A Community-Based Pancreatic Cancer Screening Study in High-Risk Individuals: Preliminary Efficacy and Safety Results

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INTRODUCTION: Pancreatic cancer (PC) screening recommendations have been based on studies performed solely at high-volume academic centers. To make PC screening more widely available, community-based efforts are essential. We implemented a prospective PC screening study in the community of Fairfield County, CT, and report our early safety and efficacy results.

METHODS: Eligible individuals were enrolled into an investigator-initiated study and underwent a baseline and 3 annual magnetic resonance imagings/magnetic resonance cholangiopancreatographies (MRIs/MRCPs) with gadolinium, biannual blood donations for biobanking, and assessments for anxiety and depression. All MRIs were presented at a multidisciplinary board to determine whether further investigation was warranted.

RESULTS: Seventy-five individuals have been enrolled and 201 MRIs performed over a 2.6-year average length of follow-up. Abnormal pancreatic findings (predominantly small cysts) were detected in 58.7% of the participants. Among these, 6.7% underwent endoscopic ultrasound, with 1 case complicated by postprocedural pancreatitis. One surgical resection was performed on a 4.7-cm intraductal papillary mucinous neoplasm with a focus on low-grade pancreatic intraepithelial neoplasia. One incidental finding of fibrosing mediastinitis was detected. Anxiety and depression scores decreased over the course of this study from 21.4% to 5.4% and 10.7% to 3.6%, respectively.

DISCUSSION: This preliminary report supports the feasibility of performing MRI/magnetic resonance cholangiopancreatographies-based PC screening as part of a clinical trial in a community setting. A longer follow-up is needed to better assess safety and efficacy. To the best of our knowledge, this is the first report from a community-based PC screening effort (clinicaltrials.gov ID: NCT03250078).

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A848, http://links.lww.com/CTG/A849

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INTRODUCTION
Recent advances in systemic chemotherapy for the treatment of pancreatic cancer (PC) have resulted in improved survival rates for those undergoing upfront resection and an increase in resection rates for those with cancers of “borderline” resection potential (1). Although the average 5-year survival for PC remains low at 10%, this is driven by the 80% of participants who have locally advanced/unresectable (stage III) or metastatic disease (stage IV) at the time of diagnosis. By contrast, resectable stage I and II PC has a 5-year survival rate of up to 37% (2). Thus, there is a compelling need to detect PC at its earliest stages. The low incidence rate of PC of 8–12 per 100,000 per year makes it impractical to screen the general population (3). The International Cancer of the Pancreas Screening (CAPS) Consortium recommends screening high-risk participants using magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) (4). These
recommendations are reinforced in a clinical practice update issued by the American Gastroenterological Association (AGA) (5). High-risk participants have specific genetic mutations or a strong family history of PC. Genetic mutations associated with PC include BRCA1, BRCA2, ATM, PALB2, CDKN2A, and STK11; genes related to hereditary pancreatitis; and mismatch repair genes linked to Lynch syndrome (6). This population represents 5%–10% of all high-risk participants who develop PC (7). PC screening guidelines are largely based on studies performed at university and academic medical centers. It has been acknowledged that for PC screening to become widely available, high-quality community-based efforts are needed. Using the methodology suggested by the American Gastroenterological Association and CAPS Consortium, we implemented a prospective PC screening protocol for high-risk individuals in our community of Fairfield County, CT.

MATERIALS AND METHODS

All authors had access to the study data and reviewed and approved the final article.

Patient selection

All study participants signed an informed consent document that described the risks and benefits of this study. This study was performed at Danbury Hospital and Norwalk Hospital, 2 mid-sized community hospitals in CT, part of Nuvance Health. This study was registered on ClinicalTrials.gov (identifier NCT03250078) and approved by the BRANTY institutional review board. No costs were incurred by participants, and all study-related costs were funded by philanthropy. Participants were eligible for enrollment if they had at least 2 first-degree relatives (FDRs) with PC or at least 3 affected blood relatives with at least 1 affected FDR. Participants were also included if they were a known mutation carrier of BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, ATM, PALB2, and CDKN2A or had a similar gene mutation and at least 1 first-degree or second-degree relative with PC. Participants had to be at least 50 years old or 10 years younger than the youngest affected relative. All participants had their family and genetic history confirmed by a genetics counselor. Inclusion criteria also required that participants have an Eastern Cooperative Oncology Group performance status of 0 or 1, a willingness to undergo MRI, and an estimated glomerular filtration rate greater than 40 mL/min (subsequently reduced to 30 mL/min). Exclusion criteria included a history of PC, prior malignancy requiring adjuvant chemotherapy within the past 5 years, and hereditary pancreatitis. All participants were assessed for depression and anxiety using the Hospital Anxiety and Depression Scale (HADS).

