Approximately 6% of colorectal cancers can be attributed to recognizable heritable germline mutations. Familial adenomatous polyposis is an autosomal dominant syndrome classically presenting with hundreds to thousands of adenomatous colorectal polyps that are caused by mutations in the **APC** gene.

In the United States, 6% of individuals will develop colorectal cancer in their lifetime. The vast majority of colorectal cancers (approximately 65% to 85%) are considered sporadic, as they are not attributable to identified cancer syndromes or a family history of colorectal cancer. An additional 10% to 30% of cancers are termed familial, indicating that colorectal cancer is present in a first- or second-degree relative, but no specific germline mutation has been identified as responsible for increased susceptibility. Identifiable germline mutations cause approximately 6% of all colorectal cancers.[1] The purpose of this review is to outline the characteristics, diagnosis, and management of hereditary colorectal cancer syndromes caused by germline mutations, including familial adenomatous polyposis, Lynch syndrome (hereditary nonpolyposis colorectal cancer), juvenile polyposis, and Peutz-Jeghers syndromes.

**Familial Adenomatous Polyposis**

Although familial adenomatous polyposis (FAP) accounts for only about 0.5% to 1% of colon cancers, its clinical presentation can be quite distinctive, consisting of hundreds to thousands of polyps in the colon and upper gastrointestinal tract. Individuals with this syndrome, if left untreated, have a virtual certainty of developing colon cancer within their lifetime. The mean age for development of colon adenomas is 16 years for classic FAP, and the mean age for diagnosis of colon cancer in untreated individuals is 36.[2] An attenuated form of FAP, also known as the hereditary flat adenoma syndrome, consists of fewer than 100 colon polyps, rather than the hundreds or more found in the classic form of FAP. Some clinical presentations of attenuated FAP are characterized by relative sparing of the rectum and a tendency for right-sided colon lesions. The age at colon cancer diagnosis in attenuated FAP is between that of classic FAP and that of the general population; it averages 10 to 20 years later than in classic FAP, or around age 50 to 60.[3]

**Other Associated Findings**

Fundic gland polyps of the stomach and adenomas of the duodenum are other characteristic gastrointestinal lesions that are often found in this disorder. Approximately 50% of individuals with FAP have gastric fundus polyps, and 10% have adenomas of the stomach. Although gastric fundus polyps are unlikely to have malignant potential, gastric adenomas can occasionally develop into invasive disease.[4] Adenomas of the small bowel can be found in 50% to 90% of patients with FAP and most commonly occur in the distal portions of the duodenum. A substantial proportion of FAP patients may have adenomas of the ampulla of Vater or the duodenal papillae, which may cause pancreatitis and have a higher risk of malignant transformation than other polyps found in the duodenum.[5]

Benign tumors outside of the gastrointestinal tract that are associated with FAP include osteomas, desmoid tumors, adrenal adenomas, and cutaneous fibromas. Although the majority of these lesions do not cause significant morbidity or mortality, desmoid tumors have the potential to become locally invasive and can be extremely difficult to manage. Desmoid tumors develop in approximately 10% of FAP patients and are associated with pregnancy, oral contraceptive use, and abdominal surgery. Half of the patients with these tumors experience significant related morbidity and mortality. The combination of colonic adenomatous polyposis, desmoid tumors, fibromas, and osteomas has been described as Gardner syndrome, although FAP remains the more commonly used term.[6] Other physical examination findings that occur more frequently in FAP patients include supernumerary
teeth, unerupted or absent teeth, odontomas, epidermoid cysts, and congenital hypertrophy of the retinal pigment epithelium (CHRPE)-a pigmented lesion of the retina that does not affect the vision. Unilateral CHRPE lesions can be found in the general population, but bilateral or multiple CHRPE lesions suggest a diagnosis of FAP.[7]

