2-3-2021

Practice Patterns and Results of Tumor and Germline Genetic Evaluation of Women With Endometrial Cancer in South Louisiana

Morgan McDougal
LSU Health Sciences Center- New Orleans

Pallavi Nair-Fairless
LSU Health Sciences Center- New Orleans

Tova Weiss
LSU Health Sciences Center- New Orleans

Elizabeth Dao
LSU Health Sciences Center- New Orleans, edao@lsuhsc.edu

Andrew G. Chapple
LSU Health Sciences Center- New Orleans, achapp@lsuhsc.edu

See next page for additional authors

Gynecologic Oncology Reports 36 (2021) 100717

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

Practice patterns and results of tumor and germline genetic evaluation of women with endometrial cancer in south Louisiana

Morgan McDougal [a], Pallavi Nair-Fairless [b], Tova Weiss [a], Elizabeth Dao [a], Andrew G. Chapple [c], Amelia Jernigan [d,*]

[a] Louisiana State University Health Sciences Center, School of Medicine, New Orleans, LA, United States
[b] Department of Obstetrics and Gynecology; Louisiana State University Health Sciences Center, New Orleans, LA, United States
[c] Biostatistics Program, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA
[d] Division of Gynecologic Oncology, Louisiana State University Health Sciences Center, New Orleans, LA, United States

ARTICLE INFO

Keywords:
Endometrial Neoplasms
Hereditary nonpolyposis
DNA mismatch repair
Microsatellite instability
Genetic testing
Genetic counseling

ABSTRACT

The objectives were to describe rates of MMRd or MSI-H EC tumors, the prevalence of LS, the practice patterns of EC genetic evaluation and adherence to NCCN guidelines, and to identify disparities in the genetic evaluation of women with EC.

A retrospective cohort study was performed on women with EC from 1/2013 to 12/2019, and information collected included demographics, personal and family history, EC diagnosis and treatment, and details of genetic evaluation. Statistical analysis included a multivariable logistic regression to adjust for all covariate effects simultaneously and Fisher exact tests of independence and Wilcoxon rank-sum tests to compare categorical and continuous covariates, respectively.

Of the 286 women with EC, 80 EC tumors were tested, and 27.5% were MMRd or MSI-H. Of the 21 women who had germline testing, no cases of LS were identified. Before the NCCN recommended universal tumor testing, 17.6% of women had tumor testing performed compared to 60.0% after February of 2017 (OR = 2.51, 95% CI 1.89–3.32). Advanced cancer stage was nearly associated with an increased likelihood of tumor testing (OR = 1.40, 95% CI 1.00–1.97). No disparities were identified.

We described patterns of genetic evaluation and tumor testing results for women with EC in south Louisiana and found similar rates of MMRd or MSI-H EC tumors as previously reported in other populations. Rates of tumor testing increased after the NCCN recommendation for universal tumor testing, but it is critical to identify weaknesses in this process and develop an algorithm to improve care for women with EC.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, and its incidence is increasing (Morice et al., 2016). Mismatch repair (MMR) deficiency is when the system responsible for correcting insertion or deletion errors during genomic replication is faulty, often due to a loss of expression of a functional MLH1, MSH2, MLH6 or PMS2 or an EPCAM mutation resulting in epigenetic silencing of the MSH2 gene (Tutlewska et al., 2013). The loss of MMR functioning leads to microsatellite instability (MSI), which is a hypermutated phenotype that increases cancer susceptibility (Ryan, 2019). MMR deficiency is common in EC, reported to occur in 20–40% of endometrial cancers, most commonly due to somatic mutations in the tumor (Kim, xxxx), but approximately 3% of endometrial cancers are due to Lynch Syndrome (LS), an autosomal dominant germline mutation in the DNA MMR machinery (Ryan, 2019). Identifying MSI-high (MSI-H) or MMR deficient (MMRd) tumors is critical for diagnosing hereditary cancer predisposition syndromes and in guiding clinical decision making. Identification of probands allows for evaluation of at-risk family members and employment of risk reducing strategies with far reaching reductions in morbidity and mortality. Furthermore, knowledge of MMR or MSI can drive therapeutic decisions with novel immunotherapies for patients with advanced disease (Ono et al.,2019).