Study design

Study participants met with the study APRN, provided blood samples for biobanking, and underwent HADS testing every 6 months for a total of 3 years between 2017 and 2020. Participants underwent a baseline and annual MRI/magnetic resonance cholangiopancreatography (MRCP) of the abdomen.

All cases were presented at a multidisciplinary meeting that included fellowship-trained body radiologists, interventional gastroenterologists, hepatopancreatobiliary surgeons, and medical oncologists. Meeting recommendations were based on the Fukuoka guidelines for pancreatic cystic lesions and the CAPS guidelines for solid pancreatic lesions (8,9). The final recommendations were individualized to determine the need for further imaging with MRI or computed tomography (CT) and/or referral for EUS or surgery.

Recruitment

Recruitment of participants involved meeting with primary care groups in our primary and secondary service areas, promoting on social media platforms, and local press releases. This study was also registered on ClinicalTrials.gov.

Table 1. Baseline participant characteristics of the high-risk hereditary population

| Characteristic                        | Total (n = 75) |
|---------------------------------------|---------------|
| Age at first surveillance, n (%)     |               |
| 39–49                                 | 6 (8)         |
| 50–59                                 | 37 (49.3)     |
| 60–69                                 | 21 (28)       |
| 70                                    | 11 (14.7)     |
| Median age (range), yr                | 59.5 (39–80)  |
| Male, n (%)                           | 31 (44.3)     |
| Female, n (%)                         | 44 (58.7)     |
| Race and ethnicity, n (%)             |               |
| White                                 | 72 (96)       |
| Hispanic                              | 3 (4)         |
| Ashkenazi Jewish ancestry, n (%)      | 17 (22.7)     |
| Diabetes, n (%)                       | 6 (8)         |
| New-onset diabetes, n (%)             | 2* (2.7)      |
| Gene testing, n (%)                   |               |
| Mutation-positive                     | 28 (37.3)     |
| Mutation-negative                     | 44 (58.7)     |
| Unavailable                           | 3 (4)         |
| Family history of PDAC, n (%)         |               |
| 2 FDRs                                | 33 (44)       |
| 1 FDR and ≥ 2 SDRs/TDRs               | 17 (22.8)     |
| Tobacco use, n (%)                    |               |
| Never                                 | 37 (49.3)     |
| Past                                  | 30 (40)       |
| Present                               | 8 (10.7)      |
| Initial alcohol use, n (%)            |               |
| Zero                                  | 20 (26.7)     |
| Light                                 | 35 (46.7)     |
| Moderate                              | 17 (22.7)     |
| Heavy                                 | 3 (4)         |

*EEOH use: Light is defined as < 7 drinks per week; moderate is defined as 2 drinks per day; and heavy is defined as an average of ≥ 3 drinks per day or binge drinking at least once per month. This is based on definitions from the NIH. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking
Genetic testing
Genetic counseling and germline genetic testing of all participants without prior testing were provided free of charge. The Color Hereditary Cancer Test (Color Health, Burlingame, CA) was used.

Psychological assessment
This study used the HADS, which has been validated for use in trials involving hospital, non-psychiatric study populations (10,11). Participants with abnormal scores were referred for psychiatric evaluation and counseling. During the informed consent process, all participants were notified of the study process and the level of expertise involved.

Image interpretation and reporting
MRI. Gadolinium-enhanced MRI/MRCP was performed on a Philips 1.5T Ingenia MRI according to a standardized protocol (see Supplementary Appendix A, http://links.lww.com/CTG/A848). All MRIs were read first by a general or trained body radiologist with a radiology resident and then reviewed at a multidisciplinary committee consisting of fellowship-trained body radiologists with prior training at large pancreatic referral centers (as well as oncologists, interventional gastroenterologists, and hepatopancreatobiliary surgeons).

EUS. Study participants were referred for EUS for pancreatic lesions with worrisome and high-risk features. Laboratory analysis of pancreatic cystic fluid was performed through Interpace Diagnostics using the PancreaGEN Test Algorithm.

Statistical analysis
The Fisher exact test was used to find significance between participants whose baseline HADS scores were elevated and decreased or remained the same at the end of the study and participants whose baseline HADS scores were normal and increased or remained the same at any time during this study.

RESULTS
Participants
Baseline demographic characteristics of the 75 study participants are presented in Table 1. The average age was 59 years; 58% were female; 22.7% were of Ashkenazi Jewish ancestry; 8% had diabetes; 37% had a gene mutation; and 44% had 2 FDRs with PC. As summarized in Table 2, the most common genetic mutations were in the BRCA1, BRCA2, and ATM genes.

