The genetic basis of Lynch syndrome and its implications for clinical practice and risk management

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Abstract: Lynch syndrome is the most common cause of hereditary colon cancer, and accounts for as much as 3% of all colon and endometrial cancers. The identification and management of individuals with Lynch syndrome have evolved over the past 20 years, yet the syndrome remains vastly underdiagnosed. It is important for clinicians to recognize individuals and families who are at risk in order to be able to manage them appropriately and reduce their morbidity and mortality from this condition. This review will touch on the history of Lynch syndrome, the current knowledge of genotype–phenotype correlations, the cancers associated with Lynch syndrome, and management of individuals who are gene carriers.

Keywords: Lynch syndrome, hereditary cancer, hereditary nonpolyposis colorectal cancer, mismatch repair, mismatch repair genes, immunohistochemistry, microsatellite instability

Overview and genetic basis

Lynch syndrome is a dominantly inherited cancer syndrome in which predisposition to colorectal, endometrial, and other cancers occurs due to an underlying defect in the cellular mismatch repair (MMR) system. MMR proteins form a complex that detects and corrects replication errors. A compromised MMR system leads to accelerated accumulation of somatic mutations, often resulting in carcinogenesis.

MLH1, MSH2, MSH6, and PMS2 are among the genes that produce MMR proteins. Lynch syndrome is caused by a heritable mutation in one copy of an MMR gene. At a phenotypic level, Lynch syndrome is dominant with variable expressivity. Secondary, somatic loss of the corresponding normal allele compromises the function of the entire MMR complex; Lynch syndrome is therefore recessive at the cellular level. An estimated 70%–90% of Lynch syndrome is attributable to deleterious mutations in MLH1 and MSH2, with the remaining 10%–30% distributed approximately equally between MSH6 and PMS2.¹⁻³ Up to 3% of Lynch syndrome is due to mutations in the EPCAM gene, which is involved in epithelial cell adhesion, cell signaling, and proliferation. EPCAM is directly upstream of MSH2, and deletions of the 3’ end of EPCAM result in epigenetic hypermethylation of the MSH2 promoter, causing Lynch syndrome.⁴

Lynch syndrome exhibits characteristic features of cancer predisposition syndromes, including substantially elevated risks for specific cancers, earlier onset, high rates of multiple primary cancers, and the absence of typical risk factors. Cancers associated with Lynch syndrome include colorectal, endometrial, ovarian, stomach, hepatobiliary, urinary, small bowel, brain/central nervous system, and sebaceous tumors. Cancer risks are strongly influenced by which MMR gene mutation is pres-
ent but may also vary substantially between and within families, due to broader influences of the genome and gene–environment interaction.

**Historical perspective and evolution of descriptive terms**

The first colorectal cancer syndrome to be well characterized was called familial adenomatous polyposis (FAP) and was characterized by very early onset, massively prolific development of colorectal polyps. Later, when high rates of colorectal cancer were observed in some families in the absence of florid polyposis, the term “hereditary nonpolyposis colorectal cancer” (HNPCC) was used to describe this new clinical entity, distinguishing it from the previously recognized FAP. Based on clinical observations, the association of colorectal cancers with brain tumors was named Turcot syndrome, and colorectal cancers associated with sebaceous neoplasms and keratoacanthomas were termed Muir–Torre syndrome. Identifying the underlying molecular etiology led to the realization that Turcot syndrome with colorectal cancer and glioblastoma is due to an MMR deficit. Muir–Torre is also caused by underlying MMR defects, and both conditions are now recognized as part of the broader clinical spectrum of Lynch syndrome.

HNPCC became defined by an evolving series of criteria. The first was published in 1991 after an international meeting of researchers and clinicians (the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer) in Amsterdam, the Netherlands. The Amsterdam criteria, which can be remembered using a “3–2–1” mnemonic, were intended to more precisely define a homogeneous population for research purposes. The Amsterdam criteria describe families who do not have FAP and in which three closely related individuals spanning at least two generations have had colorectal cancer, with at least one diagnosis occurring prior to age 50 years. “Closely related” is defined as one of the affected trio being a first degree relative of the other two. With increasing recognition of the extracolonic manifestations of Lynch syndrome over the next decade, criteria were revised in 1999 to include extracolonic cancers.

