Recommendations for the Care of Individuals With an Inherited Predisposition to Lynch Syndrome
A Systematic Review

Noralane M. Lindor, MD
Gloria M. Petersen, PhD
Donald W. Hadley, MS, CGC
Anita Y. Kinney, PhD
Susan Miesfeldt, MD
Karen H. Lu, MD
Patrick Lynch, MD
Wylie Burke, MD, PhD
Nancy Press, PhD

Early 10 years ago, Burke et al1 published an article in JAMA that set forth recommendations for care of individuals with an inherited predisposition to hereditary nonpolyposis colorectal cancer (HNPPC). This syndrome, described as an autosomal dominant disorder, was characterized by predisposition to early onset colorectal cancer and cancers of the endometrium, small intestine, ovary, hepatobiliary system, kidney, and ureter.2,3 Discovery of the genes involved in this disorder meant that genetic testing could identify high-risk individuals. In addition, tumor phenotyping, which greatly facilitates identification of gene carriers, has become clinically available and has been recommended for a subset of individuals with colorectal cancer.3 This systematic review provides updated information and screening recommendations for family members who have inherited mutations in DNA mismatch repair genes, referred to herein as Lynch syndrome.

Context About 2% of all colorectal cancer occurs in the context of the autosomal dominantly inherited Lynch syndrome, which is due to mutations in mismatch repair genes. Potential risk-reducing interventions are recommended for individuals known to have these mutations.

Objectives To review cancer risks and data on screening efficacy in the context of Lynch syndrome (hereditary nonpolyposis colorectal cancer) and to provide recommendations for clinical management for affected families, based on available evidence and expert opinion.

Data Sources and Study Selection A systematic literature search using PubMed and the Cochrane Database of Systematic Reviews, reference list review of retrieved articles, manual searches of relevant articles, and direct communication with other researchers in the field. Search terms included hereditary non-polyposis colon cancer, Lynch syndrome, microsatellite instability, mismatch repair genes, and terms related to the biology of Lynch syndrome. Only peer-reviewed, full-text, English-language articles concerning human subjects published between January 1, 1996, and February 2006 were included. The US Preventive Services Task Force’s 2-tier system was adapted to describe the quality of evidence and to assign strength to the recommendations for each guideline.

Evidence Synthesis The evidence supports colonoscopic surveillance for individuals with Lynch syndrome, although the optimal age at initiation and frequency of examinations is unresolved. Colonoscopy is recommended every 1 to 2 years starting at ages 20 to 25 years (age 30 years for those with MSH6 mutations), or 10 years younger than the youngest age of the person diagnosed in the family. While fully acknowledging absence of demonstrated efficacy, the following are also recommended annually: endometrial sampling and transvaginal ultrasound of the uterus and ovaries (ages 30-35 years); urinalysis with cytology (ages 25-35 years); history, examination, review of systems, education and genetic counseling regarding Lynch syndrome (age 21 years). Regular colonoscopy was favored for at-risk persons without colorectal neoplasia. For individuals who will undergo surgical resection of a colon cancer, subtotal colectomy is favored. Evidence supports the efficacy of prophylactic hysterectomy and oophorectomy.

Conclusions The past 10 years have seen major advances in the understanding of Lynch syndrome. Current recommendations regarding cancer screening and prevention require careful consultation between clinicians, clinical cancer genetic services, and well-informed patients.
Box 1. Amsterdam Criteria: Family Risk for Hereditary Nonpolyposis Colorectal Cancer†

At Least 3 Relatives Have a Cancer Associated With Hereditary Nonpolyposis Colorectal Cancer†
1. One should be a first-degree relative of the other 2 relatives
2. At least 2 successive generations should be affected
3. At least 1 relative should be diagnosed before age 50 years
4. Familial adenomatous polyposis should be excluded
5. Tumors should be verified by pathological examination

†About half of the families meeting Amsterdam I Criteria will have Lynch syndrome (hereditary DNA mismatch repair gene mutation); conversely, many families with Lynch syndrome do not meet these criteria.

