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Missing a chance to prevent: disparities in completion of genetic evaluation in high-risk patients with endometrial cancer

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ABSTRACT

Objective: The primary goal of this study is to examine disparities in high-risk endometrial cancer (EC) patients in relation to rates of genetic referrals (GR), testing (GT), and counseling (GC).
Methods: This is a retrospective analysis of patients with newly diagnosed EC between January 1, 2014 and September 1, 2020 at a single institution. Patients were defined as high-risk EC patients when they were 1) diagnosed at 50 years or younger, 2) had a positive family history for cancer or 3) had evidence of loss of mismatch repair protein expression on tumor immunohistochemistry. Rates of GR, GT and GC were analyzed based on race, ethnicity, primary language and insurance status.
Results: During the study period, 674 patients were diagnosed with EC and 249 (36.9%) were considered high-risk EC patients. Among high-risk patients, 128 (51.2%) were referred to GT and GC. Of those referred, 103 (80.5%) underwent GT and 85 (66.4%) completed GC. Out of all high-risk patients, 20 (18.4%) were positive for LS on GT and 29 (28.2%) had VUS results. In multivariate analysis, the odds of GT and GC referral were lower among patients who identified as Hispanic (OR=0.40; 95% CI=0.19–0.87; p=0.020). Patients who identified as black were less likely to receive GC when compared to patients of other races (p=0.030).
Conclusion: It is our hope that through this data we will increase awareness around existing disparities in genetic evaluation for patients with EC and ultimately create strategies to improve equitable access to care for all patients.

Keywords: Endometrial Cancer; Genetic Evaluation; Lynch Syndrome

Synopsis

The primary goal of this study was to identify and to examine disparities in genetic evaluation in patients with high-risk endometrial cancer. Hispanic patients were less likely to be referred for GT and Black patients less likely to undergo GC. Black patients were less likely to receive GC when compared to patients of other races (p=0.030).

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Conceptualization: H.S., V.J.; Data curation: H.S., V.J., Z.K., B.S.V.; Formal analysis: H.S., S.M., Z.K., B.S.V.; Funding acquisition: B.S.V.; Investigation: H.S.; Methodology: V.J., S.M., P.H.M., B.S.V.; Project administration: V.J., C.S., B.S.V.; Supervision: C.S.; Validation: H.S.; Writing - original draft: H.S., V.J., S.M., C.S., P.H.M., Z.K., B.S.V.; Writing - review & editing: H.S., V.J., S.M., C.S., P.H.M., Z.K., B.S.V.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States [1]. In 2022, there were an estimated 65,950 new cases and 12,550 deaths in the United States [1]. Whereas in the general population the lifetime risk of endometrial cancer is 3%, patients with Lynch syndrome (LS) have a lifetime risk as high as 57% [2]. Among EC cases, 3%–4% are hereditary, with the majority of hereditary cases ascribed to LS [3]. LS is an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, *PMS2* or loss of expression of *MSH2* due to deletion in the *EPCAM* gene. Individuals with LS are at increased risk of developing a wide variety of cancers, including colorectal, endometrial, bladder, pancreas, stomach, renal and ovarian cancers. EC can present as the first or sentinel cancer in 50% of women with LS [4], providing an opportunity to identify at-risk patients and initiate cascade testing. Identification of a germline MMR mutation and consequential cancer screening is an opportunity to prevent subsequent cancers through preventative measures, opening the door for cancer prevention. Moreover, the adoption of molecular and genomic profiling provides useful information for prognostication and for tailoring adjuvant therapies further demonstrating the importance of GT [5].

In 1998, the National Comprehensive Cancer Network (NCCN) developed a comprehensive set of clinical guidelines to identify patients with LS which are regularly updated. The most recent NCCN guidelines recommend both universal tumors testing as well as germline evaluation for LS in women diagnosed with EC under the age of 50, with evidence of a MMR deficiency on tumor testing, or in the setting of family history of two or more LS-related cancers [6,7]. Compliance with NCCN guidelines and genetic evaluation among patients diagnosed with EC has been reported to be as low as 13.4% or as high as 100%, depending on the series [8]. Most published studies have focused on the shifting screening guidelines and examined the entire genetic evaluation process. There is minimal published data on disparities in genetic testing.

The primary goal of this study is to evaluate disparities in genetic evaluation referrals (GR) as well as disparities in completion of genetic counseling (GC) and testing (GT) in patients at high-risk for EC.

