Successful Pancreatic Cancer Screening Among Individuals at Elevated Risk Using Endoscopic Ultrasound and Magnetic Resonance Imaging

A Community Hospital Experience

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Objectives: Guidelines for testing individuals at risk (IAR) for developing pancreatic duct adenocarcinoma (PC) are being advanced from university hospital populations. We implemented a screen-in criteria and protocol for IAR for PC in our community hospital setting.

Methods: Eligibility was based on germline status and/or family history of PC. Longitudinal testing continued, alternating between endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI). The primary objective was to analyze pancreatic conditions and their associations with risk factors. The secondary objective was to evaluate the outcomes and complications resulting from testing.

Results: Over 93 months, 102 individuals completed baseline EUS, and 26 (25%) met defined endpoints of any abnormal findings in the pancreas. Average enrollment was 40 months, and all participants with endpoints continued standard surveillance. Two participants (1.8%) had endpoint findings requiring surgery for premalignant lesions. Increasing age predicted for endpoint findings. Analysis of longitudinal testing suggested reliability between the EUS and MRI results.

Conclusions: In our community hospital population, baseline EUS was effective in identifying the majority of findings; advancing age correlated with a greater chance of abnormalities. No differences were observed between EUS and MRI findings. Screening programs for PC among IAR can be successfully performed in the community setting.

Key Words: pancreatic cancer, screening, early detection, endoscopic ultrasound, magnetic resonance imaging

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In the United States, an estimated 60,000 adults will be diagnosed with pancreatic cancer (PC) in 2021, representing the eighth most common cancer in women and the tenth most common cancer in men. As the fourth leading cause of cancer death in all sexes, PC accounts for 7% of all cancer-related deaths.[1,2] Surgical removal via pancreatectomy is the only potentially curative treatment for PC. However, approximately 80% of all diagnosed patients present at an advanced stage and are ineligible for surgery. Even after potentially curative surgery, relapses are common and 5-year survival is typically only 10% to 30%.[3] Five-year survival rates for patients with unresected PC are very low, typically reported as 5% to 10%.[4]

Because of the lethal nature of this disease, efforts have been made to detect PC at an earlier stage of development than typically found, in the hope of improving survival rates. Despite the importance of early screening, there are currently no broad guidelines commonly implemented for PC screening. Pancreatic cancer (PC) is a general phenotypic consequence of a wide variety of biological contributing factors, and its pathogenesis is multifactorial, including deleterious contributions from genetic, inflammatory, and immunological processes.[5] Hereditary causes makeup at least 10% of PC cases, typically involving genes such as *BRCA1/2*, *PALB2*, *ATM*, *CDKN2A*, *PRSS1*, *MLH1*, *MSH2*, *MSH6*, and *STK11/LKB1*.[6] In addition, PC is observed in some families despite negative results from germline testing, typically referred to as familial PC when 2 or more first-degree relatives are affected.[7,8] In addition to biological heterogeneity complicating the identification of an at-risk population, the deep anatomic location of the pancreas makes the detection of precancerous lesions or cancers more difficult.

Based on previously published cohort studies largely from university settings, the International Pancreas Cancer Screening Consortium in 2013 agreed that endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) were the recommended testing modalities.[9] However, age at test initiation, frequency of testing, and testing cessation remain open areas of discussion. Because of the observed familial clusters of PC and deleterious germline mutations in our community, we recognized an unmet need: in 2014, we developed a new screening program for PC in individuals at elevated risk, adapting criteria from the International Pancreas Cancer Screening Consortium, using both EUS and MRI. Our primary objective was to analyze the number and type of pancreatic conditions and their association with genetic or family history. The secondary objective was to evaluate the outcomes and complications resulting from testing.