The Amsterdam and revised Amsterdam criteria were developed with emphasis on specificity rather than sensitivity, and were intended for use as research criteria. Nevertheless, they became widely used clinically to identify high-risk families, with an estimated sensitivity and specificity of 60% and 70%. Authors of these criteria were careful to point out that these criteria should not be used to exclude individuals or families with features of Lynch syndrome from mutation analysis. Nevertheless, these criteria continue to be utilized in ways that were not intended, and it is unfortunate that some payers still utilize these criteria to determine eligibility for coverage of genetic testing.

“Lynch syndrome”, named for Dr Henry T Lynch, who was among the first to recognize and describe families with hereditary cancer predisposition, is now the accepted and preferred term to describe a hereditary syndrome caused by germline mutations that disrupt the function of an MMR gene. Although “HNPCC” is still used somewhat interchangeably with “Lynch syndrome”, it fails to recognize the associated extracolonic features and is less specific, as not all family history-defined HNPCC has underlying MMR defects. The eponymous Dr Henry Lynch is internationally recognized for his contributions to the discovery of the syndrome, his descriptions of the natural history, raising awareness by publishing and speaking, and his graciousness and support for organizations that work directly with individuals and families with Lynch syndrome.

Not long after discovery in the mid-1990s, commercial testing became available for MLH1 and MSH2 around the turn of the decade, with genetic testing for four MMR genes plus EPCAM available within 12 years (Figure 1). Families who meet Amsterdam I criteria but do not have an MMR deficit as the underlying etiology (so-called familial colorectal cancer type X) have been described and characterized. These families have elevated colorectal cancer risk compared with a general population but not the same magnitude of risk as Lynch syndrome, and do not appear to have elevated risk for extracolonic cancers. The underlying genetic causes remain undefined, although with the recent advent of next-generation sequencing panels, additional genes will likely be implicated in some cases.

**Clinical spectrum of Lynch syndrome**

The risks of developing Lynch syndrome-associated cancers are gene and sex influenced. Initial studies tended to overestimate penetrance, due to the purposeful selection bias of the Amsterdam criteria. Penetrance data and cancer

![Figure 1](https://www.dovepress.com/)

**Figure 1** Approximate time line for availability of mismatch repair gene tests. **Abbreviations:** del, deletion; dup, duplication.
risk estimates have continued to evolve as genetic testing becomes more widespread. Generally, cancer risk estimates have trended downward, and the lower penetrance genes PMS2 and MSH6 have been found to account for a higher proportion of Lynch syndrome than previously recognized. As gene and age-specific data evolve, it becomes important from a clinical standpoint to review recent literature for the most accurate risk estimates associated with a particular gene. Specific cancer risks associated with Lynch syndrome are reviewed regularly and displayed in tabular format in the National Comprehensive Cancer Network (NCCN) colorectal screening guidelines.11

Individuals with an MLH1 or MSH2 gene mutation have the highest risks and the widest array of cancers attributable to Lynch syndrome. In particular, men with an MSH2 mutation have the highest risk for several types of cancers.12–14 MSH6 carriers have lower colorectal cancer risks but substantial gynecologic cancer risks.15,16 PMS2 carriers have lower colorectal and gynecologic cancer risks.17 Data on extracolonic, nongynecologic cancers specific to MSH6 and PMS2 are sparse. Risks associated with EPCAM deletions are being elucidated. Deletions may occur in the 3′ end of EPCAM, or may span both EPCAM and MSH2. In cases where the deletion is in EPCAM only, the epigenetic silencing of MSH2 occurs only in cells that express EPCAM, and therefore creates a mosaic pattern of MSH2 inactivation. It appears that in people with this cause for Lynch syndrome the risk of colorectal cancer remains high, but endometrial cancer risk is low. Individuals with deletions that span both EPCAM and MSH2 have cancer risks similar to those with MSH2 mutations.1,18