MATERIALS AND METHODS

This was a retrospective, single-center study. After Institutional Review Board (IRB) approval was obtained, all patients diagnosed with EC between the dates of January 1st, 2014 and September 1st, 2020 were identified. Inclusion criteria included patients older than 18 years of age, had a pathologic diagnosis of EC at our institution, and underwent surgical treatment in our health care system. Patients were excluded from our study if they were known to have LS prior to their EC diagnosis, had undergone GT or GC prior to EC diagnosis or were diagnosed at another facility without a pathology review at our institution.

Demographic data were abstracted from electronic medical records—these included race, ethnicity, primary language, prior and current cancer diagnoses, family history, and insurance status. Race and ethnicity were obtained from patients' medical records. GC referral was determined based on referral seen in the electronic medical record or documentation of referral by a provider. Completion of GT or GC was determined by the

presence of germline testing result or documentation of GC visit in the chart, respectively. For this study, high-risk EC patient was defined as patients who 1) were 50-year-old or younger at the time of EC diagnosis, 2) had positive family history defined as two or more first-degree family members with LS-related cancers including endometrial, ovarian, colon, genitourinary, gastric, small bowel, pancreatic or biliary, or 3) loss of MMR protein expression on tumor immunohistochemistry (IHC). Our institution implemented universal tumor testing for MMR proteins for all patients diagnosed with EC in 2017. Patients were considered high-risk EC due to a loss of MMR protein only if there was no documented testing for hypermethylation or no hypermethylation was identified on testing. Patient's family history was determined by information on the provider note which is part of the intake process at our institution. The process by which patients are triaged to GT and GC varies by provider; in some cases, GC occurs before or after GT, and in some, GT is first and patients undergo counseling for positive results or variants of uncertain significance following receipt of the results.

Mean values and standard deviations were used to describe continuous and categorical variables. A univariate analysis was used to compare baseline patient characteristics of the high-risk group between patients who completed genetic testing and those who did not. The Mann-Whitney U test was used for non-normally distributed continuous variables and Pearson's χ^2 test for categorical variables. Logistic regression analysis was used to determine factors contributing to genetic testing and counseling completion. All analysis was done by IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) [9], and $p<0.05$ was considered statistically significant.

RESULTS

Between January 1, 2014 and September 1, 2020, EC was diagnosed in 674 patients who underwent surgical treatment at our institution. Out of the 674 patients who were diagnosed with EC during our study period, 398 (59.1%) had MMR IHC performed and 276 (40.9%) did not undergo MMR IHC testing. Out of the patients who had MMR IHC done, 249 (36.9%) were considered at high-risk for genetic cause of EC. Patient demographics and characteristics for high-risk patients are shown in **Table 1**. High-risk patients were characterized by a median age at diagnosis of 58.5 years (range, 46.5–70.5), with 84 (33.7%) diagnosed before or at 50 years of age. Our patient population was diverse with 38 (15.3%) patients identifying as black, 38 (15.3%) as Asian and 51 (20.5%) as Hispanic. The majority of patients, 205 (82.3%), spoke English as their primary language and 137 (55%) had private insurance. Median body mass index was 30.8 (range, 24.7–37.2) and 194 (77.9%) were diagnosed at International Federation of Gynecology and Obstetrics stage I disease.

Indications for patients to be considered high-risk included 84 (33.7%) due to diagnosis at age 50 or younger, 82 (32.9%) due to loss of MMR protein expression on tumor IHC, and 83 (33.3%) due to family history of LS related cancers. Patients who had surgery for endometrial cancer after 2017, when universal testing was implemented at our institution, were more likely to have IHC completed compared to those who had surgery before 2017 ($p<0.050$). After 2017, 33 (17.6%) patients did not have IHC whereas prior to 2017, 39 (45.9%) patients did not have IHC. On univariate analysis, the only factor impacting MMR IHC testing was positive family history ($p=0.030$) and age ($p=0.017$), which was not statistically significant after controlling for the year of diagnosis.