MATERIALS AND METHODS

Study Design

The Pancreatic Cancer Early Detection Program (PCEDP) is a prospective screening program following the Strengthening the Reporting of Observational studies in Epidemiology guidelines.[10]

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Setting

White Plains Hospital is a 290-bed hospital located in the county seat of Westchester County, 30 miles north of New York City. As a member of the Montefiore Health System, it serves to a broad demographic of socioeconomic status, race, and ethnicity. The population is 45.1% non-Hispanic White, 33.2% Hispanic, 12.0% non-Hispanic Black, 7.7% Asian/Pacific Islander, and 1.8% non-Hispanic other.[11]

Participants

Eligibility for the PCEDP was adapted from the recommendations of the International Pancreas Cancer Screening Consortium,[9] with our definition of elevated risk as having either (*a*) relative risk (RR) approaching or exceeding 5.0 or (*b*) lifetime risk (LR) approaching or exceeding 7.5%. Age of initiation was dependent upon eligibility criteria (Supplemental Digital Content 1, http://links.lww.com/MPA/A995).

Intervention

Our screening protocol was based on the best available recommendations[9] along with modifications designed by our team to address questions about modality and longitudinal testing. While EUS and MRI have been recommended tests for PC screening,[9] comparison of these 2 tests in the same cohort or longitudinally across individual patients is underdeveloped in the literature. Therefore, to establish at least one comparison pairing, testing started with a baseline EUS followed by a baseline MRI 6 months later. Because the risk factors for PC were continuous, longitudinal testing was continued, alternating between EUS and MRI. There have been no formal guidelines on interval testing, but premalignant pancreatic conditions, including intraductal papillary mucinous neoplasms, can grow over a period of several months, and the pancreatic cyst growth rate is correlated with the risk of malignancy.[12,13] Therefore, for participants younger than 65 years, the frequency of testing was 12 months. Based on prior data suggesting a higher yield of abnormal findings in individuals older than 65 years,[14] participants 65 years and older were tested every 6 months. The testing method is illustrated in Figure 1. Longitudinal testing continued as scheduled until either an endpoint was found or if the participant elected to stop or became unable to continue. Endpoints were defined as any abnormal EUS or MRI findings in the pancreas, including but not limited to cysts or masses, which would require management and follow-up as per the standard of current medical care. Testing and office visits were subject to coverage and payment, as approved by the participants' insurance plans. If participants could not continue with one modality, they continued to study with a single modality tested annually. Participants were recruited largely through physician referral, pamphlets, and community programs, all of which were approved by the internal review board committee.

In addition, the subset of participants with endpoints was followed with surveillance testing per the standard of care.

The PCEDP was approved for 5 years by our institutional internal review board in 2014 and was granted another 5 years in 2019.

Data Sources/Measurement

All EUS procedures were performed by a single practitioner (C.N.) as described in Supplemental Digital Content 2, http://links.lww.com/MPA/A995. The MRI was performed with and without contrast at any institution. Adverse events were not predefined and were collected when the participants reported them to the clinical trial office. The EUS and MRI results were collected from all clinical databases (hospital and clinic electronic medical records), reviewed monthly by clinical and research personnel, and entered manually into a restricted access Microsoft Excel (version 2018; Microsoft Corporation, Redmond, Wash).