Baseline screening results
As shown in Figure 1, 75 participants underwent a baseline MRI/MRCP, 58 underwent a second MRI/MRCP, 44 underwent a third MRI/MRCP, and 24 underwent a fourth MRI/MRCP. The overall prevalence of a pancreatic lesion on initial MRI was 58.7% (Figure 2). The prevalence of pancreatic cysts with concerning abnormalities was 6.7%. Summary of pancreatic findings are listed in Table 3. The average number of pancreatic cysts observed per participant was 1.5. The average cyst size was 4 mm, and most of them were unilocular and branched duct.

Figure 2 and Table 3 describes the types of pancreatic abnormalities identified in this screening study. Five participants were referred for EUS, and the details of their cases are presented in

![ Consort diagram EUS, endoscopic ultrasound. ]
Participant 1 had a subcentimeter pancreatic cyst associated with pancreatic duct (PD) dilation. EUS revealed no high-risk features, and follow-up MRIs showed no change. Participant 2 had multiple pancreatic cysts, with the largest measuring 13 mm, and some cysts communicated with the PD. EUS with fine-needle aspiration of a 14-mm cyst was performed. Fluid analysis revealed an elevated amylase level with a low CEA level, and mucicarmine staining was negative. The lesion was diagnosed as a pancreatic pseudocyst.

**Follow-up screening results**

Fifty-eight of the initial 75 participants underwent a second surveillance MRI. Two participants had pancreatic lesions newly identified on follow-up. These lesions were retrospectively detected on the initial MRI after review in the multidisciplinary meeting. This discrepancy was because of the small cyst size (average cyst size 4 mm) compared with the MRI slice thickness (4 mm) resulting in partially imaged cysts on the initial study. Participant 3 had 2 subcentimeter pancreatic cysts associated with PD dilation. EUS revealed a subcentimeter cyst associated with an abrupt change in PD caliber, for which fine-needle biopsy was performed. No malignant cells were detected; however, the participant developed postprocedure pancreatitis. Participant 4 had pancreatic lesions that initially appeared as 3 separate cysts without worrisome features. On follow-up, this appeared as one 4.7-cm multicystic lesion. EUS revealed a microcystic and septated lesion without PD communication. Cyst fluid analysis revealed an elevated amylase and CEA level with positive mucicarmine staining, negative for mutations in the Kirsten Rat Sarcoma viral oncogene homolog and the Guanine Nucleotide binding protein, Alpha Stimulating polypeptide, and negative for loss of tumor suppressor genes. This was diagnosed as a branched duct intraductal papillary mucinous neoplasm (IPMN), for which the participant opted for surgical resection over surveillance given his family history (1 FDR and 2 SDRs). A pancreaticoduodenectomy was performed without complication; pathology revealed an IPMN and a low-grade pancreatic intra-epithelial neoplasia (PanIN-1A). Participant 5 had several pancreatic cysts without concerning abnormalities on the initial MRI. The third surveillance MRI revealed diffuse dilation of the PD to 5 mm. EUS revealed a 7-mm PD with 2 subcentimeter cystic lesions in the pancreas that were too small to sample. A follow-up MRI revealed stability of the PD without concerning features (Table 4).

Five participants were found to have incidental findings during this study. One participant with retrosternal signal abnormalities underwent CT, which revealed a 13.7-cm anterior mediastinal mass and a 2.4-cm right lower lobe nodule. Surgical biopsy revealed dense sclerotic tissue, consistent with sclerosing mediastinitis. Another participant was found to have intrahepatic biliary strictures with concern for primary sclerosing cholangitis, and follow-up imaging and serologic testing were recommended. Additional imaging for 3 participants revealed benign entities without the need for additional workup. No lesions consistent with pancreatic ductal adenocarcinoma by MRI, EUS, or surgical resection were identified in this study over a 2.6-year average length of follow-up.
Anxiety and depression
Anxiety and depression scores are outlined in Table 5. Eighteen participants had diagnoses of anxiety and/or depression at baseline; most were already seeking treatment; however, 4 were referred to a licensed marriage and family therapist for counseling.

Participants with baseline elevations in HADS scores, with scores either remaining stable or improving (group A), were compared with participants with normal baseline levels, with scores either remaining stable or worsening (group B). Analysis was performed only on participants who were captured at the 24-month mark to avoid loss of follow-up as a confounding factor.

