What the Physician Needs to Know About Lynch Syndrome: An Update

By Henry T. Lynch, MD

The Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]), is the most common form of hereditary colorectal cancer (CRC), accounting for 2% to 7% of all CRC cases. The next most common hereditary CRC syndrome is familial adenomatous polyposis (FAP), which accounts for less than 1% of all CRC. Lynch syndrome is of crucial clinical importance due to the fact that it predicts the lifetime risk for CRC and a litany of extra-CRC cancers (of the endometrium, ovary, stomach, small bowel, hepatobiliary tract, upper uroepithelial tract, and brain) through assessment of a well-orchestrated family history. A Lynch syndrome diagnosis is almost certain when a mutation in a mismatch repair gene—most commonly MSH2, MLH1, or, to a lesser degree, MSH6—is identified. Once diagnosed, the potential for significant reduction in cancer-related morbidity and mortality through highly targeted surveillance may be profound. Particularly important is colonoscopy initiated at an early age (ie, 25 years) and repeated annually due to accelerated carcinogenesis. In women, endometrial aspiration biopsy and transvaginal ultrasound are important given the extraordinarily high risk for endometrial and ovarian carcinoma. These cancer control strategies have a major impact on at-risk family members once they have been counseled and educated thoroughly about Lynch syndrome's natural history and their own hereditary cancer risk.

Colorectal Cancer and Heredity

Colorectal cancer (CRC) is the third most common cancer in the United States, where its annual incidence is estimated to be over 145,000. As the second highest cause of cancer death in the United States (surpassed only by lung cancer), its annual mortality is expected to exceed 56,200.[1] Estimating that ~10% of the total CRC burden is hereditary, this incidence translates to close to 14,500 new cases with more than 5,620 deaths. These are conservative estimates, given the striking genotypic and phenotypic heterogeneity of hereditary CRC (Figure 1).[2] In turn, its familial incidence—namely a two- to threefold excess risk of CRC in patients who have one or more first-degree relatives with CRC but who do not fit any of the hereditary criteria—is estimated to be 15% to 20%, or 22,050 to 29,400 new cases and 8,505 to 11,340 deaths annually.

The remainder of CRC cases will be "sporadic," which implies that none of the patient's first- or second-degree relatives have been diagnosed with CRC. However, more meticulous probing of the family history among so-called sporadic or familial cases may identify a hereditary syndrome (Figure 1). In most hereditary CRC syndromes, certain extra-CRC cancer types may be integral lesions. Those that have been shown to be integral to the Lynch syndrome are listed in Table 1.
Physicians must understand how powerful the family history can be in determining a patient's risk for cancer. They also must know the natural history of the Lynch syndrome, in concert with the availability and significance of molecular genetic testing, so that this knowledge can be applied to effective genetic counseling, screening, and management.[3]

**Familial and Hereditary Cancer Risk**

Public awareness of "familial" and "hereditary" cancer risk is increasing. Clinically, both physician and patient are concerned about the significance of "cancer risk." For example, first-degree relatives of patients affected with common malignances such as carcinoma of the breast and colon, have approximately a twofold increased risk for cancer at the same anatomic site.[4] Twin studies, particularly those showing higher concordance of cancer in monozygous twins than in dizygous twins, provide evidence to support this familial cancer risk, as in the case of carcinoma of the breast.[5]

When searching for an explanation for familial or hereditary cancer risk, only about 20% of this twofold excess risk to relatives of affected breast cancer patients will be attributable to mutations in the BRCA1 and BRCA2 genes.[6] The same phenomenon occurs in hereditary forms of CRC, as in the case of the Lynch syndrome and its MSH2 or MLH1 etiology.[7,8] In reviewing the familial occurrence of common cancers, Houlston and Peto[9] suggest that its magnitude may be greater than currently appreciated in that the remaining familial risk could be due to mutations in as yet unidentified genes and/or to polygenic mechanisms, the latter being a more plausible explanation for familial cancer that does not follow a Mendelian inheritance pattern.