As the science has unfolded, guidance for who and how to genetically evaluate women with EC has evolved. In November of 2014, the American College of Obstetricians and Gynecologists (ACOG) and the

* Corresponding author at: 1542 Tulane Avenue, Box T5-2, New Orleans, LA 70112, United States.
E-mail address: ajerni@lsuhsc.edu (A. Jernigan).

https://doi.org/10.1016/j.gore.2021.100717
Received 29 October 2020; Received in revised form 18 January 2021; Accepted 24 January 2021
Available online 3 February 2021

Society of Gynecologic Oncology (SGO) joint recommended one of the following three options, "tumor testing for MSI/MMR deficiency on any endometrial or colorectal tumor from a woman identified to be at risk of LS through a systematic clinical screen with focused personal and family medical history, tumor testing on all endometrial or colorectal tumors irrespective of age of diagnosis, or tumor testing on all endometrial or colorectal tumors diagnosed before age 60 years" (ACOG , xxxx). The National Comprehensive Cancer Network (NCCN) published an update to clinical practice guidelines in February 2017 to recommend "tumor screening for MMR deficiency for all colorectal and endometrial cancers regardless of age at diagnosis, reserving germline genetic testing for patients with early-age at diagnosis, positive family history, or abnormal tumor testing results" (NCCN, 2.2017.). Disparities in guideline adherence in the management of gynecologic cancers have been widely described (Fang, xxxx). Whether these disparities apply to the genetic evaluation of women with EC remains to be determined.

There have not been any published studies describing the rates of MMRd or MSI-H ECs in Louisiana to date. The Louisiana Acadian parishes are populated by a US founder population with one of the highest colorectal cancer rates in the United States, suggesting a possible genetic predisposition to a cancer that is strongly linked to LS (Karlitz et al., 2014). The objectives of this study were to describe rates of MMR-d or MSI-H EC tumors, the prevalence of LS, practice patterns with regards to EC genetic evaluations and adherence to the NCCN guideline recommendations made in February of 2017. Furthermore, we sought to determine if there were disparities in the genetic evaluation of women with endometrial cancer, specifically looking at the following covariates: age at diagnosis, race, insurance status, BMI, menopausal status, comorbidities, personal or family history of lynch-spectrum cancer (LSCa), and stage of cancer.

2. Methods

2.1. Study design and data Collection

After obtaining the appropriate approval by Louisiana State University Health Sciences Center Institutional Review Board and hospital research review committees, ICD9 (182.0) and 10 (C54) codes for EC were used to identify women who received care for EC at University Medical Center New Orleans and Touro Infirmary from 1/1/2013 to 12/31/2019. This study period was chosen based on electronic medical record availability beginning in 2013. A retrospective chart review was performed, and data was compiled into a REDCap Database. Using REDCap ensured protection of patient protected health information as it was password protected, and only the investigators of the study had access to the database. Information collected included demographics, insurance status, personal and family history, EC diagnosis and treatment course, and details of tumor and germline genetic testing and genetic counseling. Only patients with EC were included. This included patients with carcinosarcoma. Patients with adenosarcoma, leiomyosarcoma, and neuroendocrine carcinomas of the uterus were excluded from the study.

2.2. Data analysis

Statistical analysis included a logistic regression to model the probability of tumor testing, analyzing the following covariates: age at diagnosis, race, insurance status, BMI, menopausal status, comorbidities, personal or family history of LSCa, stage of cancer, as well as pre and post 2/2017 NCCN guideline changes. For the logistic regression, the following decisions for inclusion were made based on the data available:

A) Regarding race, black vs. other races was used, and "unknown/declined to state" was assumed to not include black patients.
B) There were 2 patients for which family history of LSCa was unknown. These 2 patients were assumed to not have a family history of LSCa.
C) Stage of cancer was divided into advanced stage (stages III and IV) and non-advanced stage (stages I and II).

For categorical variables, we reported the count and percentage within each tumor testing group while median and standard deviation were reported for continuous covariates (Tables 2 and 3). We compared the distribution of categorical variables across the two groups using Fisher exact tests of independence and compared continuous covariates using a Wilcoxon rank-sum test with p-values reported in Tables 2 and 3. Significance was defined as $P < .05$. We adjusted for all covariate effects simultaneously to predict tumor testing using a multivariable logistic regression with adjusted odds ratios and 95% confidence intervals reported (Fig. 1).

