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Current and emerging trends in Lynch syndrome identification in women with endometrial cancer

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Abstract

Objective—Lynch syndrome is a heritable, cancer susceptibility syndrome. This study aims to review current and emerging trends in the identification of Lynch syndrome in the endometrial cancer patient population.

Methods—We performed a comprehensive review of past and present screening algorithms for Lynch syndrome, including a review of the utility of both the Amsterdam criteria and Bethesda guidelines. Because non-colon cancers have historically not been the focus of Lynch syndrome research, current literature is ripe with questions regarding screening among this patient population. Low BMI, age less than 50, positive family history and pathologic features have all been identified as risk factors in endometrial cancer patients who might benefit from Lynch screening. Additionally, based on experience at our own institution we offer a feasible screening algorithm for these patients.

Results—A comprehensive review of the data demonstrated that immunohistochemistry is becoming an efficient, inexpensive way to screen tumors at risk for mismatch repair deficiency. The sensitivity and specificity of immunohistochemistry for predicting Lynch syndrome approaches 100%. Ideally, prospective screening of all endometrial cancer patients with IHC is a feasible, cost-efficient way to detect Lynch in this patient population given the limitations of using personal/family history of malignancy as well as pathologic risk factors.

Conclusion—It is imperative that clinicians be mindful of the risk of Lynch syndrome in women with endometrial cancer. Given the opportunity for colon cancer screening and prevention strategies to be initiated, the identification of probands with endometrial cancer as a result of Lynch syndrome will lead to a reduction in morbidity and mortality for these patients and their families.

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Conflict of interest statement

David Cohn has no conflicts of interest.

Kimberly Resnick has no conflicts of interest.

Richard Fishel is an inventor on patents for the sequencing of the MMR genes *MSH2*, *MLH1* and *PMS2*. These patents are owned by the University of Vermont.

Heather Hampel sat on the Lynch syndrome advisory board (6/08) Myriad Genetics Laboratories, Inc. She also received an honorarium for speaking at Falco Biosystems.

Keywords

Lynch syndrome; Endometrial cancer; Screening

Background

In this era of personalized medicine, genetic susceptibility to cancer is quickly becoming one of the most researched areas of the biomedical sciences. Greater public understanding of the role that genes play in the development of cancer and potential testing requires that today's physician be aware of these genetic predispositions, understand how to take a detailed family history and be knowledgeable about the genetic testing for this disorder. Lynch syndrome is one such heritable, cancer susceptibility syndrome. Lynch syndrome is caused by genetic defects in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2*. The care of patients with this syndrome requires orchestrated efforts by primary care physicians, gastroenterologists, gynecologists, surgeons, medical oncologists and geneticists.

Lynch syndrome displays Mendelian autosomal dominant inheritance with incomplete penetrance [1]. It accounts for 2%–3% of cases of colon cancer (CRC) and 2.3% of endometrial cancer (EMCA) [2-6]. In the sentinel report, Aarnio et al., observed standardized incidence ratios of colon cancer and endometrial cancer of 68% and 62% respectively in those Lynch individuals with mutations in *MHL1* or *MSH2* [7]. When men and women are examined separately, the risk of colon cancer becomes 83% and 48% respectively. Thus, a female patient with Lynch has a substantially higher lifetime risk of endometrial cancer than colon cancer. Despite the similar incidence of Lynch syndrome in probands with colon and endometrial cancers, there is a broad difference in the current management of patients with these diseases as it relates to screening for Lynch syndrome.

