

EUS-based Pancreatic Cancer Surveillance in *BRCA1/BRCA2/PALB2/ATM* Carriers Without a Family History of Pancreatic Cancer



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ABSTRACT

Carriers of a pathogenic/likely pathogenic (P/LP) *BRCA1/BRCA2/ATM/PALB2* variant are at increased risk of pancreatic ductal adenocarcinoma (PDAC), yet current guidelines recommend surveillance only for those with a family history of PDAC. We aimed to investigate outcomes of endoscopic ultrasound (EUS)-based PDAC surveillance in *BRCA1/BRCA2/ATM/PALB2* carriers without a family history of PDAC. We performed a retrospective analysis of all P/LP *BRCA1/BRCA2/ATM/PALB2* carriers who underwent EUS at a tertiary care center. Of 194 P/LP *BRCA1/BRCA2/ATM/PALB2* carriers who underwent EUS, 64 (33%) had no family history of PDAC and had at least 1 EUS for PDAC surveillance. These individuals underwent 143 total EUSs, were predominantly female (72%), and *BRCA2* carriers (73%), with the majority having a personal history of cancer other than PDAC (67%). The median age at time of first EUS was 62 years [interquartile range (IQR), 53–67 years] and a median of 2 EUSs (IQR 1–3) were performed per patient, with a median of 3 years (IQR 2–4.5 years) between the first and last EUS

for those with more than 1 EUS. Pancreatic abnormalities were detected in 44%, including cysts in 27%, and incidental luminal abnormalities in 41%. Eight percent developed a new pancreatic mass or cyst during surveillance, 2 individuals developed PDAC, and no serious complications resulted from surveillance. After discussion of the risks, limitations, and potential benefits, PDAC surveillance can be considered in *BRCA1/BRCA2/ATM/PALB2* carriers without a family history of PDAC; however, the effectiveness of PDAC surveillance in this population requires further study.

Prevention Relevance: *BRCA1/BRCA2/ATM/PALB2* carriers have increased pancreatic ductal adenocarcinoma (PDAC) risk, yet are typically not eligible for PDAC surveillance in the absence of PDAC family history. Herein we describe outcomes of PDAC surveillance in *BRCA1/BRCA2/ATM/PALB2* carriers without a family history of PDAC, showing that PDAC surveillance can be considered in this high-risk group.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth most common cause of cancer-related death in both men and women (1), and is predicted to be the second leading cause of cancer-related death in the United States in 10 years (2). While the majority of PDAC is considered sporadic, 5% to 10% of PDACs are related to familial risk (3). Individuals with familial risk include those with an identified pathogenic or likely pathogenic (P/LP) variant in a known PDAC risk gene as well as familial pancreatic cancer without a known genetic risk variant (4). A number of PDAC risk genes have been identified; genes associated with increased breast cancer risk, including *BRCA1*, *BRCA2*, *ATM*, and *PALB2*, have been of particular interest given the frequency with which P/LP variants are identified in families with PDAC (5). Increased PDAC risk has been demonstrated in carriers of P/LP *BRCA1*, *BRCA2*, *ATM*, and *PALB2* across

multiple studies (6–13), with *BRCA2* often considered to carry the highest risk (6, 8, 11).

Advanced PDAC is associated with a poor prognosis, with 5-year survival for regional and distant metastatic disease being 12% and 3% respectively (1). Conversely, a recent analysis of Surveillance Epidemiology and End Results (SEER) data demonstrated that the 5-year survival rate for Stage 1A PDAC nearly doubled from 2004 to 2012, and is now greater than 80% (14). This data highlights the compelling need to develop surveillance strategies to detect PDAC at early stages for those at increased risk including *BRCA1*, *BRCA2*, *ATM*, and *PALB2* carriers (15). PDAC surveillance is generally performed through regular imaging of the pancreas with endoscopic ultrasound (EUS) or MRI, without definitive evidence showing one imaging modality is superior (16, 17). Early surveillance results have been promising, with one large European study of high-risk individuals showing that among *CDKN2A* carriers with surveillance-detected PDAC, the resection rate was 75%, with a 5-year survival of 24% (18). A long-term study of high-risk individuals in the United States, primarily from familial pancreatic cancer families, demonstrated that surveillance-detected cancers were surgically resectable 90% of the time with a 90% 3-year survival (19). However, the effectiveness of PDAC surveillance in P/LP *BRCA1*, *BRCA2*, *ATM*, and *PALB2* carriers remains less well characterized, and is predominantly restricted to those with a family history of PDAC (20).

