Inherited Colorectal Cancer Syndromes

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ABSTRACT

Colorectal cancer is common in the Western world; ~5% of individuals diagnosed with colorectal cancer have an identifiable inherited genetic predisposition to this malignancy. Genetic testing and rational clinical management recommendations currently exist for the management of individuals with a variety of colorectal cancer syndromes, including hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome), familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP), and the hamartomatous polyposis syndromes (Peutz–Jeghers, juvenile polyposis, and Cowden disease). In addition to colorectal neoplasia, these syndromes frequently predispose carriers to a variety of extracolonic cancers. The elucidation of the genetic basis of several colorectal cancer predisposition syndromes over the past two decades has allowed for better management of individuals who are either affected with, or at-risk for inherited colorectal cancer syndromes. Appropriate multidisciplinary management of these individuals includes genetic counseling, genetic testing, clinical screening, and treatment recommendations.

KEYWORDS: Colorectal cancer, hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, hamartomatous polyps

Objectives: On completion of this article, the reader should be able to summarize the clinical and genetic characteristics of the inherited colorectal cancer syndromes: hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, MYH-associated polyposis and the hamartomatous polyposis syndromes.

Approximately 20% of patients with colorectal cancer or adenomatous polyps have a family history of these neoplasms in a first-degree relative and causative inherited genetic alterations have been identified in ~5% of patients with colorectal cancer.[1] Inherited syndromes that predispose to colorectal cancer are generally categorized based on the presence of large numbers of adenomatous polyps, few (if any) adenomatous polyps, or the presence hamartomatous polyps. In the past two decades, researchers have elucidated the genetic basis of several colorectal cancer syndromes including hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP) and the hamartomatous polyposis syndromes (Peutz–Jeghers, juvenile polyposis, and Cowden disease) (Table 1). Clinicians can now better manage individuals and families who are affected or at risk for these inherited disorders with specific genetic and clinical counseling, screening, and treatment recommendations.

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

HNPCC (also known as Lynch syndrome) is an autosomal dominant disorder characterized by colorectal cancer in the absence of marked polyposis.[1–3] HNPCC

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Table 1 Inherited Colorectal Cancer Syndromes and Their Associated Genes

Syndrome	Associated Gene
Adenomatous polyposis syndromes	
Familial adenomatous polyposis (FAP)	APC
MYH-associated polyposis (MAP)	MYH
Nonpolyposis syndrome	
Hereditary nonpolyposis colorectal cancer (HNPCC)	MSH2, MLH1, MSH6, PMS2
Hamartomatous polyp syndromes	
Peutz–Jeghers (PJS)	LKB1
Juvenile polyposis (JPS)	SMAD4, BMPR1A
Cowden disease, including Bannayan–Ruvalcaba–Riley syndrome	PTEN

appears to account for ~2 to 4% of all colorectal cancer. Although probands (the incident case) from HNPCC families are diagnosed with colorectal cancer at ~45 years, the actual median age of colorectal cancer diagnosis in HNPCC now appears to be ~60 years.[4]

Despite its designation as a colorectal cancer syndrome, numerous other cancers appear to occur at increased frequency in HNPCC kindreds (see Amsterdam II criteria, below).[3,5] Most notably, the lifetime risk for endometrial and ovarian cancer in a woman with HNPCC is 54% and 13.5%, respectively.[1,6] Historically, Turcot syndrome (colorectal and brain cancers) can be a variant of HNPCC with glioblastoma multiforme.[7] In contrast, Turcot syndrome characterized by colorectal polyps or cancers and medulloblastoma is now understood to be a variant of the familial adenomatous polyposis (FAP) syndrome. The HNPCC variant Muir–Torre syndrome is characterized by sebaceous gland adenomas or keratoacanthomas and visceral cancers.[8]

In diagnosing HNPCC, a diverse range of cancers may be observed. There is a lack of profound polyposis and penetrance is generally lower than that observed in FAP (reviewed below). Individuals affected with HNPCC have an approximate 50 to 60% lifetime risk of developing a colorectal cancer (compared with a near 100% chance of colorectal polyposis or cancer in FAP) and women with HNPCC have a 54% risk of developing endometrial cancer.[1,6]

Clinically, HNPCC has been defined by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) in terms of the Amsterdam criteria.[9] Subsequently, these criteria were expanded as the Amsterdam II criteria to include extracolonic as well as colorectal cancers as follows[3]:

1. Three or more relatives with HNPCC-associated cancer (colorectal, endometrial, stomach, ovary, ureter or renal pelvis, brain, small bowel, hepatobiliary tract cancers, or sebaceous tumors).
2. One affected individual should be a first-degree relative of the other two relatives.
3. Two or more successive generations should be affected.
4. One or more of these cancers should be diagnosed before the age of 50 years.
5. FAP should be excluded.
6. Tumors should be verified by pathologic examination.

