Hereditary Colorectal Cancer and Polyposis Syndromes

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Learning Objectives

After reading this chapter, you should be able to:

- Describe the epidemiology, genetic mutation, clinical presentation, surveillance recommendations, and treatment options for Lynch syndrome and familial adenomatous polyposis (FAP) and attenuated FAP (aFAP)
- Describe the various extracolonic manifestations associated with Lynch syndrome and FAP
- Understand the various medical and surgical treatment options for FAP and its various extracolonic manifestations especially duodenal polyps and periampullary neoplasm
- Understand the difference between FAP and aFAP
- Describe the epidemiology, genetic mutation, clinical presentation, surveillance recommendations, and treatment options for MYH-associated polyposis, Peutz–Jeghers syndrome, and juvenile polyposis syndrome

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Background

Colorectal cancer (CRC) is the leading cause of death in the United States, with an estimated diagnosis of approximately 140,000 cases per year [1]. Approximately 10–30 % of patients with CRC have a positive family history [2]. The majority of these inherited CRC are accounted by two syndromes, Lynch syndrome and familial adenomatous polyposis (FAP). Lynch syndrome accounts for approximately 2–3 % of all CRC cases. Next most common is FAP, which accounts for 1 % of CRC cases [3] (Fig. 20.1). In addition, attenuated FAP (aFAP) and MUTYH-associated polyposis (MAP) are being seen with more frequency. This chapter will also focus on two additional less common polyposis syndromes, Peutz–Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS).

Lynch Syndrome

The most common form of heritable CRC is Lynch syndrome, which accounts for 1–3 % of all cases of CRC [4, 5]. It is inherited in an

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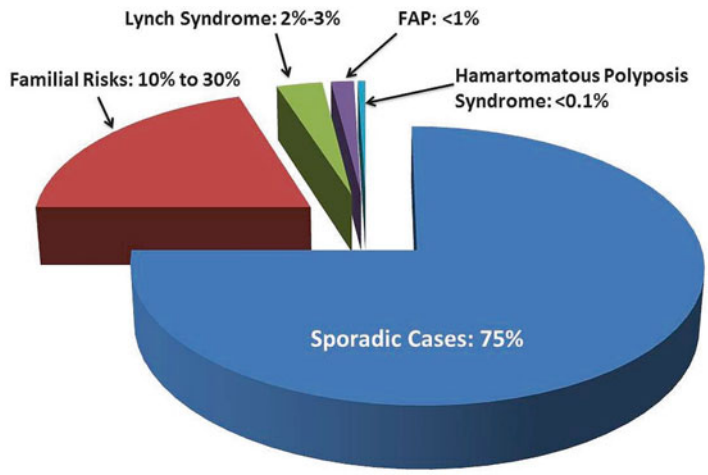

Fig. 20.1 Distribution of colorectal cancer cases (Courtesy of Quyen D. Chu, MD, MBA, FACS)

autosomal-dominant fashion. Lifetime risk of CRC in Lynch syndrome is approximately 10–69 % depending on gender and mismatch repair gene mutations [6–8]. Lynch syndrome is used in preference to hereditary nonpolyposis colorectal cancer (HNPCC) given that polyps can occur, and it involves a group of extracolonic cancer types.

Genetics

Lynch syndrome is characterized by a mutation in one of the DNA mismatch repair (MMR) genes – MLH1, MSH2, MSH6, and PMS2 (Fig. 20.2). These genetic mutations lead to errors in the number of repetitive sequences replicated, causing microsatellite instability (MSI). The errors that occur during DNA replication are not efficiently repaired, causing mutant changes and subsequent unrestrained growth that leads to adenoma and then to carcinoma. MSI occur in approximately 90–95 % of cancers in Lynch syndrome due to uncorrected errors in DNA replication [3].

In a report published by the International Collaborative Group on HNPCC, 63 % of total mutations reported in Lynch patients were MLH1 mutations, 25 % were MSH2 mutations, 6 % were MSH6 mutations, and 0.4 % were PMS2 mutations [3]. No clear genotype–phenotype relationship has been established except in Lynch patients that present with endometrial cancer, which is most commonly associated with MSH6 mutations [3]. However, patients with mutations in the other MMR genes can develop endometrial cancer.

Sometimes, patients will display mutations in mismatch repair proteins or high microsatellite instability (MSI-H) without evidence of germline mutations. This can be due to current technology that cannot identify the mutations. Also, deletions in epithelial cell adhesion molecule gene (*EpCAM*), also known as TACSTD1, located just upstream of MSH2 can account for Lynch syndrome [9]. This mutation leads to hypermethylation of MSH2 that can ultimately lead to an *EpCAM–MSH2* fusion protein that can cause aberrant protein transcription. This is responsible for the Lynch phenotype in 6–19 % of families without MMR gene mutation [10].

Clinical Evaluation

A detailed family history of at least three generations should be obtained in all patients being evaluated for Lynch syndrome. Clinical criteria such as the Amsterdam I and II were developed to identify high-risk families to aid in the discovery of the MMR genes. These criteria are useful and are still being used to identify Lynch syndrome kindreds. Lynch syndrome is suspected in those that fit the Amsterdam II criteria [11]. This criteria requires that at least three relatives, of which

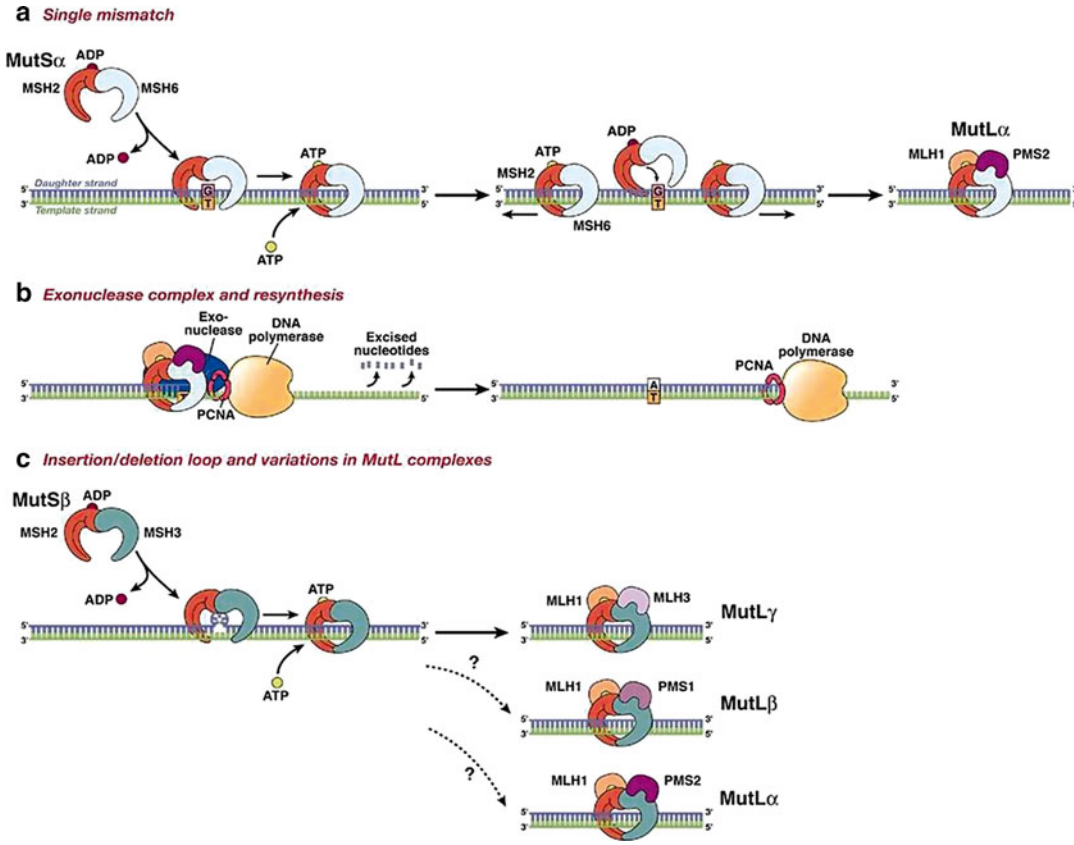

Fig. 20.2 The DNA MMR system functions through a series of steps. (**a**) MSH2–MSH6 (MutSα) recognizes single base-pair mismatches, in which the DNA polymerase has matched the wrong base (G) with the T on the template (shown on *left*), and creates a sliding clamp around the DNA. This step that requires the exchange of adenosine triphosphate (ATP) for adenosine diphosphate (ADP) (by MSH2, but not MSH6 or MSH3). The complex diffuses away from the mismatch site, which is then bound by the MLH1–PMS2 (MutLα) complex (*right*). This "matchmaker" complex moves along the new DNA chain until it encounters the DNA polymerase complex. (**b**) The DNA MMR protein sliding clamp interacts with exonuclease-1, proliferating cell nuclear antigen (PCNA), and DNA polymerase. This complex excises the daughter strand back to the site of the mismatch (shown on *left*). Eventually, the complex falls off the DNA and resynthesis occurs, correcting the error. (**c**) Variations on the DNA MMR theme. Whereas MSH2–MSH6 recognizes single-pair mismatches and small IDLs, MSH2–MSH3 (MutSα) complements this by also recognizing larger IDLs (shown on *left*). The right side shows the possible interactions with different MutL dimers, as MLH1 can dimerize with PMS2, PMS1, or MLH3. The preferred interaction with MSH2–MSH3 is MLH1–MLH3 (MutLα), but the precise roles of the other MutL heterodimers in this reaction are not entirely understood (Reprinted from Ref. [128]. With permission from W.B. Saunders Co.)