3. Results

3.1. Demographics

Two hundred eighty-six women with EC were identified, including 138 white (48.3%), 126 black (44.1%), 12 Hispanic (4.2%), 5 Asian (1.7%) and 5 "other" (1.7%) (Table 1). Most women had public insurance in the form of Medicaid (n = 71, 24.8%), Medicare (n = 85, 29.7%), or were uninsured and cared for through the Free-Care program (n = 38, 13.3%); the minority were privately insured (n = 92, 32.2%) (Table 1). The median age at diagnosis was 58.7 years (90% CI, 37.7–73.2), and BMI was 35.6 kg/m^2 (90% CI, 23.4–55.1) (Table 1). Most women in this study had multiple medical comorbidities with a median Charlson Comorbidity Index (CCI) of 4.0 (90% CI, 2.0–9.0) (Table 1).

There were 35 women (12.2%) with a family history of LSCa, 4 women (1.4%) with a prior personal history of a LSCa, and 6 women (2.1%) with a synchronous history of a LSCa (Table 1). Most women had low grade (n = 120, 42.0%), stage IA EC (n = 159, 55.6%), and the majority had surgery for initial treatment (n = 252, 88.1%) with a median time from diagnosis to last follow-up of 18.5 months (90% CI, 1.3–63.2) and 185 (64.7%) women with no evidence of disease at last follow-up (Table 1).

4. Genetic evaluation

Eighty (28.0%) of these 286 women with EC had IHC or MSI tumor testing performed with 22 (27.5% of those tested) resulting in an abnormal test (Fig. 2). Of the 80 women who had tumor testing performed, only 17 (21.3%) had both IHC and MSI testing. Of the 6 MSI-H tumors, 2 women had both IHC and MMR testing performed, and one of the two with MSI-H tumors had intact IHC expression of MMR proteins. All the MLH1 deficient tumors were also PMS2 deficient. MLH1 promoter hypermethylation testing was performed in 50.0% of the MLH1-deficient tumors, and hypermethylation was detected in all of them (Fig. 2). Of the patients with MLH-1 promoter hypermethylation, 2 were offered genetic counseling, and one attended a meeting with a genetic counselor but did not receive germline testing. Of the 22 patients with abnormal tumor testing, 6 (27.2%) were offered genetic counseling. Of the 2 patients who underwent germline testing, both resulted in variants of undetermined significance. These 2 women both had tumors that were MSI-H and no personal or first-degree relatives with a family history of LSCa. Of the 286 women with EC, 21 (7.3%) women were offered genetic counseling, and 11 had germline testing with no findings of LS-associated germline mutations (Fig. 2).

Before the February of 2017 NCCN guideline changes recommending universal tumor testing, 17.6% of women had tumor testing performed (Table 2). After February of 2017, 60.0% of women had tumor testing performed (Table 3). The tumor testing percentages for each year of the study along with the number of patients diagnosed that year are shown

Table 1
Demographics.

Covariate		
Total = 286	n	%
Race		
Black	126	44.1%
White	138	48.3%
Hispanic	12	4.2%
Asian	5	1.7%
Other	5	1.7%
Insurance Status		
Private	92	32.2%
Medicare	85	29.7%
Medicaid	71	24.8%
Uninsured	38	13.3%
BMI (kg/m^2)		
Median (90% CI)	35.6	(23.4–55.1)
Underweight	3	1.0%
Normal	22	7.7%
Overweight	54	18.9%
Class I Obese	58	20.3%
Class II Obese	47	16.4%
Class III Obese	101	35.3%
Menopausal Status		
Pre-menopausal	64	22.4%
Post-menopausal	222	77.6%
Charlson Comorbidity Index		
Median (90% CI) 4.0		(2.0–9.0)
1–3	91	31.8%
4–6	127	44.4%
>6	68	23.8%
Personal and Family History		
Family history of Lynch spectrum cancer	35	12.2%
Prior personal history of Lynch spectrum cancer	4	1.4%
Synchronous Lynch spectrum cancer	6	2.1%
Age at diagnosis (years)		
Median (90% CI)	58.7 (37.7–73.2)	
Stage		
IA	159	55.6%
IB	31	10.8%
II	23	8.0%
IIIA	11	3.8%
IIIB	6	2.1%
IIIC1	12	4.2%
IIIC2	15	5.2%
IVA	5	1.7%
IVB	24	8.4%
Tumor Grade		
1	120	42.0%
2	70	24.5%
3	84	29.4%
Unknown	12	4.2%
Tumor Histology		
Endometrioid	211	73.8%
Serous	35	12.2%
Clear Cell	10	3.5%
Mixed	10	3.5%
Other	20	7.0%
Initial Treatment		
Surgery	252	88.1%
Radiation	110	38.5%
Chemotherapy	76	26.6%
Hormonal therapy	8	2.8%
No therapy	15	5.2%
Time from diagnosis to the date of last follow up (months)		
Median (90% CI)	18.5 (1.3–63.2)	
Status at last follow up		
Alive with no evidence of disease	185	64.7%
Alive with disease	70	24.5%
Died of endometrial cancer	9	3.1%
Died of other causes	5	1.7%

