/LP variant in *STK11* (also known as *LKB1*), and it is inherited in an autosomal dominant pattern.

Current US (1) and European guidelines (44) recommend upper and lower endoscopy starting at age 8 and repeating every 1–3 years if polyps are present; if no polyps present at index examinations, can start regular surveillance at age 18. Small bowel surveillance in asymptomatic patients is also recommended using MRI or video capsule endoscopy at age 8 and repeating every 1–3 years if polyps are present. If no small bowel polyps are seen on index exam, regular surveillance should begin at age 18 or earlier if symptoms develop. Surveillance for pancreatic and breast cancers is also advocated.

PTEN Hamartoma Tumor Syndrome.

PHTS refers to a spectrum of syndromes due to germline P/LP in the tumor suppressor gene *PTEN* of which Cowden syndrome is the most common. The estimated incidence of Cowden syndrome is 1:200,000, though this is likely an underestimate. The clinical manifestations include features such as cancers (breast, endometrial, follicular thyroid, colorectal and renal cell), hamartomas in the GI tract, large head circumference and various dermatological lesions. The lifetime risk of colorectal cancer is estimated to be 9–32% with median age of diagnosis of 46–58 years (45), though studies are limited by small size and ascertainment bias. Current US guidelines list major and minor criteria for establishing a clinical diagnosis. The GI manifestations can include glycogenic acanthosis of the esophagus as well as a number of polyp types such as hamartomas, ganglioneuromas, hyperplastic, inflammatory, and adenomas.

Management guidelines for the GI tract include colonoscopy beginning at age 35 (or 5–10 years before the earliest colorectal cancer in the family) with surveillance every 5 years or earlier based on symptoms or polyps. A recent study (46) evaluated outcomes of surveillance in 70 patients with PTEN P/LP variants who had at least 2 upper or lower endoscopies at a single center. There was no difference in size of number of GI polyps during surveillance. One colon cancer and one gastric cancer were diagnosed during surveillance, both of which were associated with large polyp phenotypes underscoring the importance of close surveillance based on polyp size.

Conclusion

The title of this review posed the question “How many is too many?” when it comes to polyps in the GI tract. As discussed in this review, the answer depends on polyp histology, anatomic location, size and other features. For adenomatous polyposis syndromes, guidelines recommend multigene panel testing for 10 or more adenomas. For serrated polyposis syndrome, clinical criteria are based on number, size and location of serrated lesions. For hamartomatous polyposis syndromes, clinical criteria depend on hamartoma sub-type and anatomic location along with a host of other intestinal and extra-intestinal

manifestations. Once a polyposis syndrome is suspected, the best next step is to refer to a specialized professional, such a genetic counselor, for further evaluation and multi-gene panel testing. Based on clinical criteria and genetic test results, management and cascade testing should follow current guidelines in order to reduce the burden of cancer in high-risk families. More research is needed to understand unexplained polyposis cases, to increase recognition and testing for polyposis syndromes, to develop robust evidence-based management guidelines and to study new treatment strategies such as chemoprevention.

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Key points:

- Identification of a polyposis syndrome depends on polyp histology, number, size, anatomic location, non-gastrointestinal manifestations and/or family history.
- Multi-gene panel testing is recommended when a polyposis syndrome is suspected given the number of genes implicated and cost-effectiveness of testing multiple genes simultaneously.
- An adenomatous polyposis syndrome, such as familial adenomatous polyposis, MUTYH-associated polyposis or a number of rare syndromes, should be suspected with 10 or more cumulative adenomas.
- Serrated polyposis syndrome, the most common polyposis syndrome for which a genetic basis has not been definitively established, should be suspected based on the number, size and anatomic location of serrated lesions in the colon; once identified, patients should undergo regular surveillance given increased risk of colorectal cancer.
- Hamartomatous polyposis syndromes, Juvenile Polyposis syndrome, Peutz-Jeghers syndrome and PTEN Hamartoma Tumor syndrome, are rare and manifest with multiple malignant and benign features that should be managed by a multi-disciplinary team.