one must be a first-degree relative of the other two, have a diagnosis of some cancers associated with Lynch syndrome (CRC, endometrial, ureter/renal pelvis, small bowel), that at least two successive generations be affected, that at least one relative had a diagnosis of cancer associated with Lynch syndrome before the age of 50, and where FAP has been excluded. The Bethesda guidelines [12] linked the diagnostic criteria of Lynch syndrome to the presence of microsatellite instability (Table 20.1). However, with the advent of molecular technologies such as polymerase chain reaction (PCR) and immunohistochemistry for MMR gene protein expression in colorectal tumors (and in some cases extracolonic tumors), neoplasms can be screened for mismatch repair deficiency (and proficiency) thus identifying individuals that would be missed if only clinical

Table 20.1 Amsterdam II criteria/Bethesda guidelines

Greater than 3 relatives with Lynch/HNPCC-associated cancer and
1. One should be a first-degree relative of the other two
2. At least two successive generations should be affected
3. At least one diagnosed before the age of 50
4. FAP should be ruled out
5. Tumors verified by pathological examination
Tumors should be tested for microsatellite instability in following situations:
1. Colorectal cancer under age of 50
2. Presence of synchronous, metachronous colorectal, or other HNPCC-related cancers
3. Colorectal cancer with high microsatellite instability histology diagnosed in patients below age of 60
4. Colorectal cancer diagnosed in patient with one or more first-degree relatives with an HNPCC-related tumor confirmed under age of 50
5. Colorectal cancer diagnosed in patient with two or more first-degree relatives with an HNPCC-related tumor confirmed at any age

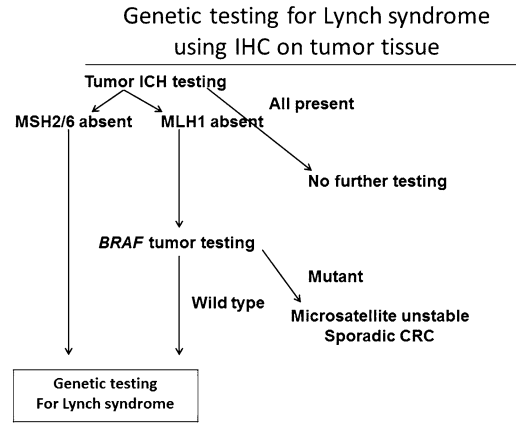

Fig. 20.3 Algorithm for genetic testing for Lynch syndrome. CRCs are tested via immunohistochemistry first for presence or absence of DNA mismatch repair proteins. If all proteins are present, then Lynch syndrome is ruled out. If MLH1 is absent, then the tumor is analyzed for BRAF mutations. If BRAF protein is present in its original state or if MSH 2 or 6 is absent, then the patient is tested genetically for Lynch syndrome. If BRAF protein is present as a mutant state, then CRC is likely a sporadic tumor due to microsatellite instability (Reprinted from Ref. [129]. With permission from Nature Publishing Group)

criteria were used for guidance in identifying Lynch syndrome patients.

Extracolonic cancers include endometrial, gastric, urinary tract, pancreas, biliary tract, brain, sebaceous gland adenomas, keratoacanthomas in Muir–Torre syndrome, carcinoma of the small bowel, and ovarian neoplasias [13, 14].

Muir–Torre variant of Lynch syndrome is associated with dermatologic manifestations such as sebaceous adenomas and carcinomas, keratoacanthomas, and basal carcinomas with sebaceous differentiation in addition to the other Lynch-associated tumors [15].

Surveillance

Those patients that meet the Bethesda guidelines should be offered screening by MSI testing or by immunohistochemistry to look for loss of MMR protein expression. However, the Bethesda guidelines were sensitive but not specific enough. There has been a move toward universal testing of colorectal tumors because it will help identify patients with Lynch syndrome as well as the status of the mismatch repair (either proficient or deficient) [16]. A more selective approach for testing colorectal cancers has been recommended by Moreira et al. and the Epicolon consortium [17]. These authors recommend testing all CRC diagnosed at age 70 or less and in older patients who fulfill the revised Bethesda guidelines. Using this approach, 4.9 % of Lynch syndrome cases were missed, but 34.8 % fewer cases required tumor MMR testing and 28.6 % fewer patients underwent germline mutation testing compared to a universal approach to all colorectal tumors [17]. It must be emphasized that tumors that show loss of protein expression of MLH 1 should undergo BRAF mutation and/or methylation testing of the promoter of MLH1. BRAF mutations are demonstrated in high levels in sporadic MSI CRC and rarely in Lynch syndrome CRC [18] (Fig. 20.3). Those patients whose tumors display loss of MSH2 protein are considered to have Lynch syndrome either secondary to the mutation in MSH2 or less commonly a mutation in EpCAM causing epigenetic silencing of MSH2. Less commonly isolated loss

of either PMS2 and MSH6 will be noted directing the clinician to test for germline mutations in these genes. Most commonly loss of MSH6 is accompanied by loss of MSH2 and loss of PMS2 by loss of MLH1.

Annual full colonoscopy starting at age 20–25 is recommended for those with diagnosis of Lynch syndrome[3]. Strong clinical evidence suggests more rapid transition from adenoma to carcinoma in those with Lynch syndrome, thus a more frequent endoscopic surveillance than for the general population is warranted. Colonoscopic surveillance in Lynch syndrome has been shown to decrease CRC incidence and decrease mortality from CRC [19].

Some literature advocates for annual transvaginal ultrasonography, measurement of CA 125 levels and annual endometrial aspiration for affected females starting at age 25–35 [20]. In those patients with Lynch syndrome and family history of gastric cancer, annual EGD is recommended. Ultrasonography and urine cytology can be considered annually or every other year to screen for urinary tract malignancy. Data for these screening tools to decrease mortality is limited at best.

Surgical Treatment

Due to a high lifetime risk of CRC, prophylactic surgical options should be presented to patients diagnosed with Lynch syndrome. However, if the colon is normal in appearance on colonoscopic exam, surgery is not recommended unless there are extenuating circumstances. The options of treatment in Lynch syndrome include total abdominal colectomy with ileorectal anastomosis (IRA) with yearly flexible sigmoidoscopy in those with normal rectal and anal sphincter function or segmental colectomy with yearly colonoscopy. To date, there have been no prospective or retrospective studies demonstrating a survival improvement in patients undergoing a total abdominal colectomy versus a segmental colectomy. What has been demonstrated is a decrease in metachronous colorectal cancer and abdominal procedures related to CRC in patients undergoing more extensive procedures [21, 22]. In the study by Parry et al., the risk of metachronous CTC after a segmental colectomy was 16 %, 41 %, and 62 % at 10, 20, and 30 years after segmental resection in MMR mutation carriers, respectively. Careful surveillance should also be advocated for those that opt for IRA, since the risk of metachronous rectal cancer after total colectomy was reported to be approximately 12 % at 10–12 years [23]. Because of the risk of metachronous CRC, most recommend a total abdominal colectomy at the time of diagnosis of colon cancer in Lynch syndrome. If the index cancer is in the rectum, the alternatives include segmental resection versus restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) if the sphincters are not involved. Similar to the colon, there is an increased incidence of metachronous colon cancer in patients undergoing segmental rectal resection. These have been reported to be 19%, 47% and 69% at 10, 20, and 30 years post-segmental rectal resection in mutation carriers [24].

Extracolonic Manifestations

Endometrial cancer risk has been reported to be from 15 % to 71 % in MMR gene carriers [6–9, 25]. Endometrial cancer can be the index cancer in a Lynch syndrome patient. Similar to CRC, the age of presentation is younger than the general populations. There is retrospective data reported where females who underwent prophylactic hysterectomy and salpingo-oophorectomy did not develop endometrial or ovarian cancer. In those that did not have the prophylactic procedure, 61 out of 315 females developed cancer [26]. In patients who have completed their families or are postmenopausal, discussion about prophylactic hysterectomy and salpingo-oophorectomy should be entertained, especially at the time of colectomy for CRC.

Other extracolonic manifestations associated with Lynch syndrome include gastric, urinary tract, pancreatic, biliary, brain cancers, sebaceous glands, and keratoacanthomas. There has been a suggestion that both prostate and breast cancer are part of the tumor spectrum of Lynch syndrome,

but because these tumors are so common in the general population, there is still controversy about their link to Lynch syndrome [24].

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is the second most common inherited colon cancer, affecting approximately 1 in 10,000 individuals and accounting for approximately 1 % of all colon cancers [27]. It is inherited in an autosomal-dominant fashion with nearly 100 % penetrance. Those affected are at nearly 100 % risk of CRC by the age of 60 [3].

Genetics

Adenomatous polyposis coli (APC) gene is a tumor suppressor gene that spans 108 kb of DNA on chromosome 5q21. The gene encodes a protein that negatively regulates the β-catenin oncoprotein. In the absence of the APC gene, the β-catenin protein interacts with various transcription factors as it accumulates in the nucleus to upregulate genes that propagate the cell cycle progression [28]. Germline mutations include deletions, insertions, nonsense, and missense mutations. Overall, it is predicted that a mutant truncated APC protein is produced as a consequence of these mutations in as much as 92 % of the cases [29] (Fig. 20.4).

Majority of the germline mutations are clustered in the 5′ portion of exon 15. Miyoshi and colleagues reported that 40 % of all mutations occurred in five specific codons (302, 625, 1061, 1309, and 1546), and 65 % of somatic mutations and 23 % of germline mutations in FAP patients occurred between codons 1286 and 1513 in exon 15 [30]. Genotype–phenotype correlation studies have demonstrated that severe polyposis in FAP patients usually have mutations between codons 1250 and 1464. Correlation between severe FAP and earlier age of onset (defined as symptoms in teen years, cancer before 30), higher number of polyps, and higher mean of diagnosis and death were seen in those with codon 1309 mutations and those more downstream [31–33]. However, subsequent studies have shown more heterogeneity and variability between and within family members with FAP and codon 1309 mutations, showing that a specific APC mutation was not the only determinant of phenotype [34].

Clinical Evaluation

Classically, FAP is diagnosed in those with greater than 100 adenomatous colorectal polyps. Polyp development is usually evident around puberty.