in Fig. 3.

There were no significant differences among the covariates that increased the likelihood of tumor testing for those tested before 2/2017 (Table 2) or after 2/2017 (Table 3). The NCCN guideline change was the only covariate that significantly increased the likelihood of tumor testing (OR = 2.51, 95% CI 1.89–3.32) (Fig. 1). Advanced cancer stage was nearly associated with an increased likelihood of tumor testing (OR = 1.40, 95% CI 1.00–1.97) (Fig. 1).

Table 2
Clinical Covariates for Tumor Testing before the February of 2017 NCCN Guideline Changes.

Covariate	Tumor tested n (%)	Not tested n (%)	P-value*
Total	38	178	
Race			
Black	19 (50.0)	75 (42.1)	0.471
Non-black	19 (50.0)	103 (57.9)	
Insurance Status			
Private	16 (42.1)	60 (33.7)	0.352
Public	21 (55.3)	89 (50.0)	0.595
Uninsured	1 (2.6)	29 (16.3)	
Family History of Lynch Spectrum Cancer	4 (10.5)	22 (12.4)	1.000
Stage			
Non-advanced (I-II)	24 (63.2)	139 (78.1)	
Advanced (III-IV)	14 (36.8)	39 (21.9)	0.062
Menopausal Status			
Pre-menopausal	12 (31.6)	34 (19.1)	
Post-menopausal	26 (68.4)	144 (80.9)	0.124
Charlson Comorbidity Index			
Median (SD)	5.24 (2.33)	4.63 (2.17)	0.151
BMI (kg/m2)			
Median (SD)	35.85 (10.90)	36.87 (10.12)	0.76
Age at Diagnosis (years)			
Median (SD)	55.9 (11.11)	58.34 (10.01)	0.328

SD indicates standard deviation.
*One-way analysis of variance with chi-square contingency tables for categorical variables and Wilcoxon rank-sum test for continuous variables.

Table 3
Clinical Covariates for Tumor Testing after the February of 2017 NCCN Guideline Changes.

Covariate	Tumor tested n (%)	Not tested n (%)	P-value*
Total	42	28	
Race			
Black	21 (50.0)	11 (39.3)	0.465
Non-black	21 (50.0)	17 (60.7)	
Insurance Status			
Private	12 (28.6)	4 (14.3)	0.246
Public	24 (57.1)	22 (78.6)	0.077
Uninsured	6 (14.3)	2 (7.1)	
Family History of Lynch Spectrum Cancer	8 (19.0)	1 (3.6)	0.075
Stage			
Non-advanced (I-II)	26 (61.9)	23 (82.1)	
Advanced (III-IV)	16 (38.1)	5 (17.9)	0.056
Menopausal Status			
Pre-menopausal	12 (28.6)	6 (21.4)	
Post-menopausal	30 (71.4)	22 (78.6)	0.584
Charlson Comorbidity Index			
Median (SD)	5.05 (2.52)	5.71 (2.43)	0.222
BMI (kg/m2)			
Median (SD)	37.64 (9.38)	38.22 (10.33)	0.901
Age at Diagnosis (years)			
Median (SD)	55.72 (10.11)	60.14 (13.19)	0.052

SD indicates standard deviation.
*One-way analysis of variance with chi-square contingency tables for categorical variables and Wilcoxon rank-sum test for continuous variables.

