The Molecular Basis of Rectal Cancer

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Abstract

Keywords

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- molecular testing
- hereditary cancer
- adenoma-carcinoma sequence

The majority of rectal carcinomas are sporadic in nature, and relevant testing for driver mutations to guide therapy is important. A thorough family history is necessary and helpful in elucidating a potential hereditary predilection for a patient's carcinoma. The adequate diagnosis of a heritable tendency toward colorectal carcinoma alters the management of a patient disease and permits the implementation of various surveillance algorithms as preventive measures.

Sporadic Colorectal Cancer

The overwhelming majority of colorectal cancer is sporadic and evolves by three main pathways: the adenoma-carcinoma sequence, CpG island hypermethylation, or mismatch repair dysfunction. Regardless of the process, multiple mutations must be acquired, with epigenetic events occurring to ultimately lead to carcinogenesis. Universally, chromosomal instability is the most common pathway to colorectal adenocarcinoma.^{1,2}

WNT signaling is the classic pathway under which most rectal cancers evolve, with an initial injury to the *APC* gene (5q21) which may be present in the germline (inherited) or somatic (acquired). In the setting of sporadic colorectal cancer, the initial mutation is acquired. Ultimately, a second *APC* mutation is acquired, which decreases the downregulation of β -catenin. The result of unregulated β -catenin activity is translocation of β -catenin to the nucleus, upregulating transcription of *MYC*, and *CyclinD1*, both of which are proliferative factors. With these changes, the mucosa now has a milieu predisposed to neoplasia, and additional genetic events further perpetuate the sequence such as acquisition of activating mutations in oncogenes such as *KRAS* (codons 12, 13, and 61), *BRAF* (V600E > > > V600K > V600H), *PIK3CA*, and others (► Fig. 1). Accumulation of such genetic aberrations is a late event; less than 10% of adenomas smaller than 1 cm in size contain activating *KRAS* mutations. However, more than 50% of adenomas greater than 1 cm in size possess

KRAS activating mutations. Additional events in the progression toward carcinoma include inactivating tumor suppressor genes such as *SMAD4*, and *SMAD2*, which are part of the *TGF β* signaling pathway, conferring autonomous growth. Deleted in colorectal cancer (*DCC*), also a tumor suppressor gene, and proximal to *SMAD4* and *SMAD2* is another gene involved in the acquisition of genetic events resulting in invasive carcinoma. It is no surprise that *p53*, the “guardian of the genome,” and the most common denominator for neoplasia, is also part of the progression toward invasive colorectal adenocarcinoma. Moreover, acquisition of a *p53* mutation is also noted in invasive lesions, but in few adenomas, implicating that this is a late event in the carcinoma progression.^{1,2}

Though less common, sporadic mismatch repair deficiency is another pathway toward development of colorectal carcinoma. This is due to hypermethylation of the promoter region of *MLH1*. *MLH1* and *PMS2* comprise a heterodimer that monitors DNA base pairing (MMR). When hypermethylated, expression of this protein is silenced and therefore not expressed in protein immunohistochemistry (IHC) studies. Microsatellite instability (MSI) studies, when performed in these cases, will be positive, due to slippage of the DNA mismatch repair mechanism. It is important to have a thorough family history as histomorphology alone does not distinguish sporadic colorectal carcinoma from its inherited counterpart, Lynch syndrome. Although a family history alone is not the only solution to this possibility, it can be very instrumental in driving the correct diagnostic algorithm

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Fig. 1 Sequence of mutations.

and therefore offering the patient the best follow-up care regarding their cancer diagnosis, especially since, like their hereditary counterparts, these lesions may reside in the right colon and may have mucinous differentiation and tumor infiltrating lymphocytes. Often, *BRAF* mutations are present in these cancers, in which testing can confirm their sporadic nature and rule out the possibility of a hereditary predisposition to colorectal carcinoma. Finally, *KRAS* activating mutations and inactivation of *p53* are not commonly associated with colorectal carcinoma due to sporadic loss of DNA mismatch repair.^{1,2}

