Feasibility of Utilizing PREMM Score for Lynch Syndrome Identification in an Urban, Minority Patient Population

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Abstract

The $PREMM_5$ model is a web-based clinical prediction algorithm that estimates the gene-specific risk of an individual carrying a Lynch syndrome germline mutation based on targeted family history questions. The objectives of our study were to determine the feasibility of screening for LS in an urban, minority patient population in a primary care setting using the $PREMM_5$ model and characterize patient barriers associated with difficulty completing the questions. Participants were recruited from Tulane Internal Medicine primary care clinics on 9 random collection dates. Our data illustrates the difficulty patients have in recalling important details necessary to answer the PREMM questionnaire.

Keywords

Introduction

Lynch syndrome (LS) is the most common cause of inherited colorectal cancer (CRC) and affected individuals carry a 50% to 70% lifetime risk of developing CRC.[1,2] LS is a defined as a germline mutation in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6, PMS2, or the EPCAM gene.[3-5] Loss of function in these genes leads to microsatellite instability,[6] which impacts mechanisms of cell growth, apoptosis, and the activity of other MMR genes, leading to increased risk of malignancy in the colon, endometrium, ovaries, stomach, intestines, kidneys, and biliary system.[7,8]

LS-associated adenocarcinomas in the colon are clinically distinct from sporadic CRC. The adenoma to carcinoma sequence takes place in about 3 years compared to 10 to 15 years in sporadic CRC.[9] The average age of onset is earlier in life, about 45 to 60 years in LS and 69 years in sporadic CRC.[10] Given these characteristics, LS associated adenomas often progress to malignancy before symptoms arise, so early diagnosis is vital not only for management of the initial cancer, but also in reducing the risk of future malignancies in the patient and in their at-risk family members.

The American College of Gastroenterology (ACGE) recommends identification of LS by universal screening of newly diagnosed CRCs for mismatch repair deficiency, or through genetic evaluation of individuals with a family history of LS or who have >5% risk of LS based on prediction models.[11] These recommendations are in accordance with a consensus statement by the US Multi-Society Task Force (USMSTF) on Colorectal Cancer.[12] $PREMM_5$ is a free web-based multivariable logistic regression model that provides gene-specific risk estimates of carrying an LS mutation

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based on family history.[13] Individuals are considered to be high risk for LS and eligible for genetic evaluation if they have a risk score greater than 2.5%. PREMM$_5$ has a sensitivity and specificity of 88% and 91%, respectively for MLH1 and MSH2 genes. Sensitivity is lower for MSH6 (74%) and PMS2 (50%).[14]

It is important to identify individuals who are high risk for LS because it makes genetic confirmation possible, allowing for further testing of at-risk family members and initiation of recommended cancer surveillance. Current indications for genetic evaluation include immunohistochemistry of newly diagnosed colorectal cancer tumors showing microsatellite instability or immunohistochemistry with deficits in MLH, MSH2, MSH6, or PMS2; individuals meeting the Revised Bethesda Guidelines (CRC under the age of 50, tumors with high microsatellite instability, or a family history of LS-associated tumors in 1 first-degree relative or 2 second-degree relatives); endometrial cancer diagnosed under the age of 50; or >5% risk based on prediction screening models, such as PREMM$_5$.[12]

Our study investigated whether it would be feasible to screen for LS using PREMM$_5$ in an urban, minority patient population in a primary care setting. We also aimed to characterize patient barriers to completing the PREMM$_5$ questions. To the best of our knowledge, no prior studies have been performed to evaluate the PREMM$_5$ model in an urban primary care setting.

Methods

This was a qualitative cross-sectional study involving a population of primary care patients with scheduled appointments in 2 different University-based outpatient clinics between April 17, 2017 and January 16, 2018. All insured patients >25 years old who arrived for their scheduled appointments during 9 random collection dates were approached to complete the PREMM survey (N=96). One of the investigators (BA) directly approached subjects after their clinic visits to obtain consent and verbally administer the PREMM$_5$ questionnaire. In addition to the standard family history items within the PREMM survey, the option of "I do not know" was added to each family history question. Participants were also asked if they had difficulty answering the PREMM survey items and individuals who reported difficulty were asked to explain their reasons. Individuals who declined participation were asked the reason for declining, and their responses were recorded.