Colorectal cancer
Features of colorectal cancer associated with Lynch syndrome include earlier average age at onset, right-sided predominance, elevated risk of synchronous and metachronous cancers, and rapid adenoma to carcinoma progression compared with sporadic adenomas.19–21 Histologic characteristics of Lynch syndrome-related colon cancers have been observed to be poorly differentiated, with tumor-infiltrating lymphocytes, mucin containing, and with signet ring or cribriform histology.22,23 There appears to be a survival advantage when matched stage for stage with non-Lynch syndrome colorectal cancers.24–26

Colorectal cancer risks are reported to be as high as 75%, with median ages reported from 44 years to 61 years in those with Lynch syndrome.27 These vary according to which gene is involved and are well documented in other publications and summarized in Table 1.12,16,17,28–34 Although 10% of colorectal cancers in the general population occur prior to age 50 years, in Lynch syndrome approximately 50% occur prior to age 50 years, before routine colorectal screening would typically commence.35,36 The rate of synchronous and metachronous colorectal cancers is dramatically elevated in colon and rectal cancer survivors with Lynch syndrome, with approximately 15%–20% developing a second colorectal cancer within 10 years, 40%–50% within 20 years, and >60% within 30 years.37 Finally, the average dwell time from onset of a polyp to onset of carcinoma is much shorter in Lynch syndrome. Polyps may progress to carcinoma within 2–3 years among individuals with Lynch syndrome, compared with from 4 years to >10 years in the general population.38,39

Endometrial cancer
Endometrial cancer is at least as likely as colorectal cancer to be the initial cancer diagnosis in women with Lynch syndrome, and synchronous endometrial/ovarian cancers are more likely.40–42 As many as 26% of female survivors of colorectal cancer due to Lynch syndrome will develop endometrial cancer within 10 years of initial diagnosis.42 Individuals with an MSH2 or MSH6 mutation have the highest risk for endometrial cancer, with a lifetime risk of up to 44% (Table 1).15,33

Lynch syndrome-associated endometrial cancers have primarily endometrioid histology, but other types, including clear cell, are observed.43 MMR-deficient endometrial cancers are more likely to exhibit specific morphological

Table 1 Colorectal and gynecologic cancer risks for people with Lynch syndrome compared with the general US population

<table>
<thead>
<tr>
<th></th>
<th>Lifetime risk</th>
<th>Cancer risks to age 70 years</th>
<th>Approximate median or mean age (years)</th>
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<tr>
<td></td>
<td>Population</td>
<td>MLH1, MSH2</td>
<td>MSH6</td>
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<tr>
<td>Colorectal</td>
<td>4.8%</td>
<td>2%</td>
<td>40%–70%</td>
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<tr>
<td>Endometrial</td>
<td>2.5%</td>
<td>&lt;2%</td>
<td>35%–40%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.4%</td>
<td>&lt;1%</td>
<td>4%–11%</td>
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Note: SEER data is presented.149
Abbreviation: SEER, Surveillance, Epidemiology and End Results Program.
features, including peritumoral lymphocytes, prominent tumor-infiltrating lymphocytes, and heterogeneous tumors displaying two morphologically distinct tumor cell populations. The reported average ages of onset vary significantly and, in general, are younger, but there is evidence that the average age of onset may not be as early as previously thought, with the advent of universal screening for Lynch syndrome among individuals with endometrial cancer.

Lynch syndrome is present in 8%–9% of women with early onset endometrial cancers, and 7%–21% of women with synchronous endometrial and ovarian cancers. Features of lower uterine segment endometrial cancers, which account for 3.5% of endometrial cancers overall, were observed in 42% of women with Lynch syndrome. As many as 30% of women with endometrial cancer of the lower uterine segment may have Lynch syndrome.

### Ovarian cancer

Approximately 2% of ovarian cancers are due to Lynch syndrome. When selected for early age of onset, specifically those diagnosed under the age of 40 years, the association with Lynch syndrome may be closer to 4%. Reported lifetime risks for ovarian cancer in women with Lynch syndrome fall primarily within the range of 6.7%–12% and appear highest for carriers of MSH2 mutations, followed by MSH6 and MLH1 (Table 1).