**Hereditary CRC Syndromes**

The two operationally defined categories of hereditary CRC are (1) tumors with chromosomal instability, which tend to be left-sided, show aneuploid DNA, harbor characteristic mutations such as K-ras, APC, and p53, and behave aggressively (eg, familial adenomatous polyposis [FAP]); and (2) tumors that show microsatellite instability, occur more frequently in the right colon, have diploid DNA, harbor characteristic mutations such as transforming growth beta type II receptor and BAX, and behave indolently (eg, Lynch syndrome).[7,8]

**Logistics of Family Studies**

Hereditary cancer syndromes can also be classified into two categories. The first includes disorders with phenotypic stigmata that can assist in establishing a hereditary cancer syndrome diagnosis. Striking examples include the multiple atypical nevi in the familial atypical multiple mole melanoma syndrome[10] and the multiple colonic adenomas in FAP.[11] The second category includes disorders that lack such phenotypic stigmata of hereditary cancer risk. Classic examples in this category are the hereditary breast-ovarian cancer (HBOC) syndrome[12,13] and Lynch syndrome.[7,8] In these latter settings, particular reliance must be given to the cancer family history coupled with knowledge of the pattern of cancer distribution within the family-factors that are mandatory for hereditary cancer syndrome diagnosis. Problems in interpreting the significance of the family history may arise. For example, the diagnosis of hereditary forms of cancer may be obfuscated by numerous factors, such as reduced penetrance of the deleterious mutations, genotypic and phenotypic heterogeneity, small families, false paternity, unavailability of medical and pathology records, slides, and/or tissue blocks, premature death of key
relatives from causes other than cancer, lack of cooperation of otherwise informative relatives, and even decreased cooperation by their physicians.

In spite of the diagnostic and cancer-control virtues embodied in a well-orchestrated family cancer history, a severe failure in its collection and/or accurate interpretation at the clinical level often exists. Confounding this omission, there may be a profound gap in knowledge between both clinical and basic science advances and their cancer-control translation at the bedside.[14] Certain of those potential barriers may delay hereditary cancer syndrome diagnosis and management.

Once the pedigree is analyzed and shown to be consonant with Lynch syndrome, certain measures can enable confirmation of the diagnosis, such as the presence of microsatellite instability in a CRC specimen from a genetically informative relative and, if positive, a search for a cancer-causing germ-line mutation (MSH2, MLH1, MSH6). The identification of a cancer-causing mutation that cosegregates with the cancer phenotype then becomes the sine qua non for a hereditary cancer syndrome diagnosis.[15] From this point on, the most important considerations will be predicated by the physician's knowledge of hereditary CRC, including its differential diagnosis in concert with the known extant phenotypic and genotypic heterogeneity of hereditary CRC syndromes (Figure 1). This information must then be coupled with knowledge of the cardinal features of hereditary cancer (Table 1), in concert with those myriad multifaceted problems that affect patient compliance and management.

**Power of a Germ-line Mutation**

The power of a cancer-causing mutation in a patient/family is truly enormous. This has been investigated in members of 75 HBOC and 47 hereditary nonpolyposis colorectal cancer (HNPCC) families.[16] Collectively, this comprised 10,910 cohort members, of whom 1,408 were tested and learned about their results. Therein, carrier risk status changed in 2,906 patients following testing of 1,408 family members. The risk change to noncarrier status was most common, accounting for 77% of risk changes. Twelve percent changed to known carrier status from a lower risk. Sixty percent of persons with a carrier risk status change were not themselves tested, and yet their risk status changed because of a relative's test result.

Conclusions of the investigation were as follows: (1) Changes from uncertainty to certainty, ie, to carrier or noncarrier status, accounted for 89% of risk changes resulting from testing; (2) because most changes were risk reductions, economic and emotional burden lessened; and (3) research into the impact of testing on untested family members is clearly needed. Thus, this study had a major impact on the clinical, economic, and emotional implications of DNA testing in two of the most common hereditary cancer syndromes, namely HBOC and the Lynch syndrome.[16]

**Molecular Genetics and the Lynch Syndrome**

Mutations in six different mismatch repair genes have been identified in HNPCC patients: MLH1, located on chromosome 3p21; MSH2 on 2p16; MSH6 on 2p15; PMS2 on 7p22; MLH3 on 14q24.3; and possibly PMS1,[17] located on 7p22.[17-22] However, only 40% to 60% of Lynch syndrome patients harbor identifiable germ-line mutations.[23] Approximately 90% of the identified HNPCC mutations involve MLH1 or MSH2, whereas mutations in the MSH6 gene account for approximately 10%. MSH6 mutations appear to predispose to a milder form of Lynch syndrome and often show an excess of endometrial cancer.[24]

