Original Article

Maximizing Cancer Prevention Through Genetic Navigation for Lynch Syndrome Detection in Women With Newly Diagnosed Endometrial and Nonserous/Nonmucinous Epithelial Ovarian Cancer

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BACKGROUND: Despite recommendations for reflex immunohistochemistry (IHC) for mismatch repair (MMR) proteins to identify Lynch syndrome (LS), the uptake of genetic assessment by those who meet referral criteria is low. The authors implemented a comprehensive genetic navigation program to increase the uptake of genetic testing for LS in patients with endometrial cancer (EC) or nonserous/nonmucinous ovarian cancer (OC). **METHODS:** Participants with newly diagnosed EC or OC were prospectively recruited from 3 cancer centers in Ontario, Canada. Family history questionnaires were used to assess LS-specific family history. Reflex IHC for MMR proteins was performed with the inclusion of clinical directives in pathology reports. A trained genetic navigator initiated a genetic referral on behalf of the treating physician and facilitated genetic referrals to the closest genetics center. **RESULTS:** A total of 841 participants (642 with EC, 172 with OC, and 27 with synchronous EC/OC) consented to the study; 194 (23%) were MMR-deficient by IHC. Overall, 170 women (20%) were eligible for a genetic assessment for LS: 35 on the basis of their family history alone, 24 on the basis of their family history and IHC, 82 on the basis of IHC alone, and 29 on the basis of clinical discretion. After adjustments for participants who died (n = 6), 149 of 164 patients (91%) completed a genetic assessment, and 111 were offered and completed genetic testing. Thirty-four women (4.0% of the total cohort and 30.6% of those with genetic testing) were diagnosed with LS: 5 with mutL homolog 1 (*MLH1*), 9 with mutS homolog 2 (*MSH2*), 15 with mutS homolog 6 (*MSH6*), and 5 with *PMS2*. **CONCLUSIONS:** The introduction of a navigated genetic program resulted in a high rate of genetic assessment (>90%) in patients with gynecologic cancer at risk for LS. ***Cancer* 2021;127:3082-3091**.

KEYWORDS: genetic navigator, genetic uptake, Lynch syndrome.

INTRODUCTION

Lynch syndrome (LS) is caused by autosomal dominant mutations in the mismatch repair (MMR) genes (mutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], mutS homolog 6 [*MSH6*], *PMS2*, and *EPCAM*), and it puts individuals at a lifetime risk of 40% to 80% for colorectal cancer (CRC), 33% to 61% for endometrial cancer (EC), and 9% to 12% for ovarian cancer (OC) as well as an increased risk of gastric, hepatobiliary, and central nervous system cancers.[1-4] Identification of LS carriers and their first-degree relatives through cascade testing is critical for cancer prevention through surveillance for

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LS-associated malignancies, chemoprevention, and risk-reducing gynecologic and colorectal surgeries. Because ECs/OCs are often the sentinel cancers in women with LS at a median age at diagnosis of 47 years,[4-6] the diagnosis of LS can open doors to effective colonoscopic surveillance, which leads to a 60% reduction in the incidence of CRC and up to a 70% reduction in CRC-related mortality.[7] Cascade testing of at-risk relatives will also identify young unaffected individuals who would benefit the most from an early diagnosis of LS.

Because of the importance of early LS identification, the National Comprehensive Cancer Network recommends tumor testing with immunohistochemistry (IHC), microsatellite instability testing, and, most recently, consideration of comprehensive molecular testing in all EC cases.[8] Multiple studies have demonstrated that universal IHC for MMR proteins in EC/CRC is the best and most cost-effective strategy for identifying patients at risk of LS, with up to 100% sensitivity reported in the literature.[8-10] In most centers, individuals with mismatch repair–deficient (MMRd) gynecologic tumors on IHC without somatic *MLH1* methylation are referred for genetic counseling for consideration of germline testing.[11]

Despite the implementation of universal IHC screening in EC and CRC to identify LS, uptake of genetic assessment remains low.[12] In a review of US institutions that had initiated reflex IHC in CRC, 67% of centers had low participant uptake of genetic testing, with less than 40% of eligible patients participating.[12] Similarly, in our previously published pilot study of 118 unselected women with EC, only 55% of eligible participants completed genetic testing.[5] Low uptake of genetic assessment has been attributed to barriers that exist on multiple levels. Systemic barriers include a lack of IHC expertise and/or a reflex IHC process, a lack of process for the disclosure of results by treating providers, a lack of clear language or directives in the pathology report, a delay between IHC results and the cancer diagnosis, and the physical distance to genetic counseling centers.[12-14] Patient-specific barriers include a lack of knowledge and awareness of the personal risk of preventable cancers and genetic services available to them.[15,16] Furthermore, there is a perceived lack of relevance and utility as well as concerns about the genetic assessment process and worries about cost and insurance coverage.[17,18] There are care provider–related barriers as well because they may not be aware of the importance of genetic assessment for their patients or lack knowledge about logistical details for the coordination of referrals. Adding to this, the workup of LS is molecularly complex because multiple genes can be involved through different mechanisms, and it sometimes requires somatic testing, which necessitates more guidance for the unfamiliar clinicians. Notwithstanding these barriers, once patients get to their genetic counseling appointment, the uptake of genetic testing is high (77%-90%).[19,20]