Studies of large numbers of cancers have shown that certain characteristics appear more commonly in HNPCC compared with sporadic colorectal cancers. Colorectal cancers in HNPCC tend to arise proximal to the splenic flexure and are associated with a variety of histologic features including tumor-infiltrating lymphocytes, Crohn disease-like lymphocytic reaction, mucinous or signet ring differentiation, and a medullary growth pattern.[3,5,10,11]

In addition to frequent differences in clinical appearances, HNPCC tumors often display a molecular phenotype known as high-frequency microsatellite instability (MSI or MSI-H, also known as replication error positive, RER+).[12,13] This molecular hallmark arises because the underlying genetic cause of HNPCC is a germline mutation in any one of several genes that participate in a DNA replication proofreading system known as mismatch repair.[2,3,13,14] As a "caretaker" system, a deficiency in mismatch repair leads to an increased mutation rate and secondary mutations in the genes that then give rise to the various cancers observed in HNPCC.[1,13] Additionally, mismatch repair-deficiency causes "bystander" mutations in short repetitive DNA repeats known as microsatellites [i.e., cytosine-adenine dinucleotide repeats (CA)n, or adenine mononucleotide repeats (A)n]. It is estimated that the human genome contains hundreds of thousands of microsatellite repeat DNA regions, largely in noncoding (intronic) regions.[15,16] Microsatellite regions are highly polymorphic and as such, microsatellite repeat numbers often differ between individuals, but are the same in all cells of any single individual. Instability of a microsatellite is apparent when the copy number of that particular microsatellite DNA region is different in a cancer when compared with normal tissue from that same individual [i.e., $(CA)_5$ versus $(CA)_4$]. MSI-H is defined as instability in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.[17] Mutations of microsatellite DNA generally have no direct functional (cancer causing) consequence on the cell, unless the microsatellite is located in the coding region of a gene.[15,17]

To date, germline mutations in four mismatch repair genes, MLH1, MSH2, MSH6, and PMS2, appear to give rise to HNPCC and the MSI-H phenotype observed in HNPCC cancers.[1,2,14] The majority of

HNPCC appears to arise from MLH1 or MSH2 mutations. Individuals predisposed to HNPCC are born with one inactivated copy of a mismatch repair gene and the second copy of this gene is then lost as a somatic event in colon epithelial cells or in cells of other organs where cancers develop. In very rare instances, biallelic germline mismatch repair gene mutations have been identified in individuals with severe cancer syndromes leading to colorectal, hematologic, and other cancers at very young ages.[18,19]

Interestingly, in addition to the majority of HNPCC-related colorectal cancer that accounts for 2 to 4% of all colorectal cancer, 10 to 15% of sporadic colorectal cancers as well display the MSI-H phenotype.[10,13,16] Thus, the majority of unselected MSI-H colorectal cancers are sporadic in nature and do not occur in the context of HNPCC. Similar to HNPCC, sporadic MSI-H colorectal cancer arises due to deficiencies in DNA mismatch repair proofreading function.[20] However, in contrast to HNPCC colorectal cancer where MSI-H arise secondary to genetic (mutational) abrogation of mismatch repair, sporadic MSI-H colorectal cancers arise due to an epigenetic (nonmutational) phenomenon causing mismatch repair-deficiency. In the majority of sporadic MSI-H colorectal cancers, the MLH1 gene has been silenced (translation and transcription have been blocked) by hypermethylation of the promoter region of the MLH1 gene.[20]

Immunohistochemical analysis of paraffin-embedded specimens is now available for the MLH1, MSH2, MSH6 and PMS2 proteins.[21] In cases of MLH1-deficiency, both MLH1 and PMS2 are immunohistochemically absent because the PMS2 protein is rapidly degraded in the absence of MLH1. Similarly, in MSH2-deficiency, both MSH2 and MSH6 protein expression are absent. In contrast, in the case of either PMS2 or MSH6-deficiency, only the gene of interest is not expressed. Though sensitive, immunohistochemistry testing may miss a proportion of mismatch repair protein deficiencies that arise due to functionally relevant substitution (missense) mutations that have been observed in 10 to 37% cases of HNPCC.[14]

Based on the previously described clinical and genetic knowledge, the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer now recommends that individuals fulfilling any one of the following Revised Bethesda Guidelines be genetically assessed for HNPCC[3]:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors (as outlined in the Amsterdam II criteria), regardless of age.
3. Colorectal cancer with the MSI-H histology (as described previously) diagnosed in a patient who is less than 60 years of age.
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