These findings suggest that other genes, including modifier genes, may be of etiologic importance in Lynch syndrome. The occurrence of mutation types that are difficult to detect and/or yet to be identified as well as environmental factors[25] and/or chance could also explain the etiology of those 40% to 60% of HNPCC families in which, to date, no known cancer-causative germ-line mutations have been identified.[7,26] The mutation database maintained by the International Collaborative Group (ICG)-HNPCC is an important source of first reference (www.nfdht.nl). Suter et al[27] reported findings of a germ-line epimutation in two individuals who lacked evidence of germline mutations in any mismatch repair genes but who nevertheless met clinical criteria for the Lynch syndrome. These authors noted that the characteristics of epigenetic states could produce patterns of disease risk that resemble those attributed to polygenic mechanisms. In addition, it is hypothesized that rare germ-line mutations and polymorphisms of low penetrance, such as those that have been identified in FAP,[28-30] may have as yet unidentified counterparts in the Lynch syndrome.

**Genetic Counseling**
We must bear in mind the absolute necessity of genetic counseling prior to DNA collection and testing, as well as at the time of disclosure of results, considering that the presence of a cancer-causing germ-line mutation will have a strong impact on the patient’s lifetime destiny for cancer. Thus, this precious and potentially lifesaving knowledge will enable disclosure of risk for cancer(s) of specific anatomic sites, average age of onset, and possibly even prognostic differences in the patient bearing the specific cancer-causing mutation. This knowledge will be limited only by the deleterious mutation’s penetrance and the possible impact of environmental carcinogenic interaction.

To maximize the cancer control potential from a family study, the proband and his or her high-risk relatives should be notified about the hereditary cancer syndrome’s natural history and the pertinent lifetime cancer risk. Genetic counseling must include an opportunity for DNA testing when this is appropriate; however, the candidates for testing must be made aware of its pros and cons. Surveillance and management opportunities for these high-risk relatives will then be highly targeted, based upon the natural history of the particular hereditary cancer disorder coupled with the presence of a cancer-causing germline mutation, when one is present. [7] Counselors must be prepared psychologically and must have an opportunity to address freely such concerns as survivor guilt if found to be negative for the deleterious mutation, or, if positive, concerns about insurance and employment discrimination, and even the possibility of stereotyping by their relatives.

**Family Information Session**

Cancer-control objectives can be significantly abetted through a family information session.[31] This involves the participation of as many family members as desire to assemble at an educational session, in a geographic area of convenience to the family. The family information session is conducted by a physician, a study coordinator (who may be a registered nurse), and a genetic counselor. Participants are educated in depth about the natural history of the particular hereditary cancer syndrome in their family, availability of genetic testing, and the surveillance and management options available to them. Blood draws for germ-line mutation testing, when indicated, will follow genetic counseling in consenting individuals.

The proband or a motivated family member can be extremely helpful in setting up the family information session in that they can notify their relatives of the upcoming family information session, assist in identifying an adequate facility for the session, and sign up family members for individual counseling appointments.

These family information sessions enable the physician and genetic counselor to discuss diagnostic and cancer control measures, as well as help to define confidentiality, psychosocial, and economic concerns that may have an impact on the family, and then determine how best to resolve them. A group psychosocial therapy situation often evolves. Family members frequently state that this was the first time a physician told them face-to-face what could kill them and, in turn, what they could do about ameliorating the many diagnostic, screening, and management problems that they may encounter and/or may have already encountered as a result of being at increased hereditary cancer risk.

**Clinical Translation of Molecular Genetic Knowledge**

Ramaswamy[32] has expressed extreme optimism regarding the current diagnosis and treatment of cancer, translating our increased comprehension of the human genome and advances in molecular technology into improvements in the individual patient’s diagnosis and management. This molecular revolution may lead to a sea change from population-based risk assessment and empiric treatment to that of a more highly predictive individualized model based on molecular diagnosis and targeted cancer treatment. Predictably, such a personalized approach will not only increase the efficacy of treatment, but it should also decrease toxicity and cost.

This knowledge has recently been applied by Lossos et al[33] through the study of gene expression signatures, which were used to predict the prognosis in patients with diffuse large B-cell lymphoma, wherein six genes were found to be sufficient to predict overall survival. This approach has also led to research showing that fluorouracil (5-FU), while proven advantageous to the treatment of CRC in general, may not be appropriate in Lynch syndrome patients with CRC tumors showing high-frequency microsatellite instability.[34,35]

Studies have strongly supported the hypothesis that CRCs with high-frequency microsatellite instability may be more immunogenic than microsatellite stable tumors. This finding has been ascribed to the increased numbers of activated cytotoxic lymphocytes in CRC tissues.[36]
Founder Mutations and the Lynch Syndrome

Founder mutation studies have many advantages compared to genetic testing in unrelated populations. For example, founder mutations enable more efficient identification of relatives who are at increased hereditary cancer risk and who thereby can benefit from genetic counseling in concert with highly targeted surveillance and management.

