Lynch Syndrome

Lynch syndrome, previously known as hereditary nonpolyposis colorectal cancer, is an autosomal dominant inherited cancer susceptibility syndrome caused by defects in the mismatch repair system. This system depends on a family of genes that are conserved across most living organisms and is responsible for repairing single-base mismatches that occur during DNA replication. In addition to colorectal cancer, hallmark diseases of Lynch syndrome include endometrial and ovarian cancer. Other tumors within the spectrum of Lynch syndrome include gastric cancer, small bowel cancer, hepatobiliary cancer, renal pelvis and ureter cancer, as well as some types of breast cancer, certain brain tumors, and sebaceous skin tumors (1–4). By identifying individuals at risk of Lynch syndrome through assessment of personal and family medical histories and genetic counseling and testing, when indicated, physicians are able to offer screening and prevention strategies to reduce morbidity and mortality from this syndrome.

Notably, the molecular abnormalities present in Lynch syndrome-associated tumors cause specific changes in the tumor tissue that can be detected by laboratory testing and, thus, identify the syndrome even in the absence of an informative family medical history. Because two of the most common types of cancer in Lynch syndrome occur in the female reproductive tract, obstetricians, gynecologists, and gynecologic oncologists are in a unique position to identify women who are at substantial risk of Lynch syndrome. The purpose of this document is to educate and provide an overview of Lynch syndrome because early identification of mutation carriers allows prevention of most Lynch syndrome-associated malignancies (5, 6).

Background

Dr. Aldred Scott Warthin first reported on a family with a hereditable aggregation of uterine and gastrointestinal neoplasms in 1913 (7). This kindred, identified as family G, was further expanded by Henry Lynch and colleagues in 1971 and 2005 (8, 9). At the time of the 2005 report, cancer history was available on 929 descendants spanning seven generations. Lynch, in addition to his work on family G, also further characterized this syndrome in a series of seminal reports starting in 1966 (10). Approximately 3–5% of cases of uterine cancer are attributable to a hereditary cause, whereas 8–13% of cases of ovarian cancer are likely inherited (11, 12). Lynch syndrome accounts for most cases of hereditary uterine and colorectal cancer and is the second most common cause of inherited ovarian cancer (after hereditary breast and ovarian cancer syndrome) (13). Lynch...
syndrome is a highly penetrant autosomal dominant inherited cancer condition characterized by defects in DNA mismatch repair and has a population prevalence of approximately 1 in 600 to 1 in 3,000 individuals (14, 15). The most common genes associated with Lynch syndrome are MLH1, MSH2, MSH6, and PMS2 (16). Deletions in the EpCAM gene also may lead to inactivation of MSH2 and result in Lynch syndrome (17). In one population-based study, the incidence of Lynch syndrome in women who presented with endometrial cancer was approximately 2.3% (18), which is comparable to the 2.2% incidence of Lynch syndrome in patients who present with colorectal cancer (19). Similar to other cancer predisposition syndromes, Lynch syndrome results in a substantially greater fraction of early-onset endometrial cancer and colorectal cancer. In women younger than 50 years, at least 5–9% of women with endometrial cancer and 5–7% of women with colorectal cancer will have a detectable deleterious repair gene mutation associated with Lynch syndrome (20–23).

Based on available data, the risk of colorectal cancer through age 70 years for women with Lynch syndrome is estimated to be 18–61%, compared with 1.7% in the general population (24). The risk of endometrial cancer through age 70 years for women with Lynch syndrome is estimated to be 16–61% and may equal or exceed their risk of colorectal cancer (13, 24). The risk of ovarian cancer through age 70 years for women with Lynch syndrome is estimated to be 5–10%, compared with approximately 1% in the general population, 39–46% in women with a BRCA1 mutation, and 12–20% in women with a BRCA2 mutation (25–27).

The risk of cancer varies according to the mismatch repair mutation. For example, in MLH1 mutation carriers, the risk of endometrial cancer is 20–54% by age 70 years (24). Carriers of an MSH2 mutation may have a slightly lower risk of endometrial cancer, which is reported to be 21–49% by age 70 years (24). For MSH6 mutation carriers, the cumulative risk of endometrial cancer is 16–61% by age 70 years and is notable for a later average age of disease onset (24, 28).

