# Pediatric Adenomatous Polyposis Syndromes: An Update

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Juvenile polyps are a common finding in the pediatric population. In contrast, colon adenomas, which are viewed as dysplastic precancerous lesions, are found sporadically in late adulthood. Adenomas in children and young adults are highly unusual and suggest one of several forms of inherited colorectal cancer. These disorders show a predilection to early adenoma formation and can present in childhood. Familial adenomatous polyposis and Lynch syndrome are autosomal dominant, often with involvement of multiple family members, or can be seen in an individual arising from a de novo mutation. The most recently described adenomatous polyposis syndrome, *MutYH*-associated polyposis, is autosomal recessive, requiring an inherited mutation from each parent. All three adenomatous polyposis disorders can display tremendous variation in expression, even within the same family, and can have a common overlapping phenotype. These disorders require regular medical care to minimize cancer risk in the digestive tract and in other organ systems.

## Introduction

Juvenile polyps are common in children presenting with rectal bleeding, abdominal pain, diarrhea, or polyp prolapse. These polyps are pedunculated hamartomas that consist of distended mucin-filled glands lined with orderly columnar epithelium on a connective tissue stalk. In contrast, adenomas are found in either sessile or pedunculated forms with hypercellular disorganized epithelium and nuclear atypia. Adenomas are dysplastic lesions that are typically found in adults and show an increasing prevalence with age. Over a period of years, a small percentage of sporadic adenomas progress to colorectal cancer, a diagnosis that annually affects 600,000 individuals worldwide [1]. Colon adenomas are highly unusual in children and adolescents, and their presence suggests a cancer predilection or inherited colorectal cancer. This group of inherited polyposis disorders displays tremendous variation in expression, even within the same family. Adenoma development can be seen at any time from early childhood into the senior years. This article reviews some of the recent discoveries that help to define the adenomatous polyposis syndromes and highlights the diagnosis and management of these syndromes in the pediatric age group.

## Lynch Syndrome: Familial Colorectal Cancer Type X

Hereditary nonpolyposis colorectal cancer (HNPCC) was described by Dr. Henry Lynch and colleagues in 1985 and is now recognized as the most common form of inherited colorectal cancer. This disorder was originally defined by clinical and family history that became the Amsterdam criteria [2]. With additional refinement, this working definition of HNPCC was revised to include other associated malignancies, including endometrial, gastric, uterine, ovarian, small bowel, pancreas, biliary, skin, and central nervous system (Table 1). This autosomal dominant disorder is characterized by the development of colorectal cancer favoring the right colon in individuals under the age of 50 years, multiple simultaneous colon cancers (synchronous malignancy), or a second primary colon or other specific cancer within 10 years of diagnosis of the original cancer (metachronous malignancy) [3••]. In contrast to the dramatic adenoma burden of familial adenomatous polyposis, HNPCC was named for the relative paucity of adenomas that are found at diagnosis. However, these adenomas undergo malignant transformation to cancer at a much faster rate (~2–3 years) than with either familial adenomatous polyposis (FAP) or sporadic adenomas (~8–10 years) [3••].

By the mid-1990s, the underlying mechanisms that caused HNPCC were shown to be due to malfunction of the DNA mismatch repair (MMR) system. Germline mutations in two MMR genes, *MLH1* and *MSH2*, account for 90% of the known disease-causing

**Table 1. The Amsterdam criteria and Bethesda guidelines for HNPCC**

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| Amsterdam II criteria |
| Families at risk for HNPCC* |
| At least 3 relatives having a HNPCC-associated cancer† |
| 1) One should be a first-degree relative (parent, child, or sibling) of the other 2 relatives |
| 2) At least 2 successive generations should be affected |
| 3) At least 1 should be diagnosed before age 50 years |
| 4) Familial adenomatous polyposis should be excluded |
| 5) Tumors should be verified by pathological examination |
| The revised Bethesda guidelines for testing of colorectal tumors for MSI‡§ |
| Tumors should be tested for MSI in the following situations |
| 1) Colorectal cancer diagnosed in a patient who is younger than 50 years |
| 2) Presence of synchronous (simultaneous) or metachronous (diagnosed at different times) colorectal or other HNPCC-associated cancers† regardless of age |
| 3) Colorectal cancer displaying histology¶ associated with MSI‡ diagnosed in a patient who is younger than 60 years |
| 4) Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related cancer†, with one of the cancers being diagnosed under the age of 50 years |
| 5) Colorectal cancer or HNPCC-associated tumor† diagnosed in 2 or more first- or second-degree relatives at any age |