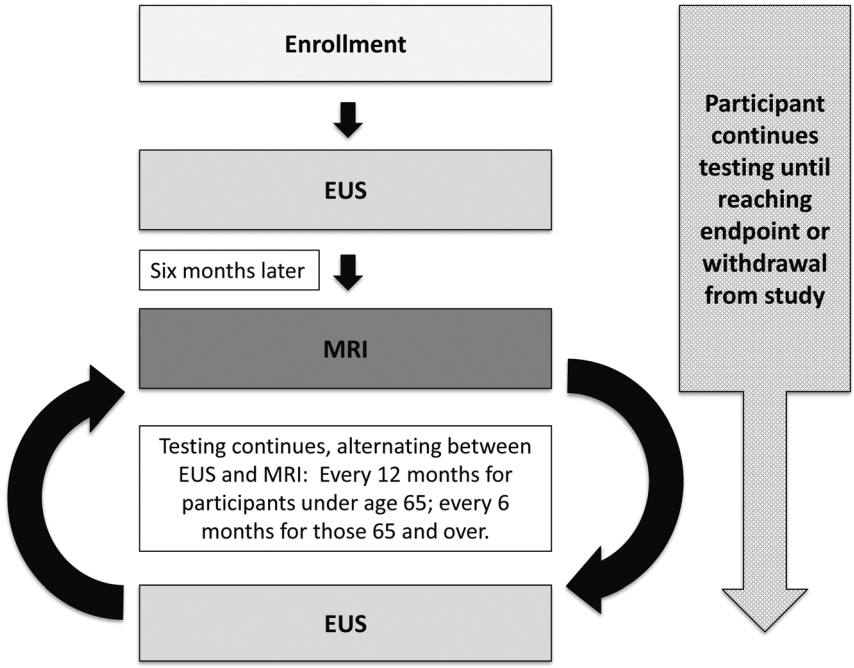

FIGURE 1. Method of testing. After enrollment, all participants began testing with a baseline EUS, followed 6 months later by a baseline MRI. Testing then continued to alternate between EUS and MRI, with the frequency of testing dependent upon age: every 12 months for those younger than 65 years, and every 6 months for those 65 years and older. Testing continued until an endpoint was reached or patient withdrew.

Bias

To minimize sampling bias, we included patients who were both referred by physicians and self-referred. Confirmation of germline mutations was required. To limit information bias, we conducted regular multidisciplinary reviews of the study, its protocols, and preliminary findings.

Study Size and Statistical Methods

Based on the volume and experience of the community, we anticipated enrolling approximately 10 to 12 individuals per year. All data were collected prospectively and stored on a secure server that was available only to members of the clinical trial office. As this was designed as an implementation and registration study, enrollment was not required to satisfy any a priori calculations.

All statistical calculations were performed using R statistical software v 4.0.2 (R Foundation, Vienna, Austria). Multivariate logistic regression was used to identify whether age, sex, race, ethnicity, germline mutations, or family history of PC contributed to positive findings. Multicollinearity was assessed using variance inflation factors and linearity with the Box-Tidwell test. Cook's distance was used to evaluate influential values, and one observation was removed. The Cohen κ was used to assess the agreement between MRI and EUS results. Given that participants followed a schedule alternating between MRI and EUS, this test was performed twice, first pairing each MRI with the preceding EUS and then pairing each MRI with the following EUS to generate two distinct κ values.

Quantitative Variables

Endpoints were met by a finding of any size on EUS or MRI; thus, quantitative variables describing positive endpoints did not impact our screening protocol. In the surveillance of the 26 patients with endpoints, changes in the size of pancreatic findings were evaluated by the standard of care with a multidisciplinary review.

RESULTS

Participants and Descriptive Data

From April 2014 to December 2021, our team received 340 queries, of which 114 individuals (33%) were enrolled in the PCEDP. At the end of 2021, 102 patients had undergone initial EUS. The other 226 individuals were either ineligible, not yet eligible, or eligible but chose not to consent. The full demographics are presented in Table 1.

Feasibility, Adherence, and Safety

No significant adverse events were observed during testing. All tests were submitted through insurance approval. Insurance

TABLE 1. Patient Demographics

Characteristic	All Patients n = 111	Patients With Positive Finding n = 26
Sex, n (%)		
Female	76 (68)	18 (69)
Male	35 (32)	8 (31)
Race, n (%)		
Asian	1 (0.9)	1 (3.8)
Black	6 (5.4)	
Other	2 (1.8)	
Unknown	3 (2.7)	3 (12)
White	99 (89)	22 (85)
Ethnicity, n (%)		
Hispanic	4 (3.6)	
Non-Hispanic	106 (95)	25 (96)
Unknown	1 (0.9)	1 (3.8)
Age at consent, median (IQR), y	56 (51–64)	61 (58–70)
Eligibility, n (%)		
Both	22 (20)	5 (19)
Family	39 (35)	8 (31)
Genetics	50 (45)	13 (50)
BRCA1, n (%)	11 (10)	2 (8)
BRCA2, n (%)	46 (41)	11 (42)
PALB2, n (%)	3 (3)	2 (8)
CDKN2A, n (%)	2 (2)	1 (4)
ATM, n (%)	4 (4)	0 (0)
PSM2, n (%)	1 (1)	0 (0)
APC, n (%)	1 (1)	1 (4)
Length of enrollment, median (IQR), d	1227 (345–1882)	1298 (497–1901)