Individuals with FAP also have an increased incidence of certain extracolonic tumors relative to the general population. Cancers of the duodenum or ampulla occur in 4% to 12% of patients with FAP and are a leading cause of morbidity and mortality among FAP patients who have been treated with a total colectomy. Stomach cancers may develop in 0.5% of FAP patients and usually arise from gastric adenomas rather than fundic gland polyps. Approximately 2% of FAP patients develop pancreatic cancer.[8] Thyroid cancer may develop in approximately 2% of FAP patients, with a mean age of 28 at diagnosis. The majority of these cancers are papillary thyroid carcinomas. Pediatric patients under age 5 have an increased incidence of hepatoblastoma, with an absolute risk of 1.6%. Turcot syndrome consists of colon cancer associated with increased risk of cancers of the central nervous system; two-thirds of these patients have FAP.[9] The tumor type most often seen in this syndrome in conjunction with FAP is medulloblastoma, which is present in less than 1% of all FAP patients. Finally, the risks of biliary and adrenal cancers, although still quite low, are increased in the FAP population relative to the general population.[10]

Genetic Testing

Most cases of classic and attenuated FAP can be attributed to mutations to the APC gene, a tumor-suppressor gene located on chromosome 5q21-q22.[11,12] Deleterious mutations in this gene cause premature truncation of the APC protein. Up to 25% of individuals with FAP will have a de novo mutation. Studies of genotype-phenotype correlations have shown that attenuated FAP is associated with mutations at the 5‘ and 3‘ ends of the gene, as well as in exon 9.[13-15] Desmoid and osteomas occur more frequently in patients with mutations of codons 1400 to 1580, and congenital hypertrophy of the retinal pigment epithelium is associated with mutations in codons 457 to 1444.[16]

Genetic testing of the APC gene that combines sequencing of the coding regions and analysis for large deletions and rearrangements will detect mutations in 90% to 95% of families with a clinical diagnosis of FAP. Once a mutation has been identified in an affected family member, other family members can be tested for the specific alteration with essentially 100% accuracy. Cost-effectiveness analysis has shown that genetic testing to identify individuals with FAP is superior to performing regular endoscopy for all individuals potentially at risk.[17] It has also been demonstrated that life expectancy is greater for individuals who are diagnosed with FAP prior to the onset of symptoms. Finally, appropriate surgical management of these patients can be determined by the results of genetic testing. As more is learned about genotype/phenotype correlations, knowledge of the specific familial mutation may play a greater role in management decisions.

Screening

Patients with classic FAP require close endoscopic surveillance starting at an early age. Screening guidelines vary, but most suggest that sigmoidoscopy or colonoscopy should be initiated between the ages of 10 and 12 and performed every 1 to 2 years until polyps are too numerous to be managed endoscopically; at that time, colectomy should be considered. After colectomy, endoscopy of the rectal remnant or ileal pouch is needed on an annual basis. Esophagogastroduodenoscopy (EGD) with use of a side-viewing scope to visualize the duodenum should begin at age 25 or at the time of detection of polyps in the lower gastrointestinal tract. A staging system for severity of duodenal adenomas has been developed by Spigelman in order to determine appropriate management.[18] Depending on Spigelman stage, EGD should be repeated every 1 to 3 years. If the duodenum is severely affected, consideration of surgery is appropriate. Small-bowel imaging by enteroclysis or capsule endoscopy may be considered when severe duodenal polyposis is detected. Individuals from families with attenuated FAP should start colonoscopy between the ages of 18 and 20 years, and colonoscopy should be done every 2 to 3 years. However, one needs to be cautious with these recommendations as it can be difficult to distinguish attenuated FAP from classic FAP in small families. There is no consensus as to whether colectomy is mandatory in these patients once polyps are identified; some elect to reserve colectomy only in patients whose polyps cannot be managed endoscopically. Similarly, upper endoscopy is recommended by most authors because of the marked phenotypic variation in this syndrome. Screening for tumors outside of the gastrointestinal tract includes regular monitoring of the liver by ultrasound and alpha-fetoprotein levels to rule out hepatoblastoma from infancy to age 5, although
consensus has not been reached for this recommendation. Annual physical examination of the thyroid is also recommended. At present, screening measures are not available for desmoid tumors and other tumors associated with FAP.

