Original Article

Current Approaches in Familial Colorectal Cancer: A Clinical Perspective

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Hereditary colon cancer, genetic testing, adenoma surveillance

Abstract
Individuals with a family history of colorectal cancer or colorectal adenomas have an increased risk for colorectal cancer. When no hereditary syndrome is evident, screening is based on empiric risk estimates. The risk is greatest for individuals with specific inherited cancer-predisposing disorders. When conditions such as familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer are diagnosed, specific neoplasm risk estimates can usually be performed based on advances in molecular genetics. These estimates lead to more straightforward and cost-effective approaches to surveillance and management. The National Comprehensive Cancer Center Network (NCCN) and other groups have provided detailed guidelines for evaluating patients based on recognition of clinical syndrome characteristics, followed by appropriate genetic counseling, genetic testing, and optimal surveillance. The NCCN guidelines are used as a frame of reference for this discussion of selected recent advances in human cancer genetics as they apply to clinical practice. (*JNCCN* 2006;4:421–430)

Colorectal cancer (CRC) ranks among lung, breast, and prostate cancer as the most common and serious malignancies. In the United States and other developed countries where CRC is common, risk is mainly attributable to environmental and particularly dietary exposures.[1,2] Because of the high frequency and steep rise in incidence of CRC after age 50, screening for individuals without additional risk factors begins at age 50. Various screening modalities offer reasonable cost and safety, along with adequate sensitivity and specificity.[3–6] Fecal occult blood testing (FOBT), air contrast barium enema (ACBE), and flexible sigmoidoscopy (FS)[7,8] are widely used, and FOBT and FS screening have individually reduced CRC mortality. Unfortunately, patient use of these tools has been relatively low, with probably only a slight impact on CRC incidence and mortality in the general population.[9,10]

Because of the limited sensitivity of FS (nonsensitive for right colon pathology), colonoscopy is used more widely to screen those older than age 50. Adenomas are now considered key targets in the field of CRC prevention, and colonoscopy is viewed as an ideal tool for finding and removing them. However, considering the cost, risk, discomfort, and relatively low *a priori* risk to the average patient, newer methods are being actively investigated. One trial showed that computed tomographic colography, also known as *virtual colonoscopy*, was sensitive enough to detect lesions smaller than 1 cm, which is equivalent to standard or optical colonoscopy.[11] Testing for mutated DNA in exfoliated colorectal epithelium has also shown promise.[12]

Disparate levels of risk exist between the average risk population and the familial/genetic group. A prior personal history of CRC, adenoma, or inflammatory bowel disease (IBD) confers an intermediate risk, and experts recommend that patients undergo colonoscopy at varying intervals. In IBD, colonoscopy with aggressive biopsy is suggested at 1- to 2-year intervals for patients with pancolitis for 8 years or more or with left-sided colitis for 15 years or more. Patients with advanced or high-risk adenomas (high-grade dysplasia, > 1 cm, or > 3 adenomas) should undergo repeat colonoscopy in 3 years. If these features are not present, colonoscopy can be performed less frequently (3–6 years).

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Family History and Colorectal Cancer Risk

For more than a century, curiosity has existed about the significance of familial clustering of cancer, including CRC. Sometimes a characteristic clinical feature immediately denotes an inherited syndrome, such as diffuse colorectal adenoma involvement as in familial adenomatous polyposis (FAP). In other cases, hamartoma or polyps readily indicate the presence of Peutz-Jeghers syndrome or juvenile polyposis. In the absence of such striking and generally pathognomonic features, conditions such as hereditary nonpolyposis colorectal cancer (HNPCC) may be diagnosed by a combination of familial clustering of cancers with typical (but nondiagnostic) presenting features. Researchers have identified responsible genes in the polyposis disorders, with clinical genetic testing available for predictive testing in at-risk offspring and siblings. Molecular testing is generally required to confirm the diagnosis of HNPCC and serves as an even more important guide to clinical screening.

When obvious polyposis is absent or when an HNPCC mutation cannot be found, familial clustering of CRC is dealt with pragmatically. Thus, the NCCN guidelines recommend screening beginning at age 40 or 10 years younger than the earliest reported case in the family and repeated at 1- to 5-year intervals. Importantly, the NCCN, like other sources, encourages clinicians to take a detailed family history before concluding that such a level of screening is warranted.