*About half of the families meeting Amsterdam criteria will have Lynch syndrome (hereditary DNA MMR gene mutation); conversely, many families with Lynch syndrome do not meet these criteria.
†Includes colorectal, endometrium, stomach, small bowel, ovarian, pancreas, ureter, renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas, and keratoacanthomas (in Muir-Torre syndrome).
‡Refers to changes in 2 or more of the 5 panels of microsatellite markers recommended by the National Cancer Institute.
§These guidelines are intended for colorectal cancer patients to identify those who may benefit from tumor microsatellite instability testing and are not intended as diagnostic criteria for hereditary nonpolyposis colorectal cancer or Lynch syndrome.
¶Presence of tumor infiltrating lymphocytes, Crohn disease–like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern.
HNPCC—hereditary nonpolyposis colorectal cancer; MMR—mismatch repair; MSI—microsatellite instability.
(*Adapted from* Vasen et al. [2] and Umar et al. [5]; with permission.)

mutations, whereas mutations of *MSH6* and *PMS2* make up the remainder. As tumor suppressor genes, the MMR genes are necessary for the repair of DNA base-pair mismatches that develop during DNA replication. These replication errors can be seen throughout the genome and can affect specific genes that are critical to the regulation of cell growth and differentiation. When MMR function is defective, a "mutator phenotype" is established, allowing mutations to become propagated in the adenomas and cancers of the affected patient. The propensity toward mutation can be documented through the sequencing of non-encoding repetitive segments of DNA, known as microsatellites, which exist in spans of 20 to 40 base pairs throughout the genome. The microsatellites of HNPCC adenomas and cancers display mutations when compared with DNA extracted from normal surrounding tissue. The documentation of mutations in two or more different microsatellites from an adenoma or colon cancer, known as microsatellite instability, is diagnostic of MMR dysfunction and of HNPCC [4]. The Bethesda guidelines, which focus on tumor characteristics as well as family history, were outlined to assist in the identification of patients with adenomas and cancers that should undergo testing for microsatellite instability (Table 1) [5]. Most, but not all MMR gene mutations (nonsense, frame shift, splice site, large genomic rearrangement) result in a truncated nonfunctional protein that does not bind to specific visualizing antibody on immunohistochemistry. This technique can be used as a diagnostic screening tool to document the absence of functional MMR proteins in adenomas and cancers. The absence of staining by immunohistochemistry is predictive of a truncating mutation for that specific MMR protein. However, DNA hypermethylation of the promoter region can also silence *MLH1* gene expression, resulting in absent immunohistochemical staining [3••]. Sequencing demonstrating the presence of a MMR gene mutation confirms the diagnosis. The term "Lynch syndrome" is now applied to all patients and families with colorectal or other cancers associated with a germline mutation of any of the four MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Still, some mutation-positive Lynch syndrome families do not have a family history that fulfills the Amsterdam criteria. Confusion still surrounds the HNPCC label, and elimination of the phrase has been suggested [6].

Soon after the discovery of the MMR genes, it became apparent that roughly half of the Amsterdam-positive families had colon cancers that did not show microsatellite instability or have an identifiable MMR gene mutation, suggesting that the Amsterdam criteria described more

than one disorder. Dividing Amsterdam-positive families into two groups based on microsatellite status showed that families with microsatellite stable tumors had a different spectrum of involvement, with fewer affected family members that developed cancer at an older age. The group with microsatellite stable cancers had a milder cancer phenotype with tumors distributed throughout the colon. This distinctive subset of Amsterdam-positive families lacking MMR gene dysfunction has recently been described as familial colorectal cancer type X. This group likely represents one or more additional subsets of inherited colorectal cancer [6–8].

With a careful family history, the astute pediatric care provider can identify families at risk of having an inherited MMR gene defect or other inherited colorectal cancer syndromes. Clinical suspicion and a complete family history have taken on greater importance in light of recent reports of children and adolescents presenting with digestive complaints who were ultimately found to have colorectal cancer and Lynch syndrome [9–11]. Although extremely rare, homozygous and compound heterozygous MMR gene mutations have been seen in children presenting with an aggressive phenotype that can include leukemia, lymphoma, and skin findings in addition to highly aggressive colon cancer [11,12]. The Amsterdam criteria can help to identify at-risk families that should be referred for genetic counseling and evaluation. However, because of incomplete penetrance, variable age of cancer development, cancer risk reduction as a result of screening or prophylactic surgery, or early death, not all adolescents who are at risk of having a MMR gene mutation will have a parent with cancer. Spontaneous or de novo mutation is also a consideration in a patient with adenomas or early colorectal cancer who lacks a family history of cancer [13].