A retrospective review of women with gastrointestinal and gynecologic metastatic malignancies (ie, separate malignancies arising at different times) and documented Lynch syndrome found that in more than one half of cases, the gynecologic cancer was the presenting cancer (29). Importantly, when endometrial cancer was the presenting diagnosis, there was a median of 11 years before the diagnosis of colon cancer; thus, women’s health care providers frequently have the opportunity to identify women at risk and prevent subsequent metachronous Lynch syndrome-associated malignancies through implementation of appropriate risk-reduction strategies.

Cancer Characteristics

Women with Lynch syndrome-associated endometrial cancer have been compared with women with sporadic disease matched for age and stage of disease. Endometrial cancer that is associated with Lynch syndrome occurs at a significantly younger age (mean age, 47–49 years) than in the general population (30). It is, however, controversial as to whether Lynch syndrome-associated endometrial cancer is more likely to be associated with aggressive histologic subtypes or worse prognosis. In one study, researchers compared women with Lynch syndrome-associated endometrial cancer with two different groups: 1) women younger than 50 years with sporadic endometrial cancer and 2) women of all ages with endometrial cancer with sporadic loss of MLH1 expression caused by promoter younger than 50 years methylation (30). Within the Lynch syndrome group, there was a trend toward nonendometrioid histology, and despite earlier disease stage, approximately one quarter of patients had pathologic characteristics that would have warranted adjuvant therapy after hysterectomy. However, in an earlier study that compared 50 patients with Lynch syndrome-associated endometrial cancer with 100 controls matched for age and disease stage, the distribution of histologic subtypes and the 5-year survival rate were not statistically different between the two groups (31).

Women with Lynch syndrome-associated ovarian cancer also have a younger mean age of diagnosis (mean age, 42–49 years) but, interestingly, earlier disease stage on presentation compared with women with sporadic ovarian cancer (32). These researchers also reported that endometrioid and clear cell histologies are overrepresented compared with sporadic ovarian cancer (32). Of note, another group of researchers reported a 22% incidence of synchronous endometrial primaries in the setting of Lynch syndrome-associated ovarian cancer (33). In terms of survival, in a study that compared 26 patients with Lynch syndrome-associated ovarian cancer with 52 controls matched for age and disease stage, the 5-year survival rate was not statistically different between the two groups. However, this study was limited by small numbers and underrepresentation of the serous subtype in both groups (34).

Pathogenesis of Lynch Syndrome-Associated Cancer

Defects in mismatch repair are the fundamental etiology of the genomic instability that allows the development of the types of cancer seen in Lynch syndrome and is essential to understanding genetic testing for Lynch syndrome. This genomic instability is not limited to coding...
regions of genes, but instead affects the entire genome, including noncoding single nucleotide and dinucleotide repeats scattered throughout the DNA. These noncoding single nucleotide and dinucleotide repeats are termed microsatellites. For patients with defects in mismatch repair, the insertion or deletion of additional nucleotides into or from these microsatellites leads to a phenomenon called microsatellite instability.

Although almost all Lynch syndrome-associated tumors demonstrate microsatellite instability, microsatellite instability also can result from noninherited methylation of the MLH1 promoter (35). This is a common phenomenon in noninherited endometrial and colorectal cancer and is seen in 20–30% of cases of endometrial cancer and 15–20% of cases of colon cancer (36, 37). Determining whether microsatellite instability is secondary to MLH1 promoter methylation or a germline mutation in one of the mismatch repair genes is one of the challenges of testing potential Lynch syndrome-associated tumors.

### Risk Assessment

For obstetrician–gynecologists, a number of clinical criteria and tumor features can be used to identify individuals at risk of Lynch syndrome. Before the availability of genetic testing, the Amsterdam Criteria, developed in 1990, were used to identify families for research studies of Lynch syndrome (38). These criteria demonstrate high specificity, but because of their low sensitivity they were not useful as referral guidelines. One of the limitations of these initial criteria was that extracolonic malignancies were not included as defining diagnoses. To address this issue, these criteria were revised to include extracolonic cancer in 1999 (39). Although these revised criteria remained quite specific for Lynch syndrome, they were still not adequately sensitive for clinical use, with only 13–36% of families in population-based studies with molecularly confirmed Lynch syndrome meeting these criteria (19, 22).