If the Revised Bethesda Guidelines are met, the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer recommends the following approach to genetic testing[3]:

1. The optimal approach to evaluation is microsatellite instability or immunohistochemical analysis of tumors, followed by germline MSH2/MLH1 testing in patients with MSI-H tumors or tumors with a loss of expression of one of the mismatch repair genes.
2. After the mutation is identified, at-risk relatives should be referred for genetic counseling and testing if they wish.
3. An alternative approach, if tissue testing is not feasible, is to proceed directly to germline analysis of the MSH2/MLH1 genes.
4. If no mismatch repair gene mutation is found in a proband with an MSI-H tumor and/or a clinical history of HNPCC, the genetic test result is noninformative. The patients and the at-risk individuals (i.e., relatives) should be counseled as if HNPCC was confirmed and high-risk surveillance should be undertaken.
5. There is a need to assure patients of confidentiality to allay fears related to discrimination based on genetic status.

In addition to these recommendations, recent publications would suggest that MSH6 and PMS2 immunohistochemistry should be performed if MSH2 and MLH1 expression are intact.[3] Furthermore, despite theoretical concerns, studies showing high sensitivity of mismatch repair protein immunohistochemistry as an initial screening tool for HNPCC detection raise the possibility that more laborious microsatellite instability testing may not be necessary in future clinical screening algorithms.[21,22]

To perform genetic testing for HNPCC and other inherited cancer syndromes, germline genetic analysis begins with an affected individual.[1] Prior to genetic testing, informed consent must be obtained and according to practice parameters published by The American Society of Clinical Oncology (ASCO) these include[23]

1. Information on the specific test being performed
2. Implications of positive and negative results

3. Possibility that the test may not be informative
4. Options for risk estimation without genetic testing
5. Risk of passing a mutation to children
6. Technical accuracy of the test
7. Fees involved in counseling and testing
8. Risks of psychological distress
9. Risks of insurer or employment discrimination
10. Confidentiality issues
11. Options and limitations of medical surveillance and screening following testing

Mutational analysis in HNPCC is complex because (1) there are four different genes to potentially screen, (2) mutations observed in the mismatch repair genes generally do not occur at specific, recurrent "hotspots," (3) pathologic mismatch repair gene mutations may be either truncating (nonsense) mutations or nontruncating (missense) mutations, and (4) large genomic rearrangements of germline mismatch repair gene mutations can cause HNPCC and require different, specific mutation detection techniques.[1,14]

If tumor tissue is available for analysis, the question of which mismatch repair gene to best assess initially can be screened using immunohistochemistry.[22] In certain populations, such as Finland, recurrent founder mutations account for a large percentage of HNPCC germline mutations and thus, genetic analysis begins with sequence-specific analysis for the specific founder mutation.[24] In most populations, founder mutations are not common and genetic analysis incorporates methods to detect large genomic rearrangements and smaller genetic mutations.[14,25] Large genomic rearrangements account for 10 to 20% of MSH2 mutations and a lesser percentage of MLH1 mutations. These mutations are effectively screened for using a recently developed assay known as multiplex ligation-dependent probe amplification (MLPA). In MLPA specific probes are hybridized to genomic DNA and then the probes (as opposed to the DNA) are amplified and quantified. Although germline mutations predisposing to HNPCC often lead to a truncated mismatch repair protein, 10 to 37% of mutations reported in MSH2, MLH1, and MSH6 are thought to be nontruncating, missense mutations.[14,17] Furthermore, germline mutations in HNPCC appear to be roughly equally distributed throughout all exons of the mismatch repair genes. Thus, screening of these genes is optimally performed using full sequencing or other methods that may detect either missense or nonsense mutations. When detected, truncating nonsense mutations are considered to be pathologic. However, determining the pathogenicity of sequence changes that lead to amino acid substitutions, splice site changes, or in-frame nucleotide deletions/additions is less straightforward.[26] Predicting whether these alterations are variants of normal or disease-causing relies on several factors. Favoring disease causation would be (1) a nonconservative amino acid substitution (versus conservative or semiconservative), (2) a change in an amino acid evolutionarily conserved between diverse species, (3) the absence of the genetic variant in normal populations, (4) cosegregation of the genetic alteration with disease, (5) the association of the alteration with tumor MSI-H or lack of specific mismatch repair protein expression, and (6) reports of the same mutation in other HNPCC kindred.[17]