Accumulating data about benefits of surveillance in high-risk individuals has led to recommendations endorsing PDAC surveillance in certain high-risk groups. The recent International Cancer of the Pancreas Screening (CAPS) Consortium recommended that individuals with a P/LP *BRCA1*, *BRCA2*, *ATM*, or *PALB2* variant who also have a first-degree relative (FDR) with PDAC are eligible to consider PDAC surveillance starting at age 45 to 50 years (21). Further broadening the family history requirement, more recent guidelines from the National Comprehensive Cancer Network (NCCN) recommend consideration of PDAC surveillance in P/LP *BRCA1*, *BRCA2*, *ATM*, or *PALB2* carriers with either a FDR or second-degree relative (SDR) with PDAC (22). Similar criteria requiring a family history of PDAC in *BRCA1*, *BRCA2*, *ATM*, and *PALB2* are also proposed by other societies (23, 24). Additionally, ongoing multicenter early detection studies, such as the CAPS5 study (25, 26) as well as the PanFAM-1 study (27), utilize similar inclusion criteria.

While PDAC surveillance recommendations have focused on carriers of a P/LP variant in *BRCA1*, *BRCA2*, *ATM*, or *PALB2* with a family history of PDAC, it remains unclear whether individuals without a family history of PDAC may also potentially benefit. This is especially important as small family size, unknown/incorrect family history, or premature deaths due to other cancers/causes may significantly influence reported family history, and therefore influence whether PDAC surveillance is recommended. In fact, the majority of indi-

viduals with PDAC who carry a P/LP *BRCA1*, *BRCA2*, *ATM*, or *PALB2* variant did not have a prior known family history of PDAC (28). Therefore, to investigate outcomes of PDAC surveillance for *BRCA1*, *BRCA2*, *ATM*, and *PALB2* carriers without a family history of PDAC, we herein describe our institution's experience with PDAC surveillance in this cohort.

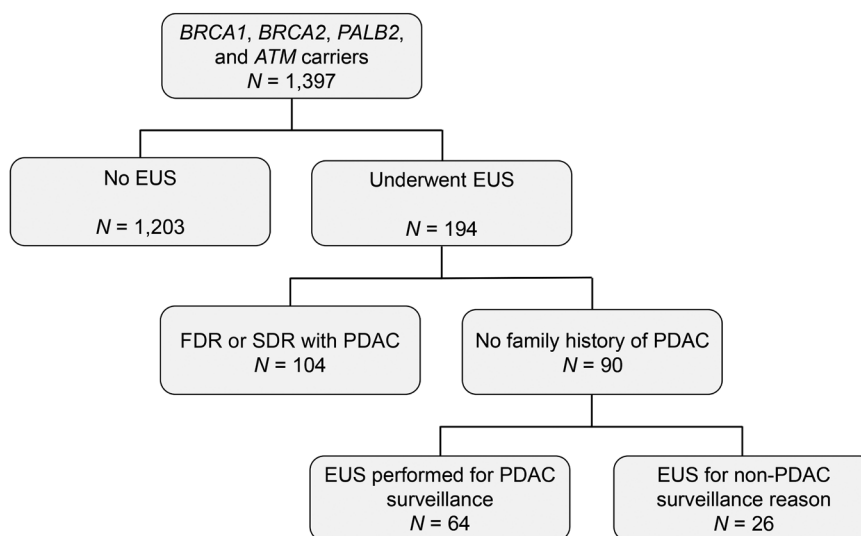
Materials and Methods

This is a retrospective analysis of all individuals with a *BRCA1*, *BRCA2*, *PALB2*, or *ATM* P/LP variant who had an EUS performed at our tertiary care referral center at the University of Pennsylvania (Philadelphia, PA) between January 1, 2008 and February 1, 2021. This study was approved by the University of Pennsylvania Institutional Review Board (IRB) and was conducted in accordance with the U.S. Common Rule, and a waiver of informed consent was granted by the IRB. At the University of Pennsylvania, *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers are often presented with the option to consider PDAC surveillance, irrespective of family history of PDAC, after an extensive discussion of the risks, potential benefits, and uncertainties about PDAC surveillance.