A third pathway to sporadic colorectal carcinoma, and the least common of all, is CpG island hypermethylation. *BRAF* mutations are associated with CpG island hypermethylation, but *p53* and *KRAS* mutations are not. In fact, *p53* mutations distinguish the cancer as evolving outside of the CpG island hypermethylation genotype. Also, CpG island hypermethylation-associated colon cancers often occur in the right colon.^{1,3}

KRAS and BRAF Testing in CRC

From a treatment perspective, targeted therapy is available for patients with rectal cancer. Somatic mutations (mutations occurring in the tumor DNA) in *KRAS* are known to confer resistance to anti-EGFR therapy such as cetuximab and panitumumab.⁴⁻⁶ The National Cancer Comprehensive Network (NCCN) guidelines recommend "expanded" *RAS* testing to include both *KRAS* and *NRAS* codons 12, 13 and 61 (and codon 146 in *KRAS*) in metastatic cases.⁴ *BRAF* testing, specifically for V600E mutations, is known to have prognostic implications, and, at the time of this paper, trials with drugs that target *BRAF* are in the initial phases. Other potentially clinically relevant targets in the future include *PIK3CA* and *PTEN*.^{5,6} Additional genomic considerations regarding therapy that are not currently tested universally include pharmacogenetic considerations of drug therapy such as *UGT1A1**28 mutations and irinotecan toxicity, and *DYPD* mutations for 5-fluorouracil or capecitabine toxicity. All of these mutations are germline in origin (present in every nucleated cell in the

body, detected through blood or saliva samples).^{7,8} Lastly, determination of the presence or absence of a hereditary cancer syndrome (expanded in the subsequent sections) is important because individuals with Lynch Syndrome who are treated with 5-fluorouracil are documented to have no improvement; or, in some cases have worse outcomes.⁹

Hereditary Cancer Syndromes

Multiple syndromes exist with a predisposition to cancer that involves the rectum. The comprehensive list includes familial adenomatous polyposis coli (FAP), Lynch syndrome, Peutz-Jeghers syndrome (PJS), phosphatase and tensin homolog (*PTEN*) hamartomatous syndrome, juvenile polyposis syndrome, *MYH*-associated polyposis, hereditary mixed polyposis, serrated polyposis, and *POLE/POLD1*. With the exception of one, each of these syndromes is inherited in an autosomal dominant fashion. The exception to this is *MYH*-associated polyposis, which is autosomal recessive. It is important to consider the inheritance pattern when trying to establish the patient's genetic risk, as well as risk to the patient's relatives. Moreover, comprehensive knowledge of the features of each type of hereditary rectal cancer is important when developing the family history, since a syndrome, by definition, is a "constellation of symptoms," to avoid overlooking an individual's hereditary predilection for cancer. Each syndrome will be considered individually herein.

Familial Adenomatous Polyposis Coli

FAP was first described in 1859.¹⁰ This disorder accounts for $\leq 0.5\%$ of colorectal carcinoma and is classically characterized by hundreds to thousands of adenomas that are present throughout the length of the large bowel and rectum.¹¹⁻¹⁴ Polyps usually present in the second decade of life, and an individual with FAP's lifetime risk of colorectal carcinoma is 100%, with a mean age at diagnosis of 36 years.

Inherited in an autosomal dominant fashion, affected individuals have a 50% chance of passing the mutated allele

Fig. 2 Genotype-phenotype correlations of FAP. FAP, familial adenomatous polyposis coli.

to each offspring, and all who inherit the mutation will manifest the disease (complete penetrance). The gene involved is the APC tumor-suppressor gene, located on 5q21, and, as is the case with all hereditary disorders, the mutation is present in every nucleated cell within the body. The diagnosis is confirmed by sequencing the gene on a blood sample from an affected individual. While an inherited disorder, a high de novo mutation rate exists (as high as 25%), and greater than 95% of mutations result in a truncated protein.¹⁴ De novo mutation indicates that this is the first time the mutation is seen within the family, and that it occurred early in the embryologic development, but as a postzygotic event. Small insertions or deletions are the most common mutations that either result in a shift in the reading frame leading to a premature stop codon, hence a “truncated protein,” or confer a premature stop codon by the nature of the change in bases altogether. Deletions and duplications and splice site changes also occur.^{12,14}