The public health dilemma

The public health dilemma of screening for Lynch syndrome among the endometrial cancer population is evident in the original name for this syndrome described by Henry Lynch. The name “hereditary nonpolyposis colon cancer” seems to reduce the importance of non-colon cancer diagnoses in this syndrome. Subsequently, public and health care professional knowledge of the risk of Lynch syndrome in the endometrial cancer population is lacking. Because non-colon cancers have historically not been the focus of Lynch syndrome research, current literature is ripe with questions regarding screening among this patient population. Low BMI, age less than 50 and positive family history have all been identified as risk factors in endometrial cancer patients who might benefit from Lynch screening [8-10]. Age at diagnosis has stood out as having the highest positive predictive value for subsequent defects in MMR with authors identifying a 9%–18% risk of germline MMR mutations in two cohorts of endometrial cancer patients less than 50 years of age [8,9]. Additionally, Matthews et al., found that 34% of tumors specimens from patients less than 50 years had loss of one or more MMR proteins on immunohistochemistry (IHC) and subsequently require further genetic counseling or germline genetic testing [11].

The need for widespread screening among gynecologic and more specifically, endometrial cancer patients is obvious. Lu et al. performed a retrospective analysis of 117 women meeting clinical criteria based on family history, diagnosed with synchronous and/or metachronous colonic and gynecologic malignancies [12]. Of the women with metachronous malignancies 51% were diagnosed with a gynecologic cancer first. The median number of years between a primary gynecologic malignancy and CRC was 11 years. Given the latency period between the gynecologic malignancy and colon cancer it is imperative that women with Lynch

syndrome be identified at the time of diagnosis of a sentinel gynecologic malignancy so that timely colon cancer screening may commence.

Current screening strategies

Recent decades have seen a refinement of the tools that clinicians may use to screen high-risk patients for Lynch syndrome. While the initial inclusion criteria for screening solely included those with a personal or family history of CRC, it has now been realized that in small families, gynecologic malignancy may be the only manifestation of Lynch syndrome. Additionally, large studies of the statistical validity of these screening tools are mostly limited to the colon cancer population.

Amsterdam criteria

The original goal of the Amsterdam criteria was to identify those who could be classified as Lynch families on the basis of clinical history. These criteria, created in 1991 by the International Collaborative Group on HNPCC, stated that Lynch syndrome could be diagnosed if the following were all met: 1) at least three family members had been diagnosed with CRC 2) two or more generations had CRC 3) one affected member was a first-degree relative of the other two and 4) at least one individual was under 50 years of age. The sensitivity and specificity of these original criteria have been documented to be as high as 60% and 70% respectively for the detection of Lynch syndrome [13].

In 1999, the Amsterdam criteria were revised to be more inclusive. The revised criteria (known as Amsterdam II) stated the following: 1) there are at least three relatives with Lynch-associated cancer (colon, endometrium, small bowel, renal pelvis or ureter; not included in this list is stomach, ovary, bladder, brain or skin) 2) one affected person is a 1st degree relative of the other two 3) at least two successive generations are involved 4) one person was diagnosed below the age of 55) familial adenomatous polyposis has been excluded and 6) tumors have been verified by a pathologist. Syngal et al. documented a sensitivity and specificity of 72% and 78% for the Amsterdam II in their evaluation of all of the criteria used to diagnose Lynch syndrome in the colon cancer population. And, while the original criteria were lacking the inclusion of the common extra-colonic malignancies such as endometrial cancer, the revised criteria failed to take into account women with sentinel gynecologic malignancies and small family pedigrees. The utility of the Amsterdam criteria in the gynecologic cancer population remained limited.

Bethesda guidelines

Although the Amsterdam criteria were revised in order to include those families with a high incidence of extra-colonic cancers associated with Lynch syndrome, the Bethesda guidelines were created in 1997 and subsequently revised in 2002. The objective of the Bethesda criteria was quite different than that of the Amsterdam criteria. The Bethesda guidelines are aimed at determining which tumors should undergo microsatellite instability (MSI) testing. The revised Bethesda guidelines state that MSI testing of tumor should be performed in the following situations: 1) colon cancer diagnosed in a patient who is less than 50 years of age 2) presence of synchronous, metachronous colon, or other Lynch syndrome-associated tumors regardless of age 3) colon cancer with the microsatellite instability-high (MSI-H) histology diagnosed in a patient who is less than 60 years of age 4) colon cancer diagnosed in one or more first-degree relatives with a Lynch syndrome-related tumor, with one of the cancers being diagnosed under age 50 years and 5) colon cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age [14]. To this end, tumor MSI testing involves PCR amplification of the markers involved in the NCI consensus panel. Previously, the NCI had come to a consensus on the genotypic definition of microsatellite instability. The