Individuals with a *BRCA1*, *BRCA2*, *PALB2*, or *ATM* P/LP variant and those who had undergone an EUS were identified through several mechanisms, including enrollment in a University of Pennsylvania PDAC surveillance study entitled "Preliminary Evaluation of Screening for Pancreatic Cancer in Patients with Inherited Genetic Risk," the University of Pennsylvania Gastrointestinal Cancer Genetics Program Registry, and the University of Pennsylvania Bassler Center Registry. Additional carriers who had undergone EUS were identified through an IRB-approved search of the medical records to identify patients with an appropriate International Classification of Diseases (ICD)–9/10 diagnostic code (ICD-9: V84.01. ICD-10: Z15.0, Z15.01, Z15.02, Z15.03, Z15.09, Z13.7, Z13.79, Z15.89) as well as an appropriate EUS-related current procedural terminology (CPT) procedure code (CPT 43237, 43231, 43232, 43237, 43238, 43240, 43242, 43253, 43259). All patients identified by these mechanisms had their electronic records manually reviewed to confirm each patient had undergone genetic testing identifying a P/LP *BRCA1*, *BRCA2*, *PALB2*, or *ATM* variant, or was an obligate carrier of a P/LP *BRCA1*, *BRCA2*, *PALB2*, or *ATM* variant. Individuals with only a *BRCA1*, *BRCA2*, *PALB2*, or *ATM* variant of uncertain significance were not included in the analysis. Records were manually reviewed to confirm that each patient had at least 1 EUS performed during the study period, including medical encounters and endoscopy reports from our center, as well as all available data from outside of our institution.

Information collected on the entire cohort included sex, race, genetic testing, and whether there was a family history of PDAC, which was defined as having at least 1 FDR or SDR with PDAC. All individuals had a family history recorded in the electronic medical record, with the majority having been seen in a dedicated cancer genetics clinic where a 3-generation

Figure 1. Individuals with a *BRCA1*, *BRCA2*, *PALB2*, or *ATM* P/LP variant who underwent an EUS.



family pedigree was obtained by a genetic counselor or cancer genetics focused physician. Individuals who were carriers of a P/LP variant in *BRCA1*, *BRCA2*, *PALB2*, or *ATM* and who had a family history of PDAC in a FDR or SDR were then excluded, followed by exclusion of individuals who had an EUS performed for a reason other than PDAC surveillance. Of the remaining cohort, information collected included demographics, personal history, family history, and EUS records including findings and complications. Descriptive statistics were presented as medians with associated interquartile ranges (IQR) or as percentages.

Results

Of 1397 P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers seen at our institution over the study period, 194 (13%) underwent at least 1 EUS (Fig. 1). This cohort was predominantly female (76%) and White (93%), with 65% having a P/LP *BRCA2* variant and 21% having a P/LP *BRCA1* variant (Supplementary Table S1). Of this group, 104 (54%) had at least 1 FDR or SDR with PDAC, compared with 244 (17%) of our total cohort of 1397 P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers. Of the 90 individuals who underwent EUS without a family history of PDAC, 26 (29%) underwent EUS for reasons other than PDAC surveillance, including evaluation of abnormal imaging ($n = 20$), further evaluation of prior endoscopic findings ($n = 2$), or for cancer staging ($n = 4$; Fig. 1).