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Table 1. Patient characteristics and demographics for patients diagnosed with endometrial cancer and categorized as high-risk (n=249)

Variable	Value
Race	
White	110 (44.2)
Black	38 (15.3)
Asian	38 (15.3)
Other	51 (20.5)
Unknown	12 (4.8)
Ethnicity	
Non-Hispanic	197 (79.1)
Hispanic	51 (20.5)
Unknown	1 (0.4)
Primary language	
English	205 (82.3)
Language other than English	44 (17.7)
Age at diagnosis (yr)	58.5±12.0
BMI (kg/m^2)	30.8 (24.7–37.2)
Smoking	
Yes	68 (27.3)
No	181 (72.7)
Insurance	
Private	137 (55.0)
Public	112 (45.0)
Family history of colon or endometrial cancer	
Yes	122 (49.0)
No	127 (51.0)
IHC tumor test	
Yes	191 (76.7)
No	58 (23.3)
Histology	
Endometroid	213 (85.5)
Serous	18 (7.2)
MMMT	8 (3.2)
Clear cell	8 (3.2)
Mixed	1 (0.4)
Dedifferentiated	1 (0.4)
FIGO stage*	
I	194 (77.9)
II	11 (4.4)
III	37 (14.9)
IV	7 (2.8)
LND	
Yes	156 (62.7)
No	93 (37.3)
SLN	
Yes	100 (40.2)
No	149 (59.8)
Vital status*	
Alive	233 (95.1)
Dead	12 (4.9)

Values are presented as number (%), median (interquartile range), or mean ± standard deviation.
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; LND, lymphadenectomy; MMMT, malignant mixed mullerian tumor; SLN, sentinel lymph node.
*Missing <5% of the data.

Among patients classified as high-risk for all reasons, 128 (51.4%) were referred for GC and GT. Of those, 103 (80.5%) underwent GT and 85 (66.4%) underwent GC (**Fig. 1**). Patients were referred to GT by their gynecologic oncologist in 75.0% of cases, medical oncologists in 22.1% of cases, and other healthcare providers in 2.9% of the cases. Among those who underwent genetic testing, 20 (19.4%) were positive for LS and 29 (28.2%) had variant of unknown

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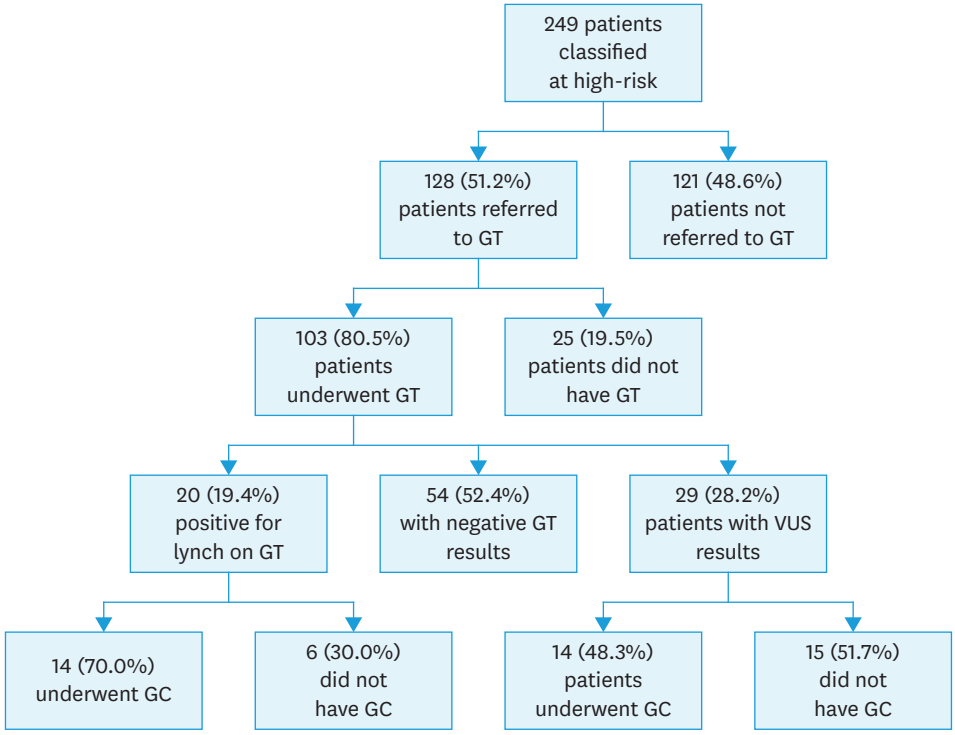

Fig. 1. Genetic evaluation flow sheet in patients with high-risk endometrial cancer.
GC, genetic counseling; GT, genetic testing; VUS, variant of unknown significance.

significance results. Our outcomes of interest, including GR, GC, and GT were stratified by primary predictors of interest including race, ethnicity and primary language (**Figs. 2-4**).