Familial Adenomatous Polyposis

FAP is rare, with a gene frequency of about 1/10,000, and it is typically easy to diagnose. When a patient has more than 100 adenomas, FAP is present. Unsurprisingly, it was the first of the inherited CRC-predisposing conditions to be described and the first for which useful clinical surveillance and management plans were established. It was also the first CRC predisposing condition whose gene, the *adenomatous polyposis coli* (*APC*) gene, was discovered.

Because FAP is inherited as an autosomal dominant disorder, each child of an affected parent is born with a 50% risk of being a carrier. Until researchers discovered the *APC* gene, clinical screening consisted of rigid or flexible lower endoscopy. Some form of mucosal inspection is still the screening method used in known carriers or in any situation in which molecular diagnosis is lacking. Surgical prophylaxis, whether subtotal colectomy with ileorectal anastomosis or proctocolectomy with end-ileostomy or, more recently, so-called *restorative proctectomy* (ileal pouch-anal anastomosis), is performed when adenomas begin to evolve. Clinical testing for mutations in the *APC* gene[13,14] is now readily available and is generally recommended for any patient with FAP when the information gained will benefit other relatives or when there is any question about the diagnosis of FAP.

Mutation testing in FAP has evolved since the responsible genetic locus was identified in 1988. Before the *APC* gene was identified and sequenced in 1991,[13,14] it was possible to conduct segregation analysis to see if the FAP phenotype segregated with haplotypes of informative polymorphic markers flanking the implicated locus. This procedure was cumbersome and required multiple affected family members, and this approach is not used today because of the newer, more direct testing methods available. Many laboratories use various forms of single-strand conformation analysis (SSCP), alone or in combination with other methods.[15] Such analysis is useful but can identify variants of uncertain significance. During the late 1990s, researchers often used the so-called *protein truncation* (PTT) or in vitro synthesized protein (IVSP) assay. Because this method tests for mutations that result in prematurely truncated protein products, essentially all positive tests demonstrated clearly pathologic mutations. This method was limited by the need for RNA as opposed to DNA, inability to characterize the specific mutation (unless additional sequencing was performed), and a sensitivity of about 75%, with a lower sensitivity for the attenuated form of FAP. Full-length, or end-to-end, sequencing is a more recently marketed tool in the United States. However, each of the methods mentioned previously is insensitive for large allelic deletions. Increasingly, gene-rearrangement studies are offered as a "reflex" test when other methods are nondiagnostic.[16]

Attenuated FAP

Before researchers identified the *APC* gene, patients and families were described with colorectal adenoma counts less than the arbitrary 100 threshold for FAP diagnosis. In addition, some patients were older at diagnosis, often in their 40s to 60s or older. Whether these families had a variant of FAP or HNPCC or represented a unique entity was uncertain until *APC* test-

ing became available and confirmed that many such families showed phenotypic variants with underlying *APC* mutations.

A common issue for clinicians is the minimal polyp count for an older patient whose family history is not compelling. This mild, or attenuated, variant of FAP is mainly accounted for by mutations in the 5' and 3' extremes of the *APC* gene.[17,18] A representative presentation may be several unremarkable polyps in the left colon accompanied by smaller, flatter, more numerous adenomas in the right colon. Such diminutive flat adenomas are ideally shown through application of Indigo Carmine dye spray. With dye spray, the polyp count may reach 100. Upper gastrointestinal (UGI) endoscopy helps confirm the diagnosis by revealing plaque-like adenomas of the duodenum and fundic gland polyps of the body and fundus of the stomach, similar to those seen in more classic FAP. The diagnosis is not excluded by an absence of UGI findings, and families with mutations in the alternately spliced Exon 9 generally will not have duodenal adenomas.

End-to-end sequencing of the *APC* gene is perhaps the ideal means for detecting attenuated FAP (AFAP). Mutations were sometimes missed using the protein truncation assay because the protein product was unstable.