Synchronous endometrial cancer is reported in ~22%, and 55% have a synchronous or metachronous Lynch syndrome-related cancer. Mean ages for diagnosis of ovarian cancer in Lynch syndrome are primarily in the 40 to 50-year range, with up to 30% of Lynch syndrome-related ovarian cancers diagnosed prior to age 35 years. Although Lynch syndrome-associated ovarian cancers are predominantly epithelial, unlike BRCA-related ovarian cancers, which are characteristically high grade serous, Lynch syndrome-associated ovarian cancers tend to display a higher proportion of endometrioid, clear cell, and mucinous cancers.

### Gastric cancer

Gastric cancer is primarily, but not exclusively, the intestinal type, with diffuse-type gastric cancers representing 12.5%–23%. Lynch syndrome-related gastric cancer is primarily, but not exclusively, the intestinal type, with diffuse-type gastric cancers representing 12.5%–23%.

### Small bowel cancer

Up to 6% of individuals with Lynch syndrome develop small bowel cancer at a median age of <50 years for carriers of MLH1 and MSH2 mutations, and 54 years for MSH6 carriers (Table 2). As with several Lynch syndrome-associated extracolonic cancers, the risk appears highest in men with MSH2 mutations and lowest in carriers of MSH6 mutations, with scant data available for carriers of PMS2 mutations.

### Urinary tract cancer

Renal pelvis and urothelial (transitional cell) cancers are exceedingly rare in the general population. In contrast, people with Lynch syndrome have up to an 8% risk of developing upper urothelial cancers by age 70 years, at a median age of 58–62 years, with the highest risk occurring in men with MSH2 mutations (Table 2). Recent data suggest a two- to four-fold elevated risk of bladder cancer as well, such that for men with MSH2 mutations the risk of developing a urinary tract cancer by age 70 years may approach or exceed 20%.

### Sebaceous neoplasms

The presence of sebaceous neoplasms in individuals and families with other internal malignancies was referred to as Muir–Torre syndrome before molecular genetic testing demonstrated a common underlying etiology. Sebaceous neoplasms, particularly carcinomas, are exceedingly rare. Sebaceous neoplasms in people with Lynch syndrome are more likely than sporadic neoplasms to occur prior to age 60 years (median age 56 years), be multiple rather than isolated, and occur in the context of a personal or family history of Lynch syndrome-related cancer(s).
The incidence of sebaceous neoplasms among individuals with Lynch syndrome has been reported to be as high as 9% (Table 2).71,72

Other rare tumors associated with Lynch syndrome

The spectrum of Lynch syndrome-associated tumors is wide, and several very rare cancers in the general population are seen more frequently in Lynch syndrome (Table 2).75 Although the risks for these rare tumors are greatly increased above the general population risks, the absolute risks are low. Individuals with Lynch syndrome have a risk of up to nearly 4% to develop pancreatic cancer by age 70 years. Pancreatic cancers appear most frequently in families with MSH2 mutations, followed by MLH1 and MSH6.73 Up to 4% of people with Lynch syndrome develop hepatobiliary cancer by age 70 years (median 50–57 years), another rare cancer in the general population.13 Finally, individuals with Lynch syndrome have up to a 3% lifetime risk of developing cancers of the brain and central nervous system, particularly glioblastoma.74

Evolving spectrum of Lynch syndrome-associated cancers

Prostate cancer has recently been associated with Lynch syndrome, and data are beginning to emerge regarding the risks and ages of onset. Several studies have found the lifetime risk for prostate cancer in Lynch syndrome to be increased by two- to five-fold.75–77 Additional studies are needed to determine whether Lynch syndrome-associated prostate cancers occur at an earlier average age or are more aggressive.75,76

The relationship between breast cancer and Lynch syndrome remains unresolved. Studies have not consistently demonstrated a higher than expected incidence of breast cancer among individuals with Lynch syndrome.78,79 Several studies have demonstrated evidence of MMR with loss of immunohistochemical staining in breast cancers found among known carriers of a mismatch gene mutation.80–82 As breast cancer is fairly common in the general population, larger studies are needed to determine whether breast cancer is indeed part of the Lynch syndrome cancer spectrum.