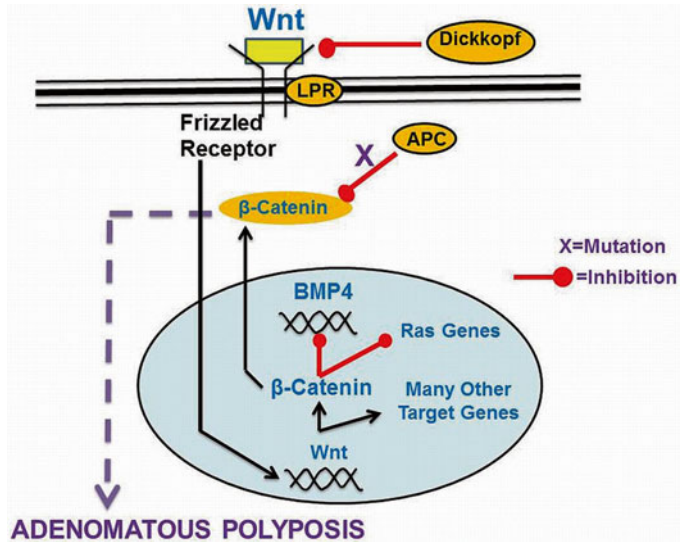

Fig. 20.4 Wnt/β-catenin pathway and adenomatous polyposis. APC (adenomatous polyposis coli) normally targets β-catenin for degradation. In familial adenomatous polyposis and in sporadic adenomatous polyps, mutations in APC are associated with an increase in β-catenin (Reprinted from Ref. [130]. With permission from Springer Verlag)

In a review of a national polyposis registry, median age for development of colorectal adenomatous polyps was 16 years (range 5–38 years), first symptoms from lower GI tract developed by median age of 29 years (range 2–73 years), and development of colorectal carcinoma occurred at a median age of 36 years (range 17–67 years) [3]. Earliest symptoms and signs of lower GI involvement in patients with FAP are blood per rectum, vague abdominal pain, tenesmus, diarrhea and/or constipation, or obstipation.

Polyps develop by age 20 in 75 % of cases and are usually less than 1 cm in size [3]. They may be pedunculated or sessile and may have tubular, villous, or tubulovillous histology. In severe polyposis, thousands may carpet the colorectal epithelium. The risk of invasive cancer is proportional to the severity of polyposis. CRC in the setting of FAP tends to be more commonly located on the left side, unlike CRC in the setting of Lynch syndrome [4].

A number of extracolonic manifestations have been reported in patients with FAP. Those include desmoid tumors, periampullary neoplasms, osteomas, odontomas, supernumerary teeth, fused teeth roots, sebaceous and epidermoid cysts, hepatoblastomas, thyroid tumors, and congenital hypertrophy of the retinal pigmented epithelium (CHRPE).

Surveillance

Patients in whom the diagnosis of FAP is suspected should undergo a complete history, paying particular attention to family history and physical examination with emphasis in areas affected by extracolonic manifestations, including neurologic, ophthalmic, dental, dermatologic, thyroid, abdominal, and digital rectal examinations.

If a mutation is known in the family, then the at-risk individual(s) should be tested for that mutation. In general, genetic testing is not recommended before age 10–12 years. Patients with normal gene study can be dismissed from further screening with a nearly 100 % certainty that any known mutation is absent. These patients should still be counseled to undergo CRC screening starting at age of 50, which is the recommendation for the general population. Surveillance for at-risk family members should begin at 10–12 years of age with a flexible sigmoidoscopy, repeated at 1–2 year intervals. Those that present with adenomatous polyps should undergo a full colonoscopy to determine the extent of polyposis. It is understood that if there are any symptoms prior to the recommended age of surveillance, at-risk individuals should be immediately evaluated at the onset of symptoms.

About 25 % of patients with FAP have no family history of polyposis; therefore, the mutation is de novo [35]. Grover et al. reported the prevalence of germline mutations in the APC gene according to the number of adenomas [36]. The prevalence of APC germline mutation in patients with 10–19 adenomas was 5 %, whereas if there are greater than 1,000 adenomas, it was 80 %.

Treatment

Surgical

Due to the nearly 100 % risk of colorectal cancer, prophylactic surgery has become the standard of care in patients with FAP. The timing of surgical treatment partially depends on the age of the patient, extent of polyposis, symptoms, family history of desmoids, genetic test results (if available), experience of the surgeon, and patient's input. The risk of CRC in FAP patients less than 20 years of age is less than 1 % [37]. If a prophylactic colectomy is to be performed due to severe polyposis, then ideally it should be performed between high school and college. Patients with severe polyposis, severe dysplasia, adenomas greater than 5 mm, and those with severe symptoms that impair quality of life should undergo surgery as soon as possible [38]. Prophylactic colectomy may also be delayed in those with a family history of aggressive desmoids tumors because the risk of desmoids-related complications may outweigh the risk of developing CRC. In females, Ileal pouch anal anastomosis (IPAA) has been associated with decreased fecundity. Therefore, it is also reasonable to delay surgery if deemed safe [39].

The three basic surgical options are: (1) total proctocolectomy (TPC) with permanent ileostomy, (2) total abdominal colectomy with ileorectal anastomosis (IRA), or (3) restorative proctocolectomy (with or without mucosectomy) with ileal pouch-anal anastomosis (IPAA).

TPC with permanent ileostomy is rarely chosen as the first-line option for prophylactic surgery. More commonly, it is considered when sphincter sparing surgery is not feasible due to rectal cancer presenting in the lower third of the rectum, if the patient has poor sphincter function or in the extremely rare situation of a patient presenting with desmoid disease that shortens the small bowel mesentery and not enough length can be technically achieved for an IRA or IPAA. Additionally, the patient's lifestyle has to be taken into consideration.

The choice between IRA and IPAA is more challenging, and considerations for the risk of rectal cancer development and/or differences in functional outcome and quality of life must be taken into account. One of the advantages of an IRA is that it is a one-stage procedure, whereas IPAA, due to the creation of a diverting loop ileostomy to protect the distal anastomosis, is a two-stage procedure (although in expert hands, it can be a one-stage procedure). Besides the increased risk in morbidity that comes from an ileostomy takedown, IPAA has been cited by several studies to have increased rate of complications. Nyam et al. reported a complication rate of 24 % in 187 patients that underwent IPAA for FAP [39]. The most common complication reported was intestinal obstruction in 13 % of the patients. Other complications included wound infection, pelvic infection, urinary tract infection or retention, and sexual dysfunction. Later study by Kartheuser and colleagues reported similar findings, with a complication rate of 27 %. Approximately 15 % experienced small bowel obstruction, and approximately 14 % experienced other complications including pelvic sepsis, fistula formation, necrotizing enterocolitis, and anastomotic stricture (4 %). Impotence and retrograde ejaculation reported after IPAA has only been 1–3 %. More commonly seen is dyspareunia in females and stool leakage during intercourse [40].

A disadvantage with IRA is its association with rectal cancer risk. According to various studies, the risk of developing rectal cancer following IRA in patients with FAP is between 4 and 14 % after 10 years and 9 to 32 % after 20 years [41–45]. It is important to note that in some of these studies, figures were derived when only IRA was available even in the setting of more extensive rectal disease. Also clear documentation of the length of the rectal stump in some series was not provided. Therefore, rectal cancer occurrence after IRA may be overestimated. Iwama et al. noted that 3 % of patients with rectal stump shorter than or equal to 7 cm developed rectal cancer after IRA as opposed to 17 % in those with rectal stump longer than 7 cm [44].

The risk of developing rectal cancer after primary prophylactic surgery may be estimated on the basis of a specific location on the APC mutation. Those that had mutations downstream of codon 1250 had threefold higher incidence of rectal cancer than those with a mutation upstream of 1250 [46]. In another study, those that had an APC mutation between codons 1250 and 1464 were 6.2 times more likely to develop rectal cancer than those with mutations upstream of 1250 or downstream of 1464 [47]. Nevertheless, having APC mutations at other sites will not preclude potential rectal cancer after an IRA.

Furthermore, in a genotype–phenotype study, the cumulative risk of needing a secondary proctectomy within 20 years after IRA and the cumulative risk of developing rectal cancer were compared based on the location of the APC mutation. In the attenuated phenotype (discussed in separate section below) group, which correlated with codons 1–157, 312–412, and 1596–2843, the risks were 10 % and 3.7 %, respectively. In the intermediate phenotype group, correlating with codons 158–311, 413–1249, and 1465–1595, the risks were 39 % and 9.3 %, respectively. In the severe phenotype group, correlating with codons 1250–1464, the risks were 61 % and 8.3 %, respectively [48]. Church et al. correlated the number of rectal polyps at the time of prophylactic IRA with subsequent need for secondary proctectomy [49]. None of the patients with less than five rectal adenomas and less than 1,000

adenomas in the colon had to undergo proctectomy. Patients who had 5–20 rectal adenomas had a 13 % chance of subsequent proctectomy. Those with greater than 20 adenomas had a 54 % chance of subsequent proctectomy.

Patients that develop rectal cancer after IRA may undergo completion proctectomy. The rate of this procedure ranges from 36.6 % to 74 %. The 5-year survival rate following metachronous rectal cancer in FAP patients who had undergone IRA originally ranges from 60 % to 78 % [3]. Other factors that also influenced this rate were stage of the tumor, comorbidities, and performance status of the patient.

The risk of developing polyps and subsequent cancer is not limited to IRA. One report found the risk of developing polyps in the ileal pouch in patients who had undergone IPAA to be 7 % at 5 years, 35 % at 10 years, and 75 % at 15 years [50]. Another study reported a higher incidence of neoplasia occurring at the site of anastomosis in FAP patients who had undergone IPAA after staple use (31 %) versus those that received a hand-sewn anastomosis with anal mucosectomy (10 %).