Demographics and clinical criteria of patients enrolled in the screening process. Race and ethnicity were self-reported. Eligibility was determined through a combination of family history and genetic predisposition. Genes correlated with an increased risk of PC qualified patients for the study and are listed in italics.

IQR indicates interquartile range.

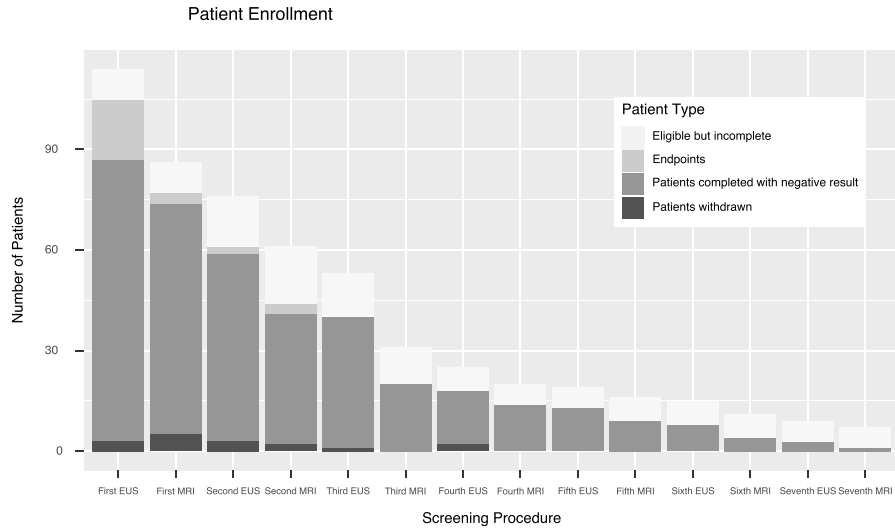

FIGURE 2. Patient enrollment. Patients alternated between EUS and magnetic resonance imaging (MRI) as screening modalities. Frequency of screening was determined by risk factors for developing PC. Patients enrolled into the study at different times over the 5-year period. As a result, patients have been eligible for a varying number of screening tests. "Eligible but incomplete" represents patients who are within the time frame of their test, and have not yet completed. "Endpoints" represents positive screenings.

approved the testing coverage in 294 of 304 tests (96%). All 10 denials were for MRIs, including 9 from private insurance. In case of insurance denial, participants were permitted to remain on study to continue testing with EUS only. Twenty-two of the 102 participants (21%) underwent MRI performed outside our institution.

Fifteen participants withdrew, including 3 who did not undergo any testing. The reasons for withdrawal were documented as follows: lost to follow-up (3), other illness (3), preference (3), insurance (2), advancing age (1), transportation (1), location (1), and moved away (1). Participation in the protocol, including the outcomes of each test, is illustrated in Figure 2.

Outcome Data and Main Results of Testing

Of the 102 participants enrolled, 26 (25.5%) had an endpoint with abnormal pancreatic findings. All endpoints were cystic or semisolid pancreatic cysts ranging from 1.0 to 29 mm (median, 7.5 mm) in size, with 18 (69%) under 10 mm. Demographic characteristics of the endpoint patients are shown in Table 1. Eighteen endpoints (69%) were found on baseline EUS, while 3 were found on baseline MRI, as shown in Figure 2. Regression analysis of clinical variables demonstrated that age was the only factor associated with an increased rate of positive endpoints, as shown in Table 2.

