

REVIEW

Genetic testing in colorectal cancer: who, when, how and why

Nicholas O. Davidson

*Division of Gastroenterology, Washington University School of Medicine,
St. Louis, MO, U.S.A.*

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Abstract. Colorectal cancer (CRC) is among the most prevalent and preventable forms of cancer worldwide, accounting for over 600,000 deaths in 2005. Both genetic and environmental factors contribute to cancer etiology and estimates suggest that at least one third of CRC has a familial component. There is increased awareness of a strong genetic component to CRC risk, with the identification of several high penetrance alleles that predict increased CRC susceptibility. These include familial adenomatous polyposis (FAP), linked to mutations or deletions of the *APC* tumor suppressor gene, as well as Lynch syndrome (formerly known as hereditary non-polyposis colorectal cancer or HNPCC), which is linked to mutations or deletions of one or more mismatch repair genes including *MLH1*, *MSH2* and *MSH6*. In addition, mutations in genes encoding key signaling molecules have been linked to autosomal dominant hamartomatous syndromes that are associated with increased susceptibility to CRC. These include Peutz-Jeghers syndrome, which is linked to mutations in *STK11/LKB* and Juvenile polyposis, which is linked to mutations in the genes encoding *SMAD4* and *BMPR1A*. In addition to these high penetrance autosomal dominant alleles, recessive mutations in the *MYH* mismatch repair gene are associated with a phenotype similar to FAP. With the widespread availability of genetic testing for these alleles, physicians will be faced with a complex array of choices in terms of advocating who should be tested, when should such testing take place, how it should be conducted and interpreted and why it changes the management and outcomes for the patient and his or her family. (Keio J Med 56 (1) : 14–20, March 2007)

Key words: tumor suppressor gene, hereditary mutations, high penetrance alleles, screening

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer related death in the United States and inflicts a major toll worldwide.¹ Advances in elucidating the genetic basis for many common polygenic disorders - which have emerged coincident with completion of the human genome sequencing project - have heightened awareness that many common cancers also have strong hereditary or familial components. Indeed, a recent review² has suggested that up to one third of patients with CRC have an identifiable familial component. Collectively then, these advances suggest that our view of CRC should be modified to reflect the consensus that it is a genetic disease. This article will attempt to summarize the background

and important new advances that support this suggestion and will outline some of the challenges in implementation of this paradigm in practice.

Who should be tested?

Genetic testing offers the opportunity to confirm a suspected diagnosis of several forms of hereditary CRC. The goal of this review is to outline specific guiding principles for each of the hereditary CRC syndromes for which genetic mutations have been defined and for which genetic screening is available [for detailed reviews, see.^{3–5} As a prelude to such discussion it is worth considering some general themes in considering who should be offered genetic testing. Genetic testing can

Table 1 Proposed categories of hereditary colorectal cancer syndromes for which genetic testing is possible

<u>Polyposis Syndromes</u>		<u>Non-polyposis Syndromes</u>		
Adenomatous Polyposis	Hyperplastic Polyposis	Hamartomatous Polyposis	Lynch Syndrome	Familial Non-polyposis CRC
Classical FAP - Autosomal dominant	• <i>K-RAS, B-RAF</i> Mutations	Peutz-Jeghers	<i>MMR</i> Gene Mutations	Undefined genetic basis
• <i>APC</i> Mutations		• <i>STK11/LKB</i> Mutations.	• <i>MLH1</i> Mutations	
Autosomal recessive		Juvenile Polyposis	• <i>MSH2</i> Mutations	
• <i>MYH</i> Mutation		• <i>SMAD4/BMPRIA</i> Mutations	• <i>MSH6</i> Mutations	
			• <i>PMS2</i> Mutations	
Attenuated FAP - Autosomal dominant				
• <i>APC</i> (I1307K)				
• Autosomal		Cowden Syndrome		
Recessive				
• <i>MYH</i> Mutation		• <i>PTEN</i> Mutations		

be offered to “at risk” family members in order to classify carrier status for known alleles and to assign a likely risk of disease. There are several categories of patients who clearly merit such genetic testing for CRC. The first group consists of patients suspected of syndromic risk based on clinical findings.^{3,5} This would include an early age of onset (<40 years), the presence of multiple (>10) polyps, synchronous or metachronous cancers (either CRC and/or associated cancers) and/or a family history positive for any of these features. A second group consists of patients within a family carrying a clinical diagnosis of hereditary CRC, but for whom the pathogenic mutation is unknown. In this instance, identification of the mutant allele in the proband could be useful in screening other members of the family in order to exclude carriers. A third group would be patients within a family known to have a genetic basis for CRC and in which the mutant allele is known. In this instance, genetic testing of other family members would be of utility in excluding carriers and in counseling affected members. Clinical genetic testing of patients who manifest these characteristics will be discussed further below under the relevant disease category