To address the identified barriers that prevent individuals from accessing genetic services, we developed a navigated genetic program to improve the uptake of genetic assessment. The primary aim of our study was to prospectively evaluate and determine whether our novel navigated genetic program increased the uptake of genetic counselling and testing in individuals with newly diagnosed EC and nonserous/nonmucinous OC.

MATERIALS AND METHODS

Participants

Participants were prospectively recruited from 3 gynecologic cancer centers in Ontario, Canada, between September 2015 and June 2019 to evaluate the impact of a navigated genetic program on the uptake of genetic counseling and testing.[4,21] Institutional research ethics board approval and written informed consent were obtained. Participants were younger than 70 years with newly diagnosed EC of all stages and histologies or with newly diagnosed nonserous, nonmucinous epithelial OC of all stages. For the pathologic diagnosis of synchronous EC/OC, previously published criteria were used: no tumor between 2 sites, no metastasis from one site to another, and the diagnosis of 2 tumor sites within 2 months of each other.[22] All participants completed an extended family history questionnaire (eFHQ; see the supporting information), and their tumors were tested with IHC for MMR protein expression reflexively. Participants with the loss of 1 or more MMR proteins in the tumor without evidence of *MLH1* methylation or with a family history suggestive of LS (as assessed by the eFHQ) were offered referrals for genetic assessment. If participants did not meet IHC or eFHQ criteria but had a concerning family history, these cases were reviewed with the genetic counselor, who then decided whether a referral was required or not (referred according to clinical discretion). Genetic testing was then offered by the genetic counsellor on the basis of his or her assessment and the standard of care. Participants had the option of consenting to a molecular assessment of their tumor and blood specimens instead of participating in the full navigated genetic program.

The eFHQ (see the supporting information) was developed as previously described to create a 3-generation pedigree, and details from this were used to determine

which participants met criteria based on Amsterdam Criteria II, the Society of Gynecologic Oncologists criteria (20-25%), and the Ontario Ministry of Health and Long-Term Care family history.[4,23,24] If participants met 1 or more criteria, they were referred for genetic counseling. *MLH1* methylation testing was not offered until December 2018, so until then, women older than 60 years with MLH1-deficient tumors were assumed to harbor *MLH1* promoter methylation and were not offered further genetic assessment unless they met family history criteria.[10] Starting in December 2018, all MLH1-deficient cases were reflexively tested for *MLH1* methylation as per the clinical standard of care in Ontario, Canada. All MMR IHC tests were performed by a gynecologic pathologist who was blinded to the germline results. IHC was used to test for the expression of MLH1, MSH2, MSH6, and PMS2 proteins as described previously.[4] Clinical and pathologic information was collected prospectively.

Navigated Genetic Program

Before the implementation of our enhanced genetic program, the standard of care relied on a genetic referral from the treating physician based on a participant's family history criteria. In response to the low uptake of genetic testing demonstrated in our pilot study,[5] we designed a novel enhanced navigated genetic program to address previously described barriers to genetic assessment to improve participant uptake.[15,17,18,25] Our intervention included the following: 1) reflex IHC results incorporated into pathology reports with standard wording and clinical directives (see the supporting information); 2) a letter to the treating physician (see the supporting information) indicating that the participant was a candidate for genetic counseling on the basis of tumor IHC results, that he or she should review these results with the participant and explain the importance of genetic assessment; and that a referral would be sent to the genetic center on his or her behalf; and 3) navigation by an individual trained by genetic counsellors who would coordinate the entire process (a genetic navigator).

The roles of the dedicated genetic navigator are highlighted in Figure 1. This individual was trained by a certified genetic counsellor before contacting study participants. The genetic navigator screened all study participants to determine their eligibility for genetic counseling on the basis of MMRd status by IHC and/or a family history. Those who met eligibility requirements were contacted by phone and informed that a genetic referral would be made. Participants were also asked for their preferred genetic counseling location because they had the option