With respect to the Lynch syndrome, there have been at least five examples of founder mutations. In the Finns, one germ-line MLH1 mutation has been found to account for as many as half of all Lynch syndrome cases, while another was found to account for 15% to 20%. Other founder mutations in the Lynch syndrome include an MSH2 germ-line mutation first detected in a large kindred in Newfoundland, subsequently found to be widespread in that population through a founder effect. Interestingly, this mutation has been seen in many other populations as well, and actually arises de novo with appreciable frequency. Thus, this mutation is a recurrent one worldwide, but its spread in Newfoundland is by the founder mechanism. A mutation of MLH1 is widespread in the Valais region of Switzerland, and a recently identified mutation in MSH2 may account for as many as one-third of all Lynch syndrome cases in the Ashkenazi Jewish population. Lynch et al have described another example of the founder mutation phenomenon. This instance involves a mutation-namely MSH2 del 1-6-in nine families that have been tracked from their "founder" in Germany in the 18th century through their migrations to and within the United States until the present day.

Practical Diagnostic Strategies

Criteria and Guidelines

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Several different sets of criteria and guidelines have been developed in the hope of resolving some of Lynch syndrome's diagnostic pitfalls. The most commonly used-the Amsterdam I and Amsterdam II criteria, and the Bethesda guidelines-are shown in Table 2.

Pattern Recognition

For diagnostic purposes, one may also consider so-called "pattern recognition" of the cancer phenotype in probands and their immediate firstand second-degree relatives. Thus, the presence of a striking phenotype such as proximal CRC occurring before age 40, possibly metachronous CRC, mucoid features with signet cell pathology, or the early onset of one or more colonic adenomas, even in only a single first- or second-degree relative, should prompt further investigation of the possibility of Lynch syndrome, even though the findings may fail to qualify for the Amsterdam Criteria or Bethesda Guidelines (Table 2).

The presence in even one relative in a pedigree showing early age of CRC onset, and/or one or more key extracolonic cancer types, should raise a high index of suspicion for a Lynch syndrome.
diagnosis. This is clearly illustrated by the pedigree shown in Figure 2,[49] which reveals multiple primary cancer and extracolonic cancer types that constitute the Lynch syndrome. Noteworthy in this pedigree is the presence of patients with the Muir-Torre syndrome variant of the Lynch syndrome (sebaceous adenomas, sebaceous carcinomas, and multiple keratoacanthomas in concert with visceral cancer).

**FIGURE 2**

Multiple Primary Cancer and Extracolonic Cancer Types

Microsatellite instability testing of the CRC tissue block should be made and, if positive, one should then search for a germ-line mutation in a mismatch repair gene.[7,8,50] Finally, given the relatively high frequency of CRC in the general population, certain HNPCC-like families may be attributed to chance alone, or there may be cancer phenotypes (such as those attributable to the MSH6 mutation) that constitute an atypical or more benign form of HNPCC.[24,51]

**Cancer Control in Lynch Syndrome**

Cancer-related morbidity and mortality may be reduced significantly through highly targeted surveillance measures that are based on knowledge of the natural history and cardinal features of the Lynch syndrome (Table 1). Particularly important is full colonoscopy (due to the syndrome's predilection toward proximal CRC), initiated at the age of 25 years (due to early onset of CRC) and repeated annually (due to accelerated carcinogenesis). In women, endometrial aspiration biopsy and transvaginal ultrasound are important, given the extraordinarily high risk for endometrial and ovarian carcinoma. These cancer-control strategies have a strong impact on family members at risk once they have been counseled and educated thoroughly about Lynch syndrome's natural history and their own hereditary cancer risk.

Jrvinen and colleagues[52] demonstrated the benefit of colonoscopic screening in HNPCC through a controlled clinical trial extending over 15 years. The incidence of CRC was compared in two cohorts of at-risk members of 22 HNPCC families. CRC developed in 8 screened subjects (6%), compared with 19 unscreened controls (16%; \( P = .014 \)). The CRC rate was reduced by 62% in those who were screened. All CRCs in the screened group were local, causing no deaths, compared with nine deaths caused by CRC in the controls. The researchers concluded that CRC screening at 3-year intervals reduces the risk of CRC by more than half, prevents CRC deaths, and decreases overall mortality by about 65% in HNPCC families. The relatively high incidence of CRC even in the screened subjects (albeit without deaths) argues for shorter screening intervals (eg, 1 year). Indeed, Vasen and colleagues[53] discovered five cancers in Lynch syndrome patients within a 3½-year interval following a normal colonoscopy.

