Published in final edited form as:

Clin Gastroenterol Hepatol. 2018 December ; 16(12): 1911–1918.e2. doi:10.1016/j.cgh.2018.08.038.

Low Referral Rate for Genetic Testing in Racially and Ethnically Diverse Patients Despite Universal Colorectal Cancer Screening

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Abstract

BACKGROUND & AIMS: Guidelines recommend that all colorectal tumors be assessed for mismatch repair deficiency, which could increase identification of patients with Lynch syndrome. This is of particular importance for minority populations, in whom hereditary syndromes are under diagnosed. We compared rates and outcomes of testing all tumor samples (universal testing) collected from a racially and ethnically diverse population for features of Lynch syndrome.

METHODS: We performed a retrospective analysis of colorectal tumors tested from 2012 through 2016 at 4 academic centers. Tumor samples were collected from 767 patients with colorectal cancer (52% non-Hispanic white [NHW], 26% African American, and 17% Hispanic patients). We assessed rates of tumor testing, recommendations for genetic evaluation, rates of attending a genetic evaluation, and performance of germline testing overall and by race/ethnicity. We performed univariate and multivariate regression analyses.

RESULTS: Overall, 92% of colorectal tumors were analyzed for mismatch repair deficiency without significant differences among races/ethnicities. However, minority patients were significantly less likely to be referred for genetic evaluation (21.2% for NHW patients vs 16.9% for African American patients and 10.9% for Hispanic patients; $P = .02$). Rates of genetic testing were also lower among minority patients (10.7% for NHW patients vs 6.0% for AA patients and 3.1% for Hispanic patients; $P < .01$). On multivariate analysis, African American race, older age, and medical center were independently associated with lack of referral for genetic evaluation and genetic testing.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2018.08.038>.

Conflicts of interest

The authors disclose no conflicts.

CONCLUSION: In a retrospective analysis, we found that despite similar rates of colorectal tumor analysis, minority patients are less likely to be recommended for genetic evaluation or to undergo germline testing for Lynch syndrome. Improvements in institutional practices in follow up after tumor testing could reduce barriers to diagnosis of Lynch diagnosis in minorities.

Keywords

CRC; Hereditary Nonpolyposis Colorectal Cancer; Genetic Counseling; Mutation

In the United States, colorectal cancer (CRC) is the third most common malignancy, and the second and third leading causes of cancer mortality in men and women, respectively.^{1,2} African American (AA) patients are disproportionately affected by CRC, with both the highest incidence and mortality of all U.S. populations.³ On average, AA patients are younger at diagnosis and have higher rates of proximal and advanced stage tumors than non-Hispanic White (NHW) patients.^{4–6} Disparities have also been described in Hispanic patients, including earlier age of onset and disparate outcomes.^{7,8} Previous studies have demonstrated both differences in tumor biology^{9–11} and environmental factors, such as socioeconomic status,^{12,13} that could account for the observed racial and ethnic disparities.

Lynch syndrome is the most common hereditary colon cancer syndrome, accounting for 3%–5% of all CRC,¹⁴ and is associated with increased risk of endometrial, ovarian, gastric, small bowel, urothelial, pancreaticobiliary and sebaceous skin cancers.¹⁵ This syndrome results from germline mutations in mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, *PMS2*, as well as deletions in *EPCAM*, resulting in microsatellite instability (MSI). Diagnosis of Lynch syndrome is important for identification of affected family members and also for implementation of surveillance programs and prophylactic treatments.^{16,17} Patients at risk for Lynch syndrome traditionally have been identified using family history-based risk assessment tools such as the Amsterdam and Bethesda criteria.¹⁷ However, clinical risk assessment tools miss up to 28% percent of cases of Lynch syndrome.¹⁸ Molecular approaches that directly test tumors for MSI with polymerase chain reaction or immunohistochemistry (IHC) for MMR proteins enable identification of Lynch syndrome with greater sensitivity.¹⁹ Improved characteristics of tumor testing, along with evidence of cost effectiveness,^{20,21} has led several professional organizations to advocate for universal testing of colorectal and endometrial cancers using MSI or IHC.^{17,22,23} As a result, universal tumor testing for Lynch syndrome has been implemented in recent years.²⁴

Although minority patients with CRC tend to be diagnosed at younger ages, previous studies have reported on only a modest number of AA and Hispanic families with Lynch syndrome.^{25–28} While the true prevalence of Lynch syndrome in minority populations is not known, the paucity of identified families is likely due to under-diagnosis. Implementation of universal tumor testing has the potential to increase Lynch syndrome diagnosis by removing traditional barriers experienced by minority populations, though this has not been studied. To address this gap, we studied universal CRC testing in a racially and ethnically diverse cohort of patients from 4 U.S. academic medical centers.