Figure. Suggested Algorithm for Laboratory Testing for Lynch Syndrome*

METHODS

Studies were identified by PubMed and the Cochrane Database of Systematic Reviews, reference list review of retrieved articles, manual searches of relevant articles, and direct communication with other researchers in the field. Search terms included hereditary non-polyposis colon cancer, Lynch syndrome, microsatellite instability, mismatch repair genes, and terms related to the biology of Lynch syndrome. Articles selected for consideration included data on carriers of HNPCC, Lynch syndrome, or DNA mismatch repair gene mutations, individuals who underwent germline mutation testing, or persons who were members of high-risk families. Only peer-reviewed, full-text articles concerning human subjects published in the English language between January 1, 1996, and February 2006 were included. Case reports and articles in which the study population was not fully described were excluded.

We adopted the US Preventive Services Task Force's 2-tier system to assess the quality of evidence and to assign strength to the recommendations for each guideline. Ultimately, recommendations for clinicians are provided and are supported by either high-quality evidence, if it exists, or by expert opinion when a strong evidentiary consensus does not exist.

HNPCC and Lynch Syndrome

Historically, HNPCC has been defined by an algorithm including clinical and family history criteria. Recently, molecular testing (Box 1 and Figure) has become available and accepted as a basis for the diagnosis of Lynch syndrome. We favor use of the term Lynch syndrome to specify families that transmit an inherited mutation in 1 of the genes that encode proteins in the DNA mismatch repair complex (MLH1, MSH2, MSH6, and PMS2), regardless of whether any pedigree criteria has been fulfilled.

The DNA mismatch repair complex functions as a “spell-check” system to repair errors occurring when DNA
Box 2. Revised Bethesda Guidelines**

Tumors Should Be Tested for Microsatellite Instability When 1 or More of the Following Exist:

1. Colorectal cancer diagnosed in a patient who is younger than 50 years
2. Presence of colorectal cancers that are synchronous (simultaneous) or metachronous (diagnosed at different times) or other tumors associated with hereditary nonpolyposis colorectal cancer,† regardless of age
3. Colorectal cancer with a high amount of microsatellite instability+ or histology§ diagnosed in a patient who is younger than 60 years||
4. Colorectal cancer or tumor associated with hereditary nonpolyposis colorectal cancer† diagnosed before age 50 years in at least 1 first-degree relative\l
5. Colorectal cancer or tumor associated with hereditary nonpolyposis colorectal cancer† diagnosed at any age in 2 first- or second-degree relatives\l

*These guidelines are intended for colorectal cancer patients to identify those who may benefit from tumor microsatellite instability testing. The guidelines are not diagnostic criteria for hereditary nonpolyposis colorectal cancer or Lynch syndrome. When a tumor is not available for testing, germline DNA testing can be offered if clinical presentation is strongly suggestive of Lynch syndrome.
†Includes colorectal, endometrial, stomach, ovarian, pancreas, uterine and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas, and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.
‡Refers to changes in 2 or more of the 5 panels of microsatellite markers recommended by the National Cancer Institute.
§Presence of tumor infiltrating lymphocytes, Crohn disease–like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern.
¶There was no consensus among the Bethesda workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep age younger than 60 years in the guidelines.
\Criteria 4 and 5 have been reworded to clarify the revised Bethesda Guidelines.

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in which the clinical suspicion for Lynch syndrome is still strong.25 No laboratory test or combination of tests is completely sensitive nor specific for diagnosing or excluding Lynch syndrome. Clinical judgment should not necessarily be overridden by laboratory results if the clinical presentation for Lynch syndrome is compelling.

We provide recommendations primarily for individuals or families with Lynch syndrome, that is, families with confirmed or suspected hereditary DNA mismatch repair gene mutations. The screening recommendations may also be applicable to individuals whose family mutation status is unknown but where there is an autosomal dominant predisposition to early onset colorectal cancer in the family, especially if the colorectal cancer has a high amount of microsatellite instability, or if endometrial cancer or another tumor characteristic of Lynch syndrome also has been diagnosed in the family.26 We also summarize the recommendations made by other experts for individuals with familial colorectal cancer not due to Lynch syndrome.

It is important to note that about 45% of families that fulfill strict Amsterdam criteria will not have evidence of a DNA mismatch repair gene mutation or deficiency of DNA mismatch repair in their tumor.27 These families (designated familial colorectal cancer type X) appear to have increased risks of colorectal cancer compared with the general population but lower risks than seen in those with Lynch syndrome. In 2 studies of such families, the colorectal cancers were reported to have occurred at older ages than in Lynch syndrome, rates of second primary tumors were lower, fewer tumors occurred in the proximal colon, and extracolonic cancer risks were not appreciably elevated.27,28 The optimal screening for familial colorectal cancer type X has not been defined and clinical judgment is required to determine if Lynch syndrome screening guidelines are appropriate based on the profile of cancer in the family, or if less aggressive screening may be advised.