The Amsterdam II criteria were introduced as a specific means to identify HNPCC kindreds in an era when the genetic cause of this syndrome remained unknown.[3] Though specific for HNPCC, these criteria lack sensitivity required for clinical screening, identifying only 10 to 40% of individuals with germline mismatch repair gene mutations.[22,27–29] Utilization of the Revised Bethesda Guidelines improved detection of germline mutation carriers to 70 to 80%.[22,28] In comparison to these predominantly clinically based criteria, recent studies have suggested that the sensitivity and specificity of the MSI-H tumor phenotype for germline mismatch repair mutation was 90 to 100% and ~90%, respectively; similarly, sensitivity and specificity of mismatch repair protein immunohistochemistry was 87 to 94% and 86 to 88%.[22,28]

In addition to the high incidence of proximal colon cancer in HNPCC, it is believed that the timeframe of adenoma to carcinoma progression may be markedly accelerated as compared with sporadic colorectal cancer.[30] Thus, a polyp may progress to an invasive cancer in 2 to 3 years, rather than the 8 to 10 years this process is estimated to require in sporadic colorectal carcinogenesis. Mechanistically, this is believed to occur due to the rapid accumulation of somatic mutations associated with neoplastic initiation and progression secondary to mismatch repair-deficiency.[13] Practically, this has led to the recommendation that those at-risk of HNPCC undergo full colonoscopy, as opposed to flexible sigmoidoscopy, every 1 to 2 years beginning between ages 20 and 25 years and at least 10 years younger than the youngest affected relative in the particular HNPCC kindred.[31] Individuals who harbor germline HNPCC mutations and first-degree relatives of those with HNPCC who were compliant with colonoscopic screening recommendations have been observed to have significantly reduced risks of both colorectal cancer and death, compared with similar at-risk individuals who were noncompliant with the same endoscopic recommendations.[32] In addition to colorectal cancer screening, some authors have recommended transvaginal ultrasonography, endometrial aspiration for pathologic assessment and plasma CA-125 (an ovarian cancer genetic marker) determination annually beginning at age 30 years in women at-risk for HNPCC due to the high incidence of endometrial or ovarian cancers in HNPCC.[33]

Surgical recommendations in HNPCC remain controversial. This primarily stems from a relative lack of high level evidence to support or refute the theoretical advantages of prophylactic surgery or extended resection beyond what would normally be oncologically necessary. Given these relative uncertainties, proper counseling is critical to all decision-making and informed consent. Recommendations from The American Society of Clinical Oncology, The Society of Surgical Oncology, and The American Society of Colon and Rectal Surgeons for HNPCC include that individuals who fulfill the Amsterdam criteria or carry a known germline mismatch repair gene mutation who are diagnosed with colon cancer may be offered subtotal colectomy with ileorectal anastomosis, or standard segmental colectomy.[34,35] Similarly, those with rectal cancer may be offered total proctocolectomy with ileal-pouch anal anastomosis or anterior resection, assuming the sphincters can be oncologically salvaged. Extended, prophylactic resections may be considered for patients with HNPCC diagnosed with more than one advanced adenoma. In addition, prophylactic hysterectomy should be considered in women with HNPCC undergoing other abdominal surgery or once their family is complete. A significant reduction in endometrial cancer and to a lesser extent, ovarian cancer, was observed with prophylactic hysterectomy and bilateral salpingo-oopherectomy for woman who have germline HNPCC mutations; however, in this retrospective study, there was no standardized clinical screening for those woman who did not undergo prophylactic surgery.[36] Furthermore, this study provided no evidence that prophylactic surgery ultimately provided a survival advantage compared with clinical screening with therapeutic intervention when necessary in woman with germline HNPCC mutations.

Both survival prognosis and the predicted response to chemotherapy may be different in HNPCC compared with sporadic colorectal cancer. A large body of high-level evidence exists to support the notion that individuals with MSI-H/mismatch repair-deficient colorectal cancer have a stage-independent survival advantage compared with those whose cancers were microsatellite stable (MSS)/mismatch repair-proficient.[10,37] These studies have generally not differentiated patients with MSI-H colorectal cancer into HNPCC versus sporadic. Analyses of individuals with germline mismatch repair mutations ascertained through HNPCC registries in Finland and the United States have observed a survival benefit in HNPCC compared with population controls.[38,39] However, better quality studies comparing population-based germline mismatch repair gene mutation carriers and noncarriers have not observed a prognostic advantage for those with HNPCC.[29,40]