Although the most devastating result of FAP is colorectal cancer, extraintestinal manifestations exist. Congenital hyperpigmentation of the retinal epithelium is one of these features, as well as fundic gland polyps in the stomach, and duodenal polyps. Extraintestinal malignancies are also seen involving the duodenum and the brain. Medulloblastoma is the brain malignancy associated with FAP, and the concomitant presence of FAP and medulloblastoma is known as Turcot syndrome. The presence of desmoids, osteomas (especially in the face or jaw), dental abnormalities, and epidermal cysts is Gardner syndrome. Papillary thyroid carcinoma, periampullary adenocarcinoma, pancreatic adenocarcinoma, hepatoblastoma, and gastric adenocarcinoma are additional extracolonic malignancies seen in FAP.^{12,14}

FAP is a classic example of a disorder with genotype-phenotype correlations which means that mutations occur-

ring in particular regions of the gene confer a specific phenotype (► **Fig. 2**). Specifically, mutations occurring toward the 5' end of the gene, involving exons 1–9, and the extreme 3' end are associated with fewer than 100 polyps, and therefore individuals with this presentation are diagnosed with attenuated FAP. In addition, individuals with attenuated FAP tend to have right-sided carcinoma, and present with colorectal carcinoma later in life (56 years of age, on average) than individuals with the other forms of FAP. Mutations occurring in the middle portion of the gene, including exons 5 through the 5' end of exon 15 are associated with manifestations of classic FAP. Severe polyposis is associated with codons 1250–1464, and desmoids tumors with mutations in codons 1445–1578, both of which exist in codon 15, upstream from the second mutation hotspot associated with an attenuated FAP phenotype.^{12,14}

In patients with classic FAP, the risk of developing carcinomatous change in the colon and rectum is 100% if left untreated. Similarly, patients with FAP who undergo ileorectal anastomosis (IRA) are at risk of developing a rectal cancer, with reports of the development of carcinoma in up to 29%.^{15–17} Furthermore, the survival rate of patients with FAP who develop a rectal cancer following IRA is significantly reduced.^{18,19} Therefore, restorative prophylactic proctocolectomy with ileoanal pouch anal anastomosis (IPAA) is the surgical treatment of choice offered to patients with FAP.

Although less controversial now, handsewn with mucosectomy versus stapled IPAA continues to be debated. Stapled IPAA is associated with improved functional outcomes with the primary concern being the rectal mucosa remaining along the transitional zone. However, the actual risk of cancer in the anal transition zone is quite low with only case reports described.^{20–27} In contrast, mucosectomy and handsewn technique removes this residual rectal mucosa. However,

islets of primary rectal mucosa have been reported in up to 20% of pouches excised, thus allowing for the potential of malignancy.²⁸

In patients with attenuated FAP, rectal sparing may allow for sparing of the rectum and creation of an IRA. However, the rectum must be free of polyps and the patient must be compliant with intense screening of the remaining rectum.

Lynch Syndrome

Lynch syndrome, also historically referred to as hereditary nonpolyposis colorectal cancer syndrome, occurs in approximately 2 to 3% of colorectal carcinomas, with a prevalence of 1:440 in the population. Early description of clustering of malignancies ultimately identified as Lynch syndrome began in 1895 with observations by Aldred Scott Warthin, MD, PhD, at the University of Michigan in Ann Arbor. The family Dr. Warthin described emigrated from Germany to Michigan before the Civil War. The family included his patient with a sibship comprised 10 members with the following cancers: two uterine, two stomach, and one "abdominal" cancer. All five of these siblings with a personal history of cancer had descendants with multiple cancers, demonstrating Lynch syndrome's autosomal dominant pattern of inheritance. Moreover, the offspring of the five siblings without cancer also did not develop cancer. This family was entitled "Family G" (for their German origin). Some time passed with intermittent descriptions of and interest in familial colorectal carcinoma other than FAP, which was ultimately embraced by Henry T. Lynch, MD, for whom the eponym derives its designation, so betrothed by C. Richard Boland, MD, PhD. Specifically, the term Lynch syndrome implies colorectal carcinoma or associated extraintestinal manifestations in families with a germline mutation in DNA MMR genes. More research was conducted, and ultimately, in 1993, nearly 100 years following its first description of familial gastrointestinal cancers, MSI was discovered by independent groups including Thibodeau at the Mayo Clinic, Rochester, and Vogelstein at Johns Hopkins and international colleagues from Finland de la Chapelle, Aaltonen, and Peltomaki. This began a rush to discover the genes involved in producing these microsatellites, which were already understood to be part of the MMR system in DNA. Although several MMR proteins have been described, including MLH1, MLH3, PMS1, PMS2, MSH2, MSH3, MSH6, TGF β R2, and EXO1, the main contributors to the development of Lynch syndrome are MLH1, PMS2, MSH2, and MSH6 (**Fig. 3**). The proteins function as heterodimers, MLH1 coupled with PMS2, and MSH2 coupled with MSH6.^{3,29,30}