Finally, there are other forms of familial colorectal cancer,13 including classic or attenuated familial adenomatous polyposis, sibships with homozgyous mutations in the mismatch repair genes, hamartomatous polyposis syndromes, and families with germline mutations in MYH,29,30 but guidelines for their management are beyond the scope of this review.

Risk of Cancer in Lynch Syndrome

Precise cumulative and relative risk estimates for Lynch syndrome–related cancers are not available. There is mounting evidence that the 4 most commonly mutated DNA mismatch repair genes, MLH1, MSH2, MSH6, and PMS2, are associated with different risks for cancer,31,32 but because of their low prevalence, aggregate risk data are often presented. Mutations in MLH1 and MSH2 account for about 90% of families with identified mutations.13,30 Genetic epidemiological data on MSH6 and PMS2 are limited. The frequencies of specific mismatch repair mutation variations are variable between different ethnic groups.41-48 Cancer risks for males and females are different. Families ascertained in high-risk clinics appear to have higher risks than gene carriers ascertained in the general population.30,49,50 Insufficient evidence is available to know if cancer risk varies by type of mutation within a given gene.51-53

Acknowledging these limitations, the estimated risk for colorectal cancer in those with mismatch repair gene mutations ascertained from high-risk clinics is 70% by age 70 years, with most studies reporting a mean age of diagnosis of the first cancer in the mid 40s compared with 64 years for colorectal cancer in the general population.11,23 In contrast, a recent population-based study of MLH1 and MSH2 mutation carriers identified a mean age at diagnosis closer to 54 years for men and 60 years for women.54 About two thirds of the colorectal cancers are right-sided.13,35 Several studies suggest higher colorectal cancer risks for men compared with women and higher risks in MLH1 mutation carriers than in MSH2 mutation carriers, whereas MSH2 carriers have greater risks for extracolonic tumors.33-35 Development of a second primary colorectal cancer is common in Lynch syndrome; 1 study reported a risk of 40% for a second primary colorectal cancer within 7 years of the first tumor.35 The colorectal cancer risk in MSH6 mutation carriers is reported to be about one third less than in MLH1 or MSH2 carriers and the average age at first diagnosis is older (54 years).36,37

The estimated lifetime risk for endometrial adenocarcinoma is 40% to 60%, with the mean age at diagnosis around age 50 years.22,24 Unlike colorectal cancer, endometrial cancer risk is not apparently lower in MSH6 mutation carriers.36,38

Studies have consistently reported modestly increased risks for cancers in additional sites including the stomach, ovary, urinary tract, hepatobiliary tract, brain, small intestine, and skin (sebaceous adenomas or carcinomas and keratoacanthomas) with a trend toward increased risks for pancreatic cancer.32-35 Of these sites, gastric cancer shows marked variation in risk between different populations. In Finland, with mostly MLH1 carriers, a cumulative risk was found to be 13% up to age 70 years with a mean age of 56 years.56 Vasen et al37 reported cumulative risks to age 70 years of 2.1% in MLH1 carriers and 4.3% in MSH2 carriers in the Netherlands. The gastric cancer risks are much higher in populations that have higher gastric cancer risks in the general population. A lifetime risk for gastric cancer has been cited as approximately 30% in Koreans with Lynch syndrome58 and in China, gastric cancer is second only to colorectal cancer in families with Lynch syndrome.59-61 Cancers of many other sites have been reported in families with Lynch syndrome (breast,62-63 prostate,64 rhabdomyosarcoma,65 dermatofibrosarcoma,66 leiomyosarcoma,97 carcinoid,98 malignant fibrous histiocytoma99), sometimes with tumors showing high amounts of micro-
satellite instability. No studies have been reported that verify that these sites are statistically more frequent than in the general population and they are not currently considered as diagnostic components of the Lynch syndrome disease spectrum.