Methods

Study Population

Retrospective review of CRC patients who underwent tumor testing between January 1, 2012, and December 31, 2016, was performed. Data were collected from 4 U.S. academic centers: University of Chicago, Rush University, University of Miami, and University of Pennsylvania. By 2012 (with the exception of 1 center that adopted universal testing in 2013), each center had implemented testing all CRCs with either IHC or MSI regardless of age. Supplementary Table 1 provides details about workflow and provider networks at each participating center. Patients were excluded if they carried a known diagnosis of a hereditary CRC syndrome or inflammatory bowel disease.

Patient Demographics

Data were collected from the medical records at all centers including pathology reports and clinic notes from surgery, oncology, gastroenterology, and genetics providers and were recorded in a combined RedCap database. Demographic data included age, patient-reported race, ethnicity, gender, and insurance type. Select comorbid conditions were recorded including a diagnosis of diabetes or obesity (defined as body mass index $>30 \text{ kg/m}^2$). Family history data (when available in the medical record) of relatives with CRC or other Lynch-associated malignancies (as defined by Amsterdam II criteria)²⁹ including endometrial, small bowel, ureteral, and renal pelvis cancers were recorded. Patient tumor data including stage, histology, location, and types of treatment were also collected.

Tumor Testing

Patients were classified as having received tumor testing if endoscopic biopsies or resected tumor was tested using MSI or IHC. Tumors were classified as mismatch repair deficient (dMMR) if MSI was high (MSI-H) or if there was loss of expression of 1 or more mismatch repair proteins (MLH1, MSH2, MSH6, PMS2). For tumors with loss of MLH1 or MLH1/PMS2, it was documented whether reflex testing with either BRAF V600E mutation or MLH1 hypermethylation was performed. All tumor testing was performed at the individual academic centers according to institutional protocols.

Referral to Genetics Provider and Genetic Testing

Chart review of clinic notes and encounter details regarding referral to a genetic provider was performed. Patients were recorded as having received a recommendation for genetics evaluation if any provider: 1) documented a referral in the medical record or 2) documented discussing need for genetics evaluation with the patient. Patients were then recorded as having been seen for genetic consultation if a clinic appointment was attended as determined by the medical record. Recommendations regarding need for germline testing as well as genetic test results, if performed, were also collected from the medical record.

Statistical Analysis

Demographic data, tumor characteristics, and universal testing outcomes were compared between NHW patients and the 2 largest ethnic minority groups, AA and Hispanic patients,

using analysis of variance for continuous variables and Pearson chi-square test for categorical variables. Genetic evaluation and testing results were evaluated between ethnic and racial groups using multivariate logistic regression models. We controlled patients' demographic factors (age, gender, comorbidities, insurance type, family history, de-identified study sites) and tumor data (location and tumor stage).

Results

Demographics

A total of 767 CRC patients from 4 academic centers, Rush University (n = 122), University of Chicago (n = 305), University of Miami (n = 167), and University of Pennsylvania (n = 173), were included. The study population consisted of 52% NHW, 26% AA, 17% Hispanic, and 3% Asian patients. Given the small number of Asian patients, subsequent analyses were limited to NHW, AA, and Hispanic patients. Table 1 shows patient demographic and tumor data overall and by race and ethnicity. There was no difference in mean age at diagnosis among racial and ethnic groups ($P = .89$). Among NHW, AA, and Hispanic patients, there were significant differences in rates of obesity (14.7%, 26.4%, and 11.6%, respectively; $P = .001$) and diabetes (13.7%, 27.9%, and 20.9%, respectively; $P = .001$) with AA patients having higher rates of comorbid conditions. NHW and AA patients were nearly twice as likely to have a family history of malignancies that can be associated with Lynch syndrome as Hispanic patients (22.2% and 18.9% vs 10.8%, $P = .02$). Compared with NHW patients, AA and Hispanic patients were more likely to have Medicaid or be uninsured (8.5%, 23.4%, and 24.8%, respectively; $P = .001$). AA patients had the highest rates of right-sided tumors (47.3%; $P = .02$). Stage at diagnosis was not significantly different between groups ($P = .99$).