The remaining 64 P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers without a family history of PDAC who underwent at least 1 EUS for PDAC surveillance were predominantly female (72%) and White (95%), with 33% having Ashkenazi Jewish ancestry, and with 73% of these individuals had a P/LP *BRCA2* variant (Table 1). Twenty-five percent were either current or former smokers, and the majority (73%) reported alcohol use. Three individuals (5%) had a prior history of acute pancreatitis, however, no individuals had a history of chronic pancreatitis or hereditary pancreatitis. Additionally, 6 individuals (9%) had a

history of type II diabetes mellitus, and no individuals were reported to have type I diabetes mellitus. Sixty-seven percent of this cohort had a prior cancer, including 34 (53%) with breast cancer. All individuals in the cohort reported a family history of at

Table 1. Characteristics of P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers without a family history of PDAC who underwent EUS for PDAC surveillance.

	N = 64	
Age at first EUS, median, IQR	62	53–67
Female	46	72%
Race		
White	61	95%
Non-White	2	3%
Not reported	1	2%
Ashkenazi Jewish ancestry	21	33%
P/LP gene variant		
<i>BRCA1</i>	12	19%
<i>BRCA2</i>	47	73%
<i>PALB2</i>	2	3%
<i>ATM</i>	3	5%
Smoking		
Never	48	75%
Former	13	20%
Current	3	5%
Alcohol use	47	73%
Prior pancreatitis	3	5%
Type II DM	6	9%
Personal history of cancer		
Any cancer	43	67%
Breast	34	53%
Ovarian	1	2%
Prostate	2	3%
Family history of cancer		
Any cancer	64	100%
Breast	57	89%
Ovarian	21	33%
Prostate	23	36%

Abbreviation: DM, Diabetes mellitus.

Table 2. Number and timing of surveillance EUSs in P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers without a family history of PDAC.

	N = 64
Number of EUSs per patient, median, IQR	2 (1–3)
Number of EUSs performed	
1	29 (45%)
2	13 (20%)
3	11 (17%)
4	7 (11%)
≥5	4 (6%)
Years between first and last EUS for individuals with ≥ 2 EUS, median (range)	3 (2–4.5)
Years between first and last EUS for individuals with ≥ 2 EUS	
1	6 (17%)
2	8 (23%)
3	9 (26%)
4	3 (9%)
≥5	9 (28%)

least one cancer in either an FDR or SDR, including breast cancer in 89%, ovarian cancer in 33%, and prostate cancer in 36%.

The 64 P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers without a family history of PDAC underwent a total of 143 surveillance EUSs. Seven fine-needle aspirations (FNA) were performed; the rate of FNA use was 5%. The median age at first surveillance EUS was 62 years (IQR 53–67), and the median number of EUSs performed was 2 (IQR 1–3), with more than one third of these individuals (34%) having 3 or more EUSs performed (Tables 1 and 2). As individual surveillance patterns were highly variable, the median number of years between the first and last EUS recorded for those having 2 or more EUSs was 3 years (IQR 2–4.5 years; Fig. 2). Forty-eight percent (N = 31)

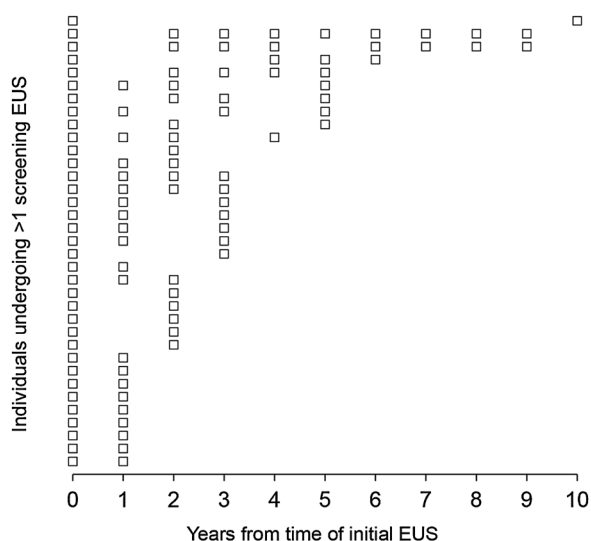


Figure 2. Plot of EUSs performed in P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers with more than 1 surveillance EUS. Each row corresponds to 1 individual's EUSs starting with the index EUS at year 0. Each square represents 1 EUS.

Table 3. EUS/EGD findings in P/LP *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers.