For depression, 6 participants (10.7%) had elevated or significant distress at baseline and 50 participants (89.2%) had normal depression scores (Figure 3). At 24 months, among the 6 participants with elevated scores, 5 showed a decline in depression. Among the 50 with normal baseline depression scores, 2 showed an increase in depression at any point within 24 months. The decline in depression in group A (83.3%) compared with the increase in depression scores in group B (4.0%) was highly significant (P < 0.001 Fisher exact).

Similar results were seen for anxiety scores, where 12 participants (21.4%) were found to have elevated or significant distress at baseline and 44 participants had normal baseline scores (group B; Figure 3). At 24 months, among group A, 10 participants showed a decline in anxiety. Among group B, 9 showed an increase in anxiety. The decline in anxiety among group A (83.3%) compared with the increase in anxiety in group B (20.4%) was highly significant (P < 0.001 Fisher exact).

DISCUSSION
In this study, we report on the preliminary results of a prospective community-based PC screening study using MRI/MRCP in high-
risk individuals based on established criteria. All MRIs were reviewed at monthly multidisciplinary conferences. We report on the safety and efficacy of the first 75 participants enrolled after an average follow-up length of 2.6 years. Furthermore, we found significant improvements in anxiety and depression in the study participants. To the best of our knowledge, this is the first community-based PC screening study of its kind.

The median age of our cohort was 59.5 years, which represents an older demographic compared with other PC screening studies whose participants’ mean ages ranged from 50 to 56 years (12,13). We observed a high rate of pancreatic lesions (58.7%), but only 6.7% warranted EUS. One participant underwent a Whipple procedure for a 4.7-cm IPMN and a low-grade PanIN, and 1 underwent surgical biopsy for incidental findings of fibrosing mediastinitis. Overall, our detection rates of pancreatic abnormalities and incidental findings are in line with those reported by tertiary care centers (12–15).

Overall, the study participants experienced improvements in depression and anxiety during the study period, despite a detectable spike in anxiety during the COVID-19 pandemic. Since 2000, there have been 15 PC screening studies in asymptomatic participants with hereditary risk factors for PC (12–14). The prevalence of pancreatic lesions identified in these studies ranged from 7.9% to 50%. (12, 13) Previous studies that had lower detection rates of pancreatic abnormalities were older, used EUS primarily, and/or only included pancreatic lesions with worrisome features. Our results are similar to the 2012 study performed by Canto et al. who discovered 42% of pancreatic abnormalities in all participants with 53% of pancreatic abnormalities detected in the 60–69-year-old age group (13). The rate of detection of a pancreatic malignancy in previous studies ranged from 0% to 6.7%. (12) The largest of these studies were performed by the CAPS Consortium, which detected a cumulative incidence of invasive PC in 3.4% of their cohort over a median follow-up period of 5.6 years (14). The groups in the studies of Al-Sukhni and Canto in 2012 published a PC detection rate of 1.1% and 0%, respectively (13,15). Our study had no positive cases of pancreatic adenocarcinoma, which we attribute to the low number of participants in our cohort (75 participants) and the short follow-up interval (2.6 years).

A successful PC screening program is able to detect and treat T1N0M0 margin-negative PC and high-grade dysplastic precursor lesions including IPMNs, mucinous cystic neoplasms, and PanINs. The current guidelines regarding screening for PC can be found in the supplemental material (see Supplementary Appendix B, http://links.lww.com/CTG/A849). The ideal screening protocol should be widely available, highly sensitive, safe to implement, and economically beneficial and should lead to improved health outcomes. In the case of PC, detection at a potentially curable stage requires accurate imaging because no biomarkers have been validated to date. The identification of biomarkers to predict PC is an area of active research, and the 75 participants have contributed 1,161 individual samples for future research. Previous PC screening protocols primarily used MRI/MRPC and/or EUS as the initial screening test. A pancreatic protocol CT is inferior at detecting subcentimeter pancreatic cysts and requires harmful ionizing radiation (13). We preferred MRI/MRPC as the primary modality because it is less invasive and cheaper than EUS. The cost-effectiveness of PC surveillance in high-risk individuals has been previously studied, and the analysis of a cohort with a 5-fold relative risk of PC revealed that MRI is the most cost-effective strategy. A threshold analysis showed that EUS became the more cost-effective strategy if the cost of MRI increases to greater than $1,600 USD (16). The cost of obtaining and reading an MRI at our institution is $1,105 USD, meeting the threshold for cost-effectiveness.

We used EUS to follow up high-risk lesions for characterization of their malignant potential. In our study, 5 participants were referred for EUS, with 1 participant developing postprocedure pancreatitis requiring a 2-day hospitalization. One participant in our study underwent surgical resection of a pancreatic lesion that was consistent with an IPMN and a low-grade PanIN.