Genetic Testing for Defined Hereditary CRC syndromes: What can we test for and how do we decide who should get tested?

Screening for carrier status in hereditary CRC syndromes can be offered for several genetic mutations, including familial adenomatous polyposis (FAP) and hamartomatous polyposis syndromes including Peutz-Jeghers syndrome and Juvenile polyposis syndrome (Table 1). In addition, genetic testing can be offered to patients with

non-polyposis forms of hereditary CRC, specifically Lynch syndrome (Table 1). The detailed application of these genetic tests, as well as their interpretation and usefulness, differs, however, depending on the syndrome under consideration and the mutant alleles involved. For the purposes of the present discussion, this review will focus predominantly on testing for familial adenomatous polyposis and hereditary non-polyposis CRC. Readers are referred to excellent reviews for expanded discussion of Juvenile polyposis and other rare hamartomatous syndromes (for example see⁵).

Familial Adenomatous Polyposis

In familial adenomatous polyposis (FAP), the classical phenotype involves development of hundreds to thousands of adenomatous polyps carpeting the colonic mucosa. This phenotype becomes manifest typically by age 35 years and demonstrates an autosomal dominant inheritance pattern with high penetrance.² FAP is found in ~1 per 7-10,000 births in the United States population and accounts for less than 1% of all CRC. In its classical form, almost 100% of these adenomatous polyps are considered to be cancer prone. FAP is typically a monogenic disease, the result of mutations or deletions of the adenomatous polyposis coli (*APC*) gene. In its classical form, FAP is relatively easy to recognize and genetic testing is important since its autosomal dominant inheritance pattern with high penetrance together imply a high likelihood of vertical transmission. Accordingly the following groups of individuals should be screened. First, individuals with some but not all the features of classical FAP should be tested. This would include individuals with more than 10 but less than 100 polyps. Secondly,

individuals should be tested who manifest clinically defined FAP (ie adenomatous colonic polyposis), but where the mutation has not been defined within the family. This would also include individuals with no family history of FAP. However, in this regard it is important to bear in mind that up to 25% of cases of FAP arise as spontaneous *APC* mutations and these patients will therefore have no family history of the disease.⁵ Thirdly, relatives within an FAP cohort family should be tested once the founder mutation is known, since genetic testing will be informative in predicting or excluding carrier status. This is a crucial issue since a negative genetic test result for a family member who has a proband with an identified mutation in the *APC* gene means that the family member (who tests negative) is at no greater risk for colon cancer than the general population, and the impact of genetic screening clearly has a major effect on the patients' perceptions and needs for future screening.⁶

There are several important issues to keep in mind when considering genetic testing for FAP. It is crucial that patients and family members fully understand the implications of genetic testing, including the value of both positive and negative results. Even with the best technology, disease-causing mutations in the *APC* gene are detectable in ~85% patients with phenotypic classical FAP. In addition, as noted above, while the typical inheritance pattern is autosomal dominant, approximately 25% of cases arise as spontaneous new mutations and these patients will not have an immediate relative with colonic polyposis.^{3,5} In these cases, where the proband presents with a phenotype consistent with classical FAP but with either a negative family history or with features consistent with an autosomal recessive pattern of inheritance (for example, skipped generations often in the presence of multiple affected members of a single generation) it is worth considering testing for *MYH* mutations.^{7,8} The *MYH* gene encodes a homolog of a bacterial DNA excision repair gene and mutations within this gene lead in turn to the accumulation of mutations within the *APC* gene. Two common mutations in the *MYH* gene (Y165C, G382D) account for the majority of cases where this proves to be the defective allele in phenotypic FAP.^{9,10}