APC mutational testing is especially important in AFAP. Because the adenoma burden is low and age at onset is late, the clinical findings for a given patient may be indistinguishable from those indicating sporadic adenoma or HNPCC. In addition to confirming the diagnosis, predictive testing within a family actually carries greater implications for screening than in the usual, more severe presentation of FAP.

MYH-Associated Polyposis

As noted, FAP may be attenuated in its clinical presentation and patients may have no antecedent family history. Although researchers know that FAP exhibits a high spontaneous mutation rate, a high proportion of "singleton" cases have been found not to carry *APC* mutations, even with a clinical presentation identical to classic FAP. Al-Tassan et al.[19] provided an explanation for some of these cases. They began with one sibship, several of whose members seemed to have AFAP. These siblings underwent extensive but ultimately nondiagnostic *APC* testing. The researchers carefully evaluated colon tumors for somatic mutations, and considered an increase in G:C to T:A transversions to be possible targets of base-excision repair system failure.

This system involves at least 3 proteins and their corresponding genes. In one of these, the *MYH* gene, germline testing showed mutations in each of the affected sibs from the family noted above. Only sibs with mutations in both parental alleles developed multiple adenomas and cancer. Subsequent investigations in larger series of *APC*-negative patients with moderate adenoma burdens (> 15–20) showed that these biallelic mutations in the *MYH* gene may account for 15% or more of such previously unclassified cases. The two alleles, Y165C and G382D, accounted for most cases whether they occurred as homozygotes or compound heterozygotes.[20] Little support exists for any increased risk for adenomas or cancer in patients with only one allele.[21] *MYH* testing has become a reflex assay process for patients with multiple colon polyps who test negative for an *APC* mutation.[21,22]

Personal and Family History of Non-Adenomatous Polyps and Polyposis

Although rare, multiple colon polyps with non-adenomatous histology may indicate a genetic condition that includes colorectal cancer risk, albeit lower than in FAP. Important conditions include Peutz-Jeghers syndrome and juvenile polyposis.

Establishing the histology of the polyps is important when clinicians first encounter a patient with multiple polyps. We have been asked to evaluate patients with FAP, only to discover that the polyps were actually hamartomas or juvenile polyps. A hamartoma or juvenile polyp commonly has a considerable degree of inflammation, such that the reactive epithelial changes can closely mimic adenomatous change on casual inspection. In addition, both hamartomas and juvenile polyps can develop true adenomatous change and even malignancy.[23–26] Therefore, clinicians should submit the entire polyp for histologic review.

The number of polyps can be important in differential diagnosis. In Peutz-Jeghers syndrome, the polyp burden in the colon and rectum is commonly low; diagnosis is often made based on characteristic perioral pigmentation. In other cases, diagnosis is based on personal or family history of small bowel polyps, typically presenting with bleeding or obstruction related to intussusception. Solitary juvenile polyps are

common in children, so the diagnosis of juvenile polyposis requires a minimal polyp count (arbitrarily 5 or more in colorectum), unless a diagnostic family history is already present.[27] Responsible genes have been identified: the *STK11* gene in Peutz-Jeghers syndrome[28] and *SMAD4*[29] and *BMPR1A*[30] in juvenile polyposis. Most patients with Peutz-Jeghers syndrome (70% in one series[31]) carry *STK11* mutations, whereas a smaller proportion of juvenile polyposis cases show informative *SMAD4I* or *BMPR1A* testing. Because juvenile polyposis lacks the characteristic pigmentation seen in Peutz-Jeghers syndrome, genetic diagnosis may be more important.

Genetic Counseling

Because understanding the implications of genetic testing requires a high degree of sophistication, clinicians must make every effort to ensure that patients fully understand the testing process and its goals and limitations. Genetic counseling and the informed consent process are critical at this point. The NCCN guidelines specifically call for risk assessment and counseling for all cases of FAP, which should include psychological assessment and support.