Tumor Testing

Tumor testing was performed in 702 of 767 (91.5%) patients. Significant negative predictors of tumor testing included older age and testing at 1 of the academic centers (Supplementary Table 2). Table 2 shows the results of tumor testing with either MSI or IHC. Most patients were tested with IHC (n = 694, 98.9%), while only 8 patients were tested by polymerase chain reaction. Overall, 13.7% of patients had dMMR tumors. There were no differences in dMMR tumors among NHW, AA, and Hispanic patients (13.7%, 12.4%, and 16.2%, respectively; $P = .96$). Hispanic patients were found to have higher rates of loss of MLH1/PMS2 compared with NHW and AA patients (90.4% vs. 60% and 48%; $P = .01$). For tumors with loss of MLH1 expression, there was no difference in the rate of reflex testing (46–70%, $P = .77$). The overall rate of MLH1 hypermethylation among those tested was 50% and did not differ between groups ($P = .52$).

Genetic Evaluation Recommendation and Genetic Testing

In the whole cohort, 18.8% of patients had a genetics evaluation recommended, whereas, among only those with abnormal tumor testing, this rate of recommendation for genetics evaluation was 48.9% (Table 3). Of all patients, 11.3% of patients were seen by a genetics provider, whereas this rate was 60.4% for those individuals who received a recommendation. Overall, 8.5% of patients had germline testing performed, and the overall prevalence of Lynch syndrome in this cohort was 2.0%.

When considering differences by race and ethnicity, AA and Hispanic patients were referred for genetics evaluation significantly less frequently than NHW were (16.9% and 10.9% vs 21.2%; $P = .02$), although after controlling for covariates, this disparity was only found for AA patients. Among patients with abnormal dMMR, NHW patients had the highest referral rate compared with AA and Hispanic patients (60.8% vs 54.2% and 6.7%; $P = .01$). NHW patients were seen by genetics providers with greater frequency than AA and Hispanic patients (13.7% vs 10.0% and 7.8%; $P = .06$). Interestingly, for patients who received a recommendation to see a genetic provider, there were no differences in attending genetics consultation among NHW, AA, and Hispanic patients (64.7%, 52.9%, and 71.4%, respectively; $P = .37$). The rate of Lynch syndrome diagnosis in this population was 2.5% for NHW, 2.0% for AA and 0.7% for Hispanic patients ($P = .48$) (Supplementary Table 3).

Multivariate analyses for recommendation for a genetics evaluation, being seen by genetics and for having germline genetic testing are included in Table 4. An independent positive predictor of a recommendation for a genetics evaluation included family history (odds ratio [OR], 5.54), while negative predictors included AA ethnicity (OR, 0.41), age (OR, 0.91), late stage (OR, 0.57), and medical centers 3 and 4 (OR, 0.29 and 0.24, respectively). Independent positive predictors for being seen by genetics included family history (OR, 5.49), while negative predictors included age (OR, 0.92), male gender (OR, 0.58), and medical centers 2 and 3 (OR, 0.31 and 0.24, respectively). Finally, independent positive predictors of having germline genetic testing performed included family history (OR, 5.86) and obesity (OR, 2.97), while AA ethnicity (OR, 0.39), age (0.92), late stage (OR, 0.54) and center 3 (OR, 0.18) were negative predictors.

Discussion

This is the largest study of universal tumor testing and follow-up in a racially and ethnically diverse population from academic medical centers. Our results demonstrate that CRC testing was performed at a high rate and, importantly, that there were no differences in the rates of tumor testing among NHW, AA, and Hispanic patients. However, less than half of all patients were recommended to see a genetics provider based on abnormal tumor testing, and minority patients were less likely than NHW patients to receive a recommendation by a health care provider. Rates of germline testing also were lower among minority patients. Even when controlling for a number of potential confounding factors, AA ethnicity as well as older age, advanced tumor stage, and medical center where patient received care were negative predictors of a recommendation for genetics evaluation and genetic testing. These differences underscore the importance of provider recommendation and patient uptake in equitable implementation along the spectrum of universal testing from molecular analysis to diagnosis of Lynch syndrome.