As the data materialized, diagnostic guidelines were developed, the first of which was the Amsterdam Criteria. Following this, the Amsterdam Criteria was improved upon in Bethesda, MD, in 1997, with establishment of the "Bethesda Guidelines" (**Fig. 4**). The initial Bethesda guidelines were revised in 2004 with the realization that the established guidelines were missing many individuals with Lynch syndrome. Still yet, the second revisions were not comprehensive enough, leading to a consensus following a workshop in Jerusalem in 2009 that any individual younger than 70 years

Fig. 3 MMR proteins involved in Lynch syndrome.

who presents with colorectal carcinoma should be screened with either IHC for assessment of the expression of MMR proteins or with polymerase chain reaction (PCR) for MSI, both of which are conducted on tumor tissue. Each technique has advantages and disadvantages with, overall slightly greater sensitivity with MSI. Another challenge of IHC is the possibility of discordant results due to the mutation not completely eliminating the ability of the protein to be expressed, yet MSI detected in the tumor.²⁹ With the advantage of time, genotype-phenotype correlations are also observed in Lynch syndrome. For example, *PMS2* (7p22.1) is rarely involved. This gene is flanked by a pseudogene which makes the testing very complicated. As such, while the present understanding is that mutations in *PMS2* are less common in Lynch syndrome, techniques to sequence this gene have been successfully developed in the past few years, which may change the frequency of *PMS2* mutations, and hence its

<p>Medscape® www.medscape.com</p> <p>The Bethesda guidelines (1997) Just one of these criteria need to be met:</p> <ul style="list-style-type: none"> • individuals with cancer in families that fulfill the Amsterdam criteria; • individuals with two hereditary non-polyposis colorectal cancer (HNPCC)-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers (which include endometrial, ovarian, gastric, hepatobiliary or small-bowel cancer, or transitional-cell carcinoma of the renal pelvis or ureter); • individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or colorectal adenoma; one of the cancers must have been diagnosed before the age of 45 years and the adenoma diagnosed before the age of 40 years; • individuals with colorectal cancer or endometrial cancer that was diagnosed before the age of 45 years; • individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/ciriform) on histopathology, which was diagnosed before the age of 45 years; • individuals with signet-ring-cell-type colorectal cancer that was diagnosed by the age of 45 years; • individuals with adenomas that were diagnosed by the age of 40 years. <p>Revised Bethesda (2003) Just one of these criteria need to be met:</p> <ul style="list-style-type: none"> • diagnosed with colorectal cancer before the age of 50 years; • synchronous or metachronous colorectal or other HNPCC-related tumours (which include stomach, bladder, ureter, renal pelvis, biliary tract, brain (glioblastoma), sebaceous gland adenomas, keratoacanthomas and carcinoma of the small bowel), regardless of age. • colorectal cancer with a high-microsatellite-instability morphology that was diagnosed before the age of 60 years; • colorectal cancer with one or more first-degree relatives with colorectal cancer or other HNPCC-related tumours. One of the cancers must have been diagnosed before the age of 50 years (this includes adenoma, which must have been diagnosed before the age of 40 years); • colorectal cancer with two or more relatives with colorectal cancer or other HNPCC-related tumours, regardless of age. <p>Source: Nat Rev Cancer © 2004 Nature Publishing Group</p>	
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Fig. 4 Bethesda guidelines.