### Surveillance and education of Lynch syndrome children and adolescents

Current screening recommendations have focused on early identification and treatment of colorectal cancer. Surveillance strategies have been shown to reduce cancer incidence and mortality in compliant Lynch syndrome patients when compared with outcomes for family members who forgo surveillance colonoscopy [14]. Individuals with a known or suspected mutation of the MMR genes (Lynch syndrome) or who are at risk based on a documented mutation in their family should undergo screening colonoscopy every 1 to 2 years in order to detect and remove adenomas that undergo an accelerated transformation to cancer when compared with sporadic or FAP. Current guidelines suggest that surveillance colonoscopy should begin at 20 years of age [3••,15,16•]. However, this guideline is modified in Lynch syndrome families with documented colon cancer prior to the age of 30 years. In very early colon cancer, surveillance colonoscopy for at-risk children and adolescents should begin at an age 10 years before the youngest case of colon cancer in the immediate family or whenever active digestive symptoms suggestive of polyps or cancer are present. After 20 years of age, additional surveillance for endometrial and other cancers is recommended [16•,17].

## Familial Adenomatous Polyposis

Familial adenomatous polyposis is an autosomal dominant cancer syndrome with significant morbidity and mortality caused by a germline mutation of the *APC* tumor suppressor gene [18]. The development of hundreds of colonic adenomas and the near certainty of colorectal cancer if left untreated are the hallmarks of FAP. In this disorder polyp number appears to correlate with the development of gastrointestinal symptoms, including diarrhea, abdominal pain, and rectal bleeding. The age of first symptoms and the number of adenomas identified during initial endoscopy demonstrate great variability, even among family members carrying the same *APC* mutation, with 95% of FAP individuals expressing colon adenomas by the age of 35 years [18]. Up to one third of patients with classic FAP will lack a family history of the disease and represent spontaneous or de novo mutation of the *APC* gene, presenting as young as 2 years of age [19]. A milder variant of this disease known as attenuated FAP (AFAP) is associated with fewer colon adenomas (less than 100) that tend to cluster in the right colon. Mutations in either the proximal 5' or distal 3' end of the gene beyond codon 1596 are associated with AFAP. Patients with AFAP lack the typical extra-intestinal findings, develop colon cancer at a later age than classic FAP, and can present with fundic gland polyps prior to the formation of colon adenomas [20•].

### The *APC* gene and cancer development

The *APC* protein participates in the *Wnt* signaling pathway as part of a complex that regulates the intracellular levels of β-catenin. β-catenin is both a cytosolic protein, involved in cell adhesion, as well as a nuclear protein, which, when bound to specific cofactors, stimulates the transcriptional activation of genes, affecting proliferation, differentiation, and cell migration. The *APC* protein also binds to the cytoskeleton, where it has both direct and indirect influence on the microtubule system [21]. Early in life, each FAP colon stem cell is heterozygous, possessing both a normal and mutant *APC* allele. The heterozygous state, with both normal and mutant proteins, is suspected to compromise normal APC function during mitosis, allowing defective spindle formation, chromosome mis-segregation, and the deletion of large segments of DNA, resulting in aneuploidy [22]. When this *mitotic deletion* event involves the normal *APC* allele on chromosome 5q, the degradation and control of β-catenin are lost, deregulating the proliferative process. In this situation, silencing of the normal *APC* allele, known as loss of heterozygosity,

is the first and defining step in cancer development [22]. Complete loss of normal APC tumor suppressor function is critical to adenoma formation and conveys a proliferative advantage, allowing the progeny of the mutant stem cell to overtake and alter the crypt, becoming aberrant crypt foci [1]. With further cell mitosis, additional mutations and deletions occur, resulting in oncogene activation and tumor suppressor gene inactivation. During this process the adenoma shows increasing cellular and tissue disorganization or dysplasia. The dysplastic cell mass proliferates into the intramucosal space as carcinoma in situ and eventually penetrates through the muscularis mucosae, to become an invasive cancer. With further gene inactivation and loss of cellular control, the cancer invades locally into the vascular and lymphatic channels, metastasizing to distant organs. This progression from normal colon to cancer is known as the adenoma-to-carcinoma sequence and is descriptive of both sporadic and some of the inherited colon cancer syndromes such as FAP [23,24]. Untreated patients with FAP have a near 100% lifetime risk of developing one or multiple colorectal cancers, usually by the fifth decade [25]. However, in FAP, adenoma development and progression to colorectal cancer are unpredictable and can occur in the pediatric and adolescent age groups.