Given the limitations of the Amsterdam Criteria, the Bethesda Guidelines were developed in 1997, and subsequently revised in 2004, to provide more clinically useful recommendations for which patients with colorectal cancer should be considered for further evaluation of Lynch syndrome (40, 41). These criteria incorporate age of diagnosis, tumor characteristics, and personal and family cancer history. In contrast to the Amsterdam Criteria, the Bethesda Guidelines have a relatively high sensitivity but low specificity for identifying individuals with Lynch syndrome. Furthermore, neither the initial nor the revised Bethesda Guidelines identify which patients with endometrial tumors should undergo evaluation for mismatch repair defects. To address this limitation, some authors have proposed modification to the 2004 Bethesda Guidelines to include endometrial cancer as a sentinel cancer (Box 1) (23, 42).

### Testing for Lynch Syndrome

There are two methods of testing for a dysfunctional mismatch repair system: 1) direct germline DNA testing and 2) tumor testing using immunohistochemistry or microsatellite instability testing. Direct germline DNA testing involves sequencing and screening for large rearrangements of the relevant mismatch repair genes. In addition, although identification of a deleterious mutation on direct gene screening conclusively proves the

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**Box 1. The 2004 Bethesda Guidelines (Modified to Include Endometrial Cancer as a Sentinel Cancer) to Identify Individuals With Colorectal or Endometrial Cancer for Whom Genetic Risk Assessment Is Recommended**

- Patients with endometrial or colorectal cancer diagnosed before age 50 years
- Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor* at any age
- Patients with colorectal cancer with tumor-infiltrating lymphocytes, peritumoral lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern diagnosed before age 60 years
- Patients with endometrial or colorectal cancer and a first-degree relative with a Lynch/HNPCC-associated tumor* diagnosed before age 50 years
- Patients with colorectal or endometrial cancer diagnosed at any age with two or more first-degree or second-degree relatives with Lynch/HNPCC-associated tumors*, regardless of age

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Abbreviation: HNPCC, hereditary nonpolyposis colorectal cancer.

*Lynch/HNPCC-related tumors include 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.

†First-degree relatives are parents, siblings, and children. Second-degree relatives are aunts, uncles, nieces, nephews, grandparents, and grandchildren.

presence of Lynch syndrome, the absence of a deleterious mutation does not exclude Lynch syndrome. Given this, most centers begin the molecular evaluation of individuals at risk of Lynch syndrome with tumor testing using immunohistochemistry or microsatellite instability testing.

**Immunohistochemistry**

Tumor testing using immunohistochemistry to evaluate for the expression of the four mismatch repair genes (by detection of the presence of their protein products) is a relatively inexpensive test and is available through most pathology laboratories. Further, immunohistochemistry allows identification of which mismatch repair proteins are absent and can guide subsequent direct germline DNA testing. If all four mismatch proteins are present, it rules out the presence of Lynch syndrome in almost all cases. The scenario in which the presence of all four mismatch repair proteins does not rule out Lynch syndrome is the relatively uncommon situation in which a deleterious mutation allows the production of a full-length but nonfunctional mismatch repair protein. Therefore, in the setting of a very high clinical suspicion of Lynch syndrome and normal immunohistochemical testing results, the tumor can be further evaluated by microsatellite instability testing.

**Microsatellite Instability Testing**

Tumor testing for microsatellite instability requires the availability of normal tissue and tumor tissue from the patient with a potential Lynch syndrome-associated tumor. By comparing normal and abnormal tissue, a diagnostic molecular genetics laboratory can determine if there has been insertion or deletion of nucleotides to informative microsatellites. To test for microsatellite instability, many laboratories use a panel of five microsatellites recommended by the National Cancer Institute (41). If no microsatellite instability is detected, this essentially rules out the presence of Lynch syndrome.