In terms of bowel function and quality of life, stool frequency ranged from 4.5 to 5 after IPAA compared to 3–4 after IRA. Normal continence was reported in 60–87 % in patients after IPAA compared to 72–83 % after IRA [51, 52]. Night defecation was significantly less in the IRA group, although fecal urgency was reduced in the IPAA patients. Reoperation rate is higher in the IPAA group. No significant difference was shown in terms of sexual dysfunction, dietary restriction, or postoperative complications [53].

Regardless of the procedure, endoscopic surveillance is recommended at intervals of 6 months to 1 year, either to examine the rectal stump (in the case of IRA) or the ileal pouch (in the case of IPAA). After IRA, small adenomas less than 5 mm can be safely observed with biopsies taken. If adenomas increase in number, endoscopic surveillance should occur more frequently. Any polyps larger than 5 mm should be removed and examined by histology. Any development of dysplasia or a villous adenoma larger than 1 cm may be an indication for proctectomy if it cannot be addressed endoscopically. Chemoprevention is discussed in a separate section below.

Extracolonic Manifestations

Desmoid tumors are histologically collagen abundant, spindle cell populated benign tumors arising from fibroaponeurotic tissues. They are usually referred to as benign without metastatic potential but can be locally invasive with ill-defined margins[3]. The prevalence of desmoid tumors in FAP has been estimated to be as high as 38 % [54]. Desmoid tumors occur in approximately 10 % of FAP patients. One study estimated the cumulative risk of 21 % for patients with FAP to develop a desmoid tumor by age 60 [55]. Desmoid tumors are associated with high morbidity and can be the cause of death in 10–23 % of FAP patients [54]. A high proportion of desmoid tumors develop after colonic resection in FAP patients [46]. Patients that have had total colectomy with IRA more frequently developed intra-abdominal desmoids compared to those that of IPAA [56], and due to mesenteric shortening, IPAA may be technically impossible for patients needing a completion proctectomy after an initial IRA [37]. Females of reproductive age seem to be more prone to developing intra-abdominal desmoids [29], possibly due to the expression of estrogen receptors that have been shown in some desmoid tumors [57].

Pharmacological intervention has been used to treat desmoid diseases. NSAID therapy such as sulindac and indomethacin has shown to show partial to complete regression in small, non-randomized studies [58]. However, it is associated with significant side effects and delayed response. Hormonal agents such as tamoxifen have also shown variable partial or complete regression of desmoid tumors [59]. Either NSAIDs or hormonal agents are viable first-line options to treat clinically inert desmoid tumors. For fast-growing tumors or those unresponsive to NSAID or hormonal agents, cytotoxic agents such as doxorubicin and dacarbazine can achieve some degree of response [58–60]. There is no definite effective

Table 20.2 Desmoid tumor staging system

Stages	
I	Asymptomatic, less than 10 cm maximum diameter and not growing
II	Mildly symptomatic, less than 10 cm maximum diameter and not growing
III	Moderately symptomatic or bowel/ureteric obstruction or 10–20 cm or slowly growing
IV	Severely symptomatic or greater than 20 cm or rapidly growing

treatment for desmoid tumors. Church et al. proposed a classification system for desmoids in FAP patients that can serve as a guide for management of these difficult problems [61] (Table 20.2).

Surgical resection is limited to those that are symptomatic (e.g., from intestinal obstruction) (Fig. 20.5). Unfortunately, resection is associated with a high rate of and more aggressive recurrence.

Duodenal cancer has become the leading cause of death in patients with FAP who have already undergone prophylactic colectomy [60]. Nearly 90 % of patients with FAP will develop duodenal polyps, and 4.5 % will develop duodenal adenocarcinoma in their lifetime [62].

Surveillance by EGD with biopsy of suspicious polyps should begin at age 20 or at the time of prophylactic colectomy, whichever is earlier [57]. Staging for duodenal polyposis can be staged using the Spigelman classification [63] (Table 20.3).

Having no polyps is designated as stage 0. One to four points is classified as stage 1. For these stages, the surveillance should be every 5 years. Five to six points is stage 2, with surveillance recommended every 3 years. Seven to eight points is stage 3 with surveillance recommended every 1–2 years. Nine to twelve points is stage 4, which warrants surgical intervention.

Surgical options include endoscopic ablation and transduodenal excision. Duodenal surgery, specifically pancreas-preserving duodenectomy or pancreaticoduodenectomy, is currently indicated for patients with severe duodenal polyposis (Spigelman IV) or duodenal carcinoma.

Several small-powered studies have investigated the role of sulindac in stabilizing or regressing duodenal polyposis [64, 65]. So far, no significant benefits have been seen. A randomized placebo study using celecoxib showed that there was no significant difference among the groups in number of polyps, although there was significant qualitative improvement in polyposis among those on high-dose celecoxib when the patients' endoscopies were reviewed independently by other physicians [66]. Overall, chemoprevention studies of duodenal polyposis with NSAIDs have been disappointing. One plausible explanation is that because the duodenum expresses higher levels of COX-2 than colon in FAP patients [67], higher dosage of NSAIDS may be needed to suppress polyp burden in the duodenum. However, higher dosages of NSAIDs, especially COX-2 inhibitors, may be limited by the potentially serious cardiovascular side effects.

Other extracolonic manifestations include gastric cancer, osteomas, odontomas, sebaceous and epidermoid cysts, and CHRPE (congenital hypertrophy of the retinal pigment epithelium).

Attenuated Familial Adenomatous Polyposis

A milder form of FAP known as attenuated familial adenomatous polyposis (aFAP) has been defined as less than 100 adenomatous polyps in the colon. Similar to FAP, aFAP is passed onto progeny by autosomal-dominant pattern and is associated with APC gene mutations and upper GI lesions [3]. Historically, aFAP has been reported to be predominantly right sided with rectal sparing, unlike FAP. However, recent studies indicate that adenoma location be uniform throughout the colon, although rectal adenomas are considerably less common than in FAP [68]. Mean age of cancer diagnosis has been reported in the early 50's [69, 70]. Cumulative risk of CRC in patients with aFAP is estimated to be 69 % by the age of 80 [71].

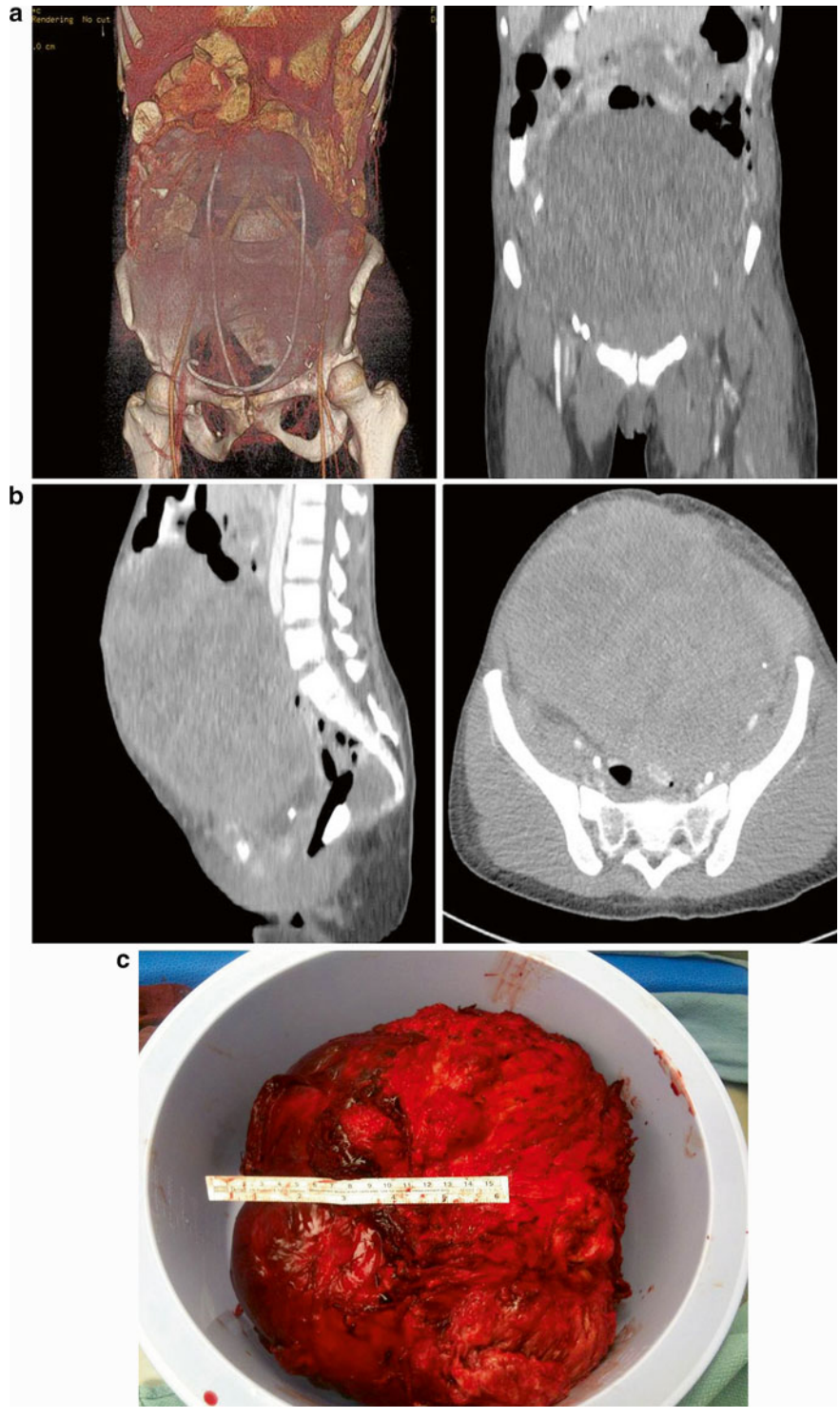

Fig. 20.5 A 24-year old woman with familial adenomatous polyposis presented with small bowel obstruction because of a large abdominal desmoids. She underwent a palliative debulking of her desmoids tumor (Courtesy of Quyen D. Chu, MD, MBA, FACS)

Table 20.3 Spigelman classification

	Points		
	1	2	3
Polyp number	1–4	5–20	Greater than 20
Polyp size (mm)	1–4	5–10	Greater than 10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Table 20.4 Clinical diagnostic criteria for attenuated FAP (aFAP)

1. No family members with > 100 adenomas diagnosed before the age of 30 and one of two below
(a) ≥2 patients with 10–99 adenomas at age >30 years
(b) One patient with 10–99 adenomas at age ≥30 years and a first-degree relative with CRC

Clinical Evaluation

The aFAP phenotype occurs in less than 10 % of FAP patients. The clinical criteria [72] for diagnosis is listed in the table (Table 20.4).