Predisposition testing is now commercially available for clinical use in the United States. Neither formal genetic counseling nor written informed consent is required for this testing, which can be performed in the community setting. If formal genetic counseling is pursued, as the NCCN and others recommend, an experienced counselor can anticipate a patient's questions and can bring up consequences of testing that may not have otherwise occurred to the patient. These commonly include implications of a positive test for distant relatives. Whenever possible, issues surrounding the so-called *duty to warn* should be identified, discussed, and resolved before testing is performed.[32]

Genetic testing is not always informative. Although sensitivity for pathologic mutations is lower for HNPCC germline testing than it is for FAP, responsible mutations are not found in about 20% of classic FAP and about 40% of AFAP. Therefore, the genetic counselor must also help patients deal with a not informative test result. We prefer terms such as *nondiagnostic* and *not informative*, rather than *negative*, because the baseline test in a patient with definite FAP can never be truly negative.

If no mutation is found in an affected subject, offering testing to at-risk unaffected members of the family is pointless, but several options are available. If the phenotype suggests AFAP, re-examining the available clinical information, repeating a colonoscopy with dye spray, performing UGI endoscopy if not already done, or re-reviewing family history details may help establish clinically that the patient really has FAP. After nondiagnostic testing, secondary approaches may be appropriate. If initial testing involved end-to-end sequencing of the *APC* gene, deletion studies may be warranted. *MYH* testing may be informative. Finally, if several living, affected family members are available, segregation analysis with intragenic or flanking markers might be informative, although sample collection may be a challenge.

Clinical Screening in FAP

The NCCN guidelines detail the clinical management of FAP. If an *APC* mutation has been identified in the family, offering testing to children of affected patients is almost always appropriate. Various models show screening based on mutational testing to be cost-effective compared with empiric clinical surveillance, based on a 50% risk to offspring of an affected parent. If a mutation is identified, clinical surveillance for adenomas begins between age 12 and 15 because this is the interval when adenomas begin to develop and multiply. Adenomas can develop even earlier than age 12, but cancer is rare at this age and exposing younger children to the trauma of endoscopic surveillance must be weighed thoughtfully against any potential advantages. FS screening is recommended because adenomas generally begin distally and progress proximally. Opinions differ about whether such examinations should be conducted without sedation in such young children. When sedation is employed, many favor use of propofol because short-acting benzodiazepines and narcotics are tolerated unpredictably in this age group. In most institutions, an anesthesiologist or anesthetist must administer propofol. If using sedation, the clinician should consider full colonoscopy. If the family wants to postpone colectomy in favor of monitoring for evidence of progression, a greater level of certainty regarding polyp burden is needed. This occurs in cases with intervention with nonsteroidal anti-inflammatory drug therapy. Clearly, full colonoscopy with monitored anesthesia care is

much more expensive than unsedated flexible sigmoidoscopy; however, no rigorous comparisons of disease outcomes, quality of life, or compliance have been performed regarding these options.

If tests confirm that a child does not carry an *APC* mutation, no special screening is recommended. Some clinicians recommended occasional sigmoidoscopy, but this procedure has lacked both a theoretical foundation and an experiential yield.[33] If no *APC* mutation has been found in a phenotypically affected family member, then screening of relatives must be empiric, as it was before discovery of the *APC* gene. In other cases, testing may not have been performed because an affected relative refused or was unavailable. *APC* testing can be performed on individuals at-risk of FAP under such circumstances, but only a positive result is helpful. A negative result may be negative only because the underlying mutation cannot be detected with available technologies. If multiple at-risk relatives are tested under this circumstance, the probability of false-negative results decreases as the number tested increases. If *APC* testing is nondiagnostic in an affected individual, clinicians may be able to rely on early physical findings, such as the presence of congenital hypertrophy of the retinal pigment epithelium (CHRPE), best identified through indirect ophthalmoscopy. These pigmented ocular fundic lesions are found in most families with FAP, are present in carriers in infancy, and generally run within a given family. The widespread prevalence of *APC* testing has reduced the frequency of examination for CHRPE, but it may still have some role when *APC* testing is uninformative.[34]