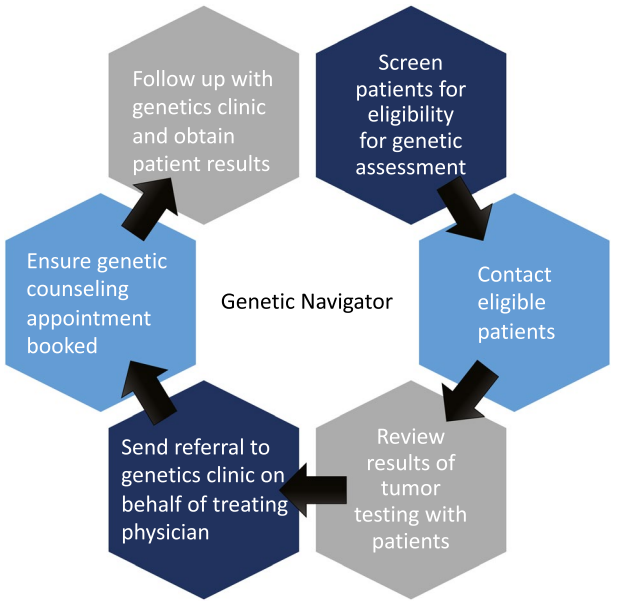

Figure 1. Facilitation of genetic counseling referrals for eligible participants by the study genetic navigator. The role of our dedicated genetic navigator throughout the genetic referral process is highlighted.

of attending the appointment at the treating institution or closer to home. Once participants were informed about the genetic counseling referral, the referral was sent to the genetics clinic on behalf of the treating physician. A letter to the treating physician was sent to inform him or her that a referral was sent and to remind the physician to discuss the importance of genetic counseling with the participant. The genetics clinics then scheduled an appointment for those participants meeting their criteria. The genetic navigator ensured that an appointment was booked and that all participants attended the clinic, with appropriate testing ordered, and also followed up on the results.

Statistical Analysis

On the basis of our prospective pilot study findings, we hypothesized that 213 of 850 participants (25% of cohort) would be eligible for a genetic assessment.[5] We also hypothesized that our navigated genetic program might increase genetic testing from the rate of 55% seen in our pilot to 80%, with an increase to 70% considered clinically important. A sample size of 213 eligible participants would achieve 99% and 100% power to detect differences of 0.15 and 0.25, respectively, with a 2-sided exact test. The type I error rate was considered to be 0.025, and the population proportion under the null hypothesis was 55%. Use of the pilot cohort as a historical control is a valid strategy in implementation research and has been

TABLE 1. Clinical Characteristics of the Participants

Characteristic	Total Cohort (n = 841)	Lynch Syndrome (n = 34)	MMR-Deficient[a] (n = 161)	MMR-Intact (n = 646)	*P*
Age at diagnosis, median (range), y	59 (20-71)	53 (34-69)	61 (42-70)	59 (20-71)	<.001
Tumor type, No. (%)					<.001
Endometrial	642 (76.3)	23 (67.7)	145 (90.0)	474 (73.4)	
Nonserous/nonmucinous ovarian	172 (20.5)	6 (17.7)	9 (5.6)	157 (24.3)	
Synchronous	27 (3.2)	5 (14.6)	7 (4.4)	15 (2.3)	
Ovarian histology, No. (%)	n = 199	n = 11	n = 16	n = 172	.005
Endometrioid	94 (47.2)	7 (63.6)	10 (62.5)	77 (44.8)	
Clear cell	84 (42.2)	2 (18)	3 (18.8)	79 (45.9)	
Mixed	13 (6.5)	1 (9.0)	2 (12.5)	10 (5.8)	
Undifferentiated	1 (0.5)	1 (9.0)	0	0	
Carcinosarcoma	6 (3.0)	0	1 (6.3)	5 (2.9)	
Other	1 (0.5)	0	0	1 (0.6)	
Endometrial histology, No. (%)	n = 669	n = 28	n = 152	n = 489	<.001
Endometrioid	512 (76.5)	21 (75.0)	128 (84.2)	363 (74.2)	
Serous	79 (11.8)	1 (3.6)	3 (2.0)	75 (15.3)	
Clear cell	5 (0.7)	1 (3.6)	1 (0.7)	3 (0.6)	
Mixed	40 (6.0)	3 (10.7)	16 (10.5)	21 (4.3)	
Undifferentiated	8 (1.2)	1 (3.6)	4 (2.6)	3 (0.6)	
Carcinosarcoma	22 (3.3)	1 (3.6)	0	21 (4.3)	
Other	3 (0.4)	0	0	3 (0.6)	
FIGO grade, No. (%)					<.001
1	381 (45.3)	12 (35.3)	64 (39.8)	305 (47.2)	
2	179 (21.3)	12 (35.3)	60 (37.3)	107 (16.6)	
3	281 (33.4)	10 (29.4)	37 (23.0)	234 (36.2)	
Ovarian FIGO stage, No. (%)[b]	n = 199	n = 11	n = 16	n = 172	.220
I	133 (66.8)	5 (45.5)	10 (62.5)	118 (68.6)	
II	32 (16.1)	4 (36.4)	5 (31.3)	23 (13.4)	
III	31 (15.6)	2 (18.1)	1 (6.3)	28 (16.3)	
IV	3 (1.5)	0	0	3 (1.7)	
Endometrial FIGO stage, No. (%)[c]	n = 669	n = 28	n = 152	n = 489	.190
I	502 (75.0)	20 (71.4)	109 (71.7)	373 (76.3)	
II	72 (10.8)	5 (17.9)	21 (13.8)	46 (9.4)	
III	69 (10.3)	3 (10.7)	19 (12.5)	47 (9.6)	
IV	26 (3.9)	0	3 (2.0)	23 (4.7)	
Met family history criteria, No. (%)					<.001
Lynch syndrome	68 (10.8)	16 (48.5)	16 (11.6)	36 (7.8)	
Hereditary breast and ovarian cancer	18 (2.9)	0	4 (2.9)	14 (3.0)	
No criteria met	546 (86.4)	17 (51.5)	118 (85.5)	411 (89.2)	
Missing	209	1	23	185	