Pathologically, adenomas may be either pedunculated or sessile and may have tubular, villous, or tubulovillous histology, much like FAP. However, there is a higher chance of sessile polyps that are seen in aFAP patients compared to FAP patients [71]. Extracolonic manifestation, such as desmoids, osteomas, and periampullary tumors, occurs in aFAP patients. CHRPE, however, has not been reported in aFAP patients [73].

Genetics

Mutations in the aFAP patients tend to be at either the 5′ end or 3′ end of APC gene, usually codons 78–167, codons 1581–2843, and in exon 9 [74]. It is hypothesized that the mutations seen in aFAP may result in a weakly functional protein, whereas other APC mutations may cause more severe phenotypes through a complete dysfunctionality of the transcribed protein. Smith et al. reported that 5′ mutations led to unstable proteins that were ultimately degraded, while 3′ mutations resulted in proteins that formed heterodimers which inhibited tumor suppressor function [75].

Surveillance

In patients with a known APC mutation and a family history of AAPC, initial colonoscopy should begin at age 15. If the study shows findings consistent with FAP, then surgery is warranted. If the polyposis is not severe, endoscopic control with regular polypectomies may be feasible and repeated annually. If no polyps are found and the patient is APC mutation positive, colonoscopy annually starting at 20 is recommended. If the APC mutation status is unknown, colonoscopy every 2 years is sufficient. If no polyps are found and the patient tests negative for the APC mutation, routine colorectal cancer screening can be applied. Individuals with a positive family history but negative APC mutation should have a screening colonoscopy at age 15. If no adenomas are found, they can be followed with a colonoscopy every 2 years starting at age 20 [3].

Treatment

Surgical

In patients with mild adenomas, repeated endoscopic polypectomies may be preferable to surgery. In those where the colonic polyps cannot be controlled, prophylactic surgery can be recommended. Most recommend total colectomy with IRA as oppose to IPAA due to rectal sparing [3]. One study reported a 10 % cumulative risk of secondary proctectomy and 3.7 % cumulative risk of rectal cancer following IRA [48].

MYH-Associated Polyposis

MYH-associated polyposis (MAP) is an autosomal recessive disorder due to biallelic mutations (pertaining to both alleles) in *MYH*, a base excision repair gene. This disease came into light in 2002 when 3 out of 7 siblings presented with multiple adenomatous colorectal polyps and cancer without germline APC mutations [76]. Subsequent APC mutation analysis revealed a result that was characteristic for a defective base excision repair.

Unaffected relatives were heterozygous for MYH mutations or wild type, confirming the autosomal recessive pattern of disease inheritance.

The mean age of diagnosis is late 40's and 50's, similar to aFAP. Approximately 60 % of MAP patients with polyposis have colorectal cancer initially [77]. Synchronous cancers occur in up to 24 % of patients [78]. The estimated cumulative risk of CRC by age 70 in biallelic MYH mutation carriers has been reported to be as high as 80 % [79]. Penetrance of CRC in MAP patients has been shown to be approximately 19 % at age 50 and 43 % by age 60 [80]. Additionally, there is a twofold increase in risk of CRC for heterozygous carriers of MYH mutations compared to the general population [81].

Genetics

The MUTYH gene, located on chromosome locus 1p34.3–p32.1, is a base excision repair gene that codes for a glycosylase protein [82]. This protein is involved in repairing guanine residues that have undergone oxidative damage. Over 105 mutations have been identified for the MUTYH gene, majority of them being missense mutations. In the western population and in the northern European descent, the most common mutations within the MUTYH gene are the Y179C and the G396D mutations, with reports of approximately 90 % of the MAP patients carrying at least one of these mutations. Different mutations in patients of Indian (E480X), Pakistani (Y90X), southern European (1395 del GGA), and Portuguese (1186–1187 insertion GG) descent have been reported.

Clinical Evaluation

Most patients with biallelic MUTYH mutations present with between 10 and a few hundred polyps. There is a slight propensity for CRC to arise proximal to the splenic flexure [83]. Phenotypic presentation for MAP patients with biallelic G396D mutations was less severe than for Y179C mutation patients [77].

Extracolonic lesions associated with MUTYH mutations include small bowel polyposis, specifically duodenal polyposis, gastric cancer, endometrial cancer, breast cancer, and low to moderate risks in skin, ovarian, and bladder cancers [82]. Very rarely, MAP patients have developed sebaceous gland tumors [84].

Surveillance

Current recommendation [85] is to begin colonoscopic surveillance for MAP patients by age 18–20 to be repeated every 2 years. If polyposis is mild, patients can be followed with polypectomy. When the polyposis becomes severe, surgery is indicated.

Upper gastrointestinal tract screening is advised to begin at the age of 25–30. Recommended screening interval is determined by the Spigelman classification (see FAP section).

Treatment

Polyposis can be controlled with endoscopic polypectomies. Surgical intervention depends on rectum involvement. If rectum is not involved, TAC/IRA is recommended. If rectum is involved, total proctocolectomy with IPAA is recommended. Postsurgically, yearly surveillance with endoscopy is warranted.

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome (PJS) is an autosomal-dominant disorder with variable penetrance characterized by mucocutaneous melanotic macules and intestinal hamartomatous polyps. Although dysplastic and carcinomatous changes in hamartomas are low (approximately 1 %), malignant transformations are found in PJS patients due to their high polyp burden, especially in the intestines. Incidence of disease varies, ranging from 1 in 8,500 to 1 in 200,000 depending on various reports in the literature [86], showing that the true incidence remains unclear.

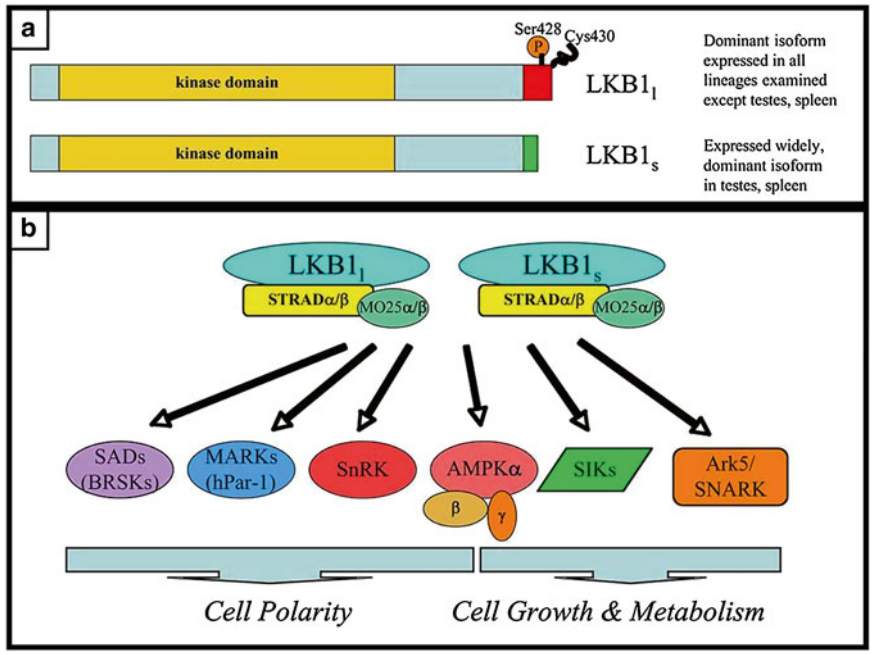

Fig. 20.6 LKB1 is a serine/threonine kinase which complexes with STRAD to phosphorylate downstream kinases in the AMP-activated protein kinase family (AMPK) (Reprinted from Ref. [131]. With permission from Portland Press Limited)

Lifetime risk of small bowel cancer risk for patients with PJS has been estimated to be approximately 57 % [87]. Cumulative risk of colonic or extracolonic cancer is 85–93 % by age 70 in PJS patients [87, 88].

Genetics

PJS is caused by a mutation in the LKB1 gene, located on the telomeric region of chromosome 19p13.3. LKB1 is a serine/threonine kinase which complexes with STE-20-related adaptor (STRAD) and mouse protein 25 (MO25) to phosphorylate and mediate downstream cell signaling cascade [89]. It is the only known tumor suppressor kinase. The Human Genome Organization designated the name serine/threonine kinase 11 (STK11) for LKB1. It is the only gene whose mutation is associated with PJS. It can be found in approximately 75 % of PJS patients [86] (Fig. 20.6).

For those without detectable LKB1 mutation, possibilities include large rearrangements of the LKB1 gene due to deletions, duplications or inversions, mutations to the LKB1 promoter, or the existence of additional PJS loci that is yet to be discovered. Thus far, no additional mutations have been found [86].

Gene sequencing is used for genetic screening. Those that come back with a negative result may opt for a multiplex ligation-dependent probe amplification (MLPA). Reported accuracy for genetic testing in at-risk individuals with established family mutations is 95 % [90]. Due to the high false-negative rate, a clinical diagnosis of PJS stands even when the genetic testing is negative. Genetic testing can also be difficult to coordinate due to a limited number of laboratories offering the test and the cost.