As adenomas emerge in a young person with FAP, several options exist.[35] One or 2 adenomas in a child 12 or 14 years old are diagnostic of FAP. If prophylactic colectomy is performed immediately, a key issue is whether extensive rectal polyp involvement is present. All things being equal, a heavy rectal adenoma burden warrants a so-called *restorative proctocolectomy with ileal pouch-anal anastomosis*. If the rectum is relatively spared, many surgeons perform an abdominal colectomy with ileorectal anastomosis.[36,37] Comorbid disease is also a consideration. The various surgical approaches and indications, advantages, and disadvantages are summarized in the Colorectal Cancer Screening Clinical Practice Guidelines in Oncology (in this issue). Most patients undergo a baseline UGI endoscopy just before colectomy/proctocolectomy, which may show fundic gland polyps, commonly with focal but clinically insignificant dysplasia. Very early duodenal adenoma may also be seen, though the frequency is generally low in the teen years.[38]

Because of the relatively indolent progression of FAP, surgery can be postponed if the baseline adenoma burden is minimal. The family may choose to postpone for social reasons, including fear of post-surgical desmoids in desmoid-prone families. The use of chemopreventive agents, typically celecoxib or sulindac, to slow adenoma progression may, for better or worse, support such a delay.[39–41]

Hereditary Nonpolyposis Colorectal Cancer

HNPCC, at one time referred to as the *cancer family syndrome* because of the variety of extracolonic tumors that may occur, is now known to arise through mutations in the DNA mismatch repair (MMR) family of genes. Like FAP, HNPCC is inherited as an autosomal-dominant disorder. A typical case involves right-sided colon cancer occurring at a relatively early age. Few or no adenomas will be seen with the primary tumor, but multiple primary colorectal and extracolonic tumors are common.[42,43] The most commonly involved extracolonic site is the endometrium,[44] but a high relative risk exists for tumors of the small bowel, ovary, stomach, uroepithelium, skin (sebaceous glands[45–47]), and brain.[48] Before discovery of the responsible genes, HNPCC recognition required an informative family history and, hence, the development of the Amsterdam and Amsterdam II criteria for HNPCC: 1) 3 or more cases of colorectal cancer or, in Amsterdam II, the characteristic extracolonic tumors; 2) involvement of 2 or more consecutive generations; 3) 1 or more cases diagnosed before age 50[49,50]; and 4) exclusion of FAP (in recognition of the possibility of AFAP).[51] With the emergence of key pathologic and molecular markers, family history no longer carries the great weight it once did.[52–55]

The discovery of the MMR genes has an interesting history. In the early 1990s, large families that appeared to have HNPCC underwent linkage analysis at loci of interest, including *APC*. As these investigations proved to be fruitless, a more genome-wide approach was undertaken and, in 1993, Peltomaki et al.[56] identified a susceptibility locus on chromosome 2 that carried a very high LOD score. At the same time, investigators found that tumors from affected

families had a high rate of microsatellite instability, a phenomenon not observed in FAP or in most sporadic CRCs. When the responsible gene was sequenced, it was found to carry a high degree of sequence homology to an MMR gene that had been studied more extensively in yeast.[57,58] It soon became evident that many HNPCC families were not linked to the chromosome 2 locus of this *hMSH2* gene. Lindblom et al.[59,60] identified another locus on chromosome 3. This locus also turned out to be an MMR gene: *hMLH1*. The *hMLH1* appears to be at least as common as *hMSH2*.[61] The other key MMR genes are *hMLH6*[62] and *hPMS2*,[63] which are both much less common than either *hMSH2* or *hMLH1*.

A major limitation of the Amsterdam Criteria for HNPCC is relative insensitivity to cases of HNPCC that are not from large, informative families. As an alternative, the so-called *Bethesda guidelines* were adopted. Individually, these are considerably more liberal and therefore more sensitive but less specific than the Amsterdam Criteria. The Bethesda guidelines, paraphrased in the NCCN guidelines, include age less than 50; multiple primary CRC or "associated" tumors; characteristic pathology (see below); or positive family history (less stringent than Amsterdam guidelines requiring only 1 other first-degree relative younger than age 50 or 2 close relatives at any age. The Bethesda Criteria constitute only a first step in a tiered approach to testing in that subjects meeting one or more criteria warrant microsatellite instability (MSI) testing of their tumor.