Numerous studies have reported on results of universal tumor testing,^{27,30–32} though there are little data on follow up in “real-world” clinical practice. The overall rate of universal tumor testing in this study is in line with a study in endometrial cancer,³³ and, importantly, showed no differences in testing rates by race or ethnicity. These contrast with a previous study showing that only 28% of patients in a national database had tumor testing and that AA patients were tested less frequently.³⁴ Notably, the strongest negative predictor of receipt

of tumor testing in our study was the medical center where testing was performed, underscoring institutional factors and quality control in successful implementation of universal testing protocols.³⁵

Nearly 14% of all patients had abnormal tumor tests in line with previous studies.^{27,30} While prior studies of Hispanic patients have reported high rates of mutation of MSH2/MSH6,^{27,36–38} our study found higher rates of MLH1/PMS2 loss among Hispanics, and further studies are required to confirm population differences in dMMR tumors. Our results suggest that a universal approach independent of the influence of patient demographics and other factors can overcome traditional barriers in identification of at-risk patients.

While tumor testing was performed at a high rate and equally across populations in this study, there were differences in the follow up of abnormal results. Overall, less than half of patients with abnormal tumor testing were referred for genetics evaluation similar to a previous study.³⁰ In this study, multivariate analysis found that independent negative predictors of genetics referral included medical center, age, and advanced tumor stage. Medical centers with lower rates of referral in our study were those with a larger network of ordering and interpreting providers which could lead to lack of communication for appropriate genetics referral as previously described.³⁹ Notably, only 1 of 15 Hispanic patients with abnormal tumor testing was referred to genetics likely because the majority of Hispanic patients were treated at a center with an overall low rate of genetics referral. Regarding lower referral in patients with late stage disease and older age, it is possible that treatment or performance status concerns had higher priority than genetics evaluation, though evidence to support this is sparse and conflicting.^{40–42}

A unique finding of this study was that AA race was also an independent negative predictor of referral for genetics evaluation. Lack of provider referral has previously been found to be a barrier for minority patients for genetics evaluation^{43–46} as well as other preventative services such as uptake of CRC screening.⁴⁷ These barriers are surmountable using a variety of strategies including automatic genetic counseling at postoperative surgical appointments to prevent loss to follow up or creation of centralized pathology cores to standardize testing procedures and reporting.^{30,31,33,35} Methods to improve application of universal testing are an ongoing area of research that should be tested for efficacy in diverse patient populations.

Minority patients were less likely to attend genetics appointments or to undergo germline testing. Interestingly, there were no population differences in being seen by a genetics provider if a recommendation was made highlighting the importance of provider recommendation. On multivariate analysis, AA race predicted reduced rate of germline testing. Lower rates of genetics evaluation among minority populations could potentially be explained by reduced knowledge of family history of cancer,⁴⁸ disparities in awareness of genetic testing for cancer risk,^{43,49} or by increased mistrust of genetic testing among minority patients.⁵⁰ Previous studies have shown that concerns regarding insurance coverage or personal cost are frequently barriers to genetic testing.^{51,52} However, even when controlling for insurance status, AA ethnicity remained a significant negative predictor of genetic testing suggesting that insurance type did not fully explain observed differences.

This study has numerous strengths. It is the first to compare outcomes of universal testing in a large, multiethnic CRC patient population. In addition, by studying the continuum of universal tumor testing, we were able to identify where disparities and differences occurred. Multivariate analyses controlled for numerous possible confounding factors including insurance status. There are also several limitations. None of the centers included in this study operate in a closed system; if a patient received genetic counseling or testing outside of the medical center, these data were not captured, and therefore the rates of genetic referral and testing might be an underestimation. Acknowledging this limitation, however, extensive chart review to capture as complete of an assessment of referral patterns as possible was performed. The retrospective design did not allow for understanding reasons for lack of genetics recommendation or genetic testing. It is possible that unmeasured factors, such as education, income level, or access to transportation could explain some of the observed differences. Furthermore, as this was not a population-based study, the true prevalence of Lynch syndrome or mutation spectrum in the populations could not be determined.