**Colon and other cancers in pediatric FAP**

The variability of adenoma and colorectal cancer development in FAP is thought to be influenced by a variety of factors, including *APC* genotype, environmental factors, and the effect of modifier genes. This marked phenotypic variability is a factor in the diagnosis and management of pediatric FAP and provides at least a partial explanation as to why the actual risk of developing colorectal cancer before the age of 20 is difficult to assess with certainty. Early reports cite a colon cancer incidence of 7% by 21 years in untreated individuals with FAP [26]. Published reports from the national polyposis registries of Denmark, Japan, and Germany, involving 2504 FAP patients, show a low incidence of colorectal cancer in early childhood, with only five cases in children under the age of 9 years. All three series report colon cancer in the 15- to 20-year-old FAP age group, with a cumulative colon cancer risk exceeding 1% by 20 years of age [27–29]. Based on a survey of 26 FAP registries, Church et al. [30] identified 14 FAP patients under the age of 20 years with invasive colon cancer out of an estimated 6600 affected individuals, providing an incidence of one case per 471. As with adults, cancer risk in adolescents correlates with an aggressive phenotype and heavy polyp burden [30,31]. In general, adenocarcinoma of the colon can be viewed as a rare, but serious, complication of FAP in children. The risk in adolescents and young adults increases with adenoma number and severity of dysplasia.

Adenomas of the duodenum and stomach are common in FAP, showing near complete penetrance by late adulthood, with the peri-ampullary region and mid-duodenum being the most consistently involved [32]. Peri-ampullary adenomas show the same pattern of genetic abnormalities as seen in colorectal cancer but progress to adenocarcinoma later in life and are a leading cause of death in the post-colectomy FAP population, with a lifetime cancer risk of 3% to 5% [27,33]. Upper gastrointestinal symptoms may not correlate with the presence of gastric or duodenal polyps in FAP adolescents [34]. Several prospectively controlled studies have shown that ampullary cancer development in FAP is likely to be a slow process that occurs beyond the pediatric age group. Recent recommendations from the National Comprehensive Cancer Network and others suggest a baseline upper gastrointestinal endoscopy at 25 to 30 years, with follow-up depending on the degree of involvement found at initial screening [15]. However, dysplastic fundic gland polyps and ampullary adenomas with advanced dysplasia have been identified in the FAP adolescent age group, prompting other authors to promote upper endoscopy beginning at diagnosis regardless of age [34,35].

Other extra-intestinal malignancies can be associated with pediatric FAP. Hepatoblastoma has an 800-fold increased incidence in children with a family history of FAP. Prospective surveillance programs to identify hepatoblastoma in genotype-positive infants and children to 5 years of age have been suggested. Surveillance involves yearly abdominal ultrasound and serum α-fetoprotein measurements. A genotype-phenotype correlation has been suggested, with FAP-associated hepatoblastoma more commonly associated with mutations in the proximal half of the *APC* gene and in the regions around the 1309 "hot-spot" codon [36].

Other less common malignancies associated with FAP include adrenocortical, pancreatic, and thyroid papillary (Cribriform-Morula variant) carcinoma. The thyroid tumors (2% lifetime risk) tend to be left sided, multicentric, non-aggressive, and associated with an excellent long-term prognosis [20•]. Brain tumors can be associated with FAP (lifetime cancer risk of 2%) and are known as Turcot's syndrome. These lesions are typically medulloblastomas and can present prior to the development of colon adenomas. Other extra-intestinal FAP findings include congenital hypertrophy of the retinal pigment epithelium, supernumerary teeth, osteomas, lipomas, fibromas, and leiomyomas [20•].

**Screening and management in FAP**

In the era of genetic testing, identification of an *APC* gene mutation is now possible in up to 90% of FAP families. The presence of a known family mutation enables the identification of affected and unaffected family members with a high degree of accuracy prior to the development of symptoms, allowing the application of preventive strategies to the affected while avoiding

unnecessary procedures in unaffected family members. Genetic testing does not always provide definitive information that assures a clear diagnosis and management plan. For this reason, genetic counseling plays a critical role in the diagnosis and management of individuals and families with FAP. Guidelines for genetic counseling and *APC* gene testing are available [18,37].