On multivariate analysis, the rates of GR were lower for individuals who were Hispanic (odds ratio=0.40; 95% confidence interval=0.19–0.87; p=0.020). There was no difference in race, ethnicity, insurance status or primary language for completion of GT. Patients considered high-risk due to positive family history were more likely to undergo GT (p<0.001) and to undergo GC (p<0.001). Rates of GC completion were lower among patients reporting black race compared to patients of other reported races (p=0.030). There was no difference in ethnicity, primary language or insurance status for patients who underwent GC.

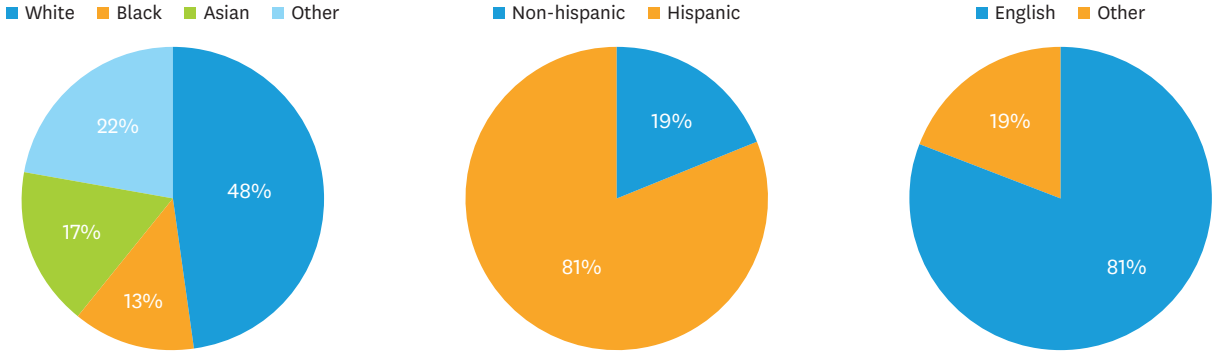

Fig. 2. Referral by race, ethnicity, primary language.

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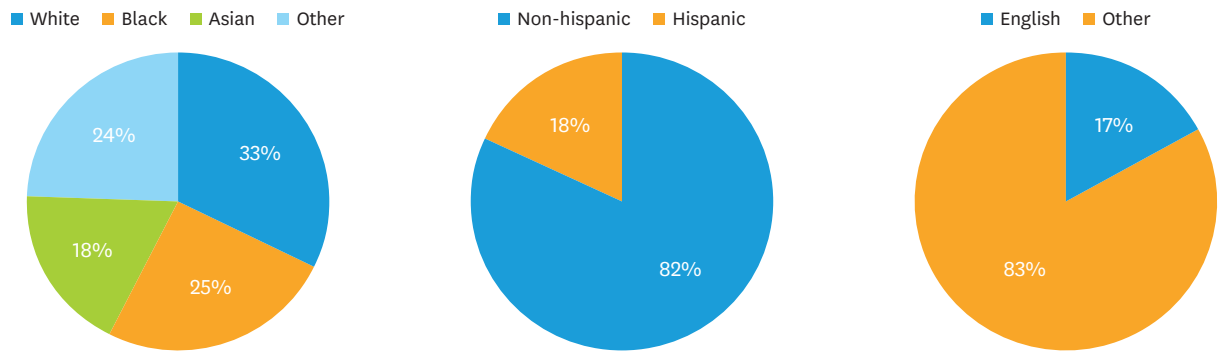

Fig. 3. Genetic testing by race, ethnicity, primary language.