	Total (N = 64)	%
EUS findings		
Any abnormality	28	44%
PDAC	2	3%
Mass	3	5%
Cyst	17	27%
Mass/cyst after initial EUS	5	8%
Parenchymal abnormality	10	16%
Heterogeneity	4	6%
Hyperechoic	2	3%
Lobularity	4	6%
Fatty	6	9%
EGD findings		
Any abnormality	26	41%
Esophagitis	8	13%
Esophageal stricture	3	5%
Barrett's esophagus	3	5%
Gastritis	10	16%
Gastric ulcer	2	3%
Gastric intestinal metaplasia	3	5%
Fundic gland polyp ^a	9	14%
<i>Helicobacter pylori</i>	1	2%

^aOne individual had a fundic gland polyp with low-grade dysplasia.

of these individuals had other non-EUS imaging of their pancreas with either an MRI or CT scan, with the median number of MRIs/CTs amongst this group being 2 (range 1–3.5; Supplementary Table S2). Taking these non-EUS pancreatic imaging studies into account, 49 (77%) individuals had more than 1 imaging study of their pancreas performed (Supplementary Table S2).

Amongst the 64 individuals undergoing EUS, 44% had an abnormal pancreatic finding, with pancreatic cysts being most common (27%, Table 3); these were reported as either side-branch intraductal papillary mucinous neoplasms (IPMN) or uncharacterized pancreatic cysts, with no main duct IPMNs nor mucinous cystic neoplasms identified. Similar results were noted for the 31 individuals who also underwent an MRI or CT surveillance scan, where 42% had an abnormal pancreatic finding that was most often a cyst (32%, Supplementary Table S3). Two individuals (3%) were diagnosed with PDAC during the study period, and although a potential pancreatic mass was noted endosonographically in 3 individuals (5%), only 1 of these masses turned out to be PDAC. The other 2 potential masses had nonspecific benign histology on FNA, with one thought to be consistent with a splenule on repeat examination, and the other not being revisualized on repeat examination. A pancreatic mass or cyst developed during surveillance in 5 individuals (8%) after having a prior normal EUS. Incidental luminal findings were identified in 41% of individuals undergoing EUS, with gastritis (16%), fundic gland polyps (14%), and esophagitis (13%) being most common (Table 3). Important luminal findings such as Barrett's esophagus, gastric intestinal metaplasia, fundic gland polyp with low grade dysplasia, and *Helicobacter pylori* infection were also

detected incidentally during the surveillance EUSs. The only procedure-related complication reported was a transient post-procedure fever, which resolved without any intervention.

Of the 2 patients who developed PDAC, the first was a female *BRCA2* carrier, with a history of a uterine leiomyosarcoma at age 57 and a family history of 2 paternal cousins with breast cancer. She was a nonsmoker with an elevated body mass index (BMI; 37 at the time of diagnosis) who on her initial surveillance EUS at age 58 was found to have a 14-mm hypoechoic cystic lesion in the pancreatic tail that communicated with the main pancreatic duct, but did not directly involve the main pancreatic duct. FNA with cytology revealed evidence of a mucinous cyst with high grade dysplasia (HGD). The patient underwent a distal pancreatectomy and splenectomy, which was the only pancreatic surgery performed in the entire cohort, with pathology revealing a 0.3 cm focus of well-differentiated invasive PDAC arising in association with a side-branch IPMN with HGD, and she remains PDAC-free more than 2 years after surgery. The second patient to develop PDAC was also a female *BRCA2* carrier (nonsmoker, BMI 25), with no personal history of cancer and a family history of breast cancer in her sister and daughter, who had undergone annual EUS surveillance from ages 72 to 74 with a normal-appearing pancreas. The patient did not have reexamination of her pancreas until age 76 where she had an EUS after developing abdominal pain revealing a 4.4 cm x 3.4 cm hypoechoic mass in the uncinate process. FNA was positive for adenocarcinoma with CT scan of the abdomen demonstrating metastatic disease to the liver, and the patient ultimately had a prolonged response to a PARP inhibitor.