Of significant clinical importance, patients with MSI-H/mismatch repair-deficient colorectal cancer do not appear to benefit from adjuvant 5-fluorouracil and leukovorin (or levamisole) chemotherapy, whereas the approximate 85% of individuals with microsatellite stable (MSS) colon cancer do appear to benefit from this adjuvant therapy.[41–47] Topoisomerase-1 inhibition with irinotecan has been postulated to specifically target mismatch repair-deficient cells.[48] A recent randomized clinical trial comparing adjuvant fluorouracil and leucovorin with or without irinotecan has shown a trend toward improved survival of patients with stage III mismatch repair-deficient colon cancer with the addition of irinotecan, raising the possibility that specific, tailored adjuvant chemotherapy based on cancer microsatellite instability status may soon be clinically possible.[48] Furthermore, one recent multicenter clinical trial, Eastern Cooperative Oncology Group (ECOG) 5202, has utilized cancer MSI-H status to exclude patients with stage II colon cancer from treatment and place them in an observation-only arm as these patients were anticipated to have good prognosis and were predicted not to benefit from adjuvant 5-fluoruracil-based chemotherapy (http://clinicaltrials.gov/ct/show/NCT00217737). Whether or not these reported predictive differences in response to chemotherapy hold true for the subset patients with HNPCC associated MSI-H/mismatch repair-deficient colorectal cancer remains to be investigated.

Approximately 40% of individuals that satisfy the Amsterdam criteria for HNPCC are not observed to have cancer MSI-H or mismatch repair-deficiency.[49] Despite fulfilling clinical criteria for HNPCC, individuals with mismatch repair intact colorectal cancers and their at-risk relatives had a significantly decreased risk of extracolonic cancers and colorectal cancer, later age of diagnosis, fewer proximal colorectal cancers, and fewer synchronous or metachronous cancers compared with those who fulfilled Amsterdam criteria and showed evidence of cancer mismatch repair-deficiency.[49–52] These results are significant both in terms of counseling recommendations including screening recommendations for a significant number of individuals usually classified as HNPCC and important in terms of future investigations including gene discovery. To distinguish these families from HNPCC with colorectal cancer MSI-H/mismatch repair-deficiency, the designation of Familial Colorectal Cancer Type X has been suggested for these kindreds.[49]

FAMILIAL ADENOMATOUS POLYPOSIS

FAP is a rare, autosomal dominant disease that is typically associated with the development of hundreds to thousands of colorectal polyps. FAP accounts for less than 1% of all colorectal cancer and occurs with a prevalence of approximately one in 8,000 births.[1,2] Adenomatous polyps usually arise during childhood or adolescence and if left untreated, colorectal cancer will

develop in young adulthood. An attenuated form of FAP has also been recognized. In attenuated FAP (AFAP), the number of adenomatous polyps is decreased (<100), onset may be later, the location of these polyps may be more proximal in the colon and cancers may not develop until 50 or 60 years of age.[1,2,53,54]

In addition to colorectal neoplasms, the occurrence rate of several extracolonic tumors is increased in FAP. The FAP variant of Gardner syndrome has been characterized by colonic polyposis, osteomas, and dermoid cysts. FAP-associated Turcot syndrome is distinguished by the occurrence of colorectal neoplasms and brain (medulloblastoma) cancer.[1,54] Extracolonic manifestations of FAP are of particular clinical relevance as the widespread use of colonic endoscopy and prophylactic proctocolectomy and colectomy has effectively decreased the likelihood of developing an advanced staged colorectal cancer. As such, FAP-associated periampullary cancer and desmoid tumors have become the leading causes of death in individuals with FAP.[55]

The underlying genetic cause of FAP is a germline mutation in the APC gene.[56,57] Somatic (as opposed to germline) mutations of the APC tumor suppressor gene initiate most sporadic adenomatous polyps and colorectal cancers; thus, the APC gene has been dubbed the "gatekeeper" of colorectal neoplasia.[13,58–60] In FAP, the affected individual is born with one mutated copy of the APC gene and somatic inactivation of the second copy of the gene in a colonic epithelial cell leads to adenoma initiation.[58] In contrast, in sporadic polyps, both copies of the APC gene must be inactivated by somatic events. In ~80% of cases of FAP there is a family history of the disease.[1] In the remaining 20% of cases, FAP occurs due to a new APC gene mutation arising shortly after conception, or when a family history is not evident due to adoption, nonpaternity, or lack of accurate knowledge.

Despite the large size of the APC gene, several characteristics of the mutations observed in FAP have lead to efficient detection strategies where mutations are identified in 80 to 90% of classic cases of FAP.[1] Up to one third of germline APC mutations occur at "hotspot" codons 1061 and 1309.[13,61] These can be assessed by several mutation specific methods which utilize polymerase chain reaction (PCR) amplification of these genomic DNA regions, such as direct sequencing, heteroduplex analysis or single-strand polymorphism.[1] Approximately 95% of APC mutations lead to a predicted truncated protein (nonsense mutations).[61] This has led to the development of an analysis technique known as the protein truncation test (PTT), where RNA is used to synthesize protein in vitro.[1,62] If a nonsense mutation exists, a faster moving, smaller band is observed (as compared with the wild-type protein) when the PTT product is subject to gel electrophoresis.