**Chemoprevention**

Chemoprevention, particularly with nonsteroidal anti-inflammatory drugs (NSAIDs), has been an area of active investigation in families with FAP. Several studies of sulindac and COX-2 inhibitors have demonstrated temporary regression of adenomas in this population. Celecoxib (Celebrex) received accelerated Food and Drug Administration approval based on data showing a reduction of polyp burden in individuals with FAP, although the clinical benefit of this drug was not established. These modestly encouraging results must be balanced with the recent data showing that rofecoxib (Vioxx, a COX-2 inhibitor that was taken off the market) increases the risk of cardiovascular events. Although COX-2 inhibitors are unlikely to play a role in colon cancer prevention in the general population, additional studies with longer follow-up may demonstrate a favorable risk-benefit ratio for these medications as chemoprevention in the FAP population. In the setting of FAP, COX-2 inhibitors currently are useful for individuals with a low polyp burden in the rectal remnant to delay the timing of complete proctectomy.

**Lynch Syndrome**

Up to 5% of all colorectal cancers are attributable to Lynch syndrome (hereditary nonpolyposis colorectal cancer, or HNPCC). This disorder, inherited in an autosomal dominant pattern, is typically characterized by a family history of colorectal cancer and the occurrence of colorectal cancer prior to the age of 50. Eighty percent of individuals with Lynch syndrome will develop colorectal cancer during their lifetime. Two-thirds of these cancers will be in the right side of the colon rather than the left side, where the majority of sporadic tumors are found. Unlike familial adenomatous polyposis, large numbers of colon polyps are not present in Lynch syndrome; however, polyps that are present undergo accelerated tumorigenesis. In patients with sporadic colorectal cancer, malignant transformation occurs over the course of 7 to 10 years; in patients with Lynch syndrome, this process occurs over approximately 3 years. The mean age of onset of colon cancer in Lynch syndrome patients is 44 years, as compared to 65 years in the general population.

**Associated Risks**

Hereditary nonpolyposis colorectal cancer is perhaps a misleading name for this syndrome, since cancers of the endometrium, stomach, ovary, small bowel, upper urinary tract, hepatobiliary tract, and central nervous system are also increased in these patients relative to the general population. The eponym Lynch syndrome is preferable for this reason, although HNPCC currently remains the more common designation. Risk for endometrial cancer is approximately 43% in women with Lynch syndrome, and in some cases, endometrial cancer may occur as the sentinel cancer in the family. The lifetime risks of gastric, biliary tract, urinary tract, and ovarian cancers range from 9% to 19% in Lynch syndrome patients; the risks for small bowel carcinoma and central nervous system tumors are approximately 1%. Within Lynch syndrome, the presence of certain extracolonic tumors is often described by other eponymous syndromes. As mentioned previously, Turcot syndrome refers to colon cancer associated with central nervous system tumors. While the majority of cases of Turcot syndrome are due to FAP, approximately one-third are due to Lynch syndrome. The characteristic central nervous system tumor in Lynch syndrome patients is glioblastoma. Muir-Torre syndrome refers to the combination of uncommon skin tumors such as sebaceous carcinomas and keratoacanthomas with the typical features of Lynch syndrome. Identification of these skin lesions may aid in the diagnosis of Lynch syndrome.

**Amsterdam Criteria**

In 1990, the Amsterdam Criteria were created in order to define a clinical diagnosis of Lynch syndrome for research purposes. An individual was identified as having Lynch syndrome if all of the following criteria were met: three family members diagnosed with colorectal cancer (one family member must be a first-degree relative of the other two), two consecutive generations affected with colon cancer, and at least one colon cancer diagnosed under the age of 50. In addition, polyposis syndromes such as FAP must be ruled out clinically. In 1999, these criteria were updated to include other Lynch syndrome-related cancers in addition to colon cancer. Recently, an Amsterdam-plus
model has been introduced, with the addition of numbers of colorectal and endometrial cancers in
the family, number of patients with more than four adenomas, number of patients with multiple
primary colorectal or endometrial cancers, and mean age of presentation in the family.[24]

In 1993, simultaneous efforts of several research groups discovered that tumor microsatellite
instability (MSI) is the molecular hallmark of Lynch syndrome.[25-28] Approximately 90% of patients
with Lynch syndrome demonstrate microsatellite instability at multiple loci in their tumor tissue,
whereas only 10% to 20% of sporadic colon tumors have MSI.[29,30] Sporadic colon cancers in older
individuals may show microsatellite instability due to epigenetic methylation, which can cause
silencing of the MLH1 gene.