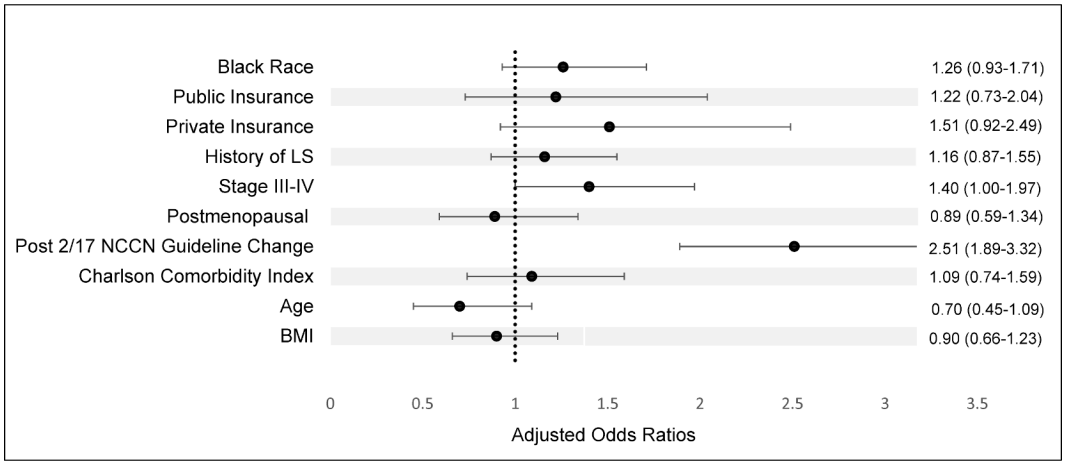

Fig. 1. Likelihood of Tumor Testing Based on Clinical Covariates.

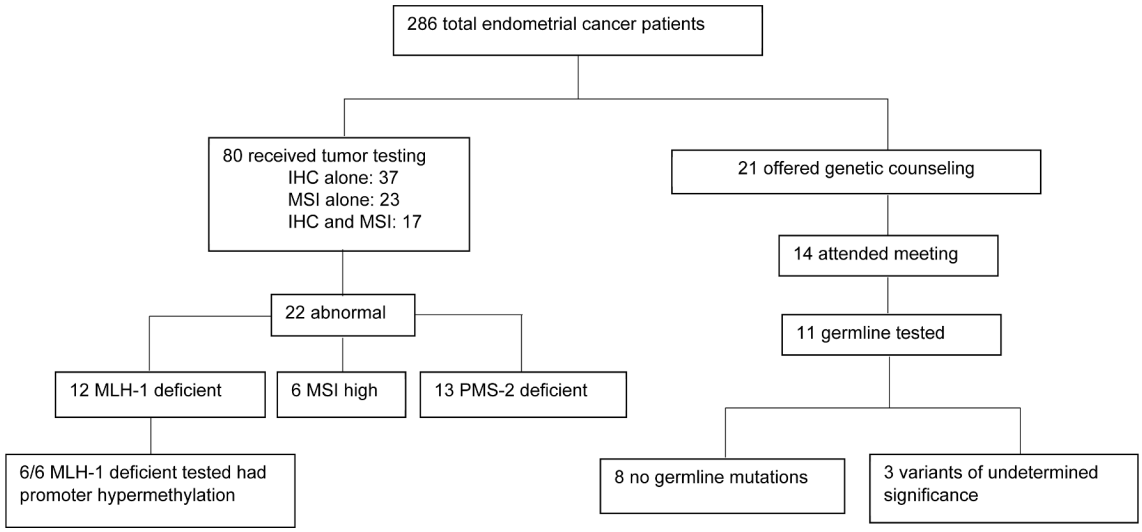

Fig. 2. Description of Genetic Evaluation.