A panel of microsatellite markers can show MSI in colon cancers and some adenomas.[64–68] A tumor that is microsatellite unstable at 2 or more of 5 markers carefully selected by a National Cancer Institute panel would be considered MSI "high" and thus appropriate for germline mutation testing.

Another clinically useful feature of HNPCC cancers is their tendency to lose expression of the wild-type MMR allele. Because the mutated allele is not expressed either, the loss of heterozygosity that occurs leaves the tumor with no expression of the protein that is otherwise associated with that particular MMR gene. After antibodies against the MMR protein were developed, immunohistochemical (IHC) stains that corresponded to each MMR gene could be made.[69]

Recently, tremendous effort has been devoted to establishing the relative usefulness of clinical criteria, MSI testing, and IHC in predicting the presence of MMR germline mutations in patients with colorectal cancer. IHC is commonly used as an alternative or adjunct to MSI testing because its application is straightforward, it is relatively inexpensive, and it correlates directly with individual MMR genes.[70–72]

Several characteristic pathologic features of CRC in HNPCC are now known. Endoscopic biopsy may show poor differentiation, extracellular mucin pools, and numerous tumor-infiltrating lymphocytes.[73] Resection specimens of HNPCC tumors commonly reveal peritumoral lymphocyte nests, the so-called *Crohn's-like* reaction. As the Bethesda guidelines suggest, such features warrant MSI or IHC testing, regardless of family history. However, MSI or loss of *hMLH1* by IHC does not necessarily imply HNPCC in older patients who lack a family history of this disease. Such cases are more likely related to hypermethylation of the *hMLH1* promoter[74] and are probably associated with *BRAF* mutations,[75] which are rarely, if ever, seen in HNPCC.[76] Thus, one series saw BRAF-V600E hotspot mutations in 40% of more than 200 nonfamilial cases of MSI-H CRCs, but in none of the more than 100 HNPCC tumors with known germline mutations.[76]

Genetic Evaluation in HNPCC as a Basis for Screening

A stepwise strategy is needed in evaluating patients with suspected HNPCC. The NCCN approach represents current thinking. The clinician begins with a personal history abetted by whatever pertinent family history may contribute to meeting Amsterdam or Bethesda criteria for HNPCC. If these threshold criteria are met, the preferred approach is to evaluate tumor tissue for evidence of MSI or loss of staining by IHC. If this tissue evaluation suggests HNPCC, germline mutation testing is recommended, ideally focusing on the particular gene suggested by IHC loss of staining. Because mutational analysis is expensive, limiting the scope of such testing shows an obvious benefit. Conversely, in cases with no abnormalities on IHC and no evidence of MSI, the yield of mutational testing will be low (less than 10%). Most centers, including the authors', now prefer to conduct IHC or MSI testing on tumor tissue before performing mutational testing. Whenever possible, genetic counseling should be offered before IHC or MSI testing is

performed, because loss of protein expression can be virtually diagnostic of HNPCC.[77–79]

Counseling about the limitations of genetic testing in HNPCC is challenging, particularly with germline mutational testing. Several different clinical laboratories conduct such testing, and their costs and testing methods vary. The sensitivity of such testing is lower than that for FAP. This is partially because a relatively high frequency of mutations that involve large deletions are not detected by routine sequencing.[80] Commercial laboratories have now begun to routinely test for deletions, although this practice increases the cost of testing. In addition, reports commonly describe mutations of uncertain significance. The database maintained by the International Society of Gastrointestinal Hereditary Tumors, formerly the International Collaborative Group for HNPCC, provides a current breakdown of MMR mutation information, including genotype-phenotype correlations.[81] Because it maintains information only on reported mutations, the group does not provide a denominator (i.e, the proportion of cases tested in which no mutation or variant is identified). Other recent studies have provided data on mutation detection sensitivity in clinical settings.