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; MMR, mismatch repair.
[a]MMR-deficient cases without Lynch syndrome.
[b]Includes the ovarian component of the synchronous cases.
[c]Includes the endometrial component of the synchronous cases.

used by other groups.[26] All categorical variables were reported as counts and percentages, whereas continuous variables were reported as medians and ranges. Statistical significance was considered to be $P < .05$. For all analyses, SAS (version 9.3) or R (version 3.5.1) was used.

RESULTS

Description of the Cohort

Table 1 describes the clinical and pathologic characteristics of the study cohort. Among the 841 participants, 34 (4%) had confirmed LS, 161 (19%) had MMRd tumors without LS, and 646 (77%) had MMR-intact tumors. The median age of the total cohort was 59 years (range, 20-71 years), with LS participants being significantly younger (53 years; range, 34-69 years) than those with MMRd tumors (61 years; range, 42-70 years) or MMR-intact tumors (59 years; range, 20-71 years; $P < .001$). Although small in number, there was a higher proportion of synchronous EC/OC cases (n = 5; 15%) in LS carriers versus those with MMRd (n = 7; 4%) or MMR-intact tumors (n = 15; 2%; $P < .001$). The majority of Lynch-associated OCs and ECs tended to be endometrioid in histology (64% of OCs and 75% of ECs)

TABLE 2. Characteristics of Participants With Lynch Syndrome According to Gene Mutations

Gene	No. of Participants	EC, No.	OC, No.[a]	Sync, No.	Age, Median (Range), y	Lynch Syndrome–Specific Family History, No. (%)	Presenting With Sentinel Malignancy, No. (%)
MLH1	5	3	1	1	45 (35-62)	5 (100)	5 (100)
PMS2	5	3	1	1	56 (54-59)	1 (20)	5 (100)
MSH2	9	8	1	0	48 (36-58)	5 (56)	8 (89)
MSH6	15	9	3	3	53 (34-69)	4 (29)	15 (100)
Total	34	23	6	5	52 (34-69)	15 (44)	33 (97)

Abbreviations: EC, endometrial cancer; MLH1, mutL homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; OC, ovarian cancer; Sync, synchronous endometrial and ovarian cancer.
[a]Nonserous/nonmucinous OC.

and low in grade (71% at grade 1 or 2) and stage (45.5% of OCs at International Federation of Gynecology and Obstetrics [FIGO] stage I and 71.4% of ECs at FIGO stage I). In the LS cohort, 16 (48.5%) had a family history of LS-associated cancers; this rate was significantly higher than the rate in the MMRd cohort (n = 16; 11.6%) or the MMRi cohort (n = 36; 7.8%; $P < .001$).

The overall incidence of LS among participants consenting to our genetic navigator–facilitated program was 4.0%: 4.0% of EC cases, 3.5% of nonserous/nonmucinous OC cases, and 18.5% of synchronous EC/OC cases (Supporting Table 1). Of the 34 participants with confirmed LS, 5 had pathogenic germline variants in *MLH1*, 5 had pathogenic germline variants in *PMS2*, 9 had pathogenic germline variants in *MSH2*, and 15 had pathogenic germline variants in *MSH6* (Table 2). Twenty-three of the 34 participants (68%) had EC, 6 (18%) had nonserous/nonmucinous OC, and 5 (15%) had synchronous EC/OC. The median age was lowest for those with *MLH1* germline mutations (45 years; range, 35-62 years) and highest for those with *PMS2* mutations (56 years; range, 54-59 years). For 33 of the 34 participants (97%), the presenting gynecologic cancer was their sentinel malignancy (Table 2). For 28 of the 34 participants (82%), their cancer was the sentinel malignancy for the family enabling the diagnosis of LS. The majority of Lynch syndrome carriers (30 of 34; 88%) had a Lynch-associated cancer in the family.