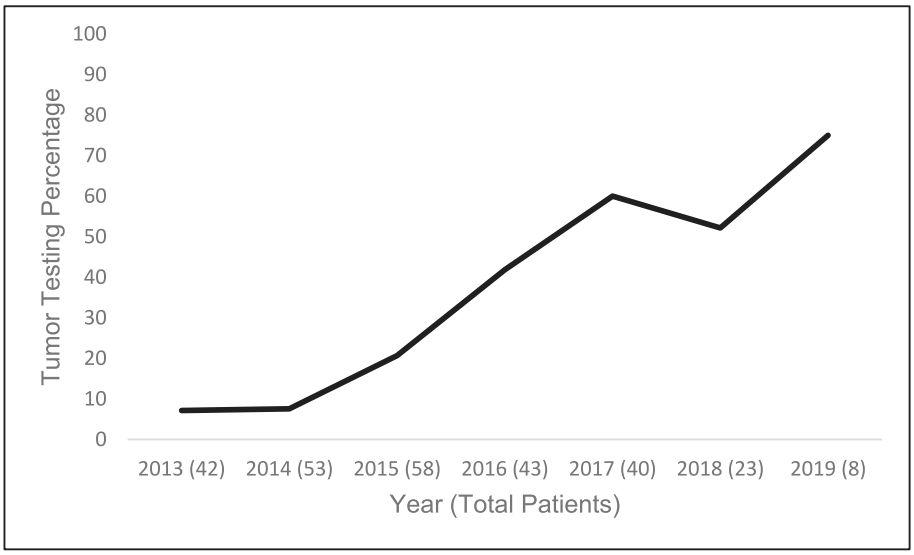

Fig. 3. Tumor Testing Percentage over Time.

5. Discussion

We set out to describe disparities in practice patterns and the results of tumor and germline genetic testing of a unique population of women with EC in south Louisiana. We did not demonstrate statistically significant disparities in guideline adherence by race, age, or insurance status, but we did document a concerning low rate of tumor or germline genetic evaluation for women with EC. After NCCN guidelines changed in February of 2017, tumor testing was more likely, but still only 60% of EC diagnosed after this time had documented tumor testing, falling far short of recommendations for universal testing. Advanced cancer stage was nearly associated with increased tumor testing likely explained by the indication for pembrolizumab monotherapy in advanced or recurrent EC. Of EC tumors tested, 27.5% were MMRd or MSI-H, and none of the women who had germline testing were diagnosed with LS.

The results of tumor and germline evaluation were consistent with prior reports, which suggest the rate of MMRd or MSI-H EC is 27–35%, and the rate of LS is 2–5% in an EC population (Dillon et al., 2017; Egoavil et al.,2013 ; Long, 2014). Previous studies have often not described the demographics of their patient populations regarding race, ethnicity, and insurance status. We were able to capture patient demographics to evaluate for disparities in practices and guideline adherence based on these factors. Our population of women is of unique interest. The Acadian region is born of a unique founder population, and our region is enriched with minority and underserved women; however, their cancer genetics have been minimally described until now.

A concern routinely voiced is that the women of south Louisiana live in "cancer alley" and experience an undue burden of malignancy. Karlitz *et al.*, found that colorectal cancer (CRC) rates in white males in the Louisiana Acadian parishes were statistically significantly higher than both Louisiana and US rates (Karlitz et al., 2014). The results suggest the possibility of hereditary CRC due to a founder effect. This was the first study to describe CRC rates in this population, but they did not look at tumor MSI or IHC analysis or germline genetic testing to explore hereditary syndromes. The authors also found disproportionately low uterine cancer rates in the Acadian parishes. However, they discuss the difficulty in interpreting uterine cancer incidence due to the high prevalence of hysterectomies in Louisiana and the lack of corrected uterine cancer rates for the Acadian population (Karlitz et al., 2014). We did not document an unusually high rate of LS; however, we must caution that our ability to comment on this definitively is severely limited by the low rates of germline evaluation. If there is an undue burden of cancers, it is important to remain open minded to environmental factors like obesity, diet, and environmental toxins as well as genetic syndromes inclusive of and beyond LS.

In this series, formal genetics counseling and germline testing were inconsistently performed. When using IHC, appropriate reflex testing to MLH1 promotor hypermethylation helps determine whether loss of MLH1 expression is due to sporadic or germline mutation (Kahn, 2019). This was documented in only half of our MLH1 deficient tumors. This landscape continues to get more complex. Roughly 9–12% of MSI-H tumors have intact MMR protein expression, which means we may miss LS if we use IHC alone (Egoavil et al 2013; Bartley, xxxx). Some recommend combined IHC and PCR approaches (Yokoyama et al., 2018; Goodfellow et al., 2015).