The participants were enrolled for an average of 40 months, with a mean of 3.7 tests.

Surveillance Testing of Endpoint Patients

All endpoint participants (EPs) were recommended to follow standard of care postprotocol, which consisted of surveillance EUS and/or MRI, for an average of 35 months after a positive finding (range, 6–87). Consent was obtained from 25 EPs to use their follow-up data, and one was lost to follow-up. Table 3 presents the characteristics and findings of the EPs cohort. Nineteen patients had stable pancreatic cysts, and 4 had slight, nonconcerning growth in cysts. Two participants had findings from their baseline EUS that resulted in pancreatic surgery. A 72-year-old man was found to have multiple anechoic branching septated cysts, with several communicating with the main pancreatic duct, the largest at the tail, and measured up to 29.2 mm. The findings were consistent with branch duct intraductal papillary mucinous neoplasm and were confirmed on MRI. He underwent laparoscopic distal pancreatectomy revealing intraductal papillary mucinous neoplasm with moderate dysplasia. A 63-year-old woman was found to have multiple simple and branching anechoic cysts up to 14 mm in the pancreatic uncinate, head, body, and tail; with several cysts in the body and tail having concerning features. These findings were also confirmed on MRI. She underwent a distal subtotal pancreatectomy, with pathology revealing multiple serous cysts and low grade pancreatic intraepithelial neoplasia. No significant adverse events were reported from any of the care delivered postprotocols, including the 2 surgeries.

Comparison of EUS and MRI Results

Cohen κ coefficient test for interrater reliability was used to evaluate the agreement between the EUS and MRI results. κ results were measured as 2 pairs: EUS followed by MRI (κ = 0.749; 95% confidence interval [CI], 0.557–0.94; n = 158) and MRI followed by EUS (κ = 0.649; 95% CI, 0.329–0.968; n = 116) both substantial in their degree of agreement.

DISCUSSION

In our single-center, community-based PC screening program, we successfully enrolled 33% of all queries and safely tested 102 participants with a 25% positive screening result at our endpoint. Longitudinal testing alternating with EUS and

TABLE 2. Factors Affecting Rate of Positive Finding

Predictors	Odds Ratio (95% CI)	*P*
Age	1.12 (1.05–1.20)	**0.001**
Sex, male	0.63 (0.19–2.06)	0.441
Eligibility: genetic	1.16 (0.32–4.23)	0.822
Eligibility: genetic and family	2.35 (0.55–9.99)	0.248
Ethnicity: Hispanic	0.00 (0.00–Inf)	0.996
Ethnicity: unknown	1.21 (0.00–Inf)	1.000

Multivariate logistic regression was used to identify factors, which increased odds of a positive finding throughout enrollment in the screening process. A bold value represents a $P < 0.05$ and is statistically significant.

Inf indicates infinite value.