Clinical Evaluation

Mucocutaneous melanin pigmentation on or around the lips generally appear by the end of the first year of life and are almost always present by

the age of 5 [91]. They can also be seen in the buccal mucosa, periorbital or periaural area, dorsal surface of fingers or toes, and around the anus and genitalia. By puberty and adulthood, these skin pigmentations can disappear so the absence of these lesions in adults does not rule out PJS. They are usually macules 1–5 mm in diameter and vary in color from light brown to black.

Gastrointestinal polyps can occur anywhere in the GI tract, with jejunum being the most common location. Other common locations include the ileum, colon, rectum, stomach, duodenum, appendix, and esophagus [92]. Polyp numbers can vary, from only a handful to thousands.

The majority of PJS patients initially present with small bowel obstruction secondary to intussusception of hamartomas. Most present between the ages of 6 and 18 [93]. Symptoms include abdominal pain, nausea, vomiting, and bloody stool. CT scan is the imaging choice for diagnosis.

According to the guidelines from Mayo Clinic [86], in patients without a family history of PJS, if either of the following two is present, a diagnosis of PJS can be made:

1. Characteristic mucocutaneous melanotic macules and one or more intestinal polyps with PJS-type histology
2. Two intestinal polyps with PJS-type histology

In patients with a family history of PJS in a parent or sibling, if any of the following are present, a diagnosis of PJS can be made:

1. Characteristic melanotic macules
2. One intestinal polyp with PJS-type histology
3. An *LKB1* mutation

Histologically, the polyps seen in PJS are disorganized hamartomas characterized by hypertrophy or hyperplasia of smooth muscle in the muscularis mucosa. Unique to PJS-type polyps, smooth muscle cells arborize into the superficial epithelial layer. Sometimes the epithelium can invade and be entrapped in the smooth muscle layer, termed pseudo-invasion [86]. This can be mistaken for malignant invasion and can be misdiagnosed as cancer. Therefore, to diagnose a malignancy in PJS polyps, cellular atypia or increased mitotic rate must be seen [94]. In a past review, 10 % of PJS-type polyp specimen examined under microscopy had pseudo-invasion.

Patients with PJS are at increased risk of developing both intestinal and extraintestinal malignancies. One study reported a 15.2 relative risk for PJS patients for all cancers, with statistically increased risk for developing cancer in the esophagus, stomach, small intestines, colon, pancreas, lung, breast, uterus, and ovary [88]. Another study reported an association of PJS and nasal polyposis [91]. Nasopharyngeal carcinoma has also been reported in PJS patients [95]. Gallbladder polyps, gallbladder cancer, and bile duct cancer have also manifested in PJS patients [96–98]. Rarely, hamartomatous polyps have been reported in the ureter [99] and respiratory tract [100] in PJS patients. Finally, several rare cancers have a special association with PJS. In female PJS patients, a highly differentiated adenocarcinoma of the cervix can develop called adenoma malignum (ADM). Special sex cord tumor with annular tubules (SCTAT) can also develop in the ovaries. In males, the corresponding sex cord tumor is the Sertoli cell testicular tumors[83].

Surveillance

Riegert-Johnson et al. outlined the surveillance protocol from two institutions, Johns Hopkins Hospital and Mayo Clinic [86]. Both institutions recommend breast self-examination at age 18 with clinical semiannual examination and optional annual mammography annually starting at age 25, endoscopy surveys for stomach and small intestines every 1–8 years starting at age 8, and colonic endoscopic examination every 2–3 years starting at age 18. Johns Hopkins recommends surveillance of pancreas (with endoscopic ultrasound, CT or MR, and/or CA 19–9 as options) and female reproductive organs (ultrasound, serum CA-125, Pap smear) at age 25 and repeated annually, whereas Mayo Clinic recommends these examinations to start at age 18. Clinical examination with ultrasound adjunct for testicular screening should begin at birth and offered annually until age 12.

Treatment

Surgical

Polyps greater than 1–1.5 cm in size should be removed [86]. The polyps should be removed by extended upper endoscopy if accessible. If not, double-balloon endoscopy (DBE) can be considered. If the polyps cannot be removed by DBE, then surgical intervention should be considered. Options are laparoscopic-assisted endoscopic polypectomy versus an open procedure with intraoperative endoscopy and polypectomy. In patients where polyps are too large to remove endoscopically, polyps are incompletely removed, or polyp-associated complications arise such as intussusception, surgery can be warranted.

If a patient presents with intussusception, the treatment is surgical, not endoscopic management. The approach depends on location, timing of extend of intussusception, and associated inflammation, bowel edema, and any degree of ischemia. Most common intussusception in PJS patients are jejunum telescoping into another segment of jejunum, and the recommended surgical technique is reduction, enterotomy, and polyp resection. In the rare case where the polyp is suspected to be malignant, enterotomy should be made first prior to reduction to prevent dissemination of cancer. Intraoperative endoscopy is an option after to inspect and remove other polyps. Another option is to prolapse the small intestine through the enterotomy incision so that the mucosa near the incision can be inspected for the presence of polyps [86].

Prophylactic colectomy in patients at risk is unclear at this time. Due to the unclear risk of CRC in PJS patients and the limited availability of genetic testing, no consensus exists at this time for prophylactic surgery.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is a rare autosomal-dominant syndrome. It is characterized by multiple distinct juvenile polyps throughout the GI tract as well as multiple extracolonic manifestations. The cumulative lifetime risk of colorectal cancer is 39 % [101]. This syndrome is defined by the presence of greater than 5 juvenile polyps in the colorectum, juvenile polyps throughout the GI tract, or any number of juvenile polyps plus a positive family history.

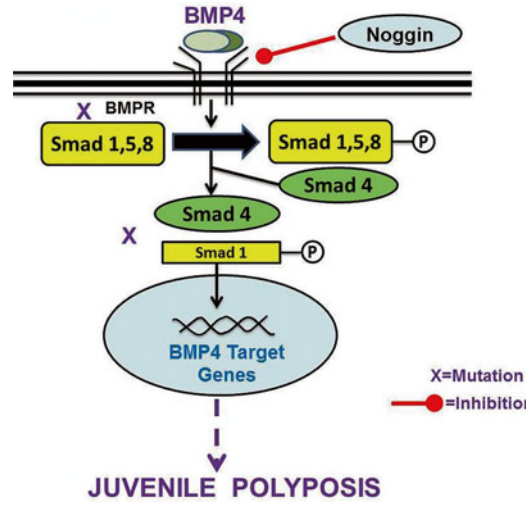

Fig. 20.7 BMP4–BMPR–Smad pathway and juvenile polyposis. Mutation of the BMP receptor 1A, introduction of Noggin, which inhibits BMP4 receptor binding, and mutation of Smad4 can suppress expression of BMP4 target genes. These interruptions of BMP4 signaling are associated with development of juvenile polyposis syndrome and related predisposition to juvenile polyps (Reprinted from Ref. [130]. With permission from Springer Verlag)

Genetics

JPS is associated with a germline mutation, usually a point mutation or small base-pair deletion, in the SMAD4 gene in chromosome 18q21.1 or BMPR1A gene on chromosome 10q22–q23 [91]. These mutations are found in about 50–60 % of JPS patients [102]. Both of these genes are involved in the bone morphogenetic protein (BMP)/transforming growth factor (TGF)-beta signaling pathway (Fig. 20.7). About 15 % of these defects are large deletions, necessitating the use of techniques such as multiplex ligation-dependent probe amplification (MLPA) for identification [103]. Upper GI polyposis and

gastric cancer have been associated with SMAD4 germline mutation [104].

Clinical Evaluation

The clinical presentation of JPS can be divided into two main variants [101]. The first is called juvenile polyposis of infancy. This is a nonsex-linked recessive condition characterized by failure to thrive, diarrhea, protein-losing enteropathy, bleeding, intussusception, rectal prolapse, and congenital abnormalities including macrocephaly and generalized hypotonia. Polyps generally are 1 mm–3 cm, sessile or pedunculated, and occur in stomach, small bowel, or colon. Death usually occurs before the age of 2. The second form, termed generalized juvenile polyposis or juvenile polyposis coli, seems to be different expressions of the same disease. GI juvenile polyps are usually present in the first decade of life or in adulthood, which are at increased risk of cancer. A number of other extraintestinal manifestations may arise. In approximately 50 % of cases, a heterozygous germline mutation in the SMAD4 or BMPR1A gene has been identified [105].

Diagnosis of JPS is made by ruling out other hamartomatous GI polyps and having:

1. Greater than 5 juvenile polyps in the colorectum
2. Juvenile polyps throughout the GI tract
3. Any number of juvenile polyps plus a family history for JPS [106]

Polyps in JPS predominantly occur in the colon and rectum, although they can be found in the stomach and small bowel. Their numbers vary from tens to hundreds. Their size can vary from 5 mm to 5 cm and typically have a spherical, lobulated, and pedunculated appearance with surface erosion. Histology shows an abundance of edematous lamina propria infiltrated with inflammatory cells and cystically dilated mucous-filled glands lined with cuboidal or columnar epithelium with reactive changes.

Extracolonic manifestations of JPS include malrotation of midgut and mesenteric lymphangiomas. Extraintestinal manifestations include hypertrophic pulmonary osteoarthropathy, cleft lip and palate abnormalities, porphyria, congenital cardiac and AV malformation, vitellointestinal duct abnormalities, and renal, uterus, and vaginal abnormalities. Cowden disease, associated with PTEN mutation and characterized by hamartomatous polyposis and is associated with other cancers including thyroid and breast, may be a phenotypic variant of JPS [4].

Surveillance

Patients with JPS or at risk should have endoscopic screening beginning at age 15 or at the time of first symptom. At diagnosis, the entire GI tract should be examined for the presence of polyps. Endoscopic examination of colon and upper GI is recommended every 2–3 years. If the patient has polyps, endoscopic exam should occur yearly until the patient is polyp free [101].

