Gynecologic Oncology 130 (2013) 121–126

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Implementation of tumor testing for lynch syndrome in endometrial cancers at a large academic medical center

Jessica Moline [a,b,c], Haider Mahdi [a,b,d], Bin Yang [e], Charles Biscotti [e], Andres A. Roma [e], Brandie Heald [a,b,c,f], Peter G. Rose [d], Chad Michener [d], Charis Eng [a,b,c,f,g,h,i,*]

[a] Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[b] Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[c] Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[d] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH 44195, USA
[e] Department of Anatomic Pathology, Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[f] Sanford R. Weiss M.D. Center for Hereditary Colorectal Cancer, Digestive Diseases Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[g] Stanley Shalom Zielony Institute of Nursing Excellence, Cleveland Clinic, Cleveland, OH 44195, USA
[h] Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, Ohio 44106, USA
[i] CASE Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH 44106, USA

HIGHLIGHTS

- There were no differences in age, histology, grade, stage, or BMI in patients with Lynch syndrome versus sporadic tumors.
- Universal screening in endometrial cancers is practical and eliminates the chance for missing eligible cases.
- Lynch syndrome screening in endometrial cancer is successfully implemented with collaboration among genetic counselors, gynecologic oncologists, and pathologists.

ARTICLE INFO

Article history:
Received 22 March 2013
Accepted 13 April 2013
Available online 20 April 2013

Keywords:
Endometrial cancer
Lynch syndrome
Microsatellite instability
Immunohistochemistry
Genetic counseling
Genetic testing

ABSTRACT

Objectives. Lynch syndrome (LS) is a hereditary condition that increases the risk for endometrial and other cancers. Recognizing women at risk for LS based on personal/family history is burdensome and imprecise. Tumor testing using microsatellite instability (MSI) testing and immunohistochemistry (IHC) for mismatch repair protein expression can be an effective strategy for identifying potential LS in patients presenting with colorectal or endometrial cancer. Here we describe our experience implementing a screening program for endometrial cancers.

Methods. Endometrial cancers diagnosed ≤50 years or those with suspicious personal history or histopathologic features were screened with MSI/IHC, June 2009–June 2011. Criteria were later (July 2011–July 2012) expanded to patients diagnosed <60 years, or at any age with suspicious features, and finally (after August 2012) universal screening was implemented. Screening techniques began with both MSI and IHC for every tumor, and later converted to IHC for two proteins, and *MLH1* promoter methylation analysis when indicated. A genetic counselor contacted patients directly to offer genetic counseling appointments.

Results. Two hundred and forty-five endometrial cancers (average age, 57 years) were screened. Sixty-two patients (25%) had abnormal results, and 42 patients were referred for genetic counseling. Of the 42 patients, 34 underwent genetic counseling, 28 pursued genetic testing, and 11 were diagnosed with LS. When age and pathology criteria were used, 27 eligible cases were overlooked for screening and 3 cases of LS were found only because a clinician requested screening.

Conclusions. Universal screening of endometrial cancers for LS is practical and successfully implemented with collaboration among genetic counselors, gynecologic oncologists, and pathologists.

Introduction

Lynch syndrome (LS) is an autosomal dominant disorder, caused by germ line mutations in the four mismatch repair (MMR) pathway genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and *EPCAM* deletion (resulting in *MSH2* promoter methylation), which increase the risk of endometrial,

* Corresponding author at: Cleveland Clinic, 9500 Euclid Avenue NE50, Cleveland, OH 44195. Fax: +1 216 445 6935.
E-mail address: engc@ccf.org (C. Eng).

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http://dx.doi.org/10.1016/j.ygyno.2013.04.022

colorectal, ovarian, gastric, small bowel, and other cancers. LS confers up to a 60% risk of endometrial cancer and accounts for 2%–6% of all endometrial cancers [1,2]. Nearly 50% of women with LS and multiple malignancies present with endometrial cancer as their first primary cancer [3]. It is therefore essential to identify endometrial cancer patients with LS to guide medical management and to help reduce the risk of additional cancers for the patient and relatives.