prevalence as a contributor to Lynch syndrome. *MSH6* (2p16.3) has an increased incidence of uterine cancer and more distally located colon cancers. *MSH6* is also associated with the finding of MSI-L in MSI studies. Mutations in *MSH2* (2p21) are associated with the greatest risk of extracolonic cancers, especially when an upstream promoter, *EPCAM* is deleted. However, a lower risk of endometrial cancer is associated with *EPCAM* deletions. Moreover, *MSH2* mutations are often seen in Muir-Torre syndrome. Of the four genes, *MLH1* (3p22.2) and *MSH2* are the most commonly involved in the colon and rectum.^{13,29,30}

Lynch syndrome-related colorectal carcinomas have a particular morphology including a poorly differentiated lesion with tumor-infiltrating lymphocytes, mucinous differentiation, signet ring cells, a pushing margin, and a Crohn-like reaction. Carcinomas tend to be located in the right colon. Moreover, these malignancies usually present at low stage.³¹⁻³³

Determination of a colorectal carcinoma as a Lynch syndrome malignancy is essential as it will influence management of the malignancy not only with respect to surgical consideration but also with chemotherapeutic regimens and surveillance follow-up. Specifically individuals with Lynch syndrome who received 5-fluorescence have a worse outcome. The known extraintestinal manifestations of Lynch syndrome include endometrial endometrioid adenocarcinoma (most commonly, occasionally clear cell, papillary serous carcinoma, malignant mixed Müllerian tumor, and less frequently other histologic patterns), ovarian endometrioid adenocarcinoma, small bowel adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, biliary carcinoma, carcinoma of the ureter, bladder, and renal pelvis, sebaceous gland tumors (Muir-Torre syndrome), keratoacanthomas, and glioblastoma multiforme (Turcot syndrome). The overall cancer risks are as follows: colorectal carcinoma 52 to 82% (mean age at diagnosis 44-61 years), endometrial carcinoma 25 to 60% (mean age at diagnosis 48-62 years), gastric cancer 6 to 13% (mean age at diagnosis 56 years), ovarian carcinoma 4 to 12% (usually diagnosed by the age of 40 years), and much lower risk for the other extraintestinal malignancies.^{13,29}

Surgeons may be the initial physician to discover a pattern consistent with Lynch syndrome, thus it is imperative for surgeons to understand the associated malignancies as well as the implications of the disease as it relates to surgery. As mentioned, the most common cancer associated with Lynch syndrome is colorectal origin with the risk of endometrial cancer approximately equal to that of colorectal. Furthermore, there is a reported approximate risk of 40% at 10 years from diagnosis in which patients with Lynch syndrome are at risk of developing metachronous colorectal cancers.^{34,35} Although the overall function in patients with segmental resection has shown to be better, the risk of metachronous cancer typically outweighs the benefit of function. Thus, most surgeons perform an extended resection consisting of a subtotal colectomy with IRA if the rectum is spared of disease as opposed to a segmental resection as is standard for a sporadic cancer. Similarly, given the increased incidence of endometrial cancer, prophylactic hysterectomy is warranted, which may be done synchronously.

The estimated risk of rectal cancer in patients with Lynch syndrome has been reported in the surgical literature to be as high as 20%. Thus, patients with Lynch syndrome and a diagnosis of rectal cancer should be evaluated preoperatively in a similar manner to patients with sporadic rectal cancer.³⁵⁻³⁸ Thus, if the staging meets criteria for neoadjuvant therapy, the patient should receive appropriate therapy. The operation offered, however, may differ in that a total proctocolectomy may be offered. In the absence of neoadjuvant chemotherapy and radiation, a total proctocolectomy with ileoanal pouch anastomosis may be constructed. The ileoanal pouch remains at risk of neoplastic change and requires surveillance regularly.