**MLH1 Promoter Methylation Testing**

Testing for methylation of the MLH1 promoter is needed when the results of immunohistochemical testing reveal the absence of the MLH1 protein (with or without the absence of the PMS2 protein) or when microsatellite instability is present. Neither of these abnormal findings is diagnostic of Lynch syndrome because approximately 15–20% of cases of colorectal cancer and 20–30% of cases of endometrial cancer will have silencing of MLH1 that is due to noninherited methylation of the MLH1 promoter (36, 37). This will lead to microsatellite instability and the absence of the MLH1 protein, the PMS2 protein, or both proteins (because the two proteins exist as a heterodimer in the cell). In order to determine if these abnormalities are due to either a noninherited methylation of the MLH1 promoter or a germline DNA mutation in MLH1 or PMS2, a diagnostic molecular genetics laboratory can directly assess the potential Lynch syndrome-associated tumor for methylation of the MLH1 promoter. When the MLH1 protein is absent and there is methylation of MLH1 promoter, then Lynch syndrome is excluded. When the MLH1 protein is absent and there is no methylation of the MLH1 promoter, then the patient requires germline DNA testing for Lynch syndrome.

**Clinical Considerations and Recommendations**

- **How should women with a personal medical history of endometrial cancer or colon cancer be evaluated for Lynch syndrome?**

  Approximately 2–3% of cases of endometrial and colon cancer are attributable to Lynch syndrome and will have a molecular signature of absent mismatch repair gene expression. This proportion increases to 5–13% of endometrial or colorectal tumors in women in whom these types of cancer are diagnosed before age 50 years. Given the substantial fraction of endometrial and colorectal tumors that are attributable to Lynch syndrome, some systematic approach to identifying women with cancer who are also at risk of Lynch syndrome likely is appropriate. Obstetric and gynecologic physicians and practices should adopt one of the following three approaches for assessing the possibility of Lynch syndrome in a woman personally affected with colorectal or endometrial cancer.

  1. Perform tumor testing on any endometrial or colorectal tumor from a woman identified to be at risk of Lynch syndrome through a systematic clinical screen that includes a focused personal and family medical history.

     A number of systematic clinical screens that incorporate a focused personal and family medical history to identify tumors that are potentially secondary to Lynch syndrome have been described (42–45). One of the more commonly used screens is the 2004 Bethesda Guidelines modified to include endometrial cancer as a sentinel cancer (Box 1). A simple four-item checklist completed by a woman who has a new diagnosis of endometrial cancer also has been described (43). The specific systematic clinical screen that is appropriate for a given physician or practice will depend on a number of factors,
including the availability of genetic counselors, local pathology resources, literacy of patients, and cost.

2. Perform tumor testing on all endometrial or colorectal tumors irrespective of age of diagnosis.

Although this approach is clearly the most sensitive, it also is the least specific. Arguments in favor of universal testing irrespective of age are that approximately 12–30% of Lynch syndrome-associated cases of endometrial and colorectal cancer will not meet the 2004 Bethesda Guidelines modified to include endometrial cancer as a sentinel cancer (18, 19, 46). However, this incremental sensitivity comes at the cost of requiring tumor testing on three to four times as many patients (46).

3. Perform tumor testing on all endometrial or colorectal tumors diagnosed before age 60 years.

As previously noted, it is estimated that 5–13% of cases of endometrial and colorectal cancer diagnosed before age 50 years and 3–5% of cases of endometrial and colorectal cancer diagnosed between age 50 years and 60 years are due to Lynch syndrome. Given operational challenges of incorporating systematic clinical screens that incorporate personal and family medical histories into pathology workflow and the decreased specificity and increased costs of performing tumor testing on all endometrial and colorectal cancer cases, regardless of age of diagnosis, several groups have suggested performing tumor testing on all endometrial or colorectal cancer cases diagnosed before age 60 years. In March 2014, this approach was endorsed by the Society of Gynecologic Oncology as an acceptable option for the screening of Lynch syndrome in patients with endometrial cancer (47).

Which of the previously mentioned approaches makes the most sense for a given practice will be determined by a number of factors, including local pathology and diagnostic molecular genetics resources, availability of genetic counseling, and cost. Further, regardless of which approach is chosen, reliable methods will need to be established to ensure systematic screening is performed and that results of tissue-based genetic risk assessment are tracked and transmitted (48, 49).