Treatment

Surgery

Patients with mild polyposis can be managed with frequent endoscopy and polypectomy. Prophylactic surgery can be considered in patients with severe polyposis that is unmanageable by endoscopy or with those with unmanageable symptoms. Surgical options include total colectomy with ileorectal anastomosis or proctocolectomy with ileal pouch-anal anastomosis [101]. Due to recurrence of rectal polyps in half of the individuals who require subsequent proctectomy [101], the initial surgery of choice is the IPAA. Patients need frequent yearly surveillance of the rectum or the ileal pouch regardless of the surgery for polyp recurrence [101].

POLE- and POLD1-Associated Polyposis

Recently, germline mutation in POLE and POLD1 has been associated with oligopolyposis inherited in an autosomal-dominant fashion [107, 108].

POLE and POLD1 are DNA polymerases ε and δ which are involved in DNA replication. The syndrome has been referred to as polymerase proofreading-associated polyposis (PPAP). In addition to oligopolyposis, colorectal cancer has been described in affected individuals, and in those with POLD1 mutations, endometrial cancer has also been described. The syndrome is relatively new and still needs to be elucidated.

A summary of all polyposis syndromes discussed above is discussed in Table 20.5.

Chemoprevention

The development of chemopreventive agents follow a standard algorithm for drug development, starting with mechanically based drug screens, preclinical, efficacy tests, toxicology assessments, and an orderly sequence of carefully designed clinical trials. Before proceeding to clinical trials, promising agents are identified and then prioritized on the basis of complementary lines of evidence. The prioritization criteria include efficacy data obtained from in vitro and in vivo animal models and observational studies.

Today, many of these agents fall short, but choosing the correct population to do the trials is crucial, and thus individuals falling into the high-risk category include the FAP and HNPCC. Table 20.6 shows some of the studies and the agents that have been utilized in hereditary colorectal cancer syndrome patients.

This section will focus on studies providing the most compelling evidence for their use in these cohorts.

Efficacy of NSAIDs such as sulindac and its metabolites (sulfide and sulfone), as well as aspirin, has been studied in patients with FAP. NSAIDs inhibit cyclooxygenase (COX), the key enzyme in the formation of prostaglandins and other eicosanoids from arachidonic acid. Prostaglandins have been postulated in having a role in altering cell adhesion, inhibiting apoptosis and promoting angiogenesis [109, 110], all important components that are implicated in transforming tumors from benign to malignant lesions. Subsequent studies have suggested that NSAIDS exert most of their antineoplastic effects via the inhibition of the COX-2 enzyme and inhibition of other biochemical pathways independent of COX suppression [111].

One of the earlier reports of chemopreventive agents in FAP came from Waddell and Loughry who in 1983 reported regression of adenomas in three patients on sulindac after ileorectal anastomosis and on one patient with an intact colon [112]. Others subsequently confirmed the efficacy of sulindac in decreasing the number and size of polyps in patients with FAP. One such study was a randomized, double-blind placebo-controlled study of 22 patients with FAP including 18 who had not undergone colectomy [113]. In this study, sulindac 150 mg twice daily was shown to reduce the size and number of polyps in patients treated compared to placebo. The effect disappeared once the study drug was discontinued. None of the patients had complete disappearance of the polyps. It must be noted that there are reports in the literature where FAP patients who were on sulindac after colectomy went on to develop colorectal adenocarcinoma [114, 115]. If sulindac is to be used, it should be used in conjunction with strict endoscopic surveillance regimen [111].

Giardello et al. also evaluated the effect of sulindac in 41 patients aged 8–25 years with APC germline mutations but not yet phenotypically affected [116]. In this double-blind placebo-controlled trial over a 48-month period, sulindac did not prevent the development of adenomas in individuals with FAP.

Combination therapy has also been looked at using sulindac. In a randomized, double-blind study reported by Meyskens Jr. et al., 375 patients with a history of adenomas greater than 3 mm that were resected were assigned to receive either oral difluoromethylornithine (DFMO) and low-dose sulindac versus placebo (DFMO and sulindac trial) [117]. Follow-up colonoscopy was performed at 3 years looking for colorectal adenoma recurrence. They reported a significant decrease in recurrence of one or more adenomas and a decrease in advanced adenomas in the DFMO plus sulindac group. They reported no statistically significant increase in gastrointestinal,

Table 20.5 Summary table of hereditary polyposis syndromes

Syndrome	Genetic basis	GI manifestation	Surveillance	Extracolonic manifestation	Surgical management
Lynch	DNA mismatch genes MLH1, MSH2, MSH6, PMS2	Right-sided tumor in 60–70 % MSI high tumor	Colonoscopy starting at age 25 or 10 years younger than youngest family history affected Consider transvaginal U/S, CA 125 levels, EGD, and urine cytology	Endometrial, gastric, urinary tract, pancreas, biliary tract, brain, sebaceous gland, keratoacanthomas	TAC/IRA with annual rectal surveillance or segmental colectomy with annual colonoscopy
FAP	APC gene 5q21 in >90 %	>100 adenomatous polyps of colorectum or polyps positive for APC mutation	Sigmoidoscopy at age 10–12 years Consider protein truncation test Upper GI surveillance with EGD at age 20 or time of prophylactic colectomy	Desmoids, periampullary neoplasms, osteomas, odontomas, sebaceous and epidermoid cysts, and CHRPE	Options include TAC with ileostomy, TAC/IRA, or TPC with IPAA
aFAP	APC gene Usually codons 78–167 or 1581–2843	10–99 adenomatous polyps of colorectum or polyps positive for APC mutation	Initial colonoscopy at age 15. If no adenomas, colonoscopy every 2 years starting at age 20	Desmoids, periampullary neoplasms, and osteomas	Options include TAC with ileostomy, TAC/IRA, or TPC with IPAA
MYH-associated polyposis	Biallelic mutation of MYH	MYH mutation in polyp	Colonoscopy at age 18–20. Repeat every 2 years if negative or polyposis mild Upper GI screening at age 25–30	Desmoids, periampullary neoplasms, osteomas, odontomas, sebaceous and epidermoid cysts, and CHRPE	Options include TAC with ileostomy, TAC/IRA, or TPC with IPAA
PJS	LKB1	Hamartomas of GI tract and at least two of the following: Small bowel disease, mucocutaneous melanin pigmentation, or positive family history	Colonoscopy at age 18, then every 2–3 years	Mucocutaneous melanin pigmentation of perioral and buccal areas	Polypectomy If not amenable, segmental bowel resection with intraoperative endoscopy Prophylactic colectomy not recommended at this time
JPS	SMAD4 in gene 18q2 or BMPR1A gene 10q22–23	Greater than 3 juvenile colonic polyps and juvenile polyps anywhere in GI tract or any number of polyps with positive family history	Colonoscopy at age 15 with EGD and SBS. If negative, repeat every 2–3 years	Stomach, pancreas, and duodenum	Polypectomy If disease diffuse, TAC/IRA with rectal surveillance every 1–3 years
POLE- and POLD1-associated polyposis	POLE and POLD1 DNA polymerase mutations	Confirmed germline mutation in POLE and POLD1 in unexplained adenomatous polyposis	Colonoscopy at age 30	Endometrial	Polypectomy. No consensus on prophylactic colectomy

CHRPE Congenital Hypertrophy of the Retinal Pigmented Epithelium, *TAC/IRA* Total Abdominal Colectomy/Ileorectal Anastomosis, *TPC* Total Proctectomy, *IPAA* Ileal Pouch-Anal Anastomosis.

Table 20.6 Hereditary colorectal chemoprevention in colorectal neoplasia: antioxidant micronutrients and NSAIDs

Study	Sample size[a]	Design/cohort[b]	Intervention[c]	Primary results
Labayle et al. [132]	9	DBRCT/phenotypic FAP	Sulindac 100 mg po TID × 4 months	Adenoma number and size reduced*
Giardiello et al. [133, 134]	22	DBRCT/phenotypic FAP	Sulindac 150 mg po BID × 9 months	Adenoma number and size reduced* mucosal prostanoids reduced*[d]
Nugent et al. [135]	14	DBRCT/phenotypic FAP	Sulindac 200 mg po BID × 6 months	Adenoma burden reduced* proliferative index reduced*
Winde et al. [136]	38	CCTRL/phenotypic FAP	Sulindac 25–150 mg BID × 3–48 months	Adenoma number and size reduced*; proliferative index reduced*; prostonoids reduced
Steinbach et al. [137]	77	DBRCT/phenotypic FAP	Celecoxib 100, 400 mg po BID × 6 months	Focal and global adenoma number and burden reduced* (400 mg BID vs. placebo)
Bussey et al. [138]	49	DBRCT/phenotypic FAP	Vitamin C 3 g/d followed for up to 24 months	Rectal adenoma number reduced(NS)
DeCosse et al. [139]	58	DBRCT/phenotypic FAP	Placebo wheat bran fiber 2.2 g/d versus Vitamin C (4 g/d), Vitamin E (400 mg/d) +/- Wheat bran fiber (22.5 g/d) over a 4 year period	Rectal adenoma number reduced in high fiber supplement group (NS)
Burn et al. [140]	861	DBRCT/HNPCC	HNPCC versus placebo 600 mg ASA qd	44 % reduction of CRC in HNPCC at 5 years. At 2 years, 63 %. No difference in the polyps burden
Ishikawa et al. [141]	34	DBRCT/FAP	ASA 100 mg qd 6–10 months	Reduction in the number and size of polyps
Glebov et al. [142]	**	HNPCC carriers	Celecoxib 200 mg BID versus 400 mg BID for 6 months	Biomarker modulation Pattern of gene expression

*Statistically significant result ($P < 0.05$). *NS* nonsignificant
**Not disclosed
[a]Number of subjects evaluated at study completion
[b]*DBRCT* double-blind, randomized, controlled trial, *DBRXT* double-blind, randomized, crossover trial, *CCTRL* case-control, *PBRCT* partially blind, randomized, controlled trial
[c]Duration of agent administration until described effect
[d]One subject with adenocarcinoma on extended follow-up

hematologic, cardiovascular, or cerebrovascular toxicity with sulindac use, although the study was not adequately powered to identify the differences in the two treatment groups. Currently, an NIH-funded randomized double-blind study is in recruitment to determine if the combination of DFMO plus sulindac is superior to sulindac or DFMO alone in delaying the first time occurrence of any FAP pathology.