Role of Clinicians and Clinical Cancer Genetic Services

Clinicians play an important role in the identification of high-risk individuals and provision of follow-up care to members of families with Lynch syndrome after a diagnosis has been made. Identification of high-risk individuals is facilitated by the collection of a family medical history and the construction of a 3-generation pedigree. The Web-based family history tool developed as part of the US Surgeon General’s Family History Initiative may be useful for collection of a complete family history. An increased likelihood of Lynch syndrome is suggested by the presence of 2 or more relatives with colorectal cancer, particularly if 1 was affected before age 50 years (Box 1 and Box 2). The presence of other cancers associated with Lynch syndrome, in particular, endometrial cancer, is also suggestive. When possible, the first step in the diagnostic process is evaluation of the tumor in an affected individual for deficiency of mismatch repair function (Figure). Specialists in cancer genetic risk assessment and counseling can provide assistance with counseling and interpretation of genetic test results. The National Cancer Institute’s Cancer Genetics Services directory provides a national resource for locating these specialists.

Recommendations from clinicians may play a crucial role in increasing adherence rates in this population. Noting that the rate of adherence to regular colonoscopic surveillance among high-risk populations is below recommended levels, and that there are often multiple individuals at high risk in a family with Lynch syndrome, the clinician can provide important assistance to patients by facilitating intrafamily communication and education.

Recommendations for Cancer Screening

Colonoscopy. Defining optimal colorectal screening in families with known or suspected Lynch syndrome poses challenges at several levels, including variable risk levels for family members, status of mismatch repair gene testing, and family history. For at least the past 15 years, recommendations for colorectal screening have centered on colonoscopy, and data on cancer incidence and mortality reduction following colonoscopy are now available (Table 1). In an observational cohort study of HNPCC families, Jarvinen et al demonstrated that in individuals undergoing prospective asymptomatic screening (mainly colonoscopy but some having barium enema), invasive colorectal cancer incidence was reduced by 62% compared with individuals from the same families who did not undergo routine surveillance. A follow-up study of the same individuals showed reduced mortality in those undergoing surveillance with colonoscopy compared with those not screened. Another study of 114 families with proven or suspected hereditary mismatch repair mutations showed that a screening interval of 2 years or less was required to diagnose colorectal cancer at an early stage. Frequent colonoscopy is performed because of high cancer risk, subtle endoscopic appearance of such tumors, and accelerated tumor growth characteristics reported in Lynch syndrome. Missing precursor adenomas and early cancers in the course of routine endoscopy has led to increased interest in the use of chromogens such as indigo carmine or methylene blue to improve mucosal contrast.

Based on available evidence about screening risk and screening outcomes, the following surveillance for colorectal cancers in Lynch syndrome is recommended (Table 2). Individuals with known or suspected mutation in a DNA mismatch repair gene or who are at risk based on a documented mutation in their family should be offered colonoscopy every 1 to 2 years, starting at the age of 20 to 25 years (age 30 years in families with MSH6). These recommendations are consistent with recommendations by other groups.

Recommendations for Non–Lynch Syndrome Colorectal Cancer Families. Data are not available on the efficacy of colonoscopy in reducing mortality among individuals from families with multiple cases of colorectal cancer in which mismatch repair gene mutations have not been found. Nonetheless, because of the recognized increased risk among such families, and data establishing the efficacy of colonoscopy in both average and high-risk populations, professional organizations recommend enhanced screening for these high-risk individuals. The recommendations vary by family history and screening interval. For example, the American Cancer Society recommends colonoscopy every 5 to 10 years for family members in which either colorectal cancer or adenomatous polyps were diagnosed before age 60 years in any first-degree relative or in 2 or more first-degree relatives at any age. Screening is recommended to begin at age 40 years or 10 years before the youngest case in the immediate family.

Endometrial Surveillance

The average age for the development of endometrial cancer in Lynch syndrome is around age 50 years (compared with a mean of 60 years in the general population). More than 75% of women with Lynch syndrome who develop endometrial cancer present with stage 1 disease, similar to sporadic endometrial cancer. In 1 study, the overall 5-year survival rate was 88%. Given the high survival rate, it is unclear if endometrial cancer screening would improve morbidity and mortality for women with Lynch syndrome. Endometrial screening can theoretically decrease the amount of treatment needed by detecting cancer at an earlier stage, when surgery alone can be curative.
CARE FOR PATIENTS WITH PREDISPOSITION TO CANCER

Unlike colorectal cancer screening, endometrial cancer screening of the general population has not been performed because of the low prevalence of disease in the general population, good overall survival rates, and the occurrence of postmenopausal vaginal bleeding as an early symptom. Therefore, there are no background data on the sensitivity or specificity of routine endometrial cancer screening. In women with Lynch syndrome, the lifetime risk of disease is high and many at-risk women are premenopausal, and it is unknown whether they will have recognizable irregular bleeding as an early symptom. Therefore, consideration of endometrial cancer screening in this high-risk population is reasonable.