Traditional methods of identifying LS, including the Amsterdam criteria, have proven to be ineffective for endometrial cancer patients, with sensitivity <40% [1]. Tumor testing with microsatellite instability (MSI) testing and immunohistochemistry (IHC) for MMR protein expression are more sensitive methods of identifying LS. Over 90% of endometrial cancers caused by LS demonstrate MSI [1]. IHC for the MMR proteins has a sensitivity of approximately 94% and can be used alone or in conjunction with MSI to identify patients who for whom directed germ line testing is indicated [1].

Several large institutions across the United States have implemented universal screening using MSI and/or IHC in colorectal cancers due in part to the recommendation from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, stating that all newly diagnosed colorectal cancer patients should be offered testing for LS [4]. However, the only guidelines for MSI/IHC screening for LS in endometrial cancer state that testing should be considered for women diagnosed before the age of 50 years [5]. Since most women with LS are diagnosed with endometrial cancer after the age of 50 years and are more likely to be diagnosed with endometrial cancer than with colon cancer, there is a need for a better screening strategy in this population [6]. A few hospitals have begun screening endometrial cancers; however, the best screening criteria and methodology are not well established. Here we report on implementing and evaluating universal screening of endometrial cancers for LS at a large academic medical center.

Methods

Patients

MSI/IHC screening was performed for patients with endometrial cancer diagnosed at the Cleveland Clinic Main Campus based on provider request (surgeon or genetic counselor [GC]), or automatic screening criteria as outlined below. Cleveland Clinic gynecologic oncologists perform surgeries at Main Campus, as well as two regional hospitals, the latter with pathology departments that do not perform MSI/IHC. Screening criteria and methodology were determined by the Department of Anatomic Pathology and were modified over time. Data collected from the medical record included age at diagnosis, tumor characteristics, body mass index (BMI), and family history of cancer. This study was approved by the Cleveland Clinic Institutional Review Board.

Time frame 1

Beginning in June 2009, endometrial cancers in patients ≤50 years who underwent hysterectomy at the Cleveland Clinic main campus were screened for MSI with reflex to IHC for the MMR proteins MLH1, MSH2, MSH6, and PMS2 (Fig. 1). Microsatellite stable (MSS) tumors were also screened with IHC for MSH6 due to previous reports showing some MSS tumors deficient in MSH6 [1]. Individuals with a prior history of colon cancer or dedifferentiated/undifferentiated endometrial cancers regardless of age were also screened [7]. Beginning in January 2011, screening was also performed for endometrial cancers in patients <60 years old with certain pathological features previously described in LS (tumor infiltrating lymphocytes, isthmic tumor, synchronous endometrial carcinoma and ovarian clear cell carcinoma, ambiguous histology, mixed histology, and high grade tumors) [7]. In May 2011, screening was switched to an IHC-only approach, whereby eligible tumors were screened with IHC for MSH6 and PMS2. This technique is possible since MMR proteins function as heterodimers. PMS2 requires binding by MLH1, and MSH6 requires MSH2 as its binding partner. It has been shown that intact results for PMS2 and MSH6 alone confirms that all four mismatch repair proteins are intact in at least 95% of cases, while reducing testing costs [8]. If PMS2 or MSH6 were absent, additional IHC for MLH1 or MSH2 was performed, respectively.

Time frame 2

Screening criteria were expanded to all patients younger than 60 years who underwent hysterectomy at the Cleveland Clinic Main Campus July 2011–July 2012. Patients 60 years or older with pathology features as described above were also screened. Beginning in late July 2012, tumors deficient in MLH1/PMS2 were analyzed for *MLH1* promoter methylation.

Time frame 3

Starting in August 2012, all endometrial cancers diagnosed at Cleveland Clinic Main Campus were screened with IHC for MSH6 and PMS2. Data were captured until the end of December 2012.

A database search of all endometrial cancers diagnosed at the Cleveland Clinic since June 2009 was performed by the Department of Anatomic Pathology to determine the number of cases that were not screened despite meeting criteria.