We identified several weak points in the chain of events from diagnosis to tumor testing to reflex testing to referral to geneticist, and quality improvement could occur at each step. If we are to unlock the potential of tumor and genetic testing, quality improvement is called for at each step. At both institutions in this study, tumor testing is primarily driven by clinicians and is performed at the request of the treating oncologist. Until 2019, there were no specialized gynecologic pathologists in New Orleans, and there are currently none at either of the institutions in this study. At Touro Infirmary, a private hospital, either the pathologists decide to do tumor testing or the gynecologic oncologist requests for it to be performed. At University Medical Center, an academic institution, the pathologists are on a rotating schedule, and tumor testing is performed at the request of the gynecologic oncologist. Ultimately, there is no stream-lined system for tumor testing. Dillon *et al.*, reported success with the use of a systematic algorithm for universal LS screening in newly diagnosed ECs using MMR IHC, but they also reported challenges to follow-up testing in patients with abnormal tumor testing results (Dillon et al., 2017). Pathologists should be prompted to send all EC specimens for tumor testing. It is imperative that managing clinicians be literate on the interpretation of tumor testing, the recommended follow-up tests, and indications for genetic counseling and germline testing. Barriers to genetic evaluation of cancer patients include provider-mediated barriers such as lack of awareness of benefit and lack of time; payor-associated barriers such as lack of reimbursement; system-associated barriers such as lengthy authorization process and lack of ability to track which patients follow through with testing; and patient-associated barriers such as misinterpretation of purpose of counseling, disinterest in results, fear of social or financial discrimination, and racial disparities in testing due to education, access, or internal bias (Randall et al., 2017). Virtual appointments with a genetic counselor as a new and emerging option could increase access to this service and provide an option for patients with a geographic barrier.

Limitations of this study include the low rates of tumor and germline testing, which limits our ability to describe disparities in genetic evaluation of EC patients among the covariates we studied. However, adherence to recommended guidelines can prevent racial and other disparities. In addition, with more robust tumor testing, we would be able to provide a more granular, detailed report of the rates of MMRd or MSI-H EC tumors and the prevalence of LSCa in Louisiana. The study design of a retrospective chart review presents another limitation as we were unable to record what was not available in the electronic medical record.

Despite this, the study highlights the importance of guidelines for clinical practice and management decisions and calls for adherence to the guidelines that currently exist. As these recommendations evolve and testing becomes more complex, it is critical to have systems in place to ensure the women of south Louisiana have thorough, evidence-based, and high-quality evaluation. This report is the most comprehensive published series of EC somatic and germline testing in south Louisiana, an underrepresented population of interest due to historic background as a US Founder population. In addition, this cohort of patients has almost equal representation of black and white races and more publicly insured or uninsured than privately insured patients, which increases the generalizability of the study findings. This study describes critically needed genetic information of EC in black women, a traditionally understudied population.

In conclusion, we were unable to identify any major disparities in tumor testing. However, we did describe the patterns of genetic evaluation and tumor testing results for women with EC in a safety net hospital in south Louisiana with an almost equal black and white population of patients. The results suggest similar rates of MMRd or MSI-H EC tumors as previously reported in other populations. However, after the NCCN recommended universal testing of tumors, rates increased significantly but fell short of 100% adherence. To provide the best care to women with EC, it is critical to identify weaknesses in the entire process from diagnosis to genetic evaluation and to develop a process that promotes adherence to national guidelines.

Author contribution

Conception and design: Amelia Jernigan, Pallavi Nair-Fairless, Morgan McDougal

Provision of study material or patients: Amelia Jernigan

Collection and assembly of data: Morgan McDougal, Pallavi Nair-Fairless, Tova Weiss, Elizabeth Dao

Data analysis and interpretation: Andrew G. Chapple, Morgan McDougal, Pallavi Nair-Fairless, Amelia Jernigan

Manuscript writing: Morgan McDougal, Pallavi Nair-Fairless, Amelia Jernigan, Andrew G. Chapple

Supervision: Amelia Jernigan

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Morice, P., Leary, A., Creutzberg, C., Abu-Rustum, N., Darai, E., 2016. Endometrial cancer. The Lancet 387 (10023), 1094–1108.