Results

Of the patients approached, 78 agreed and 18 declined to answer the questionnaire. The most commonly cited reasons for not participating included limited time (38%, n=7), aversion to signing forms (16.6%, n=3), or fear of the results

Table 1. Study Participants.

Category	% (n = 96)
Sex	
Male	57.7
Female	42.3
Age	
25-35	6.4
36-45	9
46-55	9
56-65	29.5
66-75	32.1
76+	12.8
Race	
Black	56.4
White	39.7
Other	3.9

(16.6%, n=3). The 78 participants had a mean age of 62.4 ± 13.9 years, were 56.4% black and 39.7% white, and consisted of 57.7% men and 42.3% women (Table 1). Overall, 28% (n=23) of patients had at least 1 positive response on the PREMM survey with risk scores ranging from 0.4% to 2.2%. One individual had a positive LS screen, with a risk score 3.2%, but declined further genetic evaluation. The remaining 70% (n=55) had no positive responses, resulting in no risk score output from PREMM (Table 2). One patient had a personal history of colorectal cancer and another had a personal history of another Lynch syndrome-associated cancer (LSAC). Notably, 23% of participants were "unsure" of at least 1 answer in the PREMM survey; these patients were on average unsure of 2.6 answers. Additionally, 26.9% of patients reported having "difficulty" filling out the survey. Reported reasons for difficulty included being uncertain of their family's medical history in general, being unsure of the cancer type in family members known to have a cancer history, and uncertainty about medical history in second degree relatives.

Discussion

Current guidelines recommend initiating screening colonoscopy for LS positive individuals at 25 years old and repeat colonoscopy every 1 to 2 years. This requires identifying high-risk individuals who should undergo diagnostic genetic testing. There are several screening tools to identify high-risk patients, but each tool depends on the patient's knowledge of his or her family history of LSACs. Given that 23% of our participants were unsure of at least 1 question, our data illustrates the difficulty that primary care patients may have in recalling important details necessary to stratify their risk of having LS.

A large portion of our population had difficulty completing PREMM$_5$. Common reasons for difficulty included

Table 2. Results of PREMM Survey + Additional Questions.

	Number of cancers	N	%
Personal hx of LSAC			
CRC		1	1.28
EC		0	0.00
Other LSAC		1	1.28
First degree relative with LSAC			
CRC	1	4	5.13
	2 or more	0	0.00
	Unsure	3	3.85
EC	1	4	5.13
	2 or more	0	0.00
	Unsure	6	7.69
Other LSAC	Yes	3	3.85
	Unsure	2	2.56
Second degree relative with LSAC			
CRC	1	4	5.13
	2 or more	0	0.00
	Unsure	15	19.23
EC	1	1	1.28
	2 or more	0	0.00
	Unsure	11	14.10
Other LSAC	Yes	8	10.26
	Unsure	10	12.82
Difficulty answering PREMM questions	Yes	21	26.92
Hx of genetic counseling/testing	Yes	3	3.85
Unsure of at least 1 answer	Yes	18	23.07
Other personal cancer history	Personal	11	14.10
Other family cancer history	Family	20	25.64

Abbreviations: CRC, colorectal cancer; EC, endometrial cancer; LSAC, lynch syndrome associated cancer.

uncertainty about the presence of cancer in second degree relatives and uncertainty about types of cancer in first and second degree relatives. Lack of information availability is a barrier to utilizing PREMM$_5$ and other screening tools for detecting LS in primary care settings. Harty et al assessed the feasibility of implementing a colorectal cancer risk assessment tool (CRISP-P) into a primary care clinic, and also found high rates of uncertainty when completing the questionnaire in a primary care setting. They found that while 90% of patients agreed to complete the questionnaire, 41% were unable to answer all questions independently due to difficulties with language and health literacy.[15] Similarly, Pieper et al[16] found that primary care patients who completed a 3-question colorectal cancer screening tool later reported that they had answered at least 1 of the questions inaccurately. This indicates that the level of detail necessary to identify high-risk patients may not be immediately available in a primary care setting. One limitation in our study is that we do not have information about educational levels or primary language of study

participants and therefore cannot determine the potential impact of these factors on patient's ability to complete questionnaire items. Patients who are older, without higher education, or who have English as a second language may be more likely to have needed assistance as was the case with the study by Harty et al.[15]