NCI recommends performing genotyping with the panel of nucleotide markers including: BAT25, BAT26, DS5123, D5S346 and D18S346 [15]. These markers are microsatellites present in regions of the genome that are irrelevant to tumor biology and malignant transformation. MSI-H is defined as 2 or more markers being unstable, MSS (microsatellite stable) tumors are without unstable markers and MSI-L is 1 unstable marker. The authors of the Bethesda guidelines were determined to create more inclusive clinical criterion to aid in determining which of those high-risk patients should proceed directly to tumor testing for MSI. With the revised guidelines, the sensitivity for the detection of Lynch syndrome improved to 94%, thereby making it more sensitive than the original and revised Amsterdam criteria and original Bethesda guidelines [16].

Limitations of Amsterdam criteria and/Bethesda guidelines

The evolution of the genetic screening criteria over the past two decades includes revisions of both the Amsterdam and Bethesda criteria. It is difficult to completely outline the performance of these clinical criteria in the gynecologic population; they were not created for this population and thus, the validity of these tests is mainly limited to the colon cancer population. The current Bethesda guidelines are the best tool we have for identifying those individuals whose tumors require further genetic testing, but by no means are they entirely sensitive, especially for individuals with small family pedigrees as well as those with a predominance of familial endometrial cancer.

The clinical utility of these criteria in identifying newly diagnosed colon cancer patients with germline mutations in *MLH1/MSH2* has been well documented [17]. In this circumstance sensitivity of both the original and revised Bethesda guidelines approaches 100%. Thus, in those with newly diagnosed colon cancer it is often a common practice to base referral to a genetic counselor upon whether or not the proband meets Amsterdam or Bethesda criteria. The picture is murky however, in those families with a clustering of late-onset colon and/or endometrial cancers. Later age of onset has been associated with germline *MSH6* mutations and both Amsterdam and Bethesda perform poorly in this circumstance. Ramsaek et al. recently examined 108 “at risk” families for Lynch-associated germline mutations [18]. In the 12 probands with *MSH6* mutations, 7 of these patients were diagnosed with endometrial cancer as the primary malignancy. The Amsterdam II criteria were positive in only 3/12 individuals; the false negative rate was 75%. The revised Bethesda guidelines performed better, identifying 10/12 individuals. The false negative rate was 16.6%. While we do have to extrapolate some in order to apply these statistical tests to our gynecologic population, Hampel et al. found that 8/13 endometrial cancer patients with Lynch syndrome did not meet any published clinical criteria for Lynch syndrome [4,5]. Thus, if personal and/or family history were used as justification for referral for genetic testing 61.5% of patients would have been missed in the patients presenting with endometrial cancer. We suggest that more general criteria of whom to screen, especially related to gynecologic cancers, are needed.

Current guidelines

The Society of Gynecologic Oncologists (SGO) recently published a committee statement on the risk assessment for inherited gynecologic malignancies [19]. In these recommendations patients are triaged to a genetic counselor or genetic testing based on the perception of risk (Table 1). This document offered the caveat that there are select patients who may not meet these extensive criteria but who may warrant genetic screening. These patients include those with few female relatives, unknown family history, or in a patient from a family in whom hysterectomy and oophorectomy was performed prior to the age of the risk of Lynch cancers. While these criteria take the necessary steps towards being more inclusive of endometrial

cancer patients, they still require extensive family or personal history before the referral of a patient for risk assessment.