Surveillance

A major reason to identify individuals with Lynch syndrome is to optimize surveillance, which ultimately minimizes morbidity and mortality. Surveillance recommendations for individuals with Lynch syndrome differ substantially from those of the general population, due to the accelerated progression from colorectal adenoma to carcinoma and the increased incidence of cancers that can be avoided with prophylactic surgery, such as endometrial and ovarian cancers.83–85 The elevated risk for colorectal cancer to occur at young ages justifies the initiation of surveillance as young as age 20–25 years, depending on the family history and genotype.11 The right-sided predominance of colon cancers with Lynch syndrome necessitates a colonoscopy rather than a sigmoidoscopy.

The NCCN has published guidelines for management of individuals with Lynch syndrome that are regularly reviewed and updated, and there are several other publications that outline recommendations for surveillance.11,86,87 It is notable that the most recent version of the NCCN guidelines reflects evolving evidence that individuals with a PMS2 or MSH6 mutation may have reduced penetrance and thus may not require the same intensity of surveillance.

Surveillance for colon cancer should include annual or biannual colonoscopy and begin around the age of 25 years.86,88,89 Individuals with family members who were diagnosed at very young ages may consider colonoscopy earlier, typically 5–10 years before the earliest age of onset in the family. Recent evidence suggests that individuals with MSH6 or PMS2 mutations may be able to delay initiation of colonoscopy until as late as 30 years, due to the reduced penetrance.11,16,17 Fewer colon cancers are identified when surveillance with polypectomy is performed at 1 to 2-year intervals and cancers are identified at earlier stages with overall improved survival rates.89,90 Studies comparing regular light colonoscopy with use of indigo carmine dye have not noted improved overall survival.91 However, there was documented improvement in detection of very small polyps, and it remains to be determined whether this benefit may ultimately translate into better outcomes.

Endometrial cancer symptoms include abnormal uterine bleeding and pain, which are usually early indicators easily recognized by patients. Patients should be educated to seek medical evaluation if they experience abnormal bleeding. There is no clear management recommendation regarding endometrial biopsy for surveillance, as it is invasive, and there appears to be no evidence to suggest that outcomes are improved.92

Surveillance for other cancers is widely debated due to the lack of evidenced-based improvement of outcomes. Therefore, most groups do not make any specific recommendations for extracolonic cancer surveillance. Some practitioners may consider small bowel X-ray and/or upper endoscopy to screen for cancers of the upper gastrointestinal tract, and urinalysis...
with cytology to screen for urothelial cancer in individual cases, but there are no guidelines to direct these surveillance methods. Finally, the issue of dermatology screening has been raised, based on a single study that found that almost 10% of individuals with Lynch syndrome had sebaceous adenomas or the Muir–Torre variant of Lynch syndrome.71

**Surgical considerations**

There continues to be a debate about colectomy versus subtotal colectomy at the time of colon cancer treatment for individuals known to have Lynch syndrome. Surgeons may opt for a subtotal colectomy at the time of a colon cancer diagnosis in an individual with Lynch syndrome, despite lack of evidence demonstrating survival benefit.93,94 Quality of life issues following total abdominal colectomy should be carefully considered, as should access and adherence to surveillance, and management should be tailored on an individual basis.95,96 Few physicians would recommend prophylactic colectomy today, although it was considered early on in the chronicle of Lynch syndrome.

There is little debate with regard to prophylactic removal of the uterus and ovaries once childbearing is complete, due to the lack of effective surveillance of the ovaries and the significant decrease in the risk for both cancers following prophylactic surgery.85 The average age of onset of endometrial cancer in Lynch syndrome is 55 years, and current recommendations suggest total abdominal hysterectomy and bilateral salpingo-oophorectomy by the age of 50 years.97 Thorough pathological examination of surgical specimens is recommended, as gynecologic malignancies may be present already at the time of prophylactic surgery.98,99 Removing ovaries after or near the time of menopause eliminates some of the issues of early surgical menopause, as seen in BRCA1/2 carriers. However, 30% of Lynch syndrome-associated ovarian cancers occur prior to age 35 years, and there is no apparent contraindication for use of hormone replacement in this population. The likelihood of endometrial and ovarian cancer after prophylactic salpingo-oophorectomy is very low.95