Mismatch Repair Genes

Lynch syndrome is caused by germline mutations in the mismatch repair genes MLH1, MSH2, MSH6,
and PMS2. These genes monitor for appropriate matching of nucleic acids within the DNA and allow
for the excision and correction of mismatched pairs. Mutation or dysregulation of these genes
permits the addition of unmatched nucleotide repeats to go unchecked, which becomes apparent on
microsatellite instability testing. Another mismatch repair gene, PMS1, had been suspected as a
cause of Lynch syndrome, but there is no compelling evidence that germline mutations in PMS1
cause this syndrome. Immunohistochemistry testing done in conjunction with microsatellite
instability testing allows for identification of the specific mismatch repair gene affected. In most
cases, the protein product of the mutated gene will be absent on immunohistochemistry staining.

Approximately one-third of Lynch syndrome cases are due to a mutation in MLH1, another third are
due to a mutation in MSH2, and a very small percentage are due to mutations in MSH6 and PMS2.

Additional genes, as yet unidentified, also play a role in Lynch syndrome, since alterations in the
known mismatch repair genes are not identified in approximately one-third of patients. This
discrepancy may be due to technique: One recent study showed that conventional DNA sequencing
missed approximately 33% of deleterious mutations detected by conversion analysis.[31] However,
cancer risk may not be the same in these patients, as another study reported decreased incidence of
colorectal cancer in families that met the Amsterdam Criteria but whose tumors did not exhibit
MSI.[32]

After mutations in DNA mismatch repair genes were identified as the molecular basis of Lynch
syndrome, subsequent studies demonstrated that the sensitivity and specificity of the Amsterdam
Criteria for these mutations were 61% and 67%, respectively.[33] The revision of the Amsterdam
criteria to include Lynch syndrome-associated cancers as well as colon cancer increased the
sensitivity to 78% but decreased the specificity.

Microsatellite Instability

More than 40 studies have been conducted to ascertain whether tumors demonstrating
microsatellite instability have differences in prognosis relative to tumors without this characteristic.
Improved survival has been documented in individuals with Lynch syndrome-associated colorectal
cancer when compared to unselected patients with the same stage of disease (hazard ratio = 0.67; P
< .0012).[34] It was originally suggested that these tumors might be more susceptible to cytotoxic
chemotherapy due to their inability to correct DNA damage; however, the reports in the literature
are conflicting. A recent meta-analysis by Popat et al confirmed that colorectal cancers with
microsatellite instability have an improved overall survival rate, with a hazard ratio of 0.65 (95%
confidence interval [CI] = 0.59-0.71), but did not identify any benefit of adjuvant fluorouracil in 184
patients with MSI tumors (hazard ratio = 1.24, 95% CI = 0.72-2.14). The meta-analysis concluded
that additional studies are needed to define the benefit of adjuvant therapy in locally advanced
tumors with MSI.[35]

The Bethesda guidelines were established in 1997 to identify colorectal cancer patients for screening
for Lynch syndrome by microsatellite instability testing of tumor tissue.[36] All individuals who meet
one or more of these criteria should undergo testing. The original Bethesda criteria had a sensitivity
of 94% and a specificity of 25% for detecting mutations in mismatch repair genes.[33] More recently,
these criteria have been expanded to offer testing to all individuals with colon cancer diagnosed
prior to age 50 and all those under 60 with tumor histology suggestive of microsatellite instability
(Table 1).[37] Some data suggest that a substantial number of Lynch syndrome cases may still be
missed despite use of the Amsterdam criteria and Bethesda guidelines.[38]

Microsatellite instability also offers insight regarding the value of genetic testing within a family.
Once microsatellite instability has been demonstrated on the tumor and immunohistochemistry has
established the absence of a protein associated with a mismatch repair gene, mutation analysis
should be conducted on the gene in question to determine the specific disease-causing mutation. After the specific mutation has been identified, family members at risk should be offered testing for that mutation.

**Surveillance and Prevention**

**TABLE 1**

Revised Bethesda Guidelines for Testing Colorectal Tumors for Microsatellite Instability

Asymptomatic individuals with a clinical or genetic diagnosis of Lynch syndrome should undergo colonoscopy at the time of diagnosis or starting from age 20 to 25. If colorectal cancer occurs before age 30 in the family, colonoscopy for at-risk individuals should start 10 years prior to the earliest age of diagnosis. Colonoscopy should be performed every 1 to 2 years. Compared to watchful waiting, increased colonoscopic surveillance has been shown to decrease the incidence of colorectal cancer and improve survival in this population.[39] In our own practice, we recommend annual colonoscopy.