A metabolite of sulindac, sulindac sulfone (exisulind), has also been investigated in FAP. Burke et al. reported a 25 % decrease in rectal adenomas in patients receiving exisulind compared to placebo [118]. In an open-label extension of the study by Burke et al., Phillips reported that patients who continued treatment with exisulind had a 58 % polyp reduction [119]. Side effects of exisulind include increase in liver enzymes and abdominal pain [120].

COX-2 inhibitors such as rofecoxib and celecoxib have been shown to reduce polyp number and polyp burden in the short term [121, 122]. However, significant side effects, especially cardiovascular adverse effects including myocardial

infarction, stroke, and heart failure, limit rofecoxib and to a lesser extent celecoxib use. In the celecoxib study, a double-blinded study by Steinbach et al., 77 patients were randomized to receive celecoxib or placebo for 6 months. Individuals receiving celecoxib at 400 mg twice daily showed a 28 % reduction in colorectal polyp numbers and a 30.7 % reduction in polyp burden (as calculated by the sum of polyp diameter) compared to a lesser dose of celecoxib or to placebo.

Aspirin has also been studied in the FAP as well as Lynch syndrome patients. In the Colorectal Adenoma/Carcinoma Prevention Program 1 (CAPP1) study, aspirin was studied alone or in combination with dietary nonabsorbable starch (resistant starch) and compared to resistant starch alone or to placebo in patients with FAP [123]. After median treatment duration of 17 months, no significant reduction in polyp size or count was noted, but the study did show a trend toward a decrease in both the polyp size and count in the aspirin 600 mg daily group with no effect noted on the resistant starch. Aspirin's role in FAP remains under investigation.

The combination of curcumin, an antioxidant and free radical scavenger, and quercetin, an antiflavonoid and antiinflammatory, both which are widely available as diet-derived nonprescription supplements, has been shown to reduce the size and number of ileal and rectal adenomas in five FAP patients with much toxicity [124]. Further studies are being planned to evaluate this combination.

In Lynch syndrome, only one prospective randomized study has been published with both short- and long-term results [125, 126]. In the CAPP2 study, Lynch syndrome patients defined as those with mismatch repair gene mutation or those whose family met the Amsterdam criteria and had a personal history of a cured Lynch syndrome neoplasm with an intact colon were randomized in a two by two design to either aspirin at 600 mg daily with or without resistant starch, placebo, and/or resistant starch alone [125]. At the 4-year follow-up, neither aspirin nor resistant starch alone or in combination had any effect on the incidence of adenoma or carcinoma [125]. However, at a mean follow-up of 55.7 months, 600 mg of aspirin daily for a mean of 25 months reduced cancer (overall) incidence [126].

CAPP3 trial is a double-blind randomized dose inferiority trial designed to compare the degree of cancer prevention in Lynch syndrome patients after administering three different doses of aspirin – 600 mg, 300 mg, and 100 mg [127]. The results are still pending.

Conclusion

Hereditary colon cancer represents a minority of colorectal cancer but with severe and life-threatening consequences. Lynch syndrome and familial adenomatous polyposis represent the majority of hereditary colon cancers. Due to their high risk of polyp formation and transformation, aggressive surveillance and prophylactic surgical intervention are indicated. Extracolonic manifestations and their increased malignant potential also necessitate frequent surveillance and possible surgical resection. Chemoprevention trials are ongoing, with NSAIDs such as aspirin showing promise in reducing polyp burden in individuals with FAP. However, at this time, chemopreventive agents are not a substitute for surgery and should be used as an adjunct to surgery. In Lynch syndrome, it appears that after about 2 years of aspirin intake, cancer incidence is reduced. The optimal dosage is yet to be determined.

Salient Points

- Approximately 10–30 % of colorectal cancer (CRC) patients have a positive family history. Of these inherited CRCs, majority are accounted by Lynch syndrome and familial adenomatous polyposis (FAP).
- Lynch syndrome is characterized by a mutation in one of the DNA mismatch repair genes that cause microsatellite instability and replication of repetitive sequences.
- Diagnosis of Lynch syndrome should follow the Amsterdam criteria and the Bethesda guidelines. If positive, screening should start with immunohistochemistry to look for loss of MMR protein expression.

- Those diagnosed with Lynch syndrome should start annual colonoscopy at age 25.
- The preferred surgical treatment in those with Lynch syndrome is subtotal colectomy with ileorectal anastomosis.
- Extracolonic manifestations occur with great frequency in those with Lynch syndrome, with a reported incidence as high as 43 % of those developing endometrial cancer.
- Majority of patients with FAP have a genetic mutation to the adenomatous polyposis coli (APC) gene, a tumor suppressor gene.
- FAP is diagnosed in those with greater than 100 adenomatous colorectal polyps, with these polyps developing by age 20 in 75 % of cases.
- Screening should begin at age 10–12 years of age.
- Three surgical options for FAP are total proctocolectomy with permanent ileostomy, total abdominal colectomy with ileorectal anastomosis, or proctocolectomy with ileal pouch-anal anastomosis. Each option has its advantages and disadvantages. Typically, the ideal time to have prophylactic surgery is the summer between high school and college.
- FAP is associated with many extracolonic manifestations. Desmoid tumors and duodenal cancers occur with high frequency. Patients with FAP should be screened routinely for these pathologies.
- Attenuated familial adenomatous polyposis (aFAP) is diagnosed in patients with APC mutations with less than 100 adenomatous polyps and is mainly located in the right side of the colon.
- In those whose colonic polyps cannot be controlled endoscopically, total abdominal colectomy with ileorectal anastomosis is the procedure of choice.
- MYH-associated polyposis (MAP) is an autosomal recessive disorder due to biallelic mutation in MYH, a base excision repair gene.
- In MAP, polyposis is controlled with endoscopic polypectomies. If surgical intervention is warranted, in patients without involvement of the rectum, total abdominal colectomy with ileorectal anastomosis is recommended. If rectum is involved, then total proctocolectomy with ileal pouch-anal anastomosis is indicated.
- Peutz–Jeghers syndrome (PJS) is an autosomal-dominant disorder caused by a mutation in the LKB1 gene, the only known tumor suppressor kinase.
- Hamartomatous polyps in PJS can occur anywhere in the GI tract, with the jejunum being the most common location.
- Dysplastic hamartomatous polyps must be distinguished from pseudo-invasion by histology.
- Patients often present with intussusceptions and/or bowel obstructive symptoms.
- Prophylactic colectomy in PJS is unclear.
- Juvenile polyposis syndrome (JPS) is a rare autosomal-dominant syndrome. Cumulative lifetime risk of colorectal cancer is 39 %.
- In JPS, polyposis is controlled with endoscopic polypectomies. If surgical intervention is warranted, the surgical procedure of choice has to be individualized.
- Polyps seen in PJS are disorganized hamartomas characterized by hypertrophy or hyperplasia of smooth muscle in the muscularis mucosa. Polyps in JPS are typically spherical, lobulated, or pedunculated in appearance with histology showing abundance of edematous lamina propria infiltrated with inflammatory cells and cystically dilated mucous-filled glands.
- There are differing reports on the efficacy of sulindac on colorectal recurrence and reducing polyp number and size. Currently, it is not recommended as a first-line treatment for polyp reduction.
- In CAPP1 study, aspirin was studied alone or in combination with dietary nonabsorbable starch (resistant starch) and compared to resistant starch alone or to placebo in patients with FAP. The study did show a trend toward a decrease in both the polyp size and count in the aspirin 600 mg daily group with no effect noted on the resistant starch. Aspirin's role in FAP remains under investigation.
- CAPP2 trial showed a reduction in all cancers in Lynch syndrome patients with when they were treated with 600 mg of aspirin daily for a

mean of 25 months and at a mean follow-up of 55.7 months.
- CAPP3 trial is investigating the effects of different doses of aspirin on cancer prevention in Lynch syndrome patients.
- NSAID such as sulindac decreases the number and size of polyps in FAP patients; however, they are not a substitute for surgical management.

Questions

1. What genetic mutations are linked with Lynch syndrome?
   A. SMAD4
   B. MMR genes
   C. APC
   D. LKB1
2. What is the next step in the algorithm for genetic testing in Lynch syndrome patients if MLH1 is found to be absent?
   A. Test for MSH2
   B. Test for PMS2
   C. Test for BRAF
   D. No more testing necessary
3. Which of the following is not an extracolonic manifestations linked with Lynch syndrome?
   A. Endometrial cancer
   B. Gastric cancer
   C. Intestinal hamartomas
   D. Keratoacanthomas
4. At what age does the colonic surveillance schedule for FAP patients recommended to start?
   A. At birth
   B. 10–12 years of age
   C. 16–18 years of age
   D. 28–30 years of age
5. Which of the following is not a surgical treatment options for FAP?
   A. Total colectomy with ileostomy
   B. Segmental colectomy with primary anastomosis
   C. Total colectomy with ileorectal anastomosis
   D. Total proctocolectomy with ileal pouch-anal anastomosis
6. Which of the following is not an extracolonic manifestation associated with FAP?
   A. Desmoid cancer
   B. Gastric cancer
   C. CHRPE
   D. Urogenital cancer
7. How is aFAP distinguished from FAP?
   A. Less than 100 adenomatous polyps in the colon
   B. Less than 150 adenomatous polyps in the colon
   C. Less than 500 adenomatous polyps in the colon
   D. Less than 1,000 adenomatous polyps in the colon
8. Which of the following studies looked at the role of aspirin in reducing cancer recurrence in FAP patients?
   A. DFMO trial
   B. CAPP2 trial
   C. CAPP1 trial
   D. CAPP3 trial

Answers

1. B
2. C
3. C
4. B
5. B
6. A
7. A
8. C

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