Uptake of Genetic Testing

Among the 880 participants who met the eligibility criteria for study inclusion, there were 39 who consented to molecular testing only. In total, 841 consented to the full navigation study: 642 EC cases, 172 nonserous/nonmucinous OC cases, and 27 synchronous cases of EC/OC. Among these 841 participants, 628 (75%) completed their eFHQ, and 68 of these participants (11%) met the family history criteria for a genetic counseling referral (Fig. 2). IHC was completed for 840 of the 841 cases, and 194 (23%) were MMRd. After the exclusion of 81 participants who were not eligible because of either confirmed *MLH1* methylation or an age older than 60 years with MLH1-deficient tumors and without a significant family history, 170 of the 841 participants (20%) were eligible for a genetic assessment. Thirty-five of these 170 participants (21%) met family history criteria alone, 82 (48%) met IHC criteria alone, and 24 (14%) met family history and IHC criteria. Twenty-nine of the 170 participants (17%) were referred on the basis of the clinical discretion of the genetic navigator (because they had a family history but did not meet the formal criteria or because they had a personal history of other cancers).

Of the 170 participants who were referred for genetic assessment, 149 (88%) attended their appointment. When we excluded the 6 (4%) who died before their appointment, the adjusted attendance rate was 90.8% (149 of 164), which was significantly higher than the rate from our pilot study (90.8% vs 55%; $P < .001$). Of the 149 participants who attended genetic appointments, 111 were offered genetic testing (74%), and all 111 (100%) consented to proceed with testing. This rate was significantly higher than the rate reported in our pilot study (100% vs 75%; $P < .001$). Thirty-eight participants were not offered any genetic testing after their assessment by the genetic counselor; 30 of these 38 participants had MMR-intact tumors, and 4 had *MLH1*-methylated tumors.

Of the 111 participants who completed genetic testing, 34 had confirmed LS (31%), 12 had a variant of unknown significance in the MMR genes (11%), and 65 had negative results (59%). Of the 77 participants with either a variant of unknown significance in MMR genes or negative germline results, 23 (30%) had *MLH1*-methylated tumors confirmed through methylation testing, whereas 20 (26%) had further somatic testing of their tumors and were found to have biallelic somatic mutations. Fifteen of the 164 participants (9%) did not attend their genetic appointments, with 11 participants (73%) declining the appointment and 4 (26%) being no-shows.