Total colectomy is recommended if a colorectal cancer is diagnosed, due to the increased incidence of synchronous and metachronous lesions. If a rectal remnant is present after surgery, surveillance of the remaining rectum should continue with yearly flexible sigmoidoscopy.

Surveillance for Lynch syndrome-associated cancers other than colorectal cancer is somewhat more controversial, as methods of screening for these cancers have not been proven to offer a clinical benefit. Yearly endometrial biopsy is usually recommended to women with Lynch syndrome, and transvaginal ultrasound to measure the endometrial stripe is a reasonable alternative.[40] Similarly, yearly transvaginal ultrasound and serum testing for CA-125 may offer a reasonable screening option for ovarian cancer, although patients should be counseled as to the shortcomings of these tests. Prophylactic hysterectomy with bilateral salpingo-oophorectomy after childbearing is complete is usually recommended in order to virtually eliminate the risk of endometrial and ovarian cancer.

Screening for upper urinary tract cancers by urine cytology may also be performed on a yearly basis, although this recommendation is not universally adopted. Cytology is also suboptimal as a screening test, but the noninvasive nature of this assessment and the potential benefit from early tumor detection make it acceptable to physicians and patients, and therefore reasonable to consider. At this time, screening upper endoscopy, capsule endoscopy, and other means of small bowel imaging are not recommended, and no screening for hepatobiliary tract or central nervous system tumors has been shown to be effective in Lynch syndrome to date.

Chemoprevention of colon polyps in at-risk individuals has not been realized to date. However, women of reproductive age should be counseled regarding the potential benefit of oral contraceptives in risk reduction for endometrial cancer and ovarian cancer.[41]

**Mutations in MYH**

Another newly described genetic cause of multiple colorectal adenomas has been attributed to germline mutations in the MutY human homolog (MYH) gene. This gene functions as an excision-repair mechanism; when mutated, it allows for the persistence of oxidative damage to genes, including APC. A guanine adduct that results from oxidative damage (8-oxo-7,8-dihydroxy-2'-deoxyguanosine) pairs with adenine rather than cytosine, leading to excess transversions of guanine-cytosine pairs to thymine-adenine pairs.[42]

Unlike most other known hereditary colorectal cancer syndromes, MYH polyposis appears to be autosomal recessive. Some studies have questioned this mode of inheritance, since it is possible that the presence of a monoallelic mutation in MYH may also confer a mildly increased risk of colorectal cancer.[43] However, it is very clear that MYH polyposis does not follow the classic autosomal dominant pattern observed in FAP, AFAP, or Lynch syndrome.
The phenotype for biallelic mutations of MYH is still under investigation. Although the risk of colon cancer for individuals with these mutations is known to be increased, ongoing efforts seek to quantify this risk and to determine the frequency of biallelic MYH mutations in the general population. Most individuals with biallelic MYH mutations have between 15 and 100 colonic polyps, although some have been reported to have polyposis with over 100 polyps. It is estimated by some reports that up to 30% of individuals with multiple colorectal adenomas within this range who have tested negative for an APC mutation are affected with biallelic mutations in MYH.

The median age of presentation of disease is in the mid 40s to late 50s. On average, individuals with MYH mutations and a polyposis phenotype also tend to require colectomy in their late 40s, which is significantly later than when FAP patients would require this procedure. Extracolonic manifestations of FAP, such as duodenal adenomas, gastric cancer, and CHRPE, have also been described in a small number of patients with biallelic MYH mutations. No patients with desmoid tumors and MYH mutations have been described to date.[44]