- **Which women without cancer should be offered hereditary cancer risk assessment for Lynch syndrome?**

Genetic risk assessment should be considered for unaffected women who have a first-degree relative affected with endometrial or colorectal cancer who was either diagnosed before age 60 years or who is identified to be at risk of Lynch syndrome by one of the systematic clinical screens that incorporates a focused personal and family medical history. For women without a personal history of malignancy, a pattern of repeated generations of Lynch syndrome-associated cancer, especially those diagnosed at a young age (before 60 years) should be recognized as a potential proband from a Lynch syndrome pedigree. From a clinical standpoint, it likely makes sense to focus primarily on individuals who are first-degree relatives (ie, parent, sibling, or child) of an individual affected with endometrial or colorectal cancer who was either diagnosed before age 60 years or who is identified as being at risk of Lynch syndrome by one of the systematic clinical screens that incorporates a focused personal and family medical history, such as the modified Bethesda criteria. However, in the presence of a family in which there are either few individuals who reached advanced age; a paucity of female relatives; or multiple individuals in a lineage who had hysterectomy or oophorectomy, it may be reasonable to offer genetic risk assessment to an unaffected individual who is more distant from an affected relative. In addition, women from families with a known mutation in a DNA mismatch repair gene who could have potentially inherited the familial mutation also should be offered genetic risk assessment (and, if needed, germline DNA testing) for Lynch syndrome, irrespective of their degree of relatedness to the affected family member.

- **What issues should be addressed during genetic risk assessment?**

Genetic risk assessment for Lynch syndrome is a process that includes assessment of personal and family medical histories and may include tumor testing, germline DNA testing, or both. Although pretest counseling before germline DNA testing is strongly advocated, there is substantial controversy regarding what is the appropriate counseling, if any, that is required before indirect tumor testing of surgical specimens using immunohistochemistry or microsatellite instability testing. Although some centers have advocated that tumor testing should not be performed until formal genetic counseling has been conducted, this approach is impractical in all but the largest centers if a pathology-based triage program using indirect testing is to be implemented. Further, because only a small fraction of patients undergoing surgery for endometrial cancer will have abnormal tumor testing results, universal genetic counseling before genetic testing would put additional strains on already limited cancer genetic counseling resources. Given these issues, it likely makes sense to explain to patients who are undergoing surgery for endometrial cancer and who meet the...
local criteria for tumor testing that this testing will be performed, and that if the results are abnormal, formal genetic risk counseling with possible germline DNA testing will be recommended. As part of this discussion, it may be helpful to provide patients with written educational materials explaining the rationale and approach of the local tissue testing protocol.

If germline DNA testing is to be performed, pretest counseling should include a discussion of possible outcomes of testing—specifically addressing the issues of positive, negative, and uninformative test results, including variants of unknown significance. Options for surveillance, chemoprevention, and risk-reducing surgery also should be discussed before testing. Further, possible psychologic and familial implications of test results should be considered.

Genetic testing should be performed by someone who has appropriate training and experience in cancer genetics and counseling. It is the job of the professional providing counseling to obtain and assess relevant information concerning an individual’s risk and to provide information and support to families and individuals who may be at increased risk. Genetic counselors, medical geneticists, and other cancer genetics professionals are available to assist and should be consulted in complex cases.

Genetic counseling also should include a discussion of the cost of genetic testing. Medicare and other insurance companies have written guidelines for covering the cost of genetic testing. An important aspect of genetic counseling is discussion of current legislation regarding genetic discrimination and the privacy of genetic information. The federal Genetic Information Nondiscrimination Act of 2008 protects individuals against health and employment discrimination based on genetic information. It does not apply to other forms of insurance, which may include life or disability insurance.

What specific genetic test should be used to evaluate for Lynch syndrome?

Whenever possible, molecular evaluation for Lynch syndrome should begin with tumor testing. This allows individuals who do not have Lynch syndrome to be ruled out and focuses germline testing on individuals at highest risk.

Personal or Family Medical History of Lynch Syndrome-Associated Cancer When Tumor Tissue Is Available

If the patient seeking genetic risk assessment has a personal history of a colorectal or endometrial cancer, and tumor tissue is available, testing should begin on this specimen. If the patient seeking genetic risk assessment is unaffected, every effort should be made to obtain a tissue block from a Lynch syndrome-associated cancer in an affected relative. Genetic counselors and other genetics professionals can frequently assist with this process.