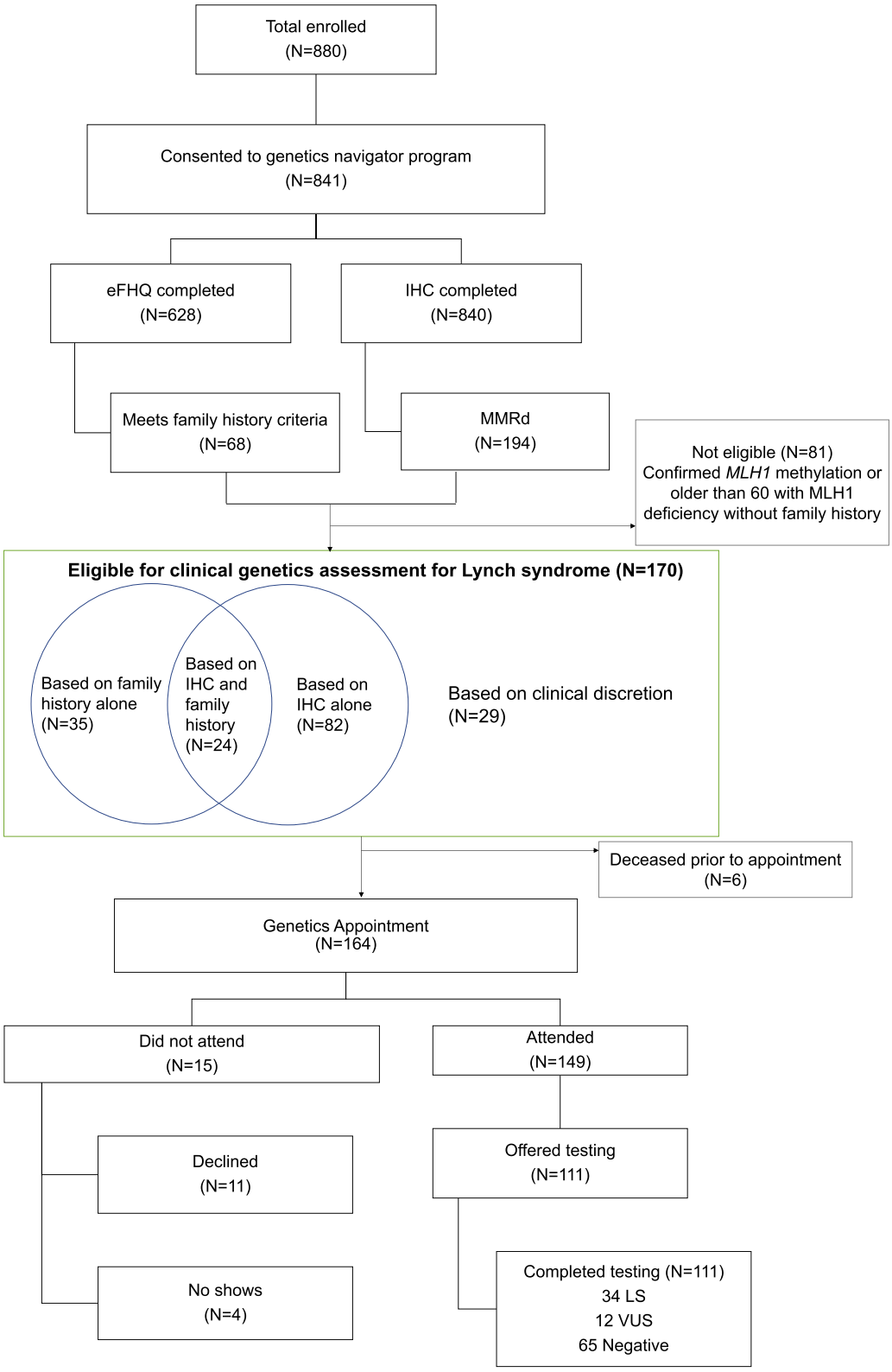

Figure 2. Overview of eligibility for genetic counseling/testing and uptake. eFHQ indicates extended family history questionnaire; IHC, immunohistochemistry; LS, Lynch syndrome; MLH1, mutL homolog 1; MMRd, mismatch repair–deficient; VUS, variant of unknown significance.

TABLE 3. Overview of All Recruited Cases by Histology and Mismatch Repair Status

	EC (n = 642)		Nonserous/Nonmucinous OC (n = 172)		Synchronous: Endometrial Component (n = 27)		Synchronous: Ovarian Component (n = 27)	
Pathology	Total, No.	MMRd, No. (%)	Total, No.	MMRd, No. (%)	Total, No.	MMRd, No. (%)	Total, No.	MMRd, No. (%)
Grade 1 endometrioid	309	63 (20)	38	0	20	5 (26)	19	5 (28)
Grade 2 endometrioid	129	52 (41)[a]	24	6 (25)	5	5 (100)	4	1 (25)
Grade 3 endometrioid	48	23 (48)	8	2 (25)	1	1 (100)	0	0
Endometrioid, grade not specified	0	0	1	0	0	0	0	0
Serous	79	4 (5)	—	—	0	0	—	—
Clear cell	5	2 (40)	82	3 (4)	0	0	2	2 (100)
Mixed	40	19 (48)	13	3 (23)	0	0	0	0
Undifferentiated	8	5 (63)	0	0	0	0	1	1 (100)
Carcinosarcoma	21	0	5	1 (20)	1	0	1	0
Other	3	0	1	0	0	0	0	0
Total by case type	642	168/641 (26)	172	15/172 (8.7)	27	11/27 (42)	27	9/27 (33)

Abbreviations: EC, endometrial cancer; MMRd, mismatch repair–deficient; OC, ovarian cancer.
Equivocal cases were counted as intact (EC, 5; OC, 2); cases with focal loss were counted as MMRd (EC, 16; OC, 3).
[a]One EC case with immunohistochemistry not completed.

Pretest Probability by Type of Cancer and MMR Status

The MMRd rate was 26% (168 of 641) in EC, 8.7% (15 of 172) in nonserous/nonmucinous OC, 42% (11 of 27) in the EC component of synchronous EC/OC, and 33% (9 of 27) in the OC component of synchronous EC/OC (Table 3). In EC, OC, and synchronous cases, the MMRd frequency was highest for the endometrioid histotype (82%, 53%, and 100% in the synchronous endometrial component and 67% in the synchronous ovarian component).

Although nonserous/nonmucinous OC had the lowest MMRd rate (8.7%), the pretest probability of LS among those with MMRd tumors was high at 40% (6 of 15; Table 4). The pretest probability of LS in MMRd EC was 13.6%, and it was 36.4% for synchronous EC/OC. The rate of LS was highest in those with a PMS2 deficiency (71%), who were closely followed by those with an MSH6 deficiency (58%) or an MSH2/MSH6 deficiency (37%). The pretest probability for LS was lowest in those with an MLH1/PMS2 deficiency (2.2%). One case of LS was missed by IHC testing, and this participant had a synchronous EC/OC with a pathogenic *PMS2* mutation. This participant was referred for genetic assessment on the basis of the genetic navigator's clinical discretion. The clinical characteristics of LS carriers are available in Supporting Table 2.