MSI and IHC

MSI was performed as previously described [9]. The following antibodies were used to perform IHC: MLH1 (clone G168.15, 1:20

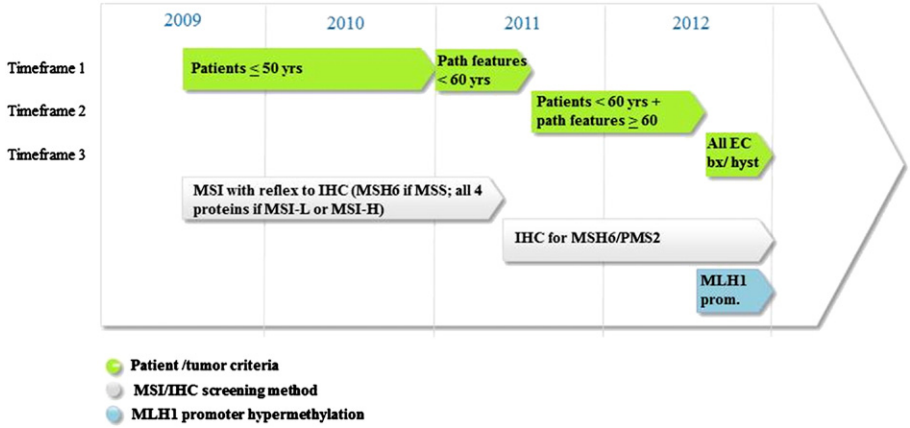

Fig. 1. Timeline of evolving criteria and methodology for Lynch syndrome screening in endometrial cancers. Path = pathology; MSI = microsatellite instability testing; IHC = immunohistochemistry; EC = endometrial cancer; bx = biopsy; hyst = hysterectomy.