Screening algorithms

While the SGO guidelines are a reflection of some of the current literature they lack recommendations regarding the form of screening that should be undertaken. Recent literature does suggest that IHC for the MMR proteins may be used as primary triage for Lynch syndrome. Walsh et al. retrospectively identified, by IHC, presumptive Lynch syndrome in 26 (18%) out of 146 newly diagnosed endometrial cancer patients less than 50 years of age [9]. Six of the twenty-six patients met Amsterdam II criteria. In a retrospective study by Matthews et al., immunohistochemical evidence of mismatch repair deficiency was evident in 34% of newly diagnosed endometrial cancer patients less than 50 years of age [11]. The caveat with both of these studies is the above numbers reflect a presumptive diagnosis; confirmation of a gene mutation was not performed in tumors lacking expression of a MMR protein. Lu et al. however, have recently provided evidence that prospective screening with IHC, followed by sequencing in all endometrial cancer patients younger than age 50, is a feasible, sensitive option [8]. In this cohort of young patients, 9% demonstrated germline mutations in *MLH1*, *MSH2* or *MSH6*, higher than the 2.3% rate in the general population of patients with endometrial cancer as a result of Lynch syndrome.

Given the fact that the incidence of Lynch syndrome in women diagnosed with endometrial cancer younger than 50 approaches 10%, many have argued to revise the Bethesda criteria in order to include MSI testing in women presenting with endometrial cancer younger than age 50; however, recent data suggests that the age of 50 to justify referral for genetic consultation may be too low. Hampel et al., in a large, prospective Lynch screening study of 562 women presenting with endometrial cancer demonstrated that the mean age at diagnosis of the 13 probands identified with Lynch syndrome was 54.1 years [4,5]. Had they used 50 years as a screening cut off, 69% of patients would have been missed. Additionally, Goodfellow et al. demonstrated a mean age of 54.8 years in 35 cases of presumptive Lynch-associated endometrial cancer [20]. These data suggest that unlike earlier studies that demonstrated that the mean age of diagnosis of endometrial cancer in patients with Lynch syndrome was 48 years [21], the diagnosis of endometrial cancer in a proband with Lynch syndrome is more commonly made after the age of 50.

Unlike colon cancer associated with Lynch syndrome, endometrial cancers in this population most commonly result from mutations in *MSH6*, and cancers resulting from mutations in *MSH6* occur at a later age than those in *MLH1* and *MSH2* (commonly mutated in Lynch syndrome-associated colon cancers). Mutations in *MSH6* confer a less “severe” clinical picture with regards to both CRC and EMCA; age of onset is later and in colon cancer, pathologic tumor features are more similar to those of general population. Importantly, for those individuals with a germline *MSH6* mutation the cumulative risk of endometrial cancer is substantially exaggerated beyond that associated with mutation in the other MMR genes [22, 23]. Hendricks et al. examined twenty families with a truncating germline mutation of *MSH6*. Women in these families were noted to have a two-fold greater risk of endometrial cancer compared to their cohorts with mutations in *MLH1* or *MSH2*. Cumulative risk by the age of 70 was 71%, substantially higher than their risk for colorectal cancer [22]. Hampel et al. noted that out of 13 germline mutations identified in a cohort of endometrial cancer patients being screened for Lynch syndrome, 9 of the mutations were in *MSH6* [4,5]. In a prospective study by Goodfellow et al., 7 germline mutations in *MSH6* were identified in a cohort of 441 consecutive endometrial cancer patients, and 71% of these patients were older than 50 [20]. It may be that by limiting Lynch syndrome screening to those patients with endometrial cancer

younger than 50, mutations in *MSH6* may be missed, and therefore patients and families with Lynch syndrome may be left undiagnosed.