Interestingly, mutational analyses in FAP have revealed significant genotype–phenotype correlations[13]:

1. Severe polyposis (>5000 polyps) is associated with mutations between codons 1250–1464.
2. Attenuated polyposis (<100 polyps) occurs when mutations are at extreme 5′ and 3′ ends of APC gene.
3. Congenital hypertrophy of the retinal epithelium (CHRPE) is associated with mutations between codons 457–1444.
4. Desmoid tumors are associated with mutations between codons 1403–1578.

The clinical management of FAP is complex and involves counseling, genetic testing, clinical screening, and treatment of multiple organ systems in not only the affected individual, but their at-risk relatives as well.[34,35,54] Practice parameters for FAP management include referral of individuals with FAP or those whose personal or family history make them at-risk for FAP, to specialized cancer registries and genetic counselors who specialize in the coordinated multidisciplinary management of these individuals. Although no consensus exists on the lower limits of adenomatous polyp numbers that would raise suspicion for attenuated FAP, the occurrence of 10 to 20 or more synchronous polyps has often been used as a guideline.[63]

Similar to HNPCC and other inherited cancer predispositions, only after an APC gene mutation is found in an affected individual can unaffected, at-risk members of the family be appropriately tested.[1] Thus, analysis in an at-risk (as opposed to affected) individual from a family with FAP is site-specific—that is the specific familial APC gene mutation is sought, not APC mutations in general. If an at-risk individual does not carry the APC gene mutation observed in their FAP-affected relative, the at-risk relative is "negative" and can be counseled to receive "normal" population colorectal cancer screening.[1,64] If an APC gene mutation is not found in testing the initial affected individual, the test is "uninformative." In these instances, all first-degree relatives of those who are genetically uninformative, but clinically affected by FAP, have a 50% chance of being clinically affected and should therefore receive counseling and clinical screening. In the case of uninformative testing, linkage analysis may be useful if sufficient affected individuals are available for testing.[1] In FAP linkage analysis, several genetic markers near the APC gene are evaluated. Depending on the pattern of these markers in an at-risk individual as compared with multiple affected individuals in the same family, the likelihood for having inherited the disease causing gene can be estimated. For clinical practicality, only likelihoods of >95% or <5% are relevant.

An analysis of commercial APC tests ordered by U.S. physicians in 1995 revealed that fewer than 20%

of patients received pretest genetic counseling, written informed consent was not obtained in nearly 85% of cases, and the referring physician could not appropriately interpret test results more than 30% of the time.[64] In the same study, testing was not indicated in 17% of cases and a further 30% of physicians employed an incorrect testing strategy. These results underscore the potential complexity of FAP management and the need to refer those affected or at-risk to centers specializing in the management of inherited colorectal cancer syndromes.

Individuals at-risk for FAP as assessed by personal or family history or those who are positive for an APC gene mutation by mutational analysis are advised to begin clinical screening every 6 to 12 months by flexible sigmoidoscopy around puberty.[34,35,54] When polyps are detected, prophylactic surgery should be undertaken. The timing and extent of surgery depends on the severity of polyposis and whether or not there is rectal sparing. Surgical options include total proctocolectomy with ileal pouch anal anastomosis, abdominal colectomy with ileal–rectal anastomosis or total proctocolectomy with end ileostomy. For most cases of classic FAP, an ileal pouch anal reconstruction is now the standard of care. Technical issues, including whether or not a mucosectomy is performed and whether or not a hand-sewn versus stapled anastomosis is created are relatively patient-specific and remain of some debate in patients undergoing ileal pouch anal reconstruction. Lifetime endoscopic surveillance of the ileal pouch, rectum, or ileostomy is required. A double-blind, placebo-control trial of the COX-2 inhibitor celecoxib (400 mg twice daily for 6 months) led to a significant, but modest, ~30% decrease in colorectal polyp number in individuals with FAP.[65] Whether these effects will lead to an effective long-term chemoprevention strategy and the avoidance of surgical resection remains unproven.