Surgical resection of the large intestine remains the only proven method of addressing the inevitability of colon cancer in FAP, for which prophylactic colectomy can dramatically reduce the risk of colon cancer. Optimal timing of surgery is best determined on a case-by-case basis, influenced by adenoma size and number, degree of adenoma dysplasia, emotional maturity of the patient, and mutation genotype. In AFAP, with a lower adenoma burden than classic FAP, endoscopic polyp ablation may allow postponement of colectomy and the consideration of different surgical options [18]. Mutations of codons 1309 and 1328 are associated with a severe phenotype showing early progression to colorectal cancer, thereby providing an impetus for early surgery [38]. *APC* genotyping can also identify mutations located in codons 1445 to 1580 that are associated with desmoid tumor formation. Abdominal surgery or trauma is associated with the development of mesenteric or abdominal wall desmoids that usually become clinically significant within 5 years of surgery. These non-malignant infiltrating bulky lesions are more common in females and can cause substantial morbidity from obstruction of the digestive or urinary tract and of the abdominal blood supply. Desmoid tumors, which can develop in up to 15% of FAP patients, can cause fatal complications from sepsis or hemorrhage and are a leading cause of death in the postcolectomy population [27,29,33].

Traditional surgery in FAP has focused on three surgical procedures: 1) proctocolectomy with ileo-pouch anal anastomosis (IPAA); 2) subtotal colectomy with ileorectal anastomosis (IRA); and 3) total proctocolectomy with a permanent ileostomy. Unless extenuating circumstances are present, such as a pelvic desmoid or metastatic cancer, a permanent ileostomy is rarely done. The IPAA removes all pre-neoplastic colonic mucosa while preserving anal function. Stooling frequency gradually improves following surgery but rarely returns to pre-surgery patterns. Fecal incontinence, pouchitis, male erectile dysfunction, and decreased female fertility are complications of this procedure. Subtotal colectomy with an IRA, which can be done laparoscopically, has a lower rate of complications and can be used when there is a low rectal adenoma burden, as with AFAP. Despite best intentions, colectomy does not completely eliminate the cancer risk, a misperception common to patients and parents following surgery. Even with careful dissection, residual colonic epithelium can be left following proctocolectomy. Ileal adenomas and adenocarcinomas can also develop in the J-pouch following surgery. For these reasons, lifelong endoscopic surveillance of the ileoanal J-pouch or ileorectal anastomosis is indicated [39,40•].

For the majority of FAP patients who undergo colectomy in middle to late adolescence, the need to establish a lifelong surveillance plan occurs just as the patient is acquiring independence from parents and established care providers. Loss of insurance coverage can also be a factor leading many young adults to avoid nonessential medical care. Being "lost to follow-up" places the FAP young adult at even greater risk and negates surveillance strategies aimed at avoiding serious complications. The pediatric care provider needs to stress the need for long-term follow-up to the patient and family and facilitate the transfer of care in an appropriate and timely manner to a qualified physician experienced in the management of hereditary colorectal cancer syndromes.

## Defects in DNA Repair: The Story of *MutYH*-associated Polyposis

In a small but significant number of individuals with classic FAP, germline mutation of the *APC* gene cannot be identified. A careful genetic analysis of the colon cancers from these phenotype positive–genotype negative individuals leads to the identification of a specific pattern of unique G:C to T:A transversions of the *APC* gene. This pattern of mutation had been observed previously in the laboratory with manipulation of the DNA base excision repair system. Under normal circumstances, this system identifies and repairs base-pair mismatches prior to replication, thus preserving DNA fidelity. These discoveries led to the identification of a new polyposis syndrome caused by mutation of the human MutY homologue gene (*MutYH*) [41]. This gene is also referred to by the abbreviation *MYH*; however, because this symbol had been assigned previously to the myosin heavy-chain gene, to avoid confusion, the symbol *MutYH* will be used in this discussion [42•].

Oxidative alteration of the DNA nucleotide guanine to 8-oxo-guanine allows for mispairing to adenine, rather than cystine, during DNA replication. As a DNA glycosolase, *MutYH* initiates the base excision repair of 8-oxoG:A and G:A mismatches by identifying and removing the mismatched adenine. Additional enzymes of the base excision system repair the 8oxoG, preventing introduction of the G to T mutation during the next cycle of DNA replication. *MutYH* also interacts with the DNA mismatch repair proteins MSH2 and MSH6, which are involved in Lynch syndrome, as previously discussed.