In recent years, specific pathologic factors associated with colon cancers have been evaluated as to their ability to predict the presence or absence of Lynch syndrome. In colon cancer, pathologic findings of poorly differentiated histology with mucoid and signet cell features, Crohn's-like reaction, tumor infiltrating lymphocytes and lack of dirty necrosis are all associated with Lynch syndrome-associated colon cancers, and may serve as an impetus for referral to a genetic counselor or for tumor testing [24]. Recently, there has been an attempt to identify certain pathologic factors in Lynch-associated endometrial cancers. Westin et al. determined that the prevalence of Lynch among women with endometrial cancer of the lower uterine segment was 29%, and concluded that in cases of pathologically confirmed endometrial cancer originating in the lower uterine segment, screening for Lynch syndrome should be considered [25]. Broaddus et al. compared three cohorts of endometrial cancer patients: those with Lynch syndrome, those with sporadic endometrial cancer younger than age 50 and those with MSI-H endometrial cancers secondary to methylation of the *MLH1* promoter (an epigenetic phenomena causing MSI and sporadic endometrial and colon cancers) [26]. While the authors did note a trend towards earlier stage and less lymph-vascular space involvement in the patients with Lynch syndrome, there was no difference in deep myometrial invasion between the cohorts. Additionally, although they did identify a distinctive "undifferentiated" subtype in those with MSI-H tumors secondary to methylation, they were unable to identify any distinct pathologic characteristics that could reliably distinguish between Lynch-associated and sporadic endometrial cancers. Shia et al. recently examined whether routinely assessed morphologic features could reliably predict MSI status (and by extension, Lynch status) in endometrial cancer [27]. As has been shown in CRC, tumor infiltrating lymphocytes (TIL) and peritumoral lymphocytes (PL) in endometrial cancer were shown to be independent predictors of MSI. Subsequently, Soslow et al. conceived an algorithm for detecting endometrial cancer patients at high risk for Lynch syndrome based on tumor morphology and epidemiologic factors. In this algorithm, immunohistochemistry for MMR proteins was performed on 1) all endometrioid carcinomas in patients younger than age 50, 2) endometrial carcinomas with TILs and PLs (suggestive of MSI) and 3) at the discretion of the treating physician. In a prospective evaluation 375 hysterectomy specimens, IHC was performed on 80 tumor samples according to this algorithm. The authors concluded that through this algorithm, they were able to enrich for high-risk patients, and identified 36 tumors with loss of one or more MMR proteins (Robert Soslow, Personal communication).

Mode of testing

As important a question as who to screen for Lynch syndrome is how to screen. Currently, both colon cancer MSI testing and IHC are used as primary triage to determine which individuals require genetic counseling regarding further analysis with sequencing. Immunohistochemistry is fast becoming an efficient, inexpensive way to screen tumors at risk for mismatch repair deficiency. Defective MMR is typically defined as lack of staining of any single MMR protein. Hampel et al. recently published the results of prospective Lynch screening in 500 newly diagnosed colon cancer patients. The sensitivity of IHC in this population was 94%. The positive predictive value of an abnormal IHC for detecting Lynch syndrome was 23.89%; significantly higher than both age<50 (10.3%) and first-degree relative with colon cancer or EMCA (8.8%) [28]. Vasen et al. described a 93% concordance between IHC and MSI testing in colon tumors when all 4 MMR proteins were examined [16]. When Cohn et al. performed IHC on 336 endometrial cancers, positive staining for *MLH1* or *MSH2* predicted an intact mismatch repair system in 95% of cases [29]. Modica et al. also demonstrated similar results; when all 4 MMR proteins were examined, they had 91% sensitivity and 83% specificity in defining the MSI-H phenotype [30]. Recent data suggests

also that IHC is not only as accurate as MSI testing but likely cost effective as well. In their large endometrial cohort Hampel et al. determined that while a similar number of cases would have required further mutation testing regardless of whether primary triage was with IHC or MSI, IHC led to fewer genes being sequenced and subjected to multiplex ligation-dependent probe amplification (MLPA) and thus, improved cost-efficiency.

Within the endometrial cancer population, there are specific considerations related to MMR screening with either MSI or IHC. While Hampel et al. have recently reported similar rates of MSI between an endometrial cancer cohort compared to a colon cohort (21.8% versus 19.6%), they determined that in the endometrial population, 1 of 6 *MSH6* mutations was noted to be MSS and 2 were MSI-L [4,5]. In contrast, in colon cancers, no mutations were detected in the MSI-L tumors [30]. Given the higher rate of *MSH6* mutations in endometrial cancer associated with Lynch syndrome and the lower predictive value of MSI in *MSH6*-associated Lynch syndrome, consideration of IHC, rather than MSI as primary screening for Lynch syndrome in patients with endometrial cancer, should be considered.