DISCUSSION

Early identification of LS leads to lifesaving interventions that start with the screening and surveillance of Lynch-associated cancers and surgical and chemoprevention strategies for affected carriers and their families. Once LS is identified, surveillance colonoscopies can significantly reduce the incidence of and deaths from CRC as well as overall mortality.[27] This presents a significant opportunity for cancer prevention in women presenting with gynecologic cancer as their sentinel malignancy because the development of EC/OC often precedes the development of CRC in these women.[1] In our study cohort, 97% of LS carriers presented with gynecologic cancer as their sentinel cancer; this rate is significantly higher than the rate of 50% reported in the literature.[6] Because of our unselected prospective population, our rate is likely a more accurate reflection of gynecologic sentinel cancer in LS carriers. The youngest LS participant in our study presenting with a gynecologic malignancy as her sentinel cancer was 34 years old. This finding clearly highlights the importance of a thorough genetic assessment in the young EC/OC population because it may significantly reduce the risk for subsequent cancers.

Our prospective study shows that a genetic navigator–facilitated program can effectively increase the rate of compliance with genetic counseling and testing in patients with gynecologic cancer at risk for LS. Our navigated program addressed multiple systems-related, patient-related, and care provider–related barriers with the end goal of patients being referred and assessed by genetic counsellors on a timely basis. Some of these systems-related barriers included the following: 1) IHC being performed in a research setting and not being included in the pathology report (hence the treating physician could not reinforce the importance of genetic counseling/testing); 2) IHC being

TABLE 4. Pretest Probability by Case Type and Immunohistochemistry Results

Case Type	LS+ Among MMRd	LS+ Among MLH1–/PMS2–	LS+ Among MSH2–/MSH6–	LS+ Among MSH6–	LS+ Among PMS2–	LS+ Among All Proteins Deficient
EC only	23/168 (14%)	2/123 (2%)	10/25 (40%)	6/13 (46%)	4/6 (67%)	1/1 (100%)
OC only[a]	6/15 (40%)	1/7 (14%)	1/4 (25%)	3/3 (100%)	1/1 (100%)	0/0
Sync EC component	4/11 (36%)[b]	1/7 (14%)	0/1	3/3 (100%)	0/0	0/0
Total	33/194 (17%)	4/137 (3%)	11/30 (37%)	12/19 (63%)	5/7 (71%)	1/1 (100%)

Abbreviations: EC, endometrial cancer; LS, Lynch syndrome; MLH1, mutL homolog 1; MMRd, mismatch repair–deficient; MSH2, mutS homolog 2; MSH6, mutS homolog 6; OC, ovarian cancer; Sync, synchronous endometrial and ovarian cancer.

[a]Nonserous/nonmucinous OC.

[b]One synchronous case with LS missed by immunohistochemistry testing (pathogenic *PMS2*).

completed in batches, which led to a delay from diagnosis; 3) the genetic referral process being solely dependent on the treating physician to initiate; and 4) the physical distance between participants and genetic counseling centers. Patient-related barriers that we addressed included 1) a lack of patient education throughout the process and 2) patients having to return to the treating center for genetic counseling. Provider-related barriers that we addressed included 1) a lack of provider education about the importance of following up with IHC results and 2) a lack of awareness of the logistics of the genetic referral process.

To address the systems-related barriers, our program instituted expert IHC testing and ensured timely disclosure of genetic results to participants and providers, and it successfully facilitated all genetic appointments with coordination by the genetic navigator. We essentially created a streamlined workflow through which reflexive IHC testing was reported with a clinical directive in the pathology report along with a letter to the treating physician. Furthermore, we addressed the patient-related and care provider–related barriers by empowering patients and their primary care providers with knowledge of the implications of screen-positive results. With the process outlined in this study, IHC and methylation testing is now reflexively performed on all EC specimen in the province of Ontario.[10] Streamlining of universal tumor screening and subsequent testing is essential to identify at-risk families and has been found to be superior to a family history alone in numerous studies.[5,28]

In breast, colorectal, and multiple other cancer types, similar issues exist with a low rate of genetic assessment and germline mutation analysis.[29,30] For example, in the population with newly diagnosed early-stage breast cancer, only 23% to 43% of patients receive genetic counseling, and only 20% to 30% receive genetic testing.[31] In all of the aforementioned cancer types, similarly to gynecologic malignancies, genetic test results can not only alter oncologic management but also offer an opportunity for cancer prevention for the patients and their family members. Various strategies to improve access and testing have been applied for these cancer types. For example, the concept of patient navigation has been a popular strategy. Given the dismal rates of genetic testing reported in the literature (eg, 10% in OC populations and 15% in breast cancer populations[32]), the American Society of Clinical Oncology has suggested improving access to genetic counseling and genetic testing by training nongenetic health care providers to perform risk assessments, obtain informed consent, and facilitate genetic testing.[33] These individuals are known as genetic counseling extenders. They are trained by certified genetic counselors to play roles similar to that of the

genetic navigator in our study; these individuals were able to increase patient access to genetic services by a factor of 4 in the context of *BRCA1/2* genetic testing.[25] Other programs have focused on training physicians or implementing "mainstreaming," in which specialties other than genetics can initiate the testing.[34] The problems with these previous strategies lie in the fact that they attempt to address 1 main barrier rather than addressing the multifaceted barriers as described in the literature. By addressing systems-related, participant-related, and care provider–related barriers, our multipronged approach significantly increased the rate of genetic counseling to 91% and the rate of genetic testing to 100%, rates that are unprecedented in comparison with those reported previously.