Unlike FAP, *MutYH*-associated polyposis, or MAP, is an autosomal recessive disorder, requiring silencing of both MutYH alleles through bi-allelic mutation. Over 24 deleterious mutations of *MutYH* have been identified, with two missense mutations, Y165C and G382D, being found in up to 70% of MAP individuals of northern European descent [43]. The Y165C and G382D mutations both affect substrate affinity and 8oxoG recognition

**Table 2. Concluding points**

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| Adenomas are precancerous lesions that are highly unusual in the pediatric age group. |
| The presence of a colon adenoma should trigger evaluation of the patient and family for possible inherited colorectal cancer/polyposis syndrome. |
| Variation in expression involving age at first symptom, rate of polyp development, and age of cancer development are typical within families with these disorders. |
| Spontaneous or de novo mutations and autosomal recessive inheritance can explain why patients with these syndromes may not have a family history that is consistent with the diagnosis. |
| Children and adolescents with these disorders require life-long care and medical supervision. |

when studied in bacteria. Both mutations also affect glycosolase activity, slowing adenine excision. Other unique mutations have been identified in several ethnic populations, arguing for whole gene sequencing as the screening method for patients suspected of having MAP [43].

As an adenomatous colorectal polyposis syndrome, MAP shows near complete penetrance by 60 years of age and typically lacks the dominant pattern of inheritance seen in FAP. Roughly half of the patients with MAP have colorectal cancer at presentation. As a group, MAP patients tend to present at an older age (40–50 years) when compared with FAP patients (39–40 years) yet can be identified as having colon cancer or adenomas in the teen years. The adenoma burden at diagnosis can show wide variation from none to hundreds, having an overlapping phenotype with AFAP. MAP-associated cancer has been diagnosed in the absence of colon adenomas [44,45]. Causing further blurring of phenotypes, MAP patients can have a variety of extracolonic manifestations that are also seen with FAP and AFAP. These include congenital hypertrophy of the retinal pigment epithelium, fundic gland polyps, duodenal adenomas, breast and other cancers, and skin findings associated with either FAP or Lynch syndrome [46]. As a bi-allelic autosomal recessive disorder, MAP, in the form of colon adenomas or cancer, would not be expected among the parents and children of the affected proband. However, *MutYH* mutations have been found in families with features that suggest other autosomal dominant polyposis syndromes [47].

**Clinical management**

MAP is a new discovery and is just now being defined. Due to the overlapping phenotypes of FAP/AFAP, MAP, and Lynch syndrome, *MutYH* genotyping should be considered for any child or adolescent with colon adenomas who does not have a germline mutation of the *APC* gene or a family history or testing suggestive for other syndromes. The importance of a genetic diagnosis is of greatest value in screening the siblings of the proband rather than the parents. Future offspring of the patient are also at risk; transmission of the disease is dependent on the genotype of the spouse. The risk for heterozygous carriers of *MutYH* mutations is also being evaluated. A recent population-based study reported a 1.68-fold increased risk of colon cancer for heterozygous carriers older than 55 years compared with control subjects, suggesting a causative role of base excision repair defects in cancer development [48]. However, this concept remains controversial [49].

## Conclusions

Important concluding points are outlined in Table 2. The inherited colon cancer/polyposis syndromes are known for their variability in expression and unpredictability. With small numbers of adenomas, FAP/AFAP, MAP, and Lynch syndrome can have overlapping phenotypes. Some families bring their asymptomatic children in for evaluation because of concerns about colon cancer in other family members or due to a recent diagnosis of an inherited colon cancer/polyposis syndrome in the family. At other times, an adenoma, or rarely colon cancer, is discovered during the evaluation of digestive complaints, which should alert the physician to the possibility of an inherited colon cancer/polyposis syndrome and trigger further evaluation. Consultation with a certified genetic counselor specialized in cancer genetics provides expertise in assessment of the family history as well as in the prioritization and interpretation of genetic testing. Children and adolescents with an inherited polyposis syndrome are at risk for the development of colorectal cancer as well as other malignant and benign tumors. For patients with FAP, colectomy remains the standard of care for the management of colon cancer risk. Regardless of the specific diagnosis, these patients require life-long surveillance, which can reduce morbidity and mortality, and should be stressed to the patients and their families beginning at diagnosis.

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