**Prophylactic Colectomy**

Subtotal colectomy as a prophylactic measure among HNPCC patients remains controversial. However, in special circumstances, patients who carry germ-line mismatch repair cancer-causing mutations should be offered this option as an alternative to lifetime colonoscopic surveillance. Church[54] and Lynch[55] have suggested that prophylactic surgery should be an option for patients who are likely to show reduced compliance with colonoscopy. Genetic counseling, coupled with a second surgical opinion, must be provided so that patients can evaluate the various available surgical management strategies.

**Prophylactic Hysterectomy and Oophorectomy**

Women at risk for Lynch syndrome should have annual screening for endometrial and ovarian cancer beginning at age 30 to 35 years. Endometrial aspiration coupled with transvaginal ultrasound is advised for screening. CA-125 testing should be performed semiannually for ovarian cancer. Women must be advised of the marked limitations in ovarian cancer screening. Prophylactic hysterectomy and oophorectomy can be considered when childbearing is completed.
Discussion

The cancer genetics diagnostician has often been thought of as someone who is obsessed with the minutiae of the cancer family history, which were believed by many colleagues to be of only minor public health significance. But no longer! The magnitude of hereditary cancer problems now compels physicians to be more strongly focused upon these concerns. Indeed, the public is demanding this attention, and malpractice attorneys are learning to deal with these multifaceted issues.[56,57]

On a more positive note, molecular geneticists have discovered countless deleterious germ-line mutations that have enabled the identification, diagnosis, and management of an increasing number of hereditary cancer syndromes. When used effectively in the clinical practice setting by informed physicians, these discoveries can significantly enhance medical management of hereditary cancer-prone families. For example, the presence of a cancer-causing mutation in a patient with a hereditary cancer syndrome enables the knowledgeable physician to offer that individual appropriate surveillance and management procedures. Conversely, in a family where a known cancer-causing mutation exists, the absence of that mutation in a family member means that general population cancer guidelines can be utilized for that individual. Such common hereditary cancers as those of the colon and endometrium in patients with Lynch syndrome (ie, MSH2, MLH1, and MSH6 mutations), and of the breast and ovary in patients with HBOC syndrome (ie, BRCA1/BRCA2 mutations) head the list of cancer disorders that are amenable to highly targeted surveillance protocols.

Research at the basic science level should one day lead to the identification of those presently elusive germine variants that confer an increased susceptibility (or resistance) to cancer. This will require a better elucidation of the myriad complex somatic genetic events that occur in the emerging cell. With increasing knowledge about cancer causality at the molecular level during the past decade, the clinical translation of cancer "running in families" has become a source of major contention.[15]

Barriers to Cancer Control

Unfortunately, these cancer control opportunities may be seriously compromised given most physicians' limited knowledge or interest in what constitutes a hereditary cancer syndrome, and the significance of highly targeted cancer surveillance and specialized management protocols for particular disorders.[58] Further confounders to cancer control center around the perception of many patients at risk for hereditary cancer that participating in genetic testing, genetic counseling, and pertinent clinical cancer control measures will identify them as being a member of a family with a hereditary cancer-prone syndrome. They may then reason that this information will result in discrimination by insurance companies or employers. To help ameliorate these concerns, we need legislation that will provide protection from such potential discrimination.

Future Projections

Finally, there remain countless areas in the etiology, pathogenesis, and control of HNPCC that require continued intensive research. Some of the questions to be answered are:

1) What is the complete tumor complement of HNPCC?
2) What are the chemotherapy and chemoprevention implications of this disease?
3) Can we improve surveillance/management strategies?
4) Can we achieve molecular-based chemoprevention?
5) What are the genotypic and phenotypic heterogeneity implications of Lynch syndrome?
6) What are the differential diagnostic implications of the disease?

Our research efforts and those of colleagues throughout the world have only grazed the tip of the proverbial iceberg in terms of the etiology, pathogenesis, surveillance, and management of Lynch syndrome. What we do know clearly is that the knowledge accrued to date, when translated clinically, can save lives!

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