**Chemoprevention**

Trials of aspirin have shown promise in reducing polyp burden among individuals with Lynch syndrome. Use of aspirin for 4 years or longer is associated with a reduction in the risk for colon cancer, although the effect is not evident until at least 5 years after the intervention.100 The optimal age to initiate the recommended dose and necessary duration of aspirin use has not been established, and studies are now ongoing. Birth control pills reduce the risk for both endometrial and ovarian cancer in the general population, and this effect was similar in a small cohort of women with Lynch syndrome.101

Recommendations for treatment and surveillance for Lynch syndrome continue to evolve. NCCN guidelines are reviewed and updated regularly, incorporating new information as it arises. Coordination of care in Lynch syndrome is essential to ensure that patients are getting the most appropriate and up-to-date care. This often requires collaboration between many different specialists, such as gastroenterologists, gynecologic oncologists or gynecologists, primary care providers, and genetic counselors.102

**Psychosocial issues**

Optimally, genetic testing should be done in a supportive setting with the expertise of a health care practitioner who is familiar with Lynch syndrome and some of the psychosocial issues that may be present. Genetic testing for Lynch syndrome may cause anxiety and distress, although studies have shown that the majority of individuals adapt to their results, and negative effects, if any, appear to be short term.103,104 Knowledge of one’s mutation and risk status may also provide individuals with a sense of control and optimism.105

There may be psychological effects of living with the threat of cancer. This may be influenced by prior experience with illness or death from cancer in the family. Feelings of guilt with regard to passing on the gene mutation or the possibility of passing on the gene mutation may also be present.105

Adherence to surveillance recommendations does not seem to be impacted by anxiety or cancer worry but may be impacted by an individual’s perceived barriers to screening.106 Barriers that have been described include discomfort, embarrassment, and lack of awareness of surveillance recommendations.106–108 Recognizing these factors in individual patients is important so that health care practitioners can maximize compliance with surveillance recommendations.

**Identification of Lynch syndrome: universal screening**

Lynch syndrome accounts for ~3% of all colorectal and endometrial cancers.2,97,109,110 Identification of Lynch syndrome has traditionally relied on multiple steps, including recognition of typical features and appropriate testing and/or referral to a genetics provider. Although there are some histological features within individual tumors that
can indicate a likelihood of MMR deficit, and other clues, such as location within the body system (eg, lower uterine segment endometrial cancer or proximal colon cancer), Lynch syndrome-associated colon and endometrial cancers are not necessarily distinguishable from sporadic colon and endometrial cancers. Systematic collection, documentation, and assessment of family history are highly variable among health care providers, and rarely is this information readily available to pathologists who may recognize histological features of Lynch syndrome. Given these limitations and the compelling reasons to identify these individuals and their at-risk family members, universal screening has been proposed as a way to adequately identify individuals with Lynch syndrome.

Universal screening for Lynch syndrome is the evaluation of all colon and/or endometrial tumors at the time of diagnosis for evidence of MMR deficit. Microsatellite instability (MSI) and immunohistochemistry (IHC) are two screening methods used to identify affected individuals who may have Lynch syndrome. MSI is a measure of whether the MMR system is functioning. Loss of MMR function, which can be caused by Lynch syndrome or by epigenetic silencing of the MLH1 gene, results in MSI, which can be detected by polymerase chain reaction on a colon tumor specimen. Evidence of MSI suggests further workup to rule out Lynch syndrome. IHC is a demonstration of the presence or absence of MMR proteins in the tumor. Absence of a protein(s) as demonstrated by IHC staining suggests the possibility of a mutation in the corresponding gene.

The Bethesda criteria were developed to define populations for which colon tumor testing with MSI and/or IHC was indicated. These evolved over time to include personal and family history of extracolonic cancers. However, studies of universal screening of all colorectal and endometrial cancers suggest that as many as 70% of people with Lynch syndrome do not meet Amsterdam or Bethesda guidelines.

Universal screening for Lynch syndrome has been demonstrated to be cost-effective, largely due to the identification of unaffected family members and subsequent prevention of colon and endometrial cancers. The issue of whether or not consent should be obtained prior to screening has been debated. However, in practice, direct informed consent prior to tumor screening is rare.