Hampel et al.[82] recruited a series of more than 1,000 otherwise unselected American patients with CRC. Tumors were tested for MSI and MMR IHC. Patients whose tumors were MSI high (MSI-H) or had loss of staining for *hMLH1*, *hMSH2*, *hMSH6*, or *hPMS2* underwent sequencing of promoter regions, exons, and intronic regions adjacent to splice sites. If this sequencing was not informative, they underwent multiplex ligation-dependent probe amplification for large deletions in *hMLH1* and *hMSH2*. About 13% of all cases showed MSI-H, which agreed with findings from other population-based studies. Most cancers that exhibit MSI are not HNPCC but are caused by silencing of the *MLH1* gene, as demonstrated by detection of hypermethylation. In the Hampel series, 78% of MSI-H cases were probably sporadic, having shown evidence of *hMLH1* hypermethylation. Of those without hypermethylation (i.e., those most likely to represent actual HNPCC), nearly 80% were found to have disease-causing mutations in one of the MMR genes.

This finding is also consistent with data from a more truly population-based CRC series in Finland.[83] Baudhuin et al.[84] were able to detect mutations in *hMLH1* or *hMSH2* in 42% of 365 cases referred because of MSI-H status or IHC loss, or for suggestive family history when no tumor was present for analysis. Eighteen percent of the *hMLH1* and 45% of the *hMSH2* mutations involved large deletions or rearrangements that would not have been detected with sequencing, protein truncation assay, denaturing gradient gel electrophoresis, and related methodologies. Every study purporting to answer the question of mutation yield in relation to clinical selection criteria and MSI/IHC findings chose to use different clinical selection criteria and different, more or less comprehensive, assays for mutation detection. These most recent studies are entirely consistent with the current NCCN guidelines, which encourage preliminary tissue evaluation using MSI/IHC, except when such tumor tissue is unavailable, followed by comprehensive mutation testing.

Clinical Colorectal Cancer Screening in HNPCC

Subjects with known MMR mutations carry a 70% to 80% lifetime risk for colorectal cancer. Risk may be slightly greater for those with *hMSH2* mutations. Full colonoscopy is the preferred method to evaluate the presence of neoplasia.[85–87] Because of the early but unpredictable age at onset, surveillance ideally begins by age 20 to 25.[88] Repeat examination should be performed at intervals as short as 1 to 2 years, even if the result is normal[89] because adenomas in HNPCC may have accelerated growth. Thus, interval cancers may develop if longer surveillance intervals are adopted.[90] Colonoscopy must be conducted with care in HNPCC carriers because adenomas are commonly very flat and show severe dysplasia disproportionate to modest size. Indigo carmine dye spray may help disclose the presence of such flat adenomas.[91] Adenomas can show IHC/MSI abnormalities although the frequency is lower than in invasive malignancies,[92] consistent with observations regarding acquired somatic mutations in the adenoma–carcinoma progression.[93]

Management of adenomas in HNPCC has not received much attention. Normally, gastrointestinal endoscopists make a great effort to remove any adenomas.[94,95] Increasingly, even very large, flat adenomas are removed from the thin-walled right colon using endoscopic mucosal resection.[96] The NCCN

guidelines recommend repeat colonoscopy at 1- to 2-year intervals after polypectomy, but imply that adenoma characteristics and patient preference may provide a basis for considering surgical resection. Adenomas not amenable to safe and complete endoscopic removal or that show high-grade dysplasia would be treated the same as invasive cancer; subtotal colectomy is recommended.

When the author encounters a large, flat, right-sided adenoma in a patient known or strongly suspected to have HNPCC, he photographs, biopsies, and tattoos the lesion. The author then reviews the situation with the patient and obtains a surgical opinion from a surgeon experienced in the nuances of HNPCC management. The benefits and disadvantages of prophylactic resection are presented from both the endoscopic and surgical perspectives.

Conclusions

A diagnosis of FAP or HNPCC should normally lead to germline mutation testing of the affected individual, providing a basis for predictive testing in at-risk relatives. Such testing, when informative, provides a concrete basis for targeted clinical screening; the search for polyps and cancer can be limited to mutation carriers, and noncarriers can be discharged. Unfortunately, germline mutation testing is fraught with pitfalls and should be conducted with formal genetic counseling whenever possible. Endoscopic surveillance is central in FAP, juvenile polyposis, Peutz-Jeghers syndrome, and HNPCC. Subjects who do not fit a syndrome classification will require empiric screening. Guidelines from several learned groups, including the NCCN, continue to emerge.

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