In summary, universal tumor testing is performed equally among minority patients. Racial and ethnic disparities become apparent in referral to genetics and genetic testing. Follow up of abnormal tumor tests requires provider action and patient uptake that are potentially modifiable factors and could be targeted with directed interventions. Such interventions could increase identification of Lynch syndrome and achieve truly universal screening among all CRC patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by R21CA215380-01 (to Sonia S. Kupfer), T32-DK007740 (to Shazia M. Siddique).

Abbreviations used in this paper:

AA	African American
CRC	colorectal cancer
dMMR	mismatch repair deficient
IHC	immunohistochemistry
MMR	mismatch repair
MSI	microsatellite instability
NHW	non-Hispanic White
OR	odds ratio

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Table 1.

Patient Demographics and Tumor Characteristics by Race or Ethnicity

	All (N = 767)	NHW (n = 401)	African American (n = 201)	Hispanic (n = 129)	P Value
Age, y	61.0 ± 14.3	60.7 ± 14.3	62.8 ± 14.2	60.1 ± 13.2	.89
Sex					
Female	376 (49.0)	186 (46.4)	112 (55.7)	61 (47.3)	.09
Male	391 (51.0)	215 (53.6)	89 (44.3)	68 (52.7)	
Comorbid conditions					
Diabetes	145 (18.9)	55 (13.7)	56 (27.9)	27 (20.9)	<.001
Obesity	130 (16.9)	59 (14.7)	53 (26.4)	15 (11.6)	<.001
Family cancer history ^a	145 (18.9)	89 (22.2)	38 (18.9)	14 (10.9)	.02
Insurance					
Private	321 (41.9)	204 (50.9)	57 (28.4)	42 (32.6)	<.001
Medicare	306 (39.9)	157 (39.2)	86 (42.8)	47 (36.4)	
Medicaid/uninsured	115 (15.0)	34 (8.5)	47 (23.4)	32 (24.8)	
Tumor location ^b					
Left	462 (60.2)	249 (62.1)	103 (51.2)	84 (65.1)	.02
Right	296 (38.6)	146 (36.4)	95 (47.3)	45 (34.9)	
Stage					
1	111 (14.5)	58 (14.5)	29 (14.4)	18 (14.0)	.99
2	233 (30.4)	120 (29.9)	60 (29.9)	41 (31.8)	
3	230 (30.0)	118 (29.4)	60 (29.9)	40 (31.0)	
4	166 (21.6)	93 (23.2)	43 (21.4)	25 (19.4)	
Medical center					
1	305 (39.8)	166 (41.4)	102 (50.7)	19 (14.7)	<.001
2	122 (15.9)	63 (15.7)	36 (17.9)	12 (9.3)	
3	167 (21.8)	37 (9.2)	36 (17.9)	94 (72.9)	
4	173 (22.6)	135 (33.7)	27 (13.4)	4 (3.1)	

NOTE. Values are mean ± SD or n (%).

NHW, non-Hispanic White.

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Family history of Lynch syndrome associated malignancy (colorectal, endometrial, ureteral or renal pelvis, or small bowel).
Left colon includes rectum to splenic flexure; right colon includes transverse colon to cecum.

Table 2.

Tumor Testing Results by Race or Ethnicity

	All (N = 767)	NHW (n = 401)	African American (n = 201)	Hispanic (n = 129)	P Value
Abnormal tumor testing (by IHC)	105 (13.7)	55 (13.7)	25 (12.4)	21 (16.2)	.96
IHC results					
MLH1/PMS2 loss	68/105 (64.8)	33/55 (60.0)	12/25 (48)	19/21 (90.4)	.01
MLH1 loss	2/105 (1.9)	1/55 (1.8)	0/25 (0)	1/21 (4.7)	.5
PMS2 loss	7/105 (6.7)	4/55 (7.3)	3/25 (12.0)	0/21 (0)	.27
MSH2/MSH6 loss	11/105 (10.5)	8/55 (14.5)	4/25 (16)	0/21 (0)	.16
MSH6 loss	7/105 (6.7)	5/55 (9.1)	2/25 (8.0)	0/21 (0)	.37
Reflex testing ^a	44/70 (62.9)	22/38 (58.0)	7/15 (46.7)	14/20 (70.0)	.77

NOTE. Values are n (%) or n/n (%).