Normal immunohistochemical testing results that indicate the presence of all four mismatch repair proteins in an appropriate tumor specimen effectively rules out the presence of Lynch syndrome in most cases. It will not, however, rule out Lynch syndrome caused by a missense mutation that leads to the production of a full-length but nonfunctional protein. This possibility should be considered in patients who have highly suspicious personal and family medical histories but have normal immunohistochemical testing results. In these cases, microsatellite instability testing, the results of which will be abnormal in the setting of Lynch syndrome, can be used to help clarify the clinical scenario.

If either the MLH1 or PMS2 protein is not present and no methylation of the MLH1 gene promoter is detected, the performance of germline DNA testing of the MLH1 gene, the PMS2 gene, or both is recommended after appropriate patient counseling. When doing this testing, it is important to remember that the MLH1 and PMS2 proteins operate as a heterodimer in the cell and that absence of the PMS2 protein can indicate either abnormal MLH1 or PMS2 gene function. Similarly, if either the MSH2 or MSH6 protein is not present, the performance of germline DNA testing of the MSH2 gene, the MSH6 gene, or both is recommended after appropriate patient counseling. In the cell, the MSH2 and MSH6 proteins also operate as a heterodimer. Therefore, the absence of the MSH6 protein can indicate loss of function of either the MSH2 gene or the MSH6 gene.

Figure 1 illustrates the flow of immunohistochemical-based endometrial tumor testing for mismatch repair gene expression to assess for the possibility of Lynch syndrome.

Personal or Family Medical History of Lynch Syndrome-Associated Cancer When Tumor Tissue Is Not Available

If tumor tissue from a Lynch syndrome-associated cancer is not available from the patient or a close family member, germline DNA testing of the mismatch repair genes may be considered after counseling. In this setting, the finding of a deleterious germline DNA mutation confirms the presence of Lynch syndrome. However, the absence of a germline DNA mutation does not exclude the syndrome, and management in these cases needs to be guided by the family medical history.
Endometrial or colorectal cancer tissue

Immunohistochemical testing for MLH1, MSH2, MSH6, and PMS2 proteins

- All mismatch repair proteins present
- MLH1 protein absent (with or without loss of PMS2 protein)
  - MLH1 promoter methylation
    - Methylation absent
      - Germline DNA testing based on protein absence
        - Mutation identified
          - Lynch syndrome
        - No mutation identified
          - Individualized management based on personal and family medical history
  - Methylation present
    - Not Lynch syndrome
- MSH2, MSH6, or PMS2 protein absent

**Tumor Testing Results Are Suspicious for Lynch Syndrome, but Germline DNA Testing Results Are Normal**

Germline DNA tests will not identify a causative mutation in 10–15% of cases of endometrial cancer with loss of either MLH1 or PMS2 gene expression and in 35–40% of cases of endometrial cancer with loss of either MSH2 or MSH6 gene expression. In the setting of suspicious tumor test results but normal germline DNA test results, consultation with a genetics professional may be helpful in determining appropriate management for the patient and her close family members. Similarly, in the setting of a particularly suspicious family medical history, even in the setting of normal results from tumor studies and germline DNA testing, follow-up with a genetics professional also may be helpful.

**How should women with Lynch syndrome be counseled to reduce their risk of endometrial and ovarian cancer?**

Women with Lynch syndrome have several options for screening and surveillance (Box 2). Options for risk reduction include chemoprevention and prophylactic hysterectomy with bilateral salpingo-oophorectomy.

**Screening**

Endometrial cancer screening is not performed in the general population because of the low prevalence of disease, typical early stage of presentation, and recognized symptoms of abnormal uterine bleeding. However, Lynch syndrome-associated endometrial cancer may reduce in the population.
occur 10–15 years earlier than the mean age of diagnosis in women with sporadic endometrial cancer. In addition, Lynch syndrome-associated endometrial cancer frequently occurs in the premenopausal years. Therefore, irregular bleeding may be less likely to be evaluated in women at risk of Lynch syndrome-associated endometrial cancer, and a strategy of surveillance is appropriate to consider.

To date, there are no proven cost-effective screening strategies for early detection of endometrial or ovarian cancer, even in high-risk populations. Limitations of studies of cancer surveillance in patients with possible Lynch syndrome include the small number of patients studied and substantial heterogeneity among the patients studied. For example, some studies have included only patients with germline DNA mutations; other studies have included families who met the Amsterdam Criteria but lacked a proven germline mutation; and yet other studies have included families with Lynch syndrome-associated cancer that neither met the Amsterdam Criteria nor had a proven germline mutation.