In addition to clinical colorectal screening, those with or at-risk of FAP are recommended to undergo regular screening esophagoduodenoscopy, including side-viewing endoscopy, starting at ~20 years of age.[34,35,54] The majority of FAP patient will develop gastric and/or duodenal polyps. In contrast, ~5% will develop duodenal or periampullary cancers. Duodenectomy or pancreaticoduodenectomy is advised in the case of persistent or recurrent severe dysplasia.[34,35,54]

Treatment of desmoid tumors complicating FAP can be difficult.[34,35,54] Small, well-defined abdominal wall desmoids may be removed surgically. Intraabdominal desmoids, particularly those involving the small bowel mesentery, should be treated according to their rate of growth and symptoms. Slow growing, mildly symptomatic tumors may be treated with sulindac, tamoxifen, or vinblastine and methotrexate. Aggressive desmoid tumors may require high-dose tamoxifen, antisarcoma combination chemotherapy such as doxorubicin and dacarbazine, and possibly radiation.

In contrast to the truncating APC gene mutations observed in FAP, APC I1307K is a single-nucleotide substitution (a nontruncating, missense mutation) that leads to a single amino acid difference in the approximate 3,000 amino acids that constitute the APC protein.[2,66,67] The APC I1307K variant is carried by an estimated 6% of the Ashkenazi Jewish population and approximately doubles the risk of developing colorectal polyps and cancers in heterozygous carriers.[68] This type of significant, but relatively modest increased cancer risk is explained by incomplete penetrence—that is those with genotype have a modestly increased risk of developing the phenotype. Given the previous successes in identifying the genetic cause of most highly penetrant colorectal cancer syndromes (such as FAP and HNPCC), it is likely that most future advances in this field will be in identifying common, lower penetrant alleles, such as APC I1307K. It does not appear however, that germline missense alterations of the APC gene, other than APC I1307K, are commonly involved in inherited colorectal cancer risk.[69]

The APC I1307K variant creates a tract of eight consecutive adenine nucleotides [$(A)_8$] in the DNA sequence that encodes APC and is not believed to significantly alter the function of the APC protein.[66,67] Mechanistically, APC I1307K behaves like a "premutation" as the $(A)_8$ offers a nucleotide sequence that is more prone to somatic mutation than the wild-type sequence. Importantly, unlike the highly penetrant, truncating APC mutations observed in FAP that almost universally lead to the development of polyps, the APC I1307K confers an approximate 10 to 15% lifetime risk of polyp or cancer development.[67] Moreover, APC I1307K carriers do not appear to develop colorectal cancer at a clinically significant younger age compared with those with sporadic cancers.[68] Although the American College of Medical Genetics and American Society of Human Genetics do have guidelines for clinical APC I1307K genetic testing, existing literature suggests that neither a positive nor a negative result of this testing would be predicted to change recommendations regarding clinical colorectal screening based on family history alone.[70] Specifically, a positive genetic test result would confirm (but not alter) a recommendation for colonoscopic screening based on family history and age on colorectal cancer onset alone, and a negative genetic result would not be sufficient to rule out the need for clinical screening should a significant family history exist.

MYH-ASSOCIATED POLYPOSIS

In addition to APC mutations associated with FAP, a second genetic predisposition to colorectal adenoma-

tous polyposis and cancer has been identified with inherited mutations of the MYH gene (MYH-associated polyposis [MAP]).[2,71–73] In general, the polyposis observed in MYH carriers is less severe and would be classified as attenuated. MYH participates in a DNA proofreading system known as base-excision repair and mutations of the MYH gene are thought to lead to somatic mutations, in particular specific mutations of the APC gene. In particular, specific G:C to T:A transversion mutations of the APC gene occur, which then give rise to colorectal neoplasia. For this reason, similar to mismatch repair genes in HNPCC, the MYH gene is thought to be a "caretaker" gene, where MYH inactivation increases the mutation rate, compared with the "gatekeeper" APC gene where mutation initiates neoplasia directly.

The clinical genetics of MYH-associated polyposis are not as well studied and are more complex than those of APC-associated FAP.[72,73] Germline mutations of the MYH gene appear to confer a codominant risk.[73] Germline mutations of both MYH alleles (biallelic) are associated with the greatest risk of adenomatous polyposis and cancer (similar to an autosomal recessive disease). In contrast, compared with noncarriers, carriers of mutations of a single copy of the MYH gene (monoallelic) are at a modestly increased risk of developing polyps and cancers (similar to an autosomal dominant disease with incomplete penetrance). However, the risk of neoplasia in monoallelic MYH gene mutation carriers is significantly lower than that for biallelic MYH mutation carriers.