Another possible reason for patient difficulty is the older age of our population. Colorectal cancer screening may have been less common in their parents or grandparents, resulting in lower likelihood of a known diagnosis or cause of death in first and second degree relatives of this patient population.

Our study showed that the majority of primary care patients were open to completing PREMM$_5$ after their clinic visits. Response rates in our population were similar to Harty et al[15] who had 90% participation. However, other studies implementing cancer risk assessment tools into primary care settings had much lower participation rates, ranging from 15% to 25%.[16,17] Our high participation rates may be skewed by chance, given our small sample size, but it is

also possible that in-person recruitment strategies improved patient participation as was noted in prior studies.[17]

Several patients also refused the questionnaire due to time restraints. Primary care visits often entail multiple competing health issues to be discussed within a limited time period, perhaps making it difficult to devote substantial time to screening for 1 potential disease if the patient or physician do not already perceive the patient to be at an elevated risk. Since time of visit was not recorded during data collection, it is unclear whether this was influenced by the time of day during which appointments were scheduled.

Luba et al[18] studied the $PREMM_{1,2,6}$ model in a community gastroenterology office and concluded that a patient self-administered version of the model could effectively be used to screen at-risk individuals in the outpatient setting. By contacting patients prior to their appointment and reviewing portions of the questionnaire, this study was likely able to improve participant completion of questions about their family history of LSAC. It is also possible that implementation in a subspecialty clinic, rather than primary care clinic, increases the probability that participants were higher risk for colorectal cancer, which has been shown to increase accuracy in answering colorectal cancer screening questions.[16] In contrast to our study, Luba et al did not report on the percentage of patients that were unsure of certain questions or had difficulty completing the questionnaire, so it is uncertain whether questionnaires were completed accurately. In addition, Luba et al did not report why 17.5% of eligible participants declined genetic testing.[18] By further investigating these questions in our study, we have addressed additional barriers to obtaining a final diagnosis of LS.

One subject screened positive for LS with a risk score 3.2%, but declined further genetic evaluation. Based on the positive screen, this individual was offered further evaluation with a genetic counselor but declined. Although we cannot draw conclusions about genetic counseling uptake due to our limited sample, there is evidence that even individuals aware of their cancer risk choose not to pursue genetic evaluation or do not receive accurate genetic testing recommendations from their providers.[19,20]

Although these results are limited by the small sample size of this study and this is only a single site study, our study demonstrates that unavailability of information needed for the $PREMM_5$ model can limit its utility in the primary care setting. Even with high questionnaire completion rates, the accuracy of questionnaire data is likely limited by patients' knowledge of a detailed family history or patient difficulty with questionnaire items, perhaps due to low health literacy. Further work would be needed to determine if interventions such as asking patients to gather a detailed family history prior to their visit would increase the yield of the in-office questionnaire. In addition, possibly further educating patients on the epidemiology of LS associated malignancies would increase their desire to complete these questions.

Author Roles

Brigid Adviento, MD, MPH: study concept and design, acquisition of data, statistical analysis, drafting of the manuscript, critical revision of the manuscript. Michael Conner, MD: drafting of the manuscript, critical revision of the manuscript for important intellectual content. Alexander Sarkisian, MD: study concept and design, drafting of the manuscript. Nicolette Walano, MS, CGC: study concept and design. Hans Andersson, MD: study concept and design. Jordan Karlitz, MD: study concept and design, study supervision.

Article Guarantor

Jordan Karlitz, MD.

Informed Consent

Every patient involved in this study completed an informed consent prior to completing the questionnaire. All patient identifiers have been removed from the pilot study.

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