Tutlewska, K., Lubinski, J., Kurzawski, G., 2013. Germline deletions in the EPCAM gene as a cause of Lynch syndrome – literature review. Hered. Cancer Clin. Pract. 11 (1) https://doi.org/10.1186/1897-4287-11-9.

Ryan, N.A.J., et al., 2019. The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. Genet. Med.: Offic. J. Am. College Med. Genet. 21 (10), 2167–2180.

Kim, S.R., et al., Does MMR status in endometrial cancer influence response to adjuvant therapy? (1095-6859 (Electronic)).

Ono, R., et al., 2019. Dedifferentiated Endometrial Carcinoma Could be A Target for Immune Checkpoint Inhibitors (Anti PD-1/PD-L1 Antibodies). Int. J. Mol. Sci., 20, 15, 3744.

ACOG Practice Bulletin No. 147: Lynch syndrome. (1873-233X (Electronic)).

NCCN, Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Colorectal. Version 2.2017.

Fang, P., et al., Racial disparities in guideline-concordant cancer care and mortality in the United States. (2452-1094 (Print)).

Karlitz, J.J., et al., 2014. Colorectal Cancer Incidence Rates in the Louisiana Acadian Parishes Demonstrated to be Among the Highest in the United States. Clin Transl Gastroenterol., 5, e60.

Dillon, J.L., Gonzalez, J.L., DeMars, L., Bloch, K.J., Tafe, L.J., 2017. Universal screening for Lynch syndrome in endometrial cancers: frequency of germline mutations and identification of patients with Lynch-like syndrome. Hum. Pathol. 70, 121–128.

Egoavil, C., et al., 2013. Prevalence of Lynch Syndrome among Patients with Newly Diagnosed Endometrial Cancers. PLoS ONE 8, 11, 1-1.

Long, Q., et al., 2014. Role of endometrial cancer abnormal MMR protein in screening Lynch-syndrome families. Int. J. Clin. Exp. Path. 7 (10), 7297–7303.

Kahn, R.M., et al., 2019. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population? Cancer 125 (18), 3172–3183.

Bartley, A.N., et al., Identification of cancer patients with Lynch syndrome: clinically significant discordances and problems in tissue-based mismatch repair testing. (1940-6215 (Electronic)).

Yokoyama, T., Takehara, K., Sugimoto, N., Kaneko, K., Fujimoto, E., Okazawa-Sakai, M., Okame, S., Shiroyama, Y., Yokoyama, T., Teramoto, N., Ohsumi, S., Saito, S., Imai, K., Sugano, K., 2018. Lynch syndrome-associated endometrial carcinoma with MLH1 germline mutation and MLH1 promoter hypermethylation: a case report and literature review. BMC Cancer 18 (1). https://doi.org/10.1186/s12885-018-4489-0.

Goodfellow, P.J., Billingsley, C.C., Lankes, H.A., Ali, S., Cohn, D.E., Broaddus, R.J., Ramirez, N., Pritchard, C.C., Hampel, H., Chassen, A.S., Simmons, L.V., Schmidt, A. P., Gao, F., Brinton, L.A., Backes, F., Landrum, L.M., Geller, M.A., DiSilvestro, P.A., Pearl, M.L., Lele, S.B., Powell, M.A., Zaino, R.J., Mutch, D., 2015. Combined Microsatellite Instability, MLH1 Methylation Analysis, and Immunohistochemistry for Lynch Syndrome Screening in Endometrial Cancers From GOG210: An NRG Oncology and Gynecologic Oncology Group Study. JCO 33 (36), 4301–4308.

Randall, L.M., Pothuri, B., Swisher, E.M., Diaz, J.P., Buchanan, A., Witkop, C.T., Bethan Powell, C., Smith, E.B., Robson, M.E., Boyd, J., Coleman, R.L., Lu, K., 2017. Multi-disciplinary summit on genetics services for women with gynecologic cancers: A Society of Gynecologic Oncology White Paper. Gynecol. Oncol. 146 (2), 217–224.