Clinical testing for MYH mutations is available. Current recommendations are that individuals with identified biallelic mutations in MYH should follow the same guidelines as those with attenuated FAP. For those with few polyps, colonoscopic surveillance is appropriate, although the frequency of screening has not been determined. If the polyps cannot be controlled by polypectomy, total colectomy should be performed. Because some individuals with biallelic MYH mutations have had duodenal adenomas, upper endoscopy should also be performed regularly in these patients.[44] For individuals with monallelic mutations in MYH, data are insufficient to develop screening guidelines at this time. Some experts recommend no increased surveillance in this group, while others advocate adherence to familial colon cancer screening guidelines.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) occurs infrequently, with an incidence rate between 1 in 16,000 and 1 in 100,000. Unlike the polyps described in FAP or Lynch syndrome, the characteristic lesions of juvenile polyposis are hamartomatous rather than adenomatous. These polyps are more commonly found in children but can occur at any age. Solitary juvenile polyps are present in 1% to 2% of the general population, but the presence of multiple juvenile polyps is suggestive of the syndrome. The diagnostic criteria for JPS are met if more than five juvenile polyps are present in the colorectum, multiple juvenile polyps are present throughout the gastrointestinal tract, or if juvenile polyps are present in an individual with a known family history of juvenile polyps.[45] Approximately 20% of patients with this syndrome will develop colorectal cancer by age 35; up to 68% will have colorectal cancer by age 60. Gastric cancer has been found in 21% of JPS patients affected with gastric polyps, and increased incidence of pancreatic and small bowel cancers relative to the general population has also been reported.

JPS is inherited in an autosomal dominant pattern and has been attributed to mutations in two genes to date. Approximately one-quarter of JPS cases arise de novo. Although the cause of juvenile polyposis has not been described in all individuals with the syndrome, 15% of JPS patients have mutations in MADH4, a tumor-suppressor gene also known as SMAD4. An additional 25% of JPS patients have mutations in BMPR1A, a serine threonine kinase. Individuals with a mutation identified in one of these two genes are more likely than other JPS patients to have a family history of gastrointestinal cancer and more than 10 polyps in the lower gastrointestinal tract. Mutations in MADH4 are also associated with hereditary hemorrhagic telangiectasia, or Osler-Weber-Rendu syndrome. Patients with this phenotype may have significant risk of visceral bleeding and should be checked for the presence of clubbing, telangiectasias, or arteriovenous malformations.[46] Genetic testing for mutations in MADH4 and BMPR1A is clinically available. The sensitivity of such testing, however, is only 40% to 60%, and therefore the absence of an identified mutation does not exclude the diagnosis of JPS. Surveillance recommendations for JPS patients include colonoscopy, upper endoscopy, and assessment of the small bowel, to be done every 1 to 2 years. The recommended age to start screening is 15 for lower endoscopy and 25 for upper gastrointestinal tract screening; endoscopy may be initiated earlier as dictated by symptoms. Less frequent screening could be considered at age 35. If polyps cannot be managed endoscopically, colectomy or gastrectomy may be indicated.[47]

The differential diagnosis of JPS should include Cowden syndrome, a hereditary syndrome caused by germline alterations in the PTEN gene. Although the gastrointestinal manifestations of this syndrome include multiple hamartomatous polyps similar to those of JPS, patients with Cowden syndrome are not considered to be at increased risk of colon cancer.[48] The primary manifestations of this syndrome...
disorder are benign skin lesions, macrocephaly, breast cancer, endometrial cancer, and thyroid cancer.

**Peutz-Jeghers Syndrome**

Like juvenile polyposis, Peutz-Jeghers syndrome (PJS) consists of hamartomatous polyps that can occur throughout the gastrointestinal tract. Estimates of its incidence range from 1 in 25,000 to 1 in 280,000. The most common site of polyps in PJS is the small intestine, but approximately 35% of PJS patients have colonic polyps, 30% have rectal polyps, and 23% have polyps in the stomach.[49] In addition to the hamartomatous polyps, adenomas are more common in all areas of the gastrointestinal tract.

For PJS patients, the risk of gastrointestinal cancers is markedly increased over the population risk. Relative risks reported for colon, stomach, and small intestine neoplasms have been as high as 84, 213, and over 500, respectively.[50] Increased risk is also present for other gastrointestinal cancers (pancreatic, esophageal), as well as neoplasms outside of the gastrointestinal tract (lung, breast, ovarian, and endometrial). Some studies report a 20-fold increase in gynecologic and breast cancer incidence in this population.[51] Other tumors associated with PJS are benign ovarian tumors called sex cord tumors with annular tubules (SCTAT), calcifying Sertoli tumors of the testes, and adenoma malignum of the cervix.