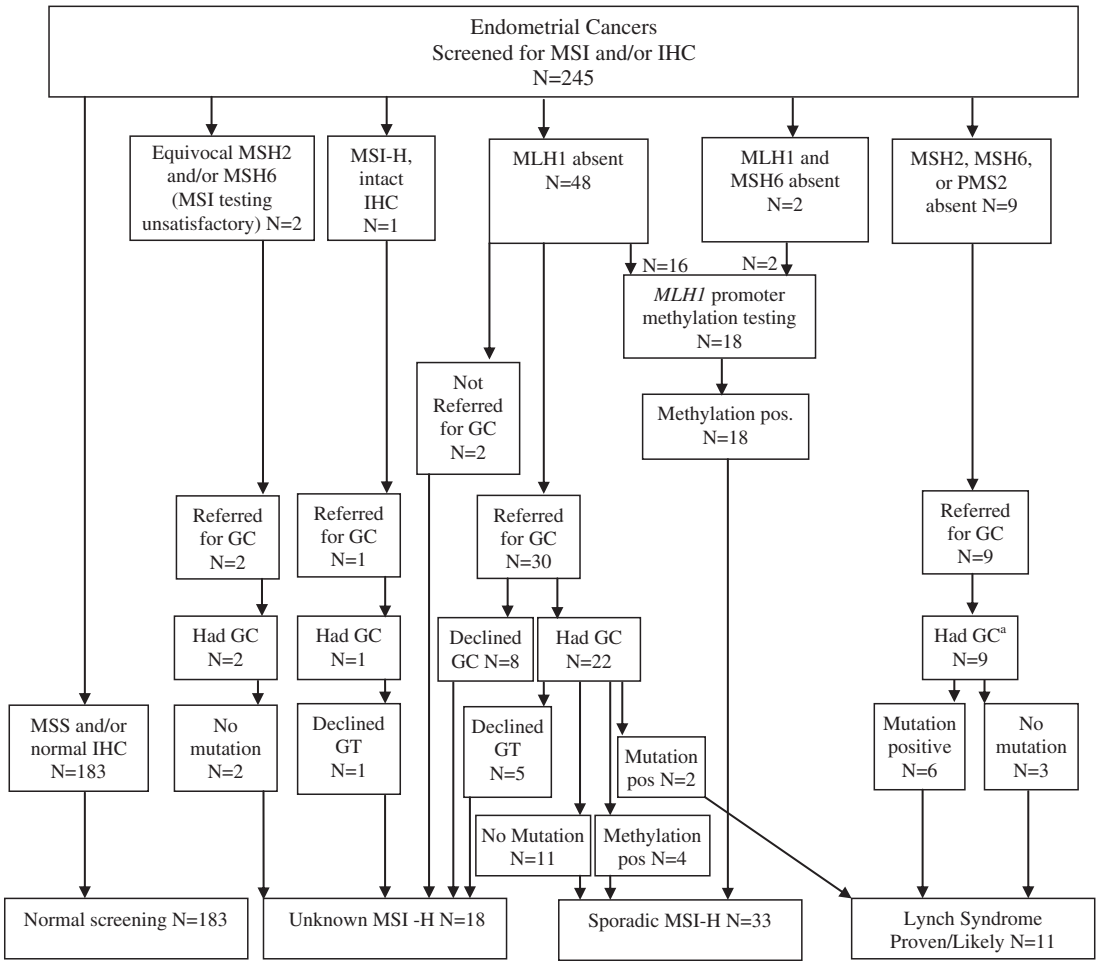

Fig. 2. Outcome of Lynch syndrome screening, genetic counseling, and genetic testing. MSI = microsatellite instability testing; IHC = immunohistochemistry; MSS = microsatellite stable; MSI-H = microsatellite instability high; GC = genetic counseling; GT = genetic testing; pos = positive. [a] Seven patients had GC based on abnormal IHC results; 2 patients had GC later on after diagnosed with colorectal cancer.

dilutions), MSH2 (clone A16-4, 1:100 dilutions), MSH6 (clone FE11, 1:100 dilutions) (Biocare Medical, Inc., Concord, CA), and PMS2 (clone BC/44, 1:1,000 dilutions) (BD PharMingen, Inc., San Diego, CA). IHC was performed using the standard streptavidin–biotin–peroxidase procedure and carried out by the Leica bond polymer refine DAB detection system (Leica Biosystem, Buffalo Grove, IL) following manufacturer's recommendations. Endometrial carcinoma and non-neoplastic endometrial tissue were used as positive and negative controls, respectively.

MLH1 promoter methylation

Tumors that lacked expression of PMS2 were sent to ARUP Laboratories for *MLH1* promoter methylation analysis. The GC would notify the primary pathologist and a pathology department coordinator when a paraffin block should be sent for testing. The analysis was performed via real-time polymerase chain reaction/fluorescence resonance energy transfer (www.aruplab.com).

Results disclosure

Results were sent to surgeons via an addendum to the surgical pathology report in the electronic medical record. A weekly report was also e-mailed to the GC by the Department of Anatomic Pathology. The GC notified the surgeon of abnormal results and also contacted the patient via telephone and/or letter to offer a genetic counseling appointment. This process was agreed upon among the gynecologic oncologists, pathologists, cancer geneticists, and GCs and was modeled after how colorectal MSI/IHC results are managed at the Cleveland Clinic [10].

Genetic counseling and testing

Typically, genetic counseling was available to the patient on the day of their post-operative visit. If MSI/IHC results or a GC was unavailable, appointments were scheduled at another time and location of the patient's choosing. Genetic counseling appointments could be made at the Cleveland Clinic Main Campus or one of four other satellite locations in the Cleveland area. Germ line testing and/or methylation studies were performed at commercial laboratories. Tumors were classified as follows: (1) sporadic MSS if they were MSS and/or had normal IHC expression; (2) sporadic MSI-H (microsatellite instability-high) if tumors lacked MLH1 expression and had negative *MLH1* germ line analysis and/or positive *MLH1* promoter methylation; (3) unknown MSI-H if there was no follow up testing, or equivocal IHC with normal germ line testing; or (4) LS proven/likely if a germ line mutation was identified or the tumor clearly lacked expression of MSH2 and/or MSH6.

Statistics

Data were analyzed using JMP Pro 9.0.0 statistical software. Descriptive statistics were calculated using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables.