TABLE 3. Characteristics of 26 Participants Who Were Found to Have an Endpoint

End Patient No.	Age at Endpoint, y	Eligibility	Endpoint Discovery	Endpoint Finding	Surveillance Duration, mo	Summary of Longitudinal Surveillance
1	54	Father, paternal grandfather, and *APC*	EUS 1	Anechoic cysts	87	Stable cysts
2	77	*BRCA2*	EUS 4	Small anechoic cyst	40	Slight growth of cysts
3	78	Father and brother	EUS 3	Anechoic cysts	44	Stable cysts
4	66	Sister and mother	EUS 2	Anechoic cyst	54	Stable cyst
5	48	Father and *PALB2*	EUS 1	Anechoic cyst	53	Stable cyst
6	71	*BRCA2*	MRI 2	Cystic lesions	34	Stable cyst
7	62	Father and brother	EUS 1	Anechoic cyst	58	Stable cyst
8	59	Sister and *PALB2*	EUS 1	Anechoic septated cyst	0	Lost to follow-up
9	56	*BRCA2*	EUS 1	Anechoic cyst	49	Slight growth of cyst
10	64	*BRCA2*	EUS 3	Parenchymal cyst	0	Too soon for any follow-up
11	55	*BRCA2*	EUS 1	Anechoic cyst	41	Stable cyst
12	70	*BRCA2*	EUS 1	Branched intraductal papillary mucinous neoplasm	29	Stable cysts
13	73	Paternal grandmother and *BRCA1*	EUS 1	Inhomogeneous structure and microcysts	39	Stable cysts/mass
14	59	*BRCA2*	EUS 1	Anechoic cyst	23	Slight growth of cysts
15	60	*BRCA2*	EUS 1	Anechoic cyst	26	Stable cysts
16	47	Father and paternal grandfather	MRI 1	Multiple cysts	12	Stable cysts
17	61	*BRCA2*	EUS 1	Anechoic cyst	31	Slight growth of cysts
18	72	Sister and *BRCA1*	EUS 1	Multiple anechoic cysts and intraductal papillary mucinous neoplasm	NA	Surgery
19	57	*BRCA2*	MRI 1	Cystic lesions	23	Stable cysts
20	64	Father, sister, and *BRCA2*	EUS 1	Multiple simple and branching cysts	NA	Surgery
21	60	Mother and *ATM*	EUS 1	Anechoic cyst	6	Stable cyst
22	62	*BRCA2*	EUS 1	Anechoic cyst	0	Too soon for any follow-up
23	72	Mother and gather	EUS 1	Anechoic cysts	7	Stable cysts
24	49	Father and paternal grandmother	EUS1	Parenchymal cyst	0	Too soon for any follow-up
25	73	Mother and maternal uncle	MRI 1	Anechoic cysts	0	Too soon for any follow-up
26	64	Brother and *BRCA2*	EUS1	Parenchymal cyst	7	Stable cyst

Demographic factors including age and eligibility criteria, as well as timing of all positive findings within the study, are illustrated in Table 3. "Endpoint Finding" represents an abnormal result on either an EUS or MRI. "Surveillance Duration, mo" details how long the patient has been in the study, as patients continue after a positive result. Any change in the positive finding during this period is shown in "Summary of Longitudinal Surveillance."

NA indicates not available.

MRI has not been routinely reported in this population and was successfully performed for an average of 40 months and 3.7 tests. The 2020 updated recommendation from the International Pancreas Cancer Screening Consortium listed 25 similar cohort studies[15] all derived from university hospitals or major cancer centers; however, only 13 (52%) used both EUS and MRI, and 10 (40%) only performed initial screening (Supplemental Table 1, http://links.lww.com/MPA/A995). A recently published preliminary report from a 456-bed community hospital using MRI to screen IAR similarly showed the feasibility of this approach.[16]

Our endpoints were defined broadly (to include any pancreatic abnormality) for 2 reasons. First, we had limited precedent to know what lesions would be found and how they would behave in our particular population. Second, we understood that there could be discrepancy between EUS and MRI in reporting cyst sizes and wanted to simplify our methodology. Although our definition of endpoint may be more inclusive than in similar studies, our 25% rate of endpoint is consistent with the most recent report from the updated International Pancreas Cancer Screening Consortium. In addition, the 2 surgeries performed here (1.9%) seem consistent with findings from 2 recent meta-analyses of pancreatic surgery in the at-risk population.[17,18] As was shown in Figure 2, most endpoints were found on baseline testing, and all by the fourth test, that is, the second MRI. We believe that the withdrawal rate of 15%, mostly occurring at earlier stages of testing, suggests a dedicated population of participants.

Limitations

The role of longitudinal testing in this patient population has not been fully described. Our decision to incorporate both serial testing and alternating modalities was likely ambitious for the scale of this study; any conclusions derived from our longitudinal testing will need to be interpreted with appropriate circumspection. Furthermore, our method of testing, which required biannual testing for individuals older than 65 years, was based on a single report of a higher yield in that age group.[14] Although there have been studies suggesting the potential for cost-effectiveness of screening in high-risk individuals,[19,20] in our small study, biannual testing led to consumption of resources without direct benefit.