An additional limitation of MSI testing is that the presence of a positive screen for MSI will not discriminate between its presence as a result of epigenetic silencing of *MLH1* or loss of function of a MMR protein. Fifteen percent of sporadic colon and 17–30% of endometrial cancers may demonstrate defective mismatch repair secondary to methylation of the *MLH1* promoter [31–33]. It is clear that the majority of MSI seen in endometrial cancer is secondary to *MLH1* promoter methylation. Gurin et al., in a study of fifty-seven consecutive cases of endometrial cancer found that 71% of the 14 MSI-H tumors demonstrated methylation of the *MLH1* promoter and subsequent epigenetic silencing and inactivation. In addition, only 7% of controls demonstrated this phenotype [34]. Hampel et al., in a study of 543 consecutive cases of endometrial cancer identified 118 (22%) cases of MSI. Of these cases, 84 (75%) demonstrated a lack of *MLH1* expression by IHC, with 79/84 (94%) being due to methylation of *MLH1*. Of the 5 unmethylated tumors, one tumor did have a germline mutation in *MLH1* [4,5]. Thus, primary screening with MSI rather than IHC would require the additional step and added cost of methylation studies to ascertain which patients with MSI require genetic counseling and potential sequencing.

Recently, screening for the mutation *BRAF* V600E has been added to algorithms for prospective screening with MSI for Lynch in colon cancer patients. *BRAF* is one of three isoforms of *RAF*, a key player in the *RAS/RAF/MEK/ERK/MAP* kinase pathway of cell signaling. Mutations in *BRAF* have been identified in 15% of colon cancers [35]. Importantly, *BRAF* mutations have been identified in a significant portion of those MSI-H colon tumors with hypermethylation of the *MLH1* promoter (sporadic cancers) but not those MSI-H tumors in patients with Lynch syndrome. In a prospective, multi-center Lynch syndrome screening trial in colon patients, the addition of sequencing of *BRAF* to either IHC or MSI testing increased the accuracy of identifying patients at risk for Lynch syndrome [37]. This increase was largest in the population where fulfillment of the Bethesda criteria was not met; here, the addition of *BRAF* testing increased specificity, positive predictive value and overall accuracy of Lynch screening. There has been disagreement however, as to the percentage of endometrial cancers displaying *BRAF* mutations and whether or not this test will be a useful adjunct to current strategies for screening for Lynch syndrome. In a study of 441 consecutive endometrial cancer patients Mutch et al. demonstrated a single *BRAF* mutation out of 146 MSI-H endometrial tumors [38]. Two other studies also documented a very low rate of *BRAF* mutations in MSI-H endometrial cancers [39,40]. This is in stark contrast to Feng et al. who demonstrated that 41% of MSI-H endometrial tumors contained a *BRAF* mutation [41]. As such, continued investigation of the role of *BRAF* in patients whose endometrial cancer lacks expression of *MLH1* is needed.

The future

The goal of a screening test for Lynch syndrome is identifying all patients with the syndrome while discriminating those without Lynch syndrome. Currently, the recommendation of testing based on family and personal history is inadequate, and many patients with endometrial cancer as a result of Lynch syndrome are not being identified. We propose general, simplified criteria that will allow community-based gynecologic oncologists, gynecologists, medical oncologists, general surgeons, primary care providers and genetic counselors to identify those patients at risk for Lynch syndrome in a timely manner so that the patients and family members may receive appropriate counseling and be included in screening for and prevention of subsequent malignancies. Currently, screening algorithms are in place for probands with colon cancer at a number of institutions including The Ohio State University Medical Center. Prospective screening of colon cancer patients with IHC for the MMR genes has been shown to be a highly effective and accurate means to identify those patients at risk for Lynch syndrome. Piñol et al. determined that the overall accuracy of IHC alone was 94.2% in predicting an *MLH1* or *MSH2* mutation [36]. This study demonstrates that large scale screening programs based on current disease in the proband instead of family and personal history is a feasible, viable option.