Table 1
Patient and tumor characteristics.

	Sporadic MSS, $N = 183$ (75%)	Sporadic MSI-H, $N = 33$ (13%)	Lynch syndrome proven/likely, $N = 11$ (5%)	Total, $N = 227$ (100%)	p-value
Age, mean (range, SD) (years)	56.5 (22–88, 11.6)	61.3 (48–76, 7.2)	53 (45–60, 5.1)	57.1 (22–88, 11.0)	0.21
Age ≤50	51 (28%)	1 (3%)	4 (36%)	56 (25%)	0.47
Age 51–59	64 (35%)	15 (45%)	6 (55%)	85 (37%)	0.34
Age ≥60	68 (37%)	17 (52%)	1 (9%)	86 (38%)	0.06
Histology					
Endometrioid	142 (78%)	26 (79%)	9 (82%)	177 (78%)	0.89
Mixed epithelial	22 (12%)	4 (12%)	2 (18%)	28 (12%)	
Serous	11 (6%)	0	0	11 (5%)	
Sarcoma	4 (2%)	2 (6%)	0	6 (3%)	
Dedifferentiated	1 (1%)	1 (3%)	0	2 (1%)	
Clear cell	3 (2%)	0	0	3 (1%)	
Grade					
1	81 (44%)	6 (18%)	5 (45%)	92 (41%)	0.22
2	45 (25%)	16 (48%)	1 (9%)	62 (27%)	
3	16 (9%)	5 (15%)	3 (27%)	24 (11%)	
High	41 (22%)	5 (15%)	2 (18%)	48 (21%)	
Stage					
I	139 (76%)	25 (76%)	9 (82%)	173 (76%)	0.86
II	11 (6%)	0	0	11 (5%)	
III	17 (9%)	5 (15%)	2 (18%)	24 (11%)	
IV	12 (7%)	2 (6%)	0	14 (6%)	
Unknown	4 (2%)	1 (3%)	0	5 (2%)	
BMI, mean (range, SD) (kg/m^2)	34.4 (17.3–61.2, 10.2)	32.2 (17.4–57.4, 9.8)	32.2 (24.5–46.8, 6.7)	34.0 (17.3–61.2, 10.0)	0.53
FDR with LS cancer	38 (21%)	7 (21%)	5 (45%)	50 (22%)	0.07

MSS = microsatellite stable; MSI-H = microsatellite instability high; BMI = body mass index; FDR = first degree relative; LS = Lynch syndrome.

Results

A total of 245 primary endometrial cancers were screened over a period of 43 months. Overall, 62/245 patients (25%) had abnormal MSI and/or IHC results (Fig. 2). Of the 62 patients, 48 (77%) lacked expression of MLH1/PMS2, 5 lacked MSH2/MSH6, 2 lacked MSH6 only, 2 lacked PMS2 only, 2 demonstrated equivocal expression of MSH2 and/or MSH6, 1 was MSI-H with intact protein expression, and 2 lacked expression of MLH1/PMS2/MSH6.

Of the 62 patients, 42 (68%) with abnormal results were referred to genetics clinics, 18 (29%) had positive *MLH1* promoter methylation and therefore were assumed to have a sporadic MSI-H cancer and did not need genetic counseling, and 2 (3%) were not included on the weekly report to the GC and were not referred by their surgeon. Of the 42 patients who were referred to genetics, 32 (76%) promptly elected to have genetic counseling. Two additional patients only underwent genetic counseling after being diagnosed with metachronous colorectal cancer. All patients were offered confirmatory germ line testing for the gene(s) implicated by IHC results and/or *MLH1* promoter methylation analyses. Of the 34 patients who had genetic counseling, 28 (82%) underwent genetic testing in which 8 (29%) had positive results confirming a diagnosis of LS (2 *MLH1*, 2 *MSH2*, 2 *MSH6*, and 2 *PMS2*). Three other patients with IHC results strongly suggestive of LS (lack of MSH2/MSH6) had negative germ line testing. Because the possibility of an undetectable germ line mutation could not be ruled out, these 3 patients were classified as having LS.