Collection of adverse events based solely on unsolicited reporting by the participants could have led to the underreporting of adverse events.

Our procedure for MRI testing was not standardized, and we did not insist on a formatted protocol for the test and reading; MRIs were read by different radiologists; tests were initially ordered as abdominal MRI and eventually ordered as magnetic resonance cholangiopancreatography; and MRIs were permitted from outside the institution. In contrast, all EUSs were performed by one practitioner, creating a uniform approach, which can be seen in a community setting where access to experienced endosonographers may be limited. In practice, EUS may have interoperator variability that was not accounted for in this study. In addition, although we did not prospectively describe the differences between parenchymal and anechoic cysts, doing so in the future may help improve accuracy of screening. Of note, our formal programmatic review of all tests allowed us to correlate the findings, comparing EUS with MRI.

Cohen κ coefficient to assess for concordance is more typically used when compared tests are performed at the same point in time, whereas we used it to evaluate EUSs and MRIs done at different points in time. Although comparisons with increased time between tests can create a tendency for discordance to emerge, we observed concordance between the EUSs and MRIs.

As some patients were self-selected and others were referred by providers, referral/volunteer bias may have affected our population. However, this may mimic the real world with a motivated population, such as people affected by PC among family members. In addition, there was the possibility of detection (information) bias because we had only one operator performing EUS. This may have been mitigated by the use of alternating MRI, which have been shown to correlate with EUS findings.

Finally, the racial and ethnic representation in our program was far from that of our community population, with the vast majority of our enrollees self-reporting as White, non-Hispanic. *BRCA1* and *BRCA2* mutations, the most common risk factors, are found in Hispanic and African-American communities.[21,22] Racial and ethnic disparities have been reported in other cancer screenings.[23,24] Ko et al[25] recently reported that racial disparities in breast cancer screening were frequently mediated by insurance status. While our marketing methods were largely based on word of mouth, physician referral, and community events, we may have overlooked the reluctance of at-risk individuals to query our study because of concerns about insurance and cost.

Future Directions

Based on these results, we believe that screening programs with EUS or MRI can be established in community settings for individuals at an elevated risk for PC. Continued testing in a longitudinal manner can be pursued as the risks for PC persist after baseline testing and because increasing age is associated with a higher rate of abnormal findings.

Detailed recommendations regarding specific eligibility and the frequency and duration of testing remain unanswered but are being actively refined.[15,26] Earlier this year, the National Comprehensive Cancer Network updated its guidelines for the first time to include PC screening for IAR.[27] While later in 2022 the American Society for Gastrointestinal Endoscopy released their updated guidelines for PC screening and genetic susceptibility,[28] with new guidelines related to *BRCA1*. Based on these results and from others, we plan to make modifications to our current methodology as our PC screening program continues, for example, by increasing the age at initiation of testing for certain eligibilities, refining certain eligibilities; changing the frequency of testing to annually for all ages, and allowing participants to select annually either EUS or MRI after their baseline tests. Our experience may serve as example for other, similar institutions.

There are no published data from any controlled studies demonstrating survival benefit from PC screening studies. New molecular tests, however, are emerging to help refine the process of PC screening, perhaps away from our traditional detection tools. These include the use of novel biomarkers (eg, epi/genetics, metabolomics, proteomics, microbiome), liquid biopsies (eg, cell-free DNA, circulating tumor cells, exosomes), and bodily fluids (eg, fecal, urinary, and salivary biomarkers).[29,30]

For any screening program that uses both EUS and MRI in a longitudinal manner, we would recommend a multidisciplinary review to ensure that all results from prior tests are consulted. Finally, increased testing efforts in Hispanic and non-White communities are needed, with attention paid to insurance concerns.

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