Discussion

Carriers of P/LP variants in *BRCA1*, *BRCA2*, *PALB2*, and *ATM* are at increased risk for PDAC, yet current pancreatic surveillance recommendations advocate for performing PDAC surveillance only if these individuals also have a family history of PDAC. Herein we present the largest report to date of PDAC surveillance with EUS in *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers without a family history of PDAC. We demonstrate that 44% of individuals had an abnormality detected on EUS, including 22% with either a pancreatic mass or cyst. Additionally, 8% developed a new pancreatic mass or cyst during surveillance, and 2 individuals in our surveillance cohort developed PDAC. Together, these results fill an important knowledge gap in PDAC surveillance in high-risk mutation carriers without a family history of PDAC, which may help guide future surveillance studies and surveillance strategies for this cohort.

Current guidelines for PDAC surveillance in *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers recommend PDAC surveillance only in the setting of a family history of PDAC in a FDR or SDR (21–24). Although the family history requirement may aid in selecting the highest risk individuals, relying on family history alone to determine PDAC surveillance candi-

dates has drawbacks. First, given the other penetrant cancer phenotypes associated with pancreatic risk genes, it is possible that early deaths due to cancers other than PDAC (i.e., breast or ovarian cancer) may limit the number of long-living individuals who develop PDAC. Second, individuals may not know their complete family history, or may have misinformation about the types of cancers present in their families (29, 30). Finally, individuals from small families naturally have fewer at-risk relatives. Taken together, these factors may lead to significant underestimation of PDAC risk in some individuals who report no family history of PDAC. This point is further exemplified by our study data, where two *BRCA2* carriers without a family history of PDAC subsequently developed PDAC during surveillance. To further address this, the field needs to develop more effective risk prediction tools, allowing more accurate risk determination and a tailored PDAC surveillance approach in all variant carriers regardless of family history. Furthermore, a similar study could also be performed in Lynch syndrome carriers, where the decision to perform surveillance is also tied to the presence of a family history of PDAC (22).

There remains minimal data assessing the uptake of PDAC surveillance among individuals with increased genetic risk, especially in the absence of a family history. We show that among *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers without a family history of PDAC, a robust number of individuals choose to undergo PDAC surveillance, even in the absence of formal guideline-based surveillance recommendations. Over two thirds of the individuals in this analysis who underwent EUS surveillance had a personal history of cancer, and every individual in the cohort had a family history of cancer. It is possible that this strong personal and family history of cancer influenced individuals' decisions about whether or not to proceed with PDAC surveillance. Furthermore, for many of these affected individuals who may have already undergone risk-reducing surgeries, such as bilateral mastectomy and/or salpingo-oophorectomy, the risk of PDAC may be one of the highest cancer risks that this group continues to face, which may also be a strong motivating factor to pursue surveillance. Of additional interest is that the majority of our cohort who underwent surveillance were *BRCA2* carriers, suggesting that *BRCA2* carriers may have a higher likelihood of wanting to pursue surveillance. Future studies exploring the motivations behind individuals' decisions to choose to undergo PDAC surveillance, even in the absence of a family history of PDAC, are certainly needed.

In our cohort we found that EUS frequently identified pancreatic abnormalities (44%), including 22% with either masses or cysts, and incidentally discovered luminal abnormalities (40%). These findings are in line other studies, including a multi-center study examining surveillance findings in high-risk individuals demonstrating that 42% had either a pancreatic mass, cyst, or dilated pancreatic duct identified (31). They are similarly comparable with a smaller series of mutation carriers without a family history of PDAC (32) and a recent

meta-analysis of high-risk individuals (17). It is well-known that pancreatic lesions are commonly observed (33), including in the general population (34), and therefore our results are not surprising. However, whether detection of these frequently found pancreatic abnormalities has clinical significance remains uncertain and will require larger and longer-term prospective studies. Furthermore, although not observed with any patients in our cohort, it is possible that pancreatic lesions identified on surveillance may lead to additional work-up and/or surgery, which carries additional potential risk for patients (35).