Screening modalities that have been suggested include transvaginal ultrasound and endometrial sampling. Transvaginal ultrasound with measurement and evaluation of the endometrial lining has been examined in 2 studies of high-risk women. Both studies reported a lack of efficacy with a high false-positive rate. Endometrial biopsy allows physicians to obtain a histologic sample of the endometrium. This office procedure is performed without sedation using a narrow catheter inserted through the cervical canal, and has similar sensitivity as a dilatation and curettage in detecting endometrial abnormalities. No studies have reported on the efficacy of this modality as a screening tool. An endometrial biopsy is necessary in women with Lynch syndrome who report abnormal symptoms including irregular vaginal bleeding or postmenopausal bleeding. Based on the high lifetime risk of endometrial

<table>
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<tr>
<th>Source</th>
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<tr>
<td>Finland, 1995</td>
<td>Observational; High-risk persons invited to participate in colorectal cancer screening*</td>
<td>252 At-risk persons from 22 families†, 133 Had a 3-y colon examination; 118 Had no planned screening; 89% Compliance in screened group</td>
<td>Colorectal cancer found in 4.5% with planned screening vs 11.9% without planned screening; 62% Reduction in colorectal cancer attributed to polypectomy (P = .03); Tumor stage more favorable and no deaths in screened group compared with 5 colorectal cancer deaths in nonscreened group; Screening intervals and modality varied initially, but after 1986-1989, colonoscopy every 3 y</td>
<td>Fair‡</td>
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<tr>
<td>Finland, 2000</td>
<td>Observational; High-risk persons invited to participate in colorectal cancer screening*</td>
<td>Follow-up of 252 at-risk persons from 22 families†</td>
<td>Colorectal cancer in 8 screened (6%) and 19 unscreened (16%) equals a 62% reduction; Rates were 18% vs 41% in mismatch repair carriers; All colorectal cancers in screened group were early stage and did not lead to death; 9 Deaths occurred in unscreened group</td>
<td>Good§</td>
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<td>The Netherlands, 2002</td>
<td>Observational; Examined stage of colorectal cancer in screen-detected tumors vs screening interval; HNPCC family registry; 114 Families with mismatch repair defect or met clinical criteria; Had at least 1 screening examination or prior resection of colorectal cancer</td>
<td>35 New colorectal cancers found; Tumors found ≤2 y from examination were classified as lower stage; 10-y Cumulative risk of 15.7% after partial colectomy and 3.4% after subtotal colectomy; Recommended screening interval of ≤2 y</td>
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<td>Fair‡</td>
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<td>United Kingdom, 2005</td>
<td>Prospective, observational; 16-y Study of colorectal cancer in high-risk families to evaluate efficacy of colonoscopy</td>
<td>554 At-risk persons from 290 families with mismatch repair gene mutations and/or fulfilled Amsterdam criteria</td>
<td>1% Diagnosed with invasive colorectal cancer and 5% with high-risk adenomas when median of 3.3 y between colonoscopies; 72% Reduction in mortality attributed to colonoscopy</td>
<td>Fair‡</td>
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<td>United States, 2006</td>
<td>Retrospective; Analysis of gene carriers who had hysterectomy or salpingo-oophorectomy for prevention or benign indications vs gene carriers who did not have a hysterectomy or salpingo-oophorectomy</td>
<td>254 Women with mismatch repair gene mutation and who did not have a hysterectomy or salpingo-oophorectomy compared with 61 women who had a hysterectomy or salpingo-oophorectomy</td>
<td>Endometrial cancer in 0% of women with a hysterectomy or salpingo-oophorectomy vs 25% in those without one; Ovarian cancer in 0% of women with a hysterectomy or salpingo-oophorectomy vs 5% in those without one</td>
<td>Good§</td>
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Abbreviation: HNPCC, hereditary nonpolyposis colorectal cancer.

*Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

†Evidence includes consistent results from welldesigned, well-conducted studies in representative populations that directly assess effects on health outcomes.

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§Evidence includes consistent results from welldesigned, well-conducted studies in representative populations that directly assess effects on health outcomes.
cancer and the potential for screening to improve outcome, the following recommendation is made. Women with a known or suspected mutation in a DNA mismatch repair gene, or who are at risk based on a documented mutation in the family, should be offered annual endometrial biopsy beginning at age 30 to 35 years (Table 2). Transvaginal ultrasound likely has no role in screening for endometrial cancer premenopausally but may assist in evaluating the ovaries and is recommended annually. Additional studies are necessary to define the most appropriate and effective gynecological cancer screening for women with Lynch syndrome.

**Screening for Other Cancers**

Although the absolute risks of other cancers are lower than for cancers of the colorectum or endometrium, noncolorectal or nonendometrial cancers account in aggregate for about 30% of cancers in MLH1/MSH2 carriers, and perhaps 50% of the cancers in MSH6 carriers. Because the risk in any 1 organ is not extremely high, no standard screening recommendations have been developed, and no studies have been conducted to support additional surveillance. However, when clini-

| Table 2. Recommended Management for At-Risk Members of Families With Lynch Syndrome |
|-----------------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Type of Intervention**                     | **Recommendation**              | **Quality of Evidence Regarding Intervention*** | **Strength of Recommendation***  |
| Screening                                     |                                 | Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes† | Strongly recommended; There is good evidence that the guideline improves important health outcomes and concludes that benefits substantially outweigh harms |
| Colonoscopy Every 1-2 y beginning at age 20-25 y (age 30 y in MSH6 families, or 10 y younger than the youngest age at diagnosis in the family, whichever comes first) |                                 | Evidence is insufficient to assess the effects on health outcomes; | Insufficient evidence to recommend for or against; Evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined |
| Endometrial resection                         |                                 | Evidence is insufficient to assess the effects on health outcomes; | Insufficient evidence to recommend for or against; Evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined |
| Transvaginal ultrasound                       |                                 | Evidence is insufficient to assess the effects on health outcomes; | Insufficient evidence to recommend for or against; Evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined |
| Urinalysis with cytology                      |                                 | Evidence is insufficient to assess the effects on health outcomes; | Insufficient evidence to recommend for or against; Evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined |
| History and examination                       |                                 | Evidence is insufficient to assess the effects on health outcomes; | Insufficient evidence to recommend for or against; Evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined |
| Prophylactic surgery                          |                                 | Evidence is insufficient to assess the effects on health outcomes; | Insufficient evidence to recommend for or against; Evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined |
| Colorectal resection (segmental vs subtotal colectomy vs complete proctocolectomy) | For at-risk persons without colorectal neoplasia: generally not recommended, discuss as alternative to regular colonoscopy, with preferences of well-informed patient actively elicited; For persons with a diagnosed cancer or polyp not resectable by colonoscopy: subtotal colectomy favored with preferences of well-informed patient actively elicited | Evidence is insufficient to assess the effects on health outcomes; | Insufficient evidence to recommend for or against; Evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined |
| Hysterectomy or oophorectomy                  | Discuss as option after childbearing completed | Good-fair || No recommendation for or against; There is at least fair evidence that the guideline can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation |

*Adapted from the US Preventive Services Task Force’s 2-tier system† to assess the quality of evidence and to assign strength of recommendations in support of each guideline. †While the quality of evidence supporting colon examination is good, the optimal frequency and initiation age have not been adequately studied. ‡Because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. §Resection of a colon neoplasm is therapeutic, not prophylactic. At issue is the extent of resection—if greater than otherwise required by usual surgical considerations, then it carries an element of prophylaxis. Because all persons in this group will be undergoing surgery, there is opportunity to consider prophylactic removal of much or all of the colon. For women, the discussion should include option of having a hysterectomy or oophorectomy at the same time. ||Defined as evidence that includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
CARE FOR PATIENTS WITH PREDISPOSITION TO CANCER

Physicians encounter individuals or families in which a particular tumor may appear to be overrepresented, or familial concerns are heightened, screening is sometimes considered. This empirical approach, while pragmatic and reassuring to the physician and patient alike, has not been validated.