In one of the earlier studies evaluating endometrial cancer surveillance in Lynch syndrome, annual or biennial transabdominal or transvaginal ultrasonography had poor sensitivity in detecting endometrial cancer, but two cases of interval early-stage cancer did present with symptoms (50). More recently, endometrial cancer surveillance using random endometrial biopsy at intervals of 1–3 years has resulted in a detection rate of hyperplasia or carcinoma of approximately 5% (51, 52). Although these data have not been validated to improve endometrial cancer stage or mortality, until further data are available, endometrial biopsy every 1–2 years, starting at age 30–35 years, is recommended for women with Lynch syndrome. Further evaluation also is recommended in women with Lynch syndrome who have a change in their normal bleeding pattern. Combined colon cancer screening and endometrial cancer screening under conscious sedation also has been demonstrated to be a feasible, highly acceptable option for women with Lynch syndrome (53).

There is no consensus on ovarian cancer surveillance in women with Lynch syndrome. Further, results of ovarian cancer surveillance in women with BRCA1 and BRCA2 mutations may not be applicable in Lynch syndrome because the biology of ovarian cancer in Lynch syndrome significantly differs from that of ovarian cancer seen in hereditary breast and ovarian cancer syndrome (32, 33). In the largest gynecologic cancer surveillance study to date, neither ultrasonography nor CA 125 testing led to the diagnosis of ovarian cancer in any of the 175 Lynch syndrome mutation carriers screened. However, there were four cases of endometrioid ovarian carcinoma diagnosed as either an interval cancer or an incidental finding at the time of an unrelated surgery (51). Given these data, it is unclear whether screening with transvaginal ultrasound or CA 125 is effective in women with Lynch syndrome.

**Chemoprevention**

Oral contraceptives are known to be chemopreventive agents for endometrial carcinoma and can reduce endometrial cancer risk in the general population by up to 50% (54, 55). Progestin therapy also is effective in the treatment of endometrial hyperplasia and early endometrial cancer (56, 57). Although specific data on either of these agents’ efficacy in the prevention of Lynch syndrome-associated endometrial cancer are lacking, a short-term study using surrogate biomarkers in women with Lynch syndrome suggested that 150-mg depot medroxyprogesterone acetate as well as 30-micrograms ethinyl estradiol/0.3-mg norgestrel oral contraceptives demonstrated a decrease in endometrial proliferation (58). Thus, progestin-based contraception, including oral contraceptives, may be considered for chemoprevention of endometrial cancer in women with Lynch syndrome. Additional studies using the levonorgestrel intrauterine system have been proposed.

**Risk-Reducing Surgery**

Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option for women with Lynch syndrome who have completed childbearing. A multicenter retrospective study of 61 women with Lynch syndrome who had undergone hysterectomy, matched to 210 controls with Lynch syndrome, demonstrated that the incidence of endometrial cancer was significantly reduced by hysterectomy (33% to 0%) after a mean follow-up time of 7 years (6). Similarly, after an 11-year mean follow-up, the risk of ovarian cancer after bilateral salpingo-oophorectomy was 0% compared with 5.5% in the control group (6).

Postoophorectomy primary peritoneal carcinoma has been observed in women with Lynch syndrome, but the magnitude of this risk is unclear (59). Hormone therapy may be considered for symptomatic surgical menopause, although this intervention has not been specifically studied in patients with Lynch syndrome.

**At what age should risk-reducing hysterectomy and salpingo-oophorectomy be considered in women with Lynch syndrome?**

The estimated endometrial cancer risk by age 40 years in women with Lynch syndrome is approximately 2–4%, and the estimated ovarian cancer risk is approximately 1–2%; by age 50 years, this risk increases to 8–17% and
3–7%, respectively (60, 61). In general, risk-reducing hysterectomy and salpingo-oophorectomy should be discussed with the patient by their early to mid-40s. Several models have been developed to consider the cost-effectiveness of risk-reducing surgery compared with surveillance for Lynch syndrome. In these studies, risk-reducing hysterectomy and salpingo-oophorectomy on completion of childbearing led to the lowest cost and the greatest increase in quality-adjusted life years (62, 63). However, issues regarding risks and benefits of prophylactic surgery, medical management of menopause, and desire for future fertility may influence a woman’s decision making.