Given the concern that current screening algorithms for Lynch syndrome are inadequate, we began prospectively screening all new endometrial cancers with IHC for *MLH1*, *MSH2*, *MSH6* and *PMS2*, with directed genetic testing based on the primary triage with IHC. At our institution, all those less than age 60 with loss of any mismatch repair protein are referred for genetic counseling. Those greater than 60 years of age with loss of *MLH1/PMS2* and no concerning family history are not referred for genetic counseling because of the high likelihood of *MLH1* promoter methylation. Loss of *MSH2/MSH6* always leads to a genetics referral. To date, we have screened more than 140 patients, and 10.7% have met the criterion for referral, and the results of genetic testing is pending (submitted for publication). For institutions in which prospective screening of all endometrial cancer patients does not seem practical, Fig. 1 offers a feasible, efficient method for screening those patients less than age 60. If this strategy were applied to all patients diagnosed annually with endometrial cancer in the United States (approximately 40,000), then 20,000 cases would be diagnosed earlier than age 60; within this group, those with any abnormal IHC staining would get triaged to a genetic counselor. Those under 60 with normal IHC but a significant family or personal history of Lynch-associated malignancies also would be referred. This screening algorithm eliminates the need for a proband's family to meet the stringent Amsterdam criteria to be referred for genetics consultation. Additionally, this strategy does not require a clinician to estimate a patient's risk of Lynch syndrome. By screening all patients and using simple triage strategies, we believe that more patients with endometrial cancer at risk for Lynch syndrome will be identified and referred for genetic assessment. Additionally, we recently performed a cost effectiveness analysis of prospective IHC testing on all newly diagnosed endometrial cancer patients for the primary triage of identifying patients at risk for Lynch syndrome. The algorithm described herein, compared with other strategies, was shown to most effectively balance cost and efficacy in the screening of patients with endometrial cancer for Lynch syndrome [42].

Conclusion

It is imperative that clinicians be mindful of the risk of Lynch syndrome in women with endometrial cancer. While most women with endometrial cancer present with early stage, curable endometrial disease, a diagnosis of colon cancer has a significantly worse prognosis. Given the opportunity for colon cancer screening and prevention strategies to be initiated, the identification of probands with endometrial cancer as a result of Lynch syndrome will lead to a reduction in morbidity and mortality for these patients and their families. Here, we present a simple algorithm for the screening of endometrial cancer patients, which is more likely to

identify patients with Lynch syndrome than current methods employing family or personal history. We believe these guidelines are feasible for use by gynecologic oncologists, surgical oncologists, general surgeons, medical oncologists, primary care providers and genetic counselors, and will lead to a decrease in the cancer burden as a result of Lynch syndrome.

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Fig. 1. Algorithm for prospective screening of all endometrial cancer patients less than age 60 using immunohistochemistry for the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*.

Table 1

SGO committee statement guidelines on risk assessment for Lynch syndrome [19].

For patients with a 20–25% risk of Lynch syndrome genetic risk assessment is strongly recommended, these patients include:

- 1 Family pedigrees meeting Amsterdam criteria
- 2 Those patients with metachronous or synchronous colorectal and endometrial or ovarian cancers prior to age 50
- 3 Those with a 1st or 2nd degree relative with a known germline mutation in a mismatch repair gene

For patients with a 5–10% risk of having Lynch syndrome genetic testing was classified as being “helpful”, these patients include:

- 1 Patients with endometrial or colorectal diagnosed prior to 50
 - 2 Patients with endometrial and/or ovarian cancer and a synchronous or metachronous Lynch-associated tumor at any age
 - 3 Patients with endometrial or colorectal cancer and a first-degree relative diagnosed with a Lynch-associated malignancy prior to 50
 - 4 Patients with colorectal or endometrial at any age with two or more 1st or 2nd degree relatives diagnosed with a Lynch-associated malignancy at any age
 - 5 A patient with a 1st or 2nd degree relative who meets the above criteria
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