There is also a distinct category of subjects with an attenuated form of FAP (AFAP), characterized by a later age of onset (over age 40), fewer adenomatous polyps (generally <50) and with a lower cumulative CRC risk. Some of these patients will be discovered to harbor mutations in the extreme 3' or 5' end of the *APC* gene.^{11,12} Others, particularly those of Ashkenazi Jewish extraction, will be found to harbor the I1307K mutation.^{13,14} This particular mutation is highly prevalent among Ashkenazim and carriers have a lifetime CRC risk in the range of 10-20%.¹⁵ Other considerations in patients presenting with an attenuated phenotype include testing for

MYH mutations, particularly those in whom *APC* testing is negative. This is important since there appear to be both low penetrance as well as high penetrance *MYH* alleles, suggesting that yet to be understood genetic and/or environmental modifiers may play a role in modulating the attenuated phenotype.² Finally, clinicians should be aware that the presence of multiple (>20) colonic polyps is consistent with a diagnosis of hyperplastic polyposis syndrome, rather than AFAP. In this situation, biopsy of the polyps will reveal hyperplastic rather than adenomatous features.¹⁶ Hyperplastic polyposis is an important entity to recognize since its genetic basis and molecular pathogenesis are distinct from that of FAP but family members are at increased risk of developing CRC.¹⁷ There is an emerging literature pointing to the importance of the hyperplastic polyposis pathway in a subset of familial CRC. In this alternative pathway, the serrated polyp represents the precursor lesion rather than the adenomatous polyp.¹⁸ Individuals and families with hyperplastic polyposis and CRC tend to present later and to demonstrate *BRAF* mutations along with microsatellite instability as a result of *hMLH1* promoter methylation (see below).¹⁸ This alternate pathway has been described in both European and North American populations and up to 16% of adenocarcinomas of the cecum and ascending colon may reveal a serrated phenotype.^{19,20} Although much remains to be understood concerning the molecular pathways that influence the progression of the serrated polyp, it is important for clinicians to recognize this distinctive manifestation of CRC risk.

Important considerations need to be kept in mind when considering genetic testing for FAP. It is essential that patients and their immediate family members be offered genetic counseling, in order that they understand the implications and potential limitations as well as the possible benefits.²¹ This includes acknowledgement of the positive and negative predictive values to such tests. There are also important psychological issues that must be confronted for these families, including access to counselors experienced in explaining in detail the concepts involved. Patients undergoing genetic testing need to provide informed consent and genetic testing should be conducted through an approved facility, where accurate interpretation is assured.²¹ Information and useful material can be accessed through the following links:

www.genetests.org
www.geneclinics.org
www3.ncbi.nlm.nih.gov
www.hereditarycc.org

Peutz Jeghers Syndrome

Peutz Jeghers syndrome (PJS) is an autosomal dominant cancer syndrome with an incomplete penetrance pattern and a variable phenotype.²² The pathological

hallmark of PJS is the presence of distinctive hamartomatous polyps throughout the gastrointestinal tract in association with pathognomonic hyperpigmented mucocutaneous spots in the perioral and buccal mucosa. Polyps typically appear during the first two decades of life and patients frequently present because of intussusception as a result of small intestinal hamartomas. In addition, patients with PJS are at greatly increased risk for a number of cancers, including throughout the GI tract (esophagus, stomach, pancreas, small intestine and colon) as well as at extraintestinal sites, principally breast.²²

PJS is caused by mutations or deletions in the *STK11* gene and informative mutations are found in 30-70% of sporadic cases and ~70% individuals with a positive family history. Genetic testing for mutations in the *STK11* gene is recommended for at-risk individuals, principally the first degree relatives of probands with confirmed PJS. This includes consideration for testing children of affected family members, since there is a very high rate of intussusception in carriers.²² Once the *STK11* gene mutation is identified in a PJS patient, family members and at-risk individuals can be tested specifically for that mutation, since the results are highly informative. At risk family members in whom a mutation is not found in the *STK11* gene are recommended to undergo small intestinal imaging and colonoscopy as well as periodic upper endoscopy in order to identify and remove large hamartomatous polyps as well to undergo regular periodic surveillance for other cancers (breast, testis, pancreas).²²

Hereditary, non-polyposis colorectal cancers (Lynch Syndrome)