A classification of sporadic MSS tumor, sporadic MSI-H tumor, or LS could be determined for 227 patients. Eighteen patients, including 2 patients who were not referred for genetic counseling, 14 patients who declined a genetics consultation or additional testing, and 2 with equivocal results, were left in an unknown MSI-H category. The mean age at diagnosis of the 227 patients was 57.1 years (range, 22–88; Table 1). The majority of tumors were of endometrioid-type histology (78%). Forty-one percent were grade 1 and 76% were stage 1. There were no statistical differences in age, BMI, tumor histology, FIGO grade, or stage in patients with LS versus those with a sporadic MSS or sporadic MSI-H tumor. There was a trend for LS patients to be diagnosed under the age of 60 years ($p = 0.06$) and to have a first-degree relative with a LS-associated cancer ($p = 0.07$).

Two hundred and twelve endometrial cancers screened met criteria as determined by the Department of Anatomic Pathology and 33 had screening ordered by the surgeon or a GC based on clinical suspicion (Table 2). Seven of the 212 that met screening criteria were initially missed for automatic screening but were later ordered by a clinician. Review of all endometrial cancer cases indicated that an additional 20 cases that met screening criteria prior to universal screening were

Table 2
Screening results per time frame.

	Time frame 1 (25 months)		Time frame 2 (13 months)		Time frame 3 (5 months)	Total	
Screened for LS	81		89		75	245	
Screening missed [a]	8		12		0	20	
	Met criteria, $N = 58$	Ordered, $N = 23$	Met criteria, $N = 79$	Ordered, $N = 10$	Met criteria, $N = 75$	Met criteria [c], $N = 212$	Ordered, $N = 33$
Abnormal IHC	17	9	14	5	17	48	14
MLH1 promoter methylation detected [b]	NA	NA	1	1	16	17	1
Lynch syndrome likely/proven	6 (10.3%)	2 (8.7%)	2 (2.5%)	0	1 (1.3%)	9 (4.2%)	2 (6.1%)

[a] Number of cases that qualified for screening based on pathology criteria but were not screened for LS.
[b] MLH1 promoter methylation analysis was automatically performed for cases lacking MLH1 expression beginning at the end of time period 2.
[c] Seven cases meeting criteria were ordered by a surgeon.

overlooked. The GC also reminded the pathology department to perform screening for 12 cases that met criteria and were discussed at tumor board (data not shown). Overall, 9 (4.2%) of 212 patients meeting criteria and 2 (6.1%) of 33 patients for whom screening was ordered were found to have LS ($p = 0.65$). A greater proportion of patients with LS were identified in time frame 1, which typically denotes underascertainment. As criteria broadened, not unexpectedly, the proportion of LS declined. However, universal screening had only been in place 5 months at the time of this analysis. The addition of *MLH1* promoter methylation testing also considerably decreased the number of patients who needed genetic counseling.

The characteristics of the 11 patients with proven or likely LS are summarized in Table 3. Five patients had MSI and IHC screening, and 6 patients had IHC only. Of note, Patient 7 had an MSS tumor with lack of expression of MSH6. Seven patients were diagnosed with endometrial cancer after the age of 50 years. Two patients diagnosed with LS did not meet automatic MSI/IHC criteria and had screening ordered by their surgeon. In the first patient (Patient 2), the reason for ordering screening was unclear as she had no concerning risk factors. The second patient (Patient 7) had screening ordered because of the history of endometrial cancer in the patient's mother. An additional patient (Patient 1) met screening criteria but was overlooked and screening was later ordered due to her personal and family history of colon cancer.

Discussion

It is well established that universal screening for LS is effective and should be offered for all colorectal cancer patients [4]. Screening for colorectal cancers has been performed at the Cleveland Clinic since 2004 and has evolved from screening only patients younger than 50 years to universal screening [10]. Our process of screening in endometrial cancers followed a similar evolution, but on a shortened timeline.