Based on evidence of cancer risk, the recommendations that appear in Table 2 are made. Individuals with confirmed or suspected mismatch repair gene mutations or their at-risk relatives should have a general examination on a regular basis, from the young adult years onward, with focus on careful review of systems and physical examination to elicit any unexplained signs or symptoms (abdominal pain, unexpected vaginal bleeding, skin lesions, adenopathy, etc) that merit further evaluation, and to update education on Lynch syndrome risk management.

Based on careful discussion of the risks and benefits, limitations, costs, and lack of demonstrated efficacy, there are additional screening tools to consider. An annual urinalysis with cytology is a noninvasive and relatively inexpensive means of evaluating the urinary tract, however, no data on efficacy is available in this population. Similarly, with an increased rate of gastric cancer, upper gastrointestinal tract endoscopy could be offered periodically. Some experts suggest this in families that have already experienced a member with gastric cancer, although there is no evidence that the presence of gastric cancer in a family indicates a predisposition above and beyond that known to be associated with having Lynch syndrome. Some experts, including some of the authors, have considered imaging of the upper abdomen, in light of the anatomic proximity of the liver, gall bladder, kidneys, ureter, and pancreas, all of which are at increased risk in Lynch syndrome. The impact of such screening is unknown. The optimal screening for noncolorectal or nonendometrial cancers in Lynch syndrome remains undefined and controversial.

Chemoprevention
Data from observational studies and randomized clinical trials have demonstrated the beneficial effects of nonsteroidal anti-inflammatory drugs and aspirin in reducing the incidence of sporadic colorectal adenomatous polyps and cancer. To date, the majority of research addressing the effectiveness of these agents among those at hereditary risk for colorectal cancer has focused on individuals with familial adenomatous polyposis. The efficacy of nonsteroidal anti-inflammatory drugs and aspirin on gastrointestinal tract disease burden among those with Lynch syndrome is unknown. Because these agents are associated with potential toxic effects that include upper gastrointestinal tract bleeding and renal insufficiency, evidence of an acceptable risk-to-benefit ratio should be available before nonsteroidal anti-inflammatory drugs or aspirin can be recommended for those with Lynch syndrome.

Oral contraceptives have been shown to decrease the risk of both endometrial cancer and ovarian cancer in the general population. There are currently no data addressing the efficacy of chemopreventive agents in reducing extracolonic cancers among those with Lynch syndrome, including gynecologic cancers.

Lifestyle Modification
Observational studies suggest that the adoption of healthy lifestyles and behaviors, particularly diet, physical activity, and weight control could have a substantial favorable impact on the national colon cancer burden. Dietary habits high in animal fats and low in fruits, vegetables, and fiber have been associated with an increased risk for cancers of the colon.

To date, there are minimal data addressing the impact of dietary or lifestyle habits on disease penetrance among those with Lynch syndrome. A randomized, placebo-controlled trial of oral calcium supplementation in individuals with Lynch syndrome failed to demonstrate a protective effect within the lower gastrointestinal tract as measured by changes in epithelial cell proliferation following 12 weeks of treatment. In a retrospective cohort study, tobacco use was associated with increased risk for colorectal cancer (hazard ratio of 1.43) whereas alcohol use did not alter colorectal cancer risk.

Although the impact of diet, exercise, and smoking cessation has not been fully explored among those with Lynch syndrome, the general health benefits of a diet rich in fruits, vegetables, and dietary fiber, combined with regular physical activity, weight control, and an avoidance of known carcinogens such as cigarettes are widely accepted. As such, it is recommended that individuals with Lynch syndrome be offered a balanced discussion of the potential benefits of dietary and lifestyle modifications on one’s overall health.

Prophylactic Surgery
Colectomy. There are anecdotal reports of prophylactic colectomy in Lynch syndrome. Strictly speaking, prophylactic colectomy involves the removal of an entirely normal-appearing colon. There is no formal research experience with this practice and there are no recommendations from expert panels for or against its use. Subtotal colectomy (the rectum is retained) or complete proctocolectomy (all of the colon and rectal mucosa are removed) have been considered or performed on the grounds of high neoplasia risk, combined with a patient-driven anxiety about cancer risk, or concern about safety of repeated colonoscopy. While the majority of colorectal cancer in Lynch syndrome develops in the right colon, the risk of rectal cancer is estimated as 11% in 1 study of 71 patients diagnosed a mean of 13 years after surgery. Long-term surveillance of the rectum after subtotal colectomy may be viewed by some patients as an acceptable alternative compared with retaining their colon and undergoing regular colonoscopy. The technical challenges of proctectomy with ileal-pouch anal anastomosis and quality of
life issues following such procedures have largely kept consideration of prophylaxis out of most discussions of surgical prophylaxis for patients with Lynch syndrome.