MUTYH Polyposis

As mentioned earlier, *MUTYH* polyposis (MAP) is inherited in an autosomal recessive fashion and therefore requires two mutations (biallelic) to manifest the disease. The *MUTYH* gene is a base excision repair gene, and *MUTYH* polyposis is characterized by multiple adenomas (> 10 on the average) and absence of a mutation in the *APC* gene (cases without polyps are also seen). These patients may present at a later age with polyps distributed along the entire length of the colon, but do not exclude the small bowel, especially the duodenum. In addition, the polyps may be the usual tubular adenomas but can also include hyperplastic polyps, serrated adenomas, and sessile serrated adenomas.³⁹ Clinically, the phenotype can parallel Lynch syndrome, including other extracolonic manifestations, and it is documented that clinical recognition of this entity is under-ascertained, with a study of 405 colorectal carcinomas in Spain containing an incidence of 27 (7% incidence) confirmed cases with *MUTYH* polyposis.³⁹⁻⁴² The phenotypic similarity to Lynch syndrome has included sebaceous lesions, and loss of MMR protein expression histologically (including *MSH2* and *MSH6*), with tumor MSI.⁴⁰ Other associated extracolonic malignancies involve the breast, thyroid, testis, and hematologic.⁴¹ Testing for *KRAS* was positive 67% of the time in individuals with confirmed biallelic *MUTYH* mutations, suggesting value of *KRAS* testing before germline testing when the question of *MUTYH* polyposis is present clinically. Specifically, the c.34G > T, p.G12C is the somatic transversion identified most often, and routine *KRAS* tests would cover the codons that have been documented thus far in *KRAS* in individuals with *MUTYH* polyposis.⁴³ When an individual is known to be affected, colonoscopy beginning at the age of 20 years is recommended. However, the autosomal recessive inheritance pattern precludes early detection, and most individuals present with invasive cancer.^{39,43}

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant condition with a frequency between 1:16,000 and 1:100,000 in which the individual is predisposed to hamartomatous polyps throughout the gastrointestinal tract beginning before the age of 20 years with an increased risk of carcinoma that varies between 9 and 50%.^{11,44-46} Nearly 75% of

individuals have an affected parent, de novo mutations occur in 25% of cases. The predominant cancer risk exists in the colon, but cases of gastric, upper gastrointestinal tract, and pancreas cancer have been documented. It is important to recall that some individuals with a mutation in *SMAD4*, one of three genes associated with this disorder, may also develop hereditary hemorrhagic telangiectasia (HHT) 15 to 22% of the time, which is subsequently referred to as HHT/JPS. Individuals with JPS who harbor *SMAD4* mutations have a greater proportion of gastric polyposis and an increased risk for gastric cancer.⁴⁵ The other identified genes are *BRMP1A* (10q22q23) and *ENG* (9Q34.11), all of which are associated with transforming-growth factor- β . Collectively, each gene accounts for the genetic diagnosis of JPS 50 to 60% of the time.⁴⁴

Although there is variability, most individuals have at least four to five polyps, presenting early in life. Some individuals will develop many polyps. Morphologically, the hamartomatous polyp of JPS is unique from that associated with Cowden syndrome (CS). Although the polyps in CS are characterized by streams of smooth muscle extending in an arborizing pattern, JPS hamartomatous polyps are characterized by a normal epithelium with a dense stroma containing an inflammatory infiltrate, mucus-filled cystically dilated glands in the lamina propria, and a smooth surface, sometimes with neoplastic changes.^{11,44,46} Additional clinical features of JPS include midgut malrotation, heart defects, cleft palate, cranial abnormalities, and polydactyly.⁴⁵

Peutz-Jeghers Syndrome

Clinically, PJS presents with mucocutaneous melanosis and hamartomatous polyps. Again, the inheritance is autosomal dominant, and it is the second most common form of intestinal polyposis, with an incidence 1/10 that of FAP. The gene responsible for up to 70% of cases is a tumor suppressor gene, *STK11* (*LKB1*), a serine threonine kinase receptor with a role in cell cycle regulation, regulation of apoptosis, and with cell cycle regulation. Penetrance is variable and incomplete. The diagnosis can be made in infancy, with macules developing within the first 2 years of life. However, the average age of diagnosis is 25 years. Small bowel lesions are often symptomatic, aiding in the diagnosis. There is a 39% increased risk of colorectal carcinoma in individuals with PJS, as well as an increased risk of malignancy in extraintestinal sites including: the breast (second most common malignancy), uterine cervix, testis, pancreas, and ovary.^{11,46,47} With respect to the uterine cervix, adenoma malignum is one diagnosis that increases the clinical suspicion of PJS. The mean age of cancer diagnosis is 43 years. The hamartomatous polyps characteristic of PJS are located throughout the gastrointestinal tract, with a predilection for the ileum, jejunum, and colon.^{11,46,47} Histologically, these polyps contain fronds of smooth muscle in an arborizing pattern, which is seen more easily in the polyps that are located in the small bowel.⁴⁷