IHC, immunohistochemistry; NHW, non-Hispanic White.

^aReflex testing for sporadic mismatch repair deficiency with MLH1 hypermethylation or BRAF V600E testing.

Table 3.
Recommendation for Genetic Evaluation and Genetic Testing Rates by Race or Ethnicity

	All (N = 767)	NHW (n = 401)	African American (n = 201)	Hispanic (n = 129)	P Value
Genetics evaluation recommended					
Total	144 (18.8)	85 (21.2)	34 (16.9)	14 (10.9)	.02
If abnormal tumor test	43/88 (48.9)	28/46 (60.8)	13/24 (54.2)	1/15 (6.7)	<.01
Seen by genetics provider					
Total	87 (11.3)	55 (13.7)	18 (10.0)	10 (7.8)	.06
If recommended	87/144 (60.4)	55/85 (64.7)	18/34 (52.9)	10/14 (71.4)	.37
Genetic testing performed	65 (8.5)	43 (10.7)	12 (6.0)	4 (3.1)	<.01
Diagnosed with Lynch syndrome	15 (2.0)	10 (2.5)	4 (2.0)	1 (0.7)	.48

NOTE. Values are n (%) or n/n (%).

NHW, non-Hispanic White.

Table 4.

Multivariate Analysis (n = 731)

	Genetics evaluation recommended		Seen by genetics		Germline testing performed	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Race						
NHW	Reference		Reference			
AA	0.41 (0.19–0.86)	.02 ^a	0.92 (0.51–1.64)	.79	0.39 (0.16–0.92)	.04
Hispanic	1.07 (0.39–2.8)	.89	1.15 (0.5–2.57)	.73	0.65 (0.15–2.22)	.52
Age	0.91 (0.88–0.93)	<.01	0.92 (0.89–0.94)	<.01	0.92 (0.89–0.95)	<.01
Sex						
Female	Reference		Reference		Reference	
Male	0.56 (0.32–1.0)	.05	0.58 (0.36–0.92)	.02	0.66 (0.33–1.28)	.22
Comorbid condition						
Diabetes	0.84 (0.31–1.99)	.70	1.03 (0.5–2.0)	.94	0.27 (0.04–1.01)	.09
Obesity	1.75 (0.89–3.39)	.10	1.57 (0.88–2.76)	.12	2.97 (1.38–6.42)	<.01
Family cancer history ^a						
Positive	5.54 (2.99–10.4)	<.01	5.49 (3.26–9.36)	<.01	5.86 (2.92–12.1)	<.01
Insurance						
Private	Reference		Reference		Reference	
Medicare	2.01 (0.88–4.66)	.10	1.22 (0.62–2.39)	.56	1.72 (0.61–4.84)	.30
Medicaid/uninsured	0.92 (0.41–2.0)	.85	0.7 (0.35–1.35)	.29	0.75 (0.28–1.9)	.55
Tumor location ^b						
Left colon	Reference		Reference		Reference	
Right colon	1.72 (0.96–3.08)	.07	1.32 (0.81–2.14)	.26	1.3 (0.65–2.6)	.45
Stage ^c						
Early	Reference		Reference		Reference	
Late stage	0.57 (0.41–0.77)	<.01	0.82 (0.64–1.04)	.10	0.54 (0.37–0.78)	<.01
Medical center						
Center 1	Reference		Reference		Reference	
Center 2	0.43 (0.17–1.0)	.06	0.31 (0.13–0.67)	.01	1.3 (0.53–3.05)	.55

	Genetics evaluation recommended		Seen by genetics		Germline testing performed	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Center 3	0.29 (0.1–0.75)	.01	0.24 (0.1–0.54)	<.01	0.18 (0.04–0.68)	.02
Center 4	0.24 (0.1–0.54)	<.01	0.55 (0.3–1.0)	.05	1.0 (0.3–3.05)	.99

AA, African American; CI, confidence interval; NHW, non-Hispanic White; OR, odds ratio.

^aFamily cancer history of Lynch syndrome associated malignancy (colorectal, endometrial, ureteral or renal pelvis, or small bowel).

^bLeft colon includes rectum to splenic flexure; right colon includes transverse colon to cecum.

^cEarly stage includes stages I–II, Late stage includes stages III–IV.