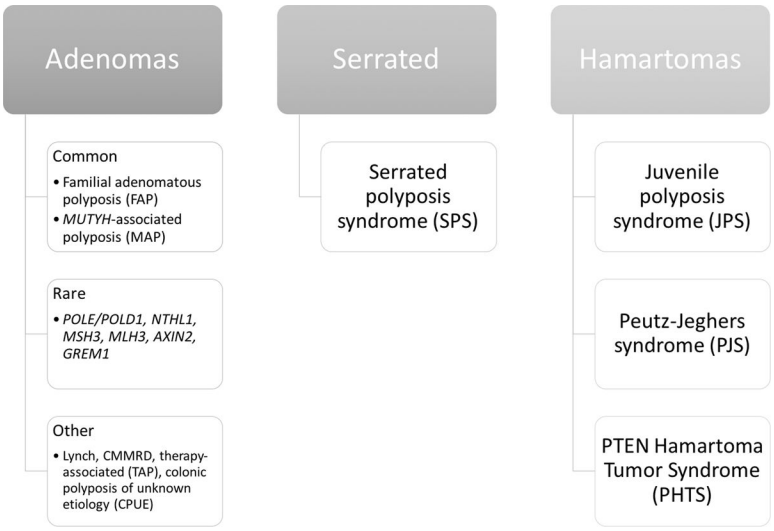

Figure 1: Gastrointestinal polyposis syndromes.

Gastrointestinal polyposis syndromes can be classified based on the predominant polyp histology: adenomas, serrated polyps and hamartomas. The most common and best characterized adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP). A number of additional genes have been implicated in adenomatous polyposis including: *POLE/POLD1, NTHL1, MSH3, MLH3, AXIN2* and *GREM1* (associated with hereditary mixed polyposis syndrome). Other conditions that present with adenomatous polyposis include Lynch syndrome (especially *MSH2* and *MSH6*), constitutional mismatch repair deficiency (CMMRD), therapy-associated polyposis (TAP) in childhood and young adult cancer survivors and colonic polyposis of unknown etiology (CPUE) which includes a heterogeneous group of patients with unexplained polyposis ranging from phenotypes similar to FAP to more attenuated phenotypes likely related to low-penetrance genetic and environmental factors (tobacco, alcohol, obesity and poor diet). Serrated polyposis syndrome is defined clinically by World Health Organization criteria based on number, size, and location of serrated lesions. Hamartomas are overgrowth of normal gastrointestinal tissue. Hamartomatous polyposis syndromes are rare and include Juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS) and PTEN Hamartoma Tumor Syndrome (PHTS) of which Cowden syndrome is the most commonly encountered.

Table 1:

Rare adenomatous polyposis syndromes

Gene(s)/ function	Inheritance	Clinical features	References
POLE/POLD1 Polymerase proofreading	AD	• Adenomas (10s-100) • Colorectal, endometrial & brain cancers • Overlap features with Lynch and CMMRD	(47–61)
NTHL1 Base excision repair	AR	• Adenomas (10s-100) • Colorectal cancer • Breast cancer • Possibly other cancers	(62–76)
MSH3 Mismatch repair	AR	• Adenomas (10s-100) • Colorectal cancer	(76, 77)
MLH3 Mismatch repair	AR	• Adenomas (10s-100) • Colorectal cancer	(79,80)
AXIN2 Wnt-signaling	AD	• Adenomas (10s-100) • Colorectal cancer • Oligodontia	(81–89)
GREM1 TGFß-signaling	AD	• Duplication found in AJ families • Mixed polyps (called Hereditary Mixed Polyposis Syndrome, HMPS) • Colorectal cancer	(90–96)

AD, autosomal dominant; AR, autosomal recessive; CMMRD, constitutional mismatch repair deficiency

Table 2:

WHO criteria for Serrated Polyposis Syndrome (SPS)

Criterion	Number	Location	Size
1	≥5 serrated polyps	Proximal to rectum	All ≥5mm in size with at least 2 polyps ≥10mm
2	≥ 20 serrated polyps	Distributed throughout colon with ≥5 polyps proximal to the rectum	Any size

Table 3:

Hamartomatous polyposis syndromes

Syndrome	Gene(s)	Clinical manifestations
Juvenile polyposis syndrome (JPS)	*BMPR1A SMAD4*	• Colonic juvenile polyps • Gastric juvenile polyps (*SMAD4* > *BMPR1A*) • Hereditary Hemorrhagic Telangiectasia, HHT (only *SMAD4*) • Congenital heart defects
Peutz-Jeghers syndrome (PJS)	*STK11*	• Small bowel Peutz-Jeghers polyps - bleeding & obstructions (in children) • Mucocutaneous pigmentation • GI and non-GI cancer risks (in adults)
PTEN Hamartoma Tumor Syndrome (PHTS)	*PTEN*	• Spectrum of condition with *PTEN* pathogenic variants • Cowden syndrome: - GI hamartomas & ganglioneuromas - esophageal glycogenic acanthosis - cancer risks (breast, endometrial, thyroid, kidney, colorectal) - macrocephaly - dermatological lesions