Biallelic germline MYH gene mutation carriers may present with attenuated polyposis, but in more than one third of these patients, colorectal cancer is diagnosed in the absence of synchronous adenomatous polyps.[74] In FAP cases that are uninformative for APC gene mutation, germline MYH mutational analysis should be undertaken as up to one third of these individuals have been observed to harbor biallelic MYH mutations.[72] The age of colorectal cancer diagnosis in biallelic MYH carriers is ~45 to 50 years and right-sided cancers appear to arise more commonly in these indiviuduals.[74,75] In addition to colorectal polyposis and cancer, adenomatous polyps of the duodenum and gastric fundic gland polyps are common in MYH-associated polyposis and duodenal cancers have been reported.[75] Similar to the Muir–Torre variant of HNPCC, benign and malignant sebaceous gland tumors have been observed in germline MYH mutation carriers.

Germline MYH genetic testing should be offered to first-degree relatives of carriers and given that the greatest risks are associated with biallelic inheritance of mutations, carrier spouses should be offered genetic testing to afford best counseling for at-risk offspring.[75] Current clinical screening recommendations for biallelic MYH mutation carriers consist of colonoscopy every second year starting at ~18 years of age and upper gastrointestinal endoscopy commencing at 25 to 30 years of age.[75] Given the significant variability in phenotype, treatment recommendations must be individualized based on patient age, polyp and cancer numbers, size, and location.

HAMARTOMATOUS POLYPOSIS SYNDROMES

Intestinal hamartomas, including colorectal hamartomas, are frequent in Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and Cowden disease (including Bannayan–Ruvalcaba–Riley syndrome). All these syndromes are very rare with incidences below 1 per 100,000.[1,2]

PJS is an autosomal dominant disease characterized by perioral pigmentation, pathologically distinct Peutz–Jeghers-type hamartomatous polyps throughout the gastrointestinal tract and an approximate 30% lifetime risk of colon cancer and 50% risk for breast cancer.[1,2] In PJS, patients are at risk for other extracolonic cancers including pancreatic, gastric, small bowel, ovarian, uterine, and lung malignancies. Approximately 50% of PJS cases are believed to occur due to autosomal dominant germline mutations of the STK11 gene.[76,77]

Although solitary colonic juvenile polyps are believed to be one of the most common sources of lower gastrointestinal bleeding in children, multiple juvenile polyps are rarely observed.[1,2,78] JPS should be considered when three or more juvenile polyps are identified in the colon. The lifetime colon cancer risk in JPS approaches 60% and patients are additionally at risk of developing stomach, small bowel, and pancreatic cancers. In ~50% of JPS cases, germline mutations of either the SMAD4 or BMPR1A genes, both involved in TGFβ signaling, are believed to confer an autosomal dominant risk.[79,80] Interestingly, germline SMAD4 mutations have been associated with a combined syndrome of juvenile polyposis and hereditary hemorrhagic telangiectasia.[81] In addition to genetic testing, colonoscopy, gastroscopy, and small bowel examination are recommended in PJS and JPS.[1,78] Endoscopic or surgical excision of large or symptomatic polyps is recommended to address symptoms (obstruction, intussusception, bleeding) and avoid malignant progression.

Cowden disease is an autosomal dominant disease characterized by facial trichilemmomas, oral papillomas, multinodular goiter, fibrocystic breast disease, esophageal glycogenic acanthosis, and intestinal hamartomas.[1,2] Breast and thyroid cancer risk are most pronounced in Cowden disease, with colon cancer developing in up to 10% of patients. Autosomal dominant germline mutations of the PTEN gene have been identified in the majority of patients with Cowden disease and as well

predispose to Bannayan–Ruvalcaba–Riley syndrome, which shares characteristics with Cowden disease and additionally includes slowed psychomotor development and pigmentary spotting of the penis.[82,83]

In comparison to the gatekeeper function of the APC gene and the caretaker roles of the mismatch repair and MYH genes, the genes predisposing to hamartomatous polyposis syndromes have been dubbed "landscaper" genes.[84] In sporadic circumstances, non-neoplastic hamartomatous polyps are not believed to confer a significant cancer risk. In comparison, germline mutations and somatic inactivation of the STK11, SMAD4, BMPR1A, and PTEN genes in hamartomatous polyposis syndromes are believed to create an epithelial milieu (or landscape) at risk for neoplastic development.

CONCLUSIONS

The elucidation of the genetic basis of several inherited colorectal cancer predispositions now allows for rational specific clinical recommendations for the counseling, investigation, and clinical management of those affected by these disorders and their at-risk relatives. It is hoped that future clinical management of individuals with these inherited syndromes will include effective chemoprevention and tailored biologic-based treatments. Additionally, current and future avenues of research aim to identify the molecular biologic factors predisposing to colorectal cancer in as yet unexplained familial colorectal cancer kindreds, as well as seemingly sporadic colorectal cancer cases and ultimately, the implementation of effective, tailored clinical counseling, prevention, screening, and treatment strategies for this common malignancy.

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