How should risk-reducing hysterectomy and salpingo-oophorectomy be performed?

Surgical removal of the uterus and adnexa may be accomplished through a vaginal or minimally invasive approach. Before hysterectomy, colonoscopy screening should be up-to-date. In a patient with Lynch syndrome undergoing surgery for colorectal cancer, a synchronous gynecologic surgery also may be considered.

Occult endometrial lesions have been found at the time of prophylactic hysterectomy (64, 65). Given this, preoperative endometrial sampling is indicated, and opening the uterine specimen for intraoperative examination of the endometrium may be considered. For women considering hysterectomy without oophorectomy, complete resection of the fallopian tubes is still advised because occult tubal malignancies also have been reported (66).

Because colorectal cancer may precede a diagnosis of Lynch syndrome, some women may have previously undergone bowel surgery or pelvic irradiation, which may complicate an elective risk-reducing surgical procedure. It is important to discuss the risks and benefits of surgery versus its effect on cancer risk and mortality when counseling these women.

How should women with Lynch syndrome be counseled to reduce the risk of colon cancer as well as other types of noncolonic cancer?

All women with Lynch syndrome should undergo colonoscopy every 1–2 years, starting at age 20–25 years or 2–5 years before the earliest colon cancer diagnosis in the family, whichever is earlier (67, 68). Colorectal cancer surveillance has been demonstrated to reduce mortality in individuals with Lynch syndrome (5). In a Finnish study that compared colonoscopy or flexible sigmoidoscopy and barium enema every 3–5 years with no screening, the incidence of colorectal cancer was reduced from 41% (19 of 46) in the control group to 18% (8 of 44) in the study group (P=.02) over a median follow-up of 15 years (5). From a chemoprevention standpoint, taking 600 mg of aspirin daily for more than 2 years also may reduce colorectal cancer incidence in women with Lynch syndrome; however, data on long-term adverse events and effect on mortality are not yet available (68).

Other methods of cancer screening that may be considered in the surveillance of unaffected women with Lynch syndrome include esophagoduodenoscopy and urine cytology, although the effect of these approaches on cancer mortality is not yet known (67, 69). Until further information is available, breast cancer screening in women with Lynch syndrome should be in accordance with the American College of Obstetricians and Gynecologists’ routine breast cancer screening guidelines for all women (70).

Summary of Recommendations

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Obstetric and gynecologic physicians and practices should adopt one of the following three approaches for assessing the possibility of Lynch syndrome in a woman personally affected with colorectal or endometrial cancer:
  1. Perform tumor testing on any endometrial or colorectal tumor from a woman identified to be at risk of Lynch syndrome through a systematic clinical screen that includes a focused personal and family medical history.
  2. Perform tumor testing on all endometrial or colorectal tumors irrespective of age of diagnosis.
  3. Perform tumor testing on all endometrial or colorectal tumors diagnosed before age 60 years.

- Genetic risk assessment should be considered for unaffected women who have a first-degree relative affected with endometrial or colorectal cancer who was either diagnosed before age 60 years or who is identified to be at risk of Lynch syndrome by one of the systematic clinical screens that incorporates a focused personal and family medical history.

- Whenever possible, molecular evaluation for Lynch syndrome should begin with tumor testing.

- Endometrial biopsy every 1–2 years, starting at age 30–35 years, is recommended for women with Lynch syndrome. Further evaluation also is recommended in women with Lynch syndrome who have a change in their normal bleeding pattern.
Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option for women with Lynch syndrome who have completed childbearing. In general, risk-reducing hysterectomy and salpingo-oophorectomy should be discussed with the patient by their early to mid-40s.

All women with Lynch syndrome should undergo colonoscopy every 1–2 years, starting at age 20–25 years or 2–5 years before the earliest colon cancer diagnosis in the family, whichever is earlier.

The following recommendation is based primarily on consensus and expert opinion (Level C):

- Progestin-based contraception, including oral contraceptives, may be considered for chemoprevention of endometrial cancer in women with Lynch syndrome.

**Proposed Performance Measure**

Percentage of women with Lynch syndrome who have had a colonoscopy within 2 years of the diagnosis of Lynch syndrome

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists’ own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–June 2014. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.