There are documented challenges to implementation of a universal screening program for Lynch syndrome. One challenge has been to establish an effective process for notification and discussion with the patient, with subsequent patient uptake of genetic testing and notification of at-risk relatives. Individuals identified by universal screening for Lynch syndrome may not return for genetic counseling and testing if it is not apparent to them how it would impact their care and/or if their perception is that further evaluation is not warranted based on their family history. There have been several studies attempting new approaches to remove barriers and improve compliance with follow-up genetic counseling and testing, with variable success. Cascade testing for at-risk relatives is complex and depends upon effective intrafamilial communication. Factors that correlate with how well information is transmitted among family members include the education of individuals with Lynch syndrome and recommendations by the health care professionals who care for them. Most individuals with Lynch syndrome inform first-degree family members but are less likely to notify more distant relatives, due to lack of closeness and concerns that relatives may not understand the information shared. Resources to assist health care providers and families in the process of notifying at-risk relatives include an online tool, informational brochures, and a searchable database to identify genetic counselors (Table 3).

Table 3 Lynch syndrome resources

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<th>Patient-focused resources</th>
<th><a href="http://www.kintalk.org">http://www.kintalk.org</a></th>
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<td>National Society of Genetic Counselors (NSGC): contact list for board-certified genetic counselors</td>
<td><a href="http://www.nsgc.org">http://www.nsgc.org</a></td>
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<td>Hereditary Colon Cancer Takes Guts: support network for individuals with Lynch syndrome</td>
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<tr>
<td>Lynch Syndrome International: support network for individuals with Lynch syndrome</td>
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<td>GeneReviews: concise yet detailed information about different hereditary syndromes</td>
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<tr>
<td>National Society of Genetic Counselors (NSGC): searchable list for board-certified genetic counselors</td>
<td><a href="http://www.nsgc.org">http://www.nsgc.org</a></td>
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Molecular testing does not always identify the underlying mutation in screen-positive individuals who are identified by tumor screening. Current technology may not detect all mutations, or there may be additional, yet-to-be-identified genes that cause Lynch syndrome. Biallelic somatic mutations may explain some cases of absent MMR proteins detected by IHC. Personal and family history may be helpful in distinguishing sporadic biallelic somatic mutations from true Lynch syndrome with no identifiable mutation.

Finally, the clinical utility of evaluating nonendometrial, extracolonic tumors for evidence of MMR continues to be unclear. The accuracy of screening ovarian tumors for MMR with IHC or MSI is questionable, although abnormal findings certainly warrant further evaluation and consideration of germline testing. Rare sebaceous tumors (including sebaceous adenomas, epitheliomas, and carcinomas) are strongly associated with the Muir–Torre variant of Lynch syndrome, and 30%–60% of sebaceous tumors are related to an MMR defect. However, there are differing opinions on the utility of screening all sebaceous tumors with IHC. Some authors have advocated for IHC screening of all sebaceous tumors. Others have argued that in the absence of a personal or family history of Lynch syndrome-associated cancers, the positive predictive value of IHC on sebaceous tumors is not high enough to warrant routine screening. A recent publication describes a scoring system based on the number of sebaceous neoplasms, age at diagnosis, and personal and family history of Lynch syndrome-associated cancers, and concludes that IHC alone is a poor predictor for identifying people with Lynch syndrome.

Other Lynch syndrome-associated cancers may display evidence of MMR, but results tend to be less reliable than screening other tumors. There is incomplete concordance between MSI and IHC analysis in gastric tumors, so one group has recommended screening gastric tumors with both MSI and IHC when meeting revised Bethesda criteria. Other tumors have much fewer data regarding reliability of MSI and IHC in assessing likelihood for Lynch syndrome. The one exception is small bowel tumors, in which the performance of MSI and IHC in assessing likelihood for Lynch syndrome. The one exception is small bowel tumors, in which the performance of MSI and IHC appears to be similar to that in colon cancers.

In conclusion, there are case reports of abnormal IHC among rare and unusual tumors in individuals with confirmed Lynch syndrome, but not enough evidence to routinely screen these tumors for evidence of MMR, nor enough evidence to be able to rule out suspected Lynch syndrome with normal IHC and/or MSI.
Disclosure

The authors have no conflicts of interest in this work.

References


The genetic basis of Lynch syndrome