MMR deficiency was most commonly observed in women with EC (26%) or synchronous EC/OC (36%-42%). The MMRd rate in EC in our study is consistent with what has been reported in the literature at 25%, with 20% of MMRd cases diagnosed with LS.[35,36] The MMRd and LS rates in synchronous EC/OC or nonserous/nonmucinous OC are less well known, with scarce data mostly from observational studies. Our prospective study reports a very high pretest probability of LS given MMR deficiency in a synchronous EC/OC case or an OC case. In most centers in Canada, reflex IHC is implemented only for EC and CRC, with OC being neglected completely. Because of the high pretest probability of LS, this study provides further impetus to implement universal IHC screening in nonserous/nonmucinous OC.[4]

This study has a number of strengths. First, it was prospective in nature, and we were able to compare the genetic counseling/testing compliance rates with those observed in our prospective pilot study (performed before implementation of our enhanced genetic uptake program).[5] Although preexisting studies have similarly shown the value of patient navigation/care coordination in improving genetic counseling uptake for LS populations, these have been observational in nature,[37] with our study being the first prospective study to validate this idea. Furthermore, we had a sizable number of participants from 3 cancer centers, with complete information on the majority of the participants as they navigated through the system. One of our limitations, however, was the lack of information on why there were some participants who were not offered germline testing even though they met criteria for referral to genetics. Furthermore, we did not have all methylation data for participants with MLH1-deficient tumors. There were 56 participants with MLH1-deficient tumors older than 60 years without an LS-specific family history who were assumed to have somatic *MLH1* promoter methylation and, therefore, were not eligible for further genetic testing. We also included only nonserous/nonmucinous OCs in our study cohort, and this may limit the generalizability of our findings; however, the majority of Lynch-associated OCs are endometrioid, clear cell, or mixed subtypes, and the incidence of LS in serous OCs is as low as 0.1%.[38] Studies have repeatedly shown that the MMRd rate is exceedingly low in serous OCs.[39] Some have reported a higher incidence of LS in serous cancers, but these studies were limited by their retrospective nature, a lack of central pathology review, and a lack of confirmatory germline testing.

In conclusion, our prospective study clearly shows that a navigated genetic program can successfully increase genetic counseling and testing uptake in patients with gynecologic malignancies at risk for LS. With this paradigm shift of providing care, there is huge potential for cancer prevention for patients with LS and their relatives. Standardization of tumor testing with IHC is futile without physician and patient compliance with genetics testing; ultimately, cancer prevention requires a holistic and comprehensive system that involves patients, physicians, allied health professionals, and infrastructure for genetic services.

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The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Soyoun Rachel Kim: Data curation, formal analysis, project administration, visualization, writing–original draft, and writing–review and editing. **Alicia Tone:** Conceptualization, data curation, investigation, methodology, and writing–review and editing. **Raymond H. Kim:** Investigation and writing–review and editing. **Matthew Cesari:** Investigation and writing–review and editing. **Blaise A. Clarke:** Investigation and writing–review and editing. **Lua Eiriksson:** Investigation, resources, and writing–review and editing. **Tae L. Hart:** Resources and writing–review and editing. **Melyssa Aronson:** Resources and writing–review and editing. **Spring Holter:** Resources and writing–review and editing. **Alice Lytwyn:** Investigation and writing–review and editing. **Manjula Maganti:** Formal analysis and writing–review and editing. **Leslie Oldfield:** Formal analysis and writing–review and editing. **Steven Gallinger:** Conceptualization and writing–review and editing. **Marcus Q. Bernardini:** Conceptualization and writing–review and editing. **Amit M. Oza:** Conceptualization and writing–review and editing. **Bojana Djordjevic:** Writing—review and editing. **Jordan Lerner-Ellis:** Investigation and writing–review and editing. **Emily Van de Laar:** Data curation, project administration, and writing–review and editing. **Danielle Vicus:** Investigation, resources, and writing–review and editing. **Trevor J. Pugh:** Formal analysis, investigation, and writing–review and editing. **Aaron Pollett:** Investigation and writing–review and editing. **Sarah E. Ferguson:** Conceptualization, formal analysis, funding acquisition, project administration, investigation, methodology, supervision, and writing–review and editing.

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