At the time we began, we were unsure if screening all endometrial cancers was feasible. Therefore, the criteria for screening were based largely on previous studies that demonstrated a high likelihood of LS in endometrial cancer patients diagnosed <50 years [11,12]. Feedback from the GC influenced modified screening criteria. For example, pointing out that 6 of 8 patients found to have LS during time frame 1 were older than 50 years prompted screening criteria to expand to all diagnosed patients younger than 60 years. Additionally, when *MLH1* promoter methylation testing was brought on, the suggestion to perform universal screening was accepted based on the fact that we would have fewer results necessitating genetic counseling. The observation that 27 eligible cases had been missed also argued for universal screening.

Screening techniques also evolved over time. Initially, MSI testing was performed for all eligible patients given input from the gastrointestinal pathologists, and our center was more experienced with MSI testing. IHC for MSH6 was performed for MSS tumors given previous reports [1], and in fact one of our patients with LS was identified this way. Results of MSI/IHC testing took anywhere from 2 weeks to 2 months. Later work showed that using a two-antibody screen was effective for LS screening [8,13]. We currently utilize the two-antibody approach and results are typically available in 7 business days. This method also cuts down on cost of screening and has allowed for complete results before a patient's post-operative visit and before the initiation of adjuvant treatment.

The benefits of tumor testing for LS can only be appreciated if providers and patients are informed of abnormal results and genetic counseling and/or high-risk screening is pursued. In our study, we found that two patients were not referred to genetics because they were missing from the weekly report to the GC. These two patients had tumors that lacked MLH1/PMS2 expression and were diagnosed over age 65 years, suggesting methylation of the *MLH1* promoter. A

Table 3
Characteristics of patients with proven or likely Lynch syndrome.

Patient no.	Age	Histology	FIGO grade	Met Amsterdam criteria	Met revised Bethesda criteria	Family history FDR	Personal history of other cancer	Met MSI/IHC screening criteria or ordered	MSI	Absent MMR protein	GC visit	Genetic testing results
1	54	Endometrioid	1	No	Yes	Yes	Colon dx 42	Met criteria[b]	5/5	MSH2	Yes	MSH2 c.1012G > C p.G338R
2	55	Endometrioid	1	No	No	No	No	Ordered	5/5	MSH2	Yes	No mutation in MSH2, EPCAM, or MSH6
3	49	Endometrioid	3	No	No	No	TCC bladder dx 49	Met criteria	ND	MSH2/MSH6	Yes	No mutation in MSH2, EPCAM, or MSH6
4	55	Mixed serous/endometrioid	High	No	No	Yes	No	Met criteria	4/5	MLH1(eq)/PMS2	Yes	PMS2 c.2113G > A p.E705K
5	59	Endometrioid	3	No	No[c]	No	Colon dx 61	Met criteria	5/5	MLH1/PMS2	No[a]	MLH1 exon 16–19 del
6	55	Endometrioid	1	No	No	No	No	Met criteria	ND	MSH2/MSH6	Yes	No mutation in MSH2, EPCAM, or MSH6
7	56	Endometrioid	3	No	No	Yes	No	Ordered	0/5	MSH6	Yes	MSH6 c.1176_1178delTGCinsGGAA
8	50	Mixed endometrioid/clear cell	High	Yes	No	Yes	No	Met criteria	ND	MLH1/PMS2	Yes	MLH1 c.1489delC
9	45	Endometrioid	2	No	No	No	No	Met criteria	ND	PMS2	Yes	PMS2 c.861_864delACAG
10	45	Endometrioid	1	No	No[c]	Yes	Rectal dx 46	Met criteria	ND	MSH2/MSH6	No[a]	MSH2 exon 8 del
11	60	Endometrioid	1	No	No	No	No	Met criteria	ND	MSH2(eq)/MSH6	Yes	MSH6 c.1421_1422dupTG

GC = genetic counseling; ND = not done; TCC = transitional cell carcinoma; eq = equivocal results.

[a] GC pursued after colorectal cancer diagnosis.

[b] Met screening criteria but initially missed by pathology and later ordered by surgeon.