Eight percent of our cohort developed a pancreatic mass or cystic lesion during surveillance after a prior normal EUS, therefore demonstrating that new lesions can be detected during surveillance. Two individuals (3%) were diagnosed with PDAC, with 1 with metastatic disease having an EUS 2 years prior to her diagnosis. Similarly, of 97 *BRCA1/BRCA2/PALB2/ATM* carriers followed by our center with a family history of PDAC and a surveillance EUS performed during the study period, 2 (2%) were diagnosed with an advanced pancreatic lesion (IPMN with HGD). It is possible that had the individual with metastatic disease continued with annual pancreatic imaging this PDAC may have been diagnosed at a resectable stage, and emphasizes the need for close monitoring of individuals who choose to undergo PDAC surveillance, ideally on an annual basis. Additionally, the 2 PDACs in our surveillance cohort of 62 individuals is a higher frequency than estimates of number-needed-to-screen amongst high-risk cohorts with a family history of PDAC, where between 111 to 135 high-risk patients are predicted to need to be screened to identify a single high-risk lesion (17, 36). In addition to the pancreatic findings, other incidentally discovered luminal findings were noted included Barrett's esophagus, gastric intestinal metaplasia, low grade dysplasia in a fundic gland polyp, and *Helicobacter pylori*. Treatment and/or follow-up of these luminal findings, which otherwise may not have been detected outside of these surveillance EUSs, may have additional long-term benefits in the patients in whom they were discovered. Alternatively, one could consider performing surveillance EUS in any *BRCA1*, *BRCA2*, *PALB2*, or *ATM* carrier who is undergoing upper endoscopy for another clinical indication.

There continues to be debate about which modality of PDAC surveillance is most effective, with no consensus as to whether EUS or MRI is preferred (16, 31). This has similarly been emphasized in guidelines recommending use of either imaging modality in appropriate high-risk individuals (21, 22). MRI may be more sensitive for detecting cystic lesions of the pancreas, whereas EUS may be better at detecting solid lesions (16, 35). Given that the majority of PDACs develop as solid lesions via the PanIN pathway, rather than from cysts (37), EUS performed by experienced endoscopists may have added benefit when incorporated into PDAC surveillance regimens (35).

There are limitations to our study including our small sample size. Our analysis focusing on carriers without a family history of PDAC limited our sample size to less than a third of the *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers who underwent EUS and less than a tenth of the total number of carriers followed at our institution, thus leading to potential selection bias. Ongoing studies (i.e., CAPS5; ref. 25, 26) that our institution is participating in are prospectively collecting data on carriers with a family history, and our data on these carriers with a family history will be reported with the collective data of these ongoing studies. Another limitation of our study is that for individuals who underwent more than 1 surveillance EUS, the intervals between EUSs were highly variable. Additionally, given the retrospective nature of this study and the inherent selection bias, it is possible that there is over-estimation of the rate of pancreatic findings and PDAC. A final limitation of our study is the reporting of family history, which in most cases was by self-report. However, the majority of these patients were seen in a dedicated cancer genetics clinic where a 3-generation family pedigree was obtained by a genetic counselor or cancer genetics focused physician.

PDAC surveillance is an important and evolving area of cancer-risk management, yet limitations and uncertainties highlight the need for continued research in the field (38). The downsides to PDAC surveillance include discovery of false positive findings with potential for unnecessary intervention (39), the small but tangible risks associated with surveillance procedures, increased health care costs (40), as well as lack of large-scale data showing surveillance is conclusively effective for preventing death from PDAC. However, at this time PDAC surveillance provides the only option for patients at increased risk to detect PDAC early and potentially allow it to be treated surgically. In the past, surveillance of *BRCA1*, *BRCA2*, *PALB2*, and *ATM* carriers has been largely governed by family history; given the limitations of family history-based surveillance outlined earlier, whether this is the optimal strategy for PDAC surveillance remains to be determined. Our data illustrates that PDAC surveillance with EUS might be considered in all carriers of a P/LP variant in *BRCA1*, *BRCA2*, *PALB2*, or *ATM*, regardless of family history, with further study of surveillance outcomes in this population being needed. However, prior to consideration of PDAC surveillance initiation, it is critical for providers to discuss the risks and potential benefits, as well as the limitations of PDAC surveillance, to allow patients to make a well-informed choice.

Authors' Disclosures

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Authors' Contributions

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