The issue of the extent of surgical resection when a cancer or endoscopically unresectable adenoma is identified has received considerable attention. 102-105 Here too, experience remains largely anecdotal. Recommendations for consideration of subtotal colectomy when performing surgery on an initial primary colon cancer are based on the subsequent increased risk of second (or more) primary cancers in the Lynch syndrome patient. Follow-up colonoscopy, otherwise standard after colon cancer resection, is the alternative to colectomy. No studies have formally compared outcomes of more standard, limited resections followed by periodic follow-up colonoscopy (as otherwise performed for sporadic tumors) vs subtotal colectomy.

For those with Lynch syndrome who will undergo surgical resection of a colon cancer, subtotal colectomy (as opposed to a segmental resection) is a reasonable choice and is favored but not proven to be superior to colonoscopic surveillance every 1 to 2 years (Table 2). Patient preference and issues related to compliance with screening will be major determinants in this decision. For those with gene mutations who have not had cancer or unresectable adenomas, colonoscopy appears to be the most reasonable option.

Hysterectomy and Oophorectomy. Given the high risk for endometrial cancer and the moderately increased risk for ovarian cancer, women with Lynch syndrome must decide between screening or prophylactic surgery. While there are no data regarding the efficacy of screening for gynecologic cancers in Lynch syndrome, there is evidence of efficacy for prophylactic surgery. Schmeler et al43 report on a retrospective cohort of 315 women who had mismatch repair gene mutations in which 61 had prophylactic surgery and were then followed up for approximately 10 years. No endometrial or ovarian cancers developed in those who had surgery whereas 33% of those who did not have surgery developed endometrial cancer and 5.5% developed ovarian cancer. These data indicate that prophylactic hysterectomy and oophorectomy is a reasonable option for those with Lynch syndrome, following a careful discussion of the risks, benefits, and limitations of this procedure (Table 2). Given the average age at diagnosis of gynecologic cancers, it may be reasonable to offer this option to women aged 35 years or older who do not want to preserve fertility. There are no specific or unique contraindications to hormone therapy related to a diagnosis of Lynch syndrome. In addition, in women with Lynch syndrome who need to undergo laparotomy for colon surgery, consideration should be given to concurrent prophylactic hysterectomy and oophorectomy.

FUTURE DIRECTIONS

The past 10 years have produced considerable basic science advances in the understanding of Lynch syndrome, the DNA mismatch repair genes, and their role in hereditary cancer susceptibility. Translation of these findings into clinically applicable information is now emerging but many questions remain. Large-scale studies are needed to better understand the cancer risks associated with each of the mismatch repair genes, and to begin to identify environmental factors that increase and reduce risks. Research is urgently needed to define optimal cancer screening techniques, initiation ages, and frequency of surveillance for colorectal and endometrial cancers, as well as for other associated cancers. Prospective clinical trials of chemoprevention and studies of the net risks and benefits of surgical options are also needed. Because Lynch syndrome is not common, multicenter collaborative studies will be required to achieve answers to these issues.

Author Affiliations: Departments of Medical Genetics (Dr Lindor and Petersen) and Health Sciences Research (Dr Petersen), Mayo Clinic College of Medicine, Rochester, Minn; Social and Behavioral Research Branch, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Md (Mr Hadley); Department of Medicine and Huntsman Cancer Institute, University of Utah, and Veterans Affairs Medical Center, Salt Lake City (Dr Kinney); Medical Oncology, Maine Center for Cancer Medicine and Blood Disorders and Maine Medical Center, Portland (Dr Miesfeldt); Departments of Gynecologic Oncology (Dr Lu) and Gastrointestinal Medicine and Nutrition (Dr Lynch), M. D. Anderson Cancer Center, University of Texas, Houston; Department of Medical History and Ethics, University of Washington, Seattle (Dr Burke); and Schools of Nursing and Medicine, Oregon Health and Science University, Portland (Dr Press).

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