The strengths of our study include the following: (i) High-risk participants did not have to leave their community to participate in a PC screening study; (ii) anxiety and depression were monitored; (iii) we had a low rate of adverse events; and (iv) this study was performed at a community hospital with easier accessibility for more individuals. The limitations of our study include the following: (i) a small cohort with 75 participants; (ii) a short median follow-up interval of 2.6 years; (iii) lack of racial and ethnic diversity; (iv) no participants with an STK11 mutation (Peutz-Jeghers syndrome) were enrolled, likely because they were already under the care of high-risk providers; and (v) participants with chronic pancreatitis were excluded because of the complexities of image interpretation.

PC screening studies have traditionally been performed at tertiary care centers. Our study highlights the possibility of expanding PC screening studies to community centers that have access to a multidisciplinary team. This model could be replicated at other community hospital settings either with their own

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### Table 5. Hospital Anxiety and Depression Scale (HADS) scores

|               | Baseline | Month 6 | Month 12 | Month 18 | Month 24 | Month 30 | Month 36 |
|---------------|----------|---------|----------|----------|----------|----------|----------|
| HADS-A score categories |          |         |          |          |          |          |          |
| Normal level of anxiety (score <8, %) | 59 (78.7) | 61 (85.9) | 55 (82.1) | 52 (89.7) | 53 (94.6) | 40 (88.9) | 35 (92.1) |
| Elevated distress (score 8–10, %) | 10 (13.3) | 4 (5.6)  | 10 (14.9)a | 4 (6.9)  | 2 (3.6)  | 5 (11.1) | 2 (5.3)  |
| Significant distress (score >10, %) | 6 (8)    | 6 (8.5) | 2 (3.0)  | 2 (3.4)  | 1 (1.8)  |          | 1 (2.6)  |
| HADS-D score categories |          |         |          |          |          |          |          |
| Normal level of depression (score <8, %) | 65 (86.7) | 66 (93.0) | 64 (95.5) | 54 (93.1) | 54 (96.4) | 43 (95.6) | 36 (94.7) |
| Elevated distress (score 8–10, %) | 7 (9.3)  | 3 (4.2)  | 2 (3.0)  | 3 (5.2)  | 1 (1.8)  |          | 1 (2.2)  |
| Significant distress (score >10, %) | 3 (4)    | 2 (2.8)  | 1 (1.5)  | 1 (1.7)  | 1 (1.8)  |          | 1 (2.2)  |

*aMarked elevations in anxiety were noted during the COVID-19 pandemic*
internal experts or in conjunction with a pancreatic referral center if trained experts are not available at the local community level. Our study focused on high-risk participants with hereditary risk factors. Further research has revealed another group of high-risk participants, specifically those with new-onset diabetes mellitus (17). The diagnosis of diabetes mellitus within 1 year has a 5.4-fold increase in relative risk of PC (18). We are in the process of screening individuals with new-onset diabetes mellitus for PC at our institution, using a similar study protocol (identifier NCT03937453).

In summary, we provide evidence that a community-based PC screening effort may be performed safely as part of a clinical trial with adequate funding that includes the participation of multiple medical specialists. We did not experience any major safety signals that would merit study stoppage. Additional time will reveal the effectiveness of our approach in detecting early target lesions and resectable PC. Support for community-based PC screening programs will be essential for the success of any future, widespread PC screening efforts.

CONFLICTS OF INTEREST
Guarantor of the article: Richard C. Frank, MD.
Specific author contributions: J.K.: drafting and editing the manuscript and interpreting data. T.L.: study planning and design, collecting and interpreting data, and writing the manuscript. D.J.: collecting and interpreting data and writing the manuscript. L.M.: interpreting data. T.L.K.: interpreting data. N.A.: collecting and interpreting data and writing and editing the manuscript. S.I.: collecting and interpreting data and editing the manuscript. P.K.: collecting data and editing the manuscript. D.P.: interpreting data, performed data analysis, and writing and editing the manuscript. A.T.: collecting and interpreting data and writing and editing the manuscript. X.D.: interpreting data and editing the manuscript. R.S.: interpreting data and editing the manuscript. J.B.: collecting and...
interpreting data and editing the manuscript. R.L.: collecting and interpreting data and editing the manuscript. R.C.F.: conceived and designed the study, collected and interpreted data, performed analysis, and contributed to writing and editing the manuscript.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

✓ Pancreatic cancer screening is recommended for high-risk individuals.
✓ Pancreatic cancer screening programs occur primarily in large-volume, tertiary care centers.

WHAT IS NEW HERE

✓ Pancreatic cancer screening can be safely and successfully implemented in a community-based setting.

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