The non-polyposis forms of hereditary colon cancer are much more common than the syndromes outlined above, with estimates that it may account for 3-5% of all cases of CRC.² Lynch syndrome is an autosomal dominant disease with pleomorphic features characterized by early onset of colon cancer (< age 40 years) often in association with a family history positive for either colon cancer or for other associated cancers, including endometrial, ovarian, brain, small intestinal, pancreatic, urinary tract cancers.^{23,24} Criteria were established over 15 years ago to establish clinical criteria for the diagnosis of this common form of hereditary CRC (the so-called Amsterdam criteria). These included the presence of at least 3 members of a kindred with CRC (excluding FAP) with at least one member being a first degree relative of the other 2, that at least two generations be involved and that one was age <50 years.¹ These criteria have been modified sequentially and the current, so-called Modified Bethesda criteria now classify a patient as having Lynch syndrome if there is CRC diagnosed <50 years, or if the patient has a synchronous or metachronous CRC or if the patient has an extracolonic cancer (see above) diagnosed at any age, or if the patient with CRC (any age)

has a first degree relative with CRC diagnosed at age <50 years and/or colorectal adenomas diagnosed at age <40 years.¹ In addition, a patient with CRC diagnosed at age <60 years would be classified as Lynch syndrome if the tumor contained the mutational signature of defective mismatch repair (microsatellite instability, MSI), which is described below. Individuals diagnosed with Lynch syndrome, as well as their immediate family members, have a greatly increased lifetime risk of developing colorectal cancer and female carriers carry an equally substantial lifetime risk of developing endometrial cancer. These features of Lynch syndrome make it particularly important to recognize in order to offer preventive screening for at-risk family members. These recommendations include frequent colonoscopy (at 1-2 year intervals) starting at age 20-25 or at least 10 years earlier than the earliest age of onset of cancer in a family member.²⁴ In addition, endometrial cancer surveillance is recommended with frequent transvaginal ultrasound examination.²⁴ These screening recommendations make it imperative to establish an unequivocal diagnosis of Lynch syndrome where possible.

The mutational signature of Lynch syndrome, MSI, is present in most if not all cancers arising in patients with this disease complex and results from mutations, deletions or defects in one of several DNA mismatch repair genes.²⁵ The genes most frequently involved are *hMLH1* and *hMSH2* (which together account for ~90% of the germline mutations that account for Lynch syndrome) as well as *hMSH6* (which accounts for the majority (~7%) of the remaining mutations) and a small minority caused by *hPMS2*.⁴ Genetic testing through commercially available conventional DNA sequence analysis is currently offered only to detect mutations in *hMLH1* and *hMSH2* genes.²⁴

Problems in diagnosing Lynch syndrome

Having outlined the basic elements of this disease complex, it is important to understand that reaching an unambiguous diagnosis of Lynch syndrome is often quite challenging. There are at least three major reasons for this difficulty. First, clinical suspicion of Lynch syndrome largely rests on a clinical diagnosis based on information concerning the extended family history of a suspected proband. In this regard, a detailed family history is often not documented in the patients' medical record-- particularly with respect to the presence of associated cancers (endometrial, ovarian, ureteric etc) in maternal or paternal relatives.²⁶ The absence of this information might lead to the clinician overlooking possible Lynch syndrome in a patient presenting with new onset CRC. The second issue that has led to confusion and ambiguity with respect to establishing a molecular diagnosis of Lynch syndrome is that less than half of patients will have a pathogenic mutation in one of the

mismatch repair genes.⁴ DNA sequencing of the two leading candidate genes (*hMLH1* and *hMSH2*) led to the realization that many of the sequence variations noted were silent polymorphisms or missense mutations of unknown significance.⁴ This is an important problem since the emerging information from several centers supports a divergence in the classification of Lynch syndrome into classical genotypic families with MSI and/or an identified mismatch repair gene mutation and families with phenotypic features only.²⁷ A rational approach to this issue is discussed in detail below. The third issue that complicates establishing an unequivocal diagnosis of Lynch syndrome is the observation that the mutational signature of DNA mismatch repair (MSI) is present in ~15% of sporadic CRC.² In this setting, MSI is associated with acquired silencing (through promoter methylation) of the *hMLH1* gene and not a heritable mutation in the germline. As noted above, promoter hypermethylation is an important epigenetic mechanism of gene silencing—as exemplified by MSI appearing in the setting of hyperplastic polyposis and the serrated adenoma to adenocarcinoma transition.