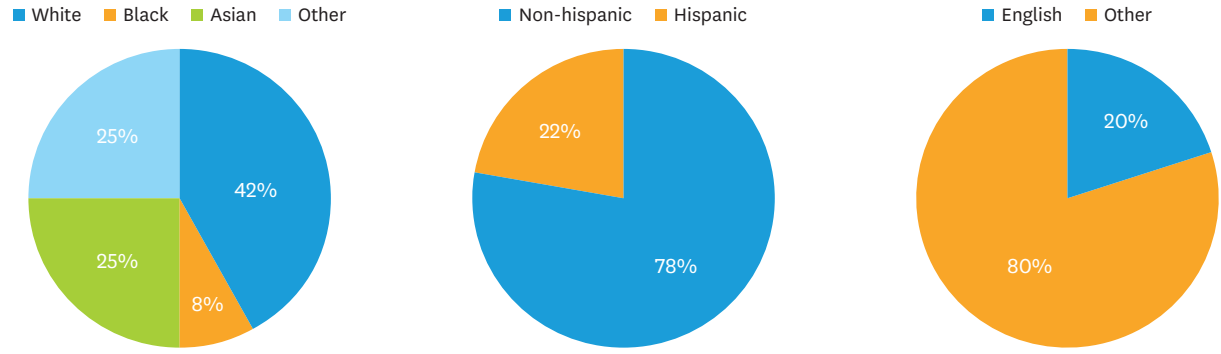

Fig. 4. Genetic counseling by race, ethnicity, primary language.

DISCUSSION

This study examines the relationship between genetic evaluation for LS and race and ethnicity. Our study demonstrated ethnicity-based disparity in GR, and a race-based disparity in completion of GC. We did not find an association between primary language spoken or insurance status with GR, GC or GT [6]. Our first level of disparity observed was GR, with GR less likely in Hispanic patients compared to non-Hispanic patients. This disparity creates an unequal opportunity for patients to undergo GT and GC and creates a decreased opportunity to understand personal future cancer risk as well as their family's future cancer risk. Given that there was no difference in patients undergoing GT after receiving a GR, the biggest barrier for GT was receiving a GR. Black patients were less likely to undergo GC compared to patients of other races representing another missed opportunity for education and cascade testing.

In separating out the components of genetic evaluation, we had hoped to tease out the factors driving the disparities observed in our study. Positive family history and younger age was initially predictive of MMR testing; however, once controlled for years of diagnosis, there was no difference in MMR testing based on the indication for being considered high-risk. Our findings are likely reflective of implementation of universal MMR testing of all patients diagnosed with EC at our institution in 2017. This demonstrates the importance of universal guidelines for all patients decreasing the chance of provider bias. While our IHC testing rates were not 100%, we did find that implementing universal testing increased the number of patients undergoing IHC testing as implementation of a new process requires time for full adoption.

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Diving deeper into our findings, we can consider both provider and patient-related factors [10]. Providers are vulnerable to implicit bias. Studies have demonstrated that a patient's race, ethnicity and socioeconomic status are associated with physician perception of patients' health literacy and adherence to medical advice [11]. Unknowingly, these stereotypes may alter and impact providers' medical care. From a patient's perspective, non-white communities have had a long history of mistreatment by the health care system creating a lack of trust between some patients and their providers [10]. Additionally, there may be cultural and community beliefs surrounding GT which contribute to lower rates of discussion and utilization of service [11].

The role of race and ethnicity in healthcare, and in particular cancer care, has long been recognized. This reality has been demonstrated within the field of gynecologic oncology as well [12-15]. White patients are more likely to receive the recommended treatment, have better overall survival compared to non-White patients, regardless of insurance status and participation in Gynecologic Oncology Group clinical trials [12-16]. Given the adoption of molecular and genomic profiling in the treatment of EC, understanding the individual patient genetics may impact treatment options [5]. Given this reality, equal genetic evaluation among all patients is important as treatment options become more personalized in the future emphasizing the importance of this study.

This study has many strengths and limitations. First, our study population was racially and ethnically diverse allowing our results to be generalized to other populations. Although the goal at our institution is referral of all high-risk patients to GT and GC, referral patterns were dependent on physician practice which creates an individual bias. Additionally, information about testing for methylation is difficult to obtain from our electronic medical records, and therefore it is likely an underestimate in the completion of genetic workup based on MMR IHC tumor testing. Lastly, there is a limitation in the accuracy of retrospective data in electronic medical records. Specifically for patient race and ethnicity, there is a barrier given that most basic demographic information is written by front desk clerks and not reported directly by the patient. Moreover, there is an inherent bias in collection and knowledge of family history within the electronic medical record. This adds an extra layer to existing differences in knowledge of family history, particularly among populations facing discrimination, racism, and other complex family situations [17].

Genetic evaluation of patients with EC provides an opportunity for risk evaluation, cascade testing and ultimately cancer prevention. While racial and ethnic disparities in healthcare exist, it is our hope that by displaying and publishing these disparities, there will be an increase in awareness, corrective actions and creation of equal opportunity for cancer prevention for all patients.

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