PTEN Hamartomatous Syndrome

As the name implies, *PTEN* hamartomatous syndrome is associated with mutations in the *PTEN* tumor suppressor

gene and includes both CS and Bannayan Riley Ruvalcaba Syndrome (BRRS). The pattern of inheritance is autosomal dominant. While breast, thyroid, and endometrial malignancies are associated with CS, rectal carcinoma is also known to occur. Again, hamartomatous lesions are present in the gastrointestinal tract of individuals with CS, as well as BRRS. Physical examination distinguishes these two entities, since macrocephaly and polyps are seen with each. In BRRS, pigmented macules are present on the penis. Dysplastic gangliocytomas of the cerebellum are said to be pathognomonic for CS, a diagnosis otherwise known as Lhermitte-Duclos. The polyps seen in *PTEN* hamartomatous syndromes can include hamartomas (most commonly), adenomas, ganglioneuromas, inflammatory polyps, and less commonly leiomyomas, lipomatous, and lymphoid polyps. Polyps have varied from few to more than hundreds in quantity, with the potential for the presence of more than one histologic type present synchronously. The colorectal cancer risk has been stated to vary from 9 to 16% lifetime risk and is thought to emerge likely from a pre-existing adenomatous polyp, or a hamartoma.^{11,46,47} Genetic confirmation of the diagnosis of CS occurs in 80% of cases when the diagnostic criteria is applied accurately.⁴⁷ Extraintestinal manifestations of CS include trichilemmomas and acral keratoses, and an increased risk of breast carcinoma, thyroid carcinoma (papillary thyroid most often), as well as renal cell carcinoma (several histologic variants), melanoma, and endometrial carcinoma (the latter two malignancies seen less often).⁴⁷⁻⁴⁹

Other syndromes associated with hamartomatous polyps include Gorlin syndrome (*PTCH1*), multiple endocrine neoplasia 2B (*RET*), neurofibromatosis type 1 (*NF1*), and Birt-Hogg Dube (*FLCN*).⁴⁷

Hereditary Mixed Polyposis

Inherited in an autosomal dominant fashion, this condition is characterized by a presentation with a variety of polyps including tubular adenomas, juvenile polyps, and hyperplastic polyps. A few genes have been identified as candidates that contribute to this syndrome, and additional details regarding extracolonic manifestations are not as well established as the previously discussed entities, as it is one of the newer polyposis syndromes described. Candidate genes identified thus far include: *BMPRIA* (note also seen in juvenile polyposis), *GREM1*, and *SCG5*.^{11,46,50,51}

Serrated Polyposis

This entity remains genetically elusive but is diagnosed in accordance with the World Health Organization criteria published by Snover et al in 2010. An increased risk of CRC is present in patients with serrated polyposis, with an autosomal dominant inheritance pattern. Tubular adenomas can also be present in individuals with serrated polyposis, and, to date, two genes have been described with a potential role in this syndrome: *PTEN*, *MUTYH*.^{11,41} However, other than the two mentioned genes, genome-wide association studies have demonstrated considerable genetic heterogeneity in individuals with serrated polyposis, making targeted testing difficult.⁵²

Polymerase Proofreading Polyposis

New genes, *POLE* (polymerase ϵ) and *POLD1* (polymerase δ), the equivalent lagging strand polymerase to *POLE*, have been identified as candidate hereditary colorectal carcinoma genes, with affected individuals presenting with 10 to 100 polyps, microsatellite stable tumors, under the age of 60 years, and an autosomal dominant pattern of inheritance. In many cases, a family history of colorectal carcinoma is present, though this is not always the case. At the time of completion of this article, these genes are just identified, and additional data regarding their status are needed.⁵³

Summary

In summary, the majority of rectal carcinomas are sporadic in nature, and relevant testing for driver mutations to guide therapy is important. However, a thorough family history is necessary and helpful in elucidating a potential hereditary predilection for the patient's carcinoma. Moreover, adequate diagnosis of a heritable tendency toward CRC will alter the management of the patient's known disease, in some instances, and permit the implementation of various surveillance algorithms as a preventive measure.

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