[c] Met revised Bethesda criteria after second cancer diagnosis.

change in the search criteria used by the Department of Anatomic Pathology has since eliminated any missed reports to the GC. In our approach, 76% of patients referred for genetic counseling made and kept their appointments. This result is similar to what has been observed in our colorectal cancer population and is higher than previous reports in endometrial cancer [10,14]. In this study, we did not survey patients to determine what their motivations were for having genetic counseling. However, a strength of our genetics program is that same-day genetic counseling appointments as well as outreach locations are available and convenient for out-of-town patients. Also, the GC contacts the patient directly and may be better equipped to explain screening results and implications for the patient and her family as well as answer questions about what genetic counseling and testing entails.

It is important to point out, however, that two patients with abnormal IHC results who initially chose not to have genetic counseling were later diagnosed with colorectal cancers. The first patient had no reported family history of cancer and was diagnosed with endometrial cancer at age 59; IHC results showed a lack of MLH1/PMS2. At that time, *MLH1* promoter methylation was not routinely analyzed. The patient was referred for genetic counseling, but an appointment was not made due to concerns regarding insurance coverage. The patient was diagnosed with colon cancer 19 months later and then made a genetic counseling appointment. Additionally, her daughter was diagnosed with colon cancer in the interim and was found to have a germ line *MLH1* mutation, but the patient did not share this information with her physician. The other patient was a 45-year-old Spanish-speaking woman whose tumor showed lack of expression of MSH2/MSH6. The recommendation for genetic counseling was presented to the patient by her surgeon at the time of her post-operative visit, with her daughter translating, and she declined the visit. The GC later phoned the daughter to ensure the family understood the results and she scheduled an appointment, but the patient did not show. The patient was finally had genetic counseling after being diagnosed with stage IIIB rectal cancer 8 months later. The first case highlights the benefit of performing *MLH1* promoter methylation testing. If this had been performed, the patient could have been counseled by her physician that her results were consistent with LS and perhaps she would have pursued genetic counseling or additional cancer screening promptly. The second case raises the issue of whether to recommend high-risk cancer screening in patients with results, strongly suggestive of LS who defer a genetic counseling visit. This patient received pelvic radiation therapy for her endometrial cancer and later presented with rectal bleeding which prompted a colonoscopy. If she underwent a colonoscopy prior to radiation therapy, perhaps her rectal cancer could have been diagnosed at an earlier stage. In future cases highly suggestive of LS, LS cancer screening recommendations will be strongly considered whether or not genetic counseling is pursued. These cases stress the importance of the gynecologic oncologists' awareness of abnormal LS screening results and outcome or deferment of genetic counseling in order to appropriately counsel and manage patients.

At our institution, universal screening of all endometrial cancers using IHC for MSH6 and PMS2 has become the method of choice. Initial studies in LS screening in endometrial cancer suggested that only patients diagnosed $\leq$50 years would benefit from screening. If we used this as or only cutoff, 7/11 patients with LS would have been missed. One could argue that screening in patients diagnosed $\leq$60 years would have identified all patients with LS in our cohort. However, universal screening had only been in place for 5 months at the time of this analysis, so additional data are needed to determine the incidence of LS in our older patient population. Other studies have found that there is still a significant risk of LS in patients older than age 60 years diagnosed with endometrial cancer [2]. Furthermore, given the inconsistencies among pathologists in recognizing patients meeting screening criteria, universal screening is our best option to avoid missing cases and to capture all at-risk patients. Since women with LS are often diagnosed with endometrial cancer as their sentinel cancer, and the incidence of LS in endometrial cancer (2%–6%) is similar to that of colon cancer (3%), universal screening in this population is extremely beneficial in identifying patients with LS [1,11,12,15]. Close partnerships among gynecologic oncologists, GCs, and pathologists are essential to the success of universal LS screening.

Conflict of interest statement

All authors declare that there are no conflicts of interest.

Acknowledgments

C.E. is the Sondra J. and Stephen R. Hardis Chair of Cancer Genomic Medicine at the Cleveland Clinic and is an American Cancer Society Clinical Research Professor, generously funded in part by the F.M. Kirby Foundation.

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