The diagnostic criteria for PJS are the presence of histologically confirmed hamartomatous polyps with at least two of the following: positive family history, hyperpigmentation of the digits and mucosa of the external genitalia, and small bowel polyposis.[52] This classic hyperpigmentation is almost a pathognomonic physical finding in PJS and characteristically occurs on the buccal mucosa or near the eyes, nose, mouth, or axilla. Pigmented macules can also be observed around the umbilicus and on the fingertips. This finding usually develops before the age of 5 years and often fades during puberty. A clinical diagnosis can be made if the characteristic pigmentation is found in a patient with a first-degree relative who has PJS.

Seventy percent of patients with PJS have mutations in the **STK11/LKB1** gene, which causes induction of apoptosis in conjunction with p53 when normally expressed.[53] The pattern of inheritance of PJS is autosomal dominant. Due to variable penetrance, only 50% of individuals with PJS have an affected parent, and the rate of de novo mutation is unknown. Genetic testing is clinically available. However, the absence of a mutation in STK11 does not preclude a diagnosis of PJS in individuals meeting the clinical diagnostic criteria.

Because of their susceptibility to multiple types of cancer, an extensive surveillance program is recommended for PJS patients. Endoscopic evaluation of the upper gastrointestinal tract and assessment of the small bowel should be done every 2 years starting at age 10. Biannual colonoscopy should be initiated at age 25. Mammography should start at age 20 and be performed every 2 to 3 years as well. Women should be instructed in breast self-examination and should have clinical breast examinations, pelvic examinations, and pelvic ultrasounds on a yearly basis after age 20. Testicular examination should be performed on a yearly basis in males over age 10.[47]

**APC I1307K and Low-Penetrance Susceptibility Alleles**

A common polymorphism in the **APC** gene, isoleucine to lysine at codon 1307 (**APC I1307K**), has been well-described as a low-penetrance susceptibility allele associated with an approximately twofold increased risk of colorectal cancer.[54] This mutation, caused by a transversion of thymine to adenine, creates a polyadenine sequence that is vulnerable to an increased rate of somatic mutation. Approximately 6% of all Ashkenazi Jews are believed to have this mutation, which confers a lifetime risk of colon cancer between 10% and 20%. Age at diagnosis and number of adenomas are similar in I1307K carriers and noncarriers, and the phenotype is generally indistinguishable from sporadic colorectal cancer.

Genetic testing for I1307K is clinically available. However, use of these test results to guide clinical care has not been firmly established. The risk conferred by this polymorphism is similar to that for individuals with a family history of colon cancer, so the utility of testing individuals with a family history is unclear. Surveillance strategies for individuals with this mutation are also a subject of debate. Our group does not routinely test for **APC I1307K**, but we recommend colonoscopy every 2 years, starting at age 35 or 5 to 10 years prior to the age of the first cancer in the family, for known carriers. Others advocate following general population screening guidelines.[55]

Other low-penetrance susceptibility alleles also contribute to the pathogenesis of colorectal cancer, although less is known about these associations. **TGFBR1** is one of the best studied examples; a
common polymorphism in this gene is associated with 1.2 times the population risk of colorectal cancer.[56] A recent meta-analysis of other studies of low-penetrance susceptibility alleles found consistent evidence linking APC I1307K, HRAS1 VNTR, and MTHFR677V with the risk of colorectal cancer, with APC I1307K and HRAS1 VNTR both conferring an increased risk, and the MTHFR677V variant associated with a reduced risk of colorectal cancer.[57,58] Other examples, such as the twofold increase in risk reported in carriers of a BLMash mutation, need to be confirmed in additional studies.[59,60] In general, low-penetrance susceptibility alleles are more important for the mechanistic insight that they provide than for direct patient care at the present time.

Conclusions

Identification of patients with high-risk colorectal cancer syndromes can lead to significant changes in screening practices and disease management, not only for the colon but for multiple sites within and outside of the gastrointestinal tract. The impact of these hereditary cancer syndromes extends beyond the patient to his or her entire family. Increased awareness and recognition facilitates appropriate management and improved survival in these patients.

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