Suggested algorithm for genetic testing of patients and family members with suspected Lynch syndrome

In view of the aforementioned problems and complications in establishing a diagnosis of Lynch syndrome, it is extremely important to elicit a detailed family history of other cancers, the age of diagnosis and where possible to obtain the tumor specimen for MSI testing. Tumors that manifest MSI should be examined by immunohistochemical staining for the protein products of the mismatch repair genes (ie *MLH1*, *MSH2*, *MSH6* and *PMS2*).²⁸ Using this approach, the clinician will be able to detect loss of staining of one of the candidate mismatch repair genes and would then conclude that there is likely to be an inactivating mutation in the corresponding gene. Loss of staining of a mismatch repair gene, coupled with MSI would then be a reasonable basis to pursue mutational analysis of the corresponding gene in order to identify informative mutations that could then be used to screen at-risk family members. A recent report has outlined a useful web-based questionnaire that uses a balanced algorithm of clinical information (age of diagnosis, gender, location of tumor, presence of synchronous or metachronous tumors, family history of CRC or endometrial cancer) as well as immunohistochemical staining to predict the likelihood of Lynch syndrome.²⁹ This questionnaire can be accessed at:

<http://www1.hgu.mrc.ac.uk/Softdata/MMRpredict.php>

Other considerations for who should be offered genetic testing for Lynch syndrome

Any patient with CRC diagnosed at <40 years impor-

tant category of patients should be offered genetic testing for Lynch syndrome.³⁰ This is important since a high proportion of young patients with CRC do not meet strict clinical criteria for Lynch syndrome. In addition, young patients with CRC tend to have less right sided predominance of their colon cancers than the typical Lynch syndrome patients.³⁰ However, almost three quarters of the tumors from young patients with CRC will show MSI and approximately half of these will have mismatch repair gene mutations. Finally, over 40% of young patients with CRC will develop a second cancer within 12 years, the majority of these being GI tract cancers.³⁰

New information concerning suspected Lynch syndrome patients who do not carry the molecular fingerprint of MSI

Three new studies have added considerable insight into the management and genetic classification of patients with phenotypic Lynch syndrome.^{29,31,32} These studies addressed the question of whether the disease process was fundamentally distinct in patients based on the presence or absence of MSI and the findings provide important new insights for the management of these patients and their at-risk family members. As discussed above, patients with classic Lynch syndrome have a constellation of clinical features in conjunction with the molecular fingerprint of MSI, frequently accompanied by alterations in the expression of mismatch repair genes.²⁷ There is, however, another group of patients who manifest the clinical features of Lynch syndrome (early onset CRC, positive family history, etc) but where the tumor does not demonstrate MSI and the genetic basis for the cancer susceptibility is unknown. There are important features concerning this subset of patients, who have been referred to as familial non-polyposis colorectal cancer type X.³¹ These include the finding that the standardized incidence ratios for CRC are elevated in first degree relatives (as in classical Lynch syndrome) but that the incidence of other Lynch syndrome associated cancers (endometrial, ovarian, stomach etc) were not higher than in an age-adjusted general population.³¹ This information is of particular relevance in terms of counseling female family members who may be at risk, since their need for intensive screening for endometrial cancer surveillance is no longer recommended. In addition, the average age at which CRC was detected in the family members from the familial non-polyposis colorectal cancer syndrome cohort (type X) was approximately 60 years, compared to less than age 50 in classical Lynch syndrome.³¹ This information is particularly useful in terms of providing guidelines for the initiation of screening colonoscopy (5-10 years younger than the earliest CRC diagnosis in the family) and for the intervals between screening (every 5 years). These patients and their family members should be counseled that they do not have a sinister can-

cer predisposition syndrome. In particular, since women family members with Lynch syndrome carry a 40-60% lifetime risk of endometrial cancer, this diagnosis carries major implications for their continued surveillance.³³

Summary comments

Newer advances in the molecular genetics of colorectal cancer pathogenesis will undoubtedly continue to evolve. As public awareness of the human genome project expands and commercialization of the tools for diagnostic genomic applications continue to expand, it will be important for physicians to stay well informed about the limitations, interpretation and utility of these approaches and to be able to apply them in a scientifically sound manner to the management of their patients.

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