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Article

Pancreatic Ductal Carcinoma Risk Associated With Hereditary Cancer-Risk Genes

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Abstract

Background: Although several hereditary cancer predisposition genes have been implicated in pancreatic ductal adenocarcinoma (PDAC) susceptibility, gene-specific risks are not well defined and are potentially biased because of the design of previous studies. More precise and unbiased risk estimates can result in screening and prevention better tailored to genetic findings. **Methods:** This is a retrospective analysis of 676 667 individuals, 2445 of whom had a personal diagnosis of PDAC, who received multigene panel testing between 2013 and 2020 from a single laboratory. Clinical data were obtained from test requisition forms. Multivariable logistic regression models determined the increased risk of PDAC because of pathogenic variants (PVs) in various genes as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Multivariable odds ratios were adjusted for age, personal and/or family cancer history, and ancestry. **Results:** Overall, 11.1% of patients with PDAC had a PV. Statistically significantly elevated PDAC risk (2-sided $P < .05$) was observed for *CDK2NA* (p16INK4a) (OR = 8.69, 95% CI = 4.69 to 16.12), *ATM* (OR = 3.44, 95% CI = 2.58 to 4.60), *MSH2* (OR = 3.17, 95% CI = 1.70 to 5.91), *PALB2* (OR = 3.09, 95% CI = 2.02 to 4.74), *BRCA2* (OR = 2.55, 95% CI = 1.99 to 3.27), and *BRCA1* (OR = 1.62, 95% CI = 1.07 to 2.43). **Conclusions:** This study provides PDAC risk estimates for 6 genes commonly included in multigene panel testing for hereditary cancer risk. These estimates are lower than those from previous studies, possibly because of adjustment for family history, and support current recommendations for germline testing in all PDAC patients, regardless of a personal or family history of cancer.

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Pancreatic ductal adenocarcinoma (PDAC) currently accounts for 3% of all cancer diagnoses in the United States but approximately 7% of all cancer deaths (1). The majority of the 60 000 cases expected in 2021 were diagnosed after disease had already metastasized regionally or to distant organs, with an overall 5-year survival rate of only 10% (1). PDAC is projected to be the second leading cause of cancer death by 2030, highlighting the need for improved strategies for prevention, early detection, and treatment (2).

Emerging evidence suggests that screening can detect premalignant lesions and malignancies at earlier stages, resulting in improved survival (3,4). Studies report that 75%-90% of screen-detected PDAC is surgically resectable at diagnosis (5). Current screening options for PDAC such as endoscopic ultrasonography are unsuitable for use in the general population, because of cost, complexity, and the potential for associated morbidity (6). However, screening targeted to those at increased risk for the disease may be a practical and effective tool for improved survival.

Germline pathogenic variants (PVs) in hereditary cancer genes are an important contributor to increased PDAC risk. Studies have found such PVs in approximately 10% of unselected PDAC cases (7,8) and in up to 30% of cases within populations enriched for family history of cancer and/or common founder variants (ie, Ashkenazi Jews) (8). In 2018, this data led the National Comprehensive Cancer Network (NCCN) to recommend germline genetic testing and counseling for all PDAC patients regardless of ancestry or additional personal and

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Table 1. PDAC-associated genes by syndrome, risk estimate, and management recommendations by professional societies

Genes	Syndrome	Previously published pancreatic cancer risk estimates, OR[a]	Professional society screening recommendations
APC	Familial adenomatous polyposis (FAP)	RR = 4.5 (10)	Yes (5)[b]
ATM	ATM-associated cancer risk	OR = 4.2 (11) OR = 5.7 (12) OR = 9.0 (13)	Yes (5,14,15)[b]
BRCA1	Hereditary breast and ovarian cancer	OR = 2.6 (12) OR = 3.0 (13)	Yes (5,14,15)[b]
BRCA2	Hereditary breast and ovarian cancer	OR = 6.2 (12) OR = 9.0 (13)	Yes (5,14,15)[b]
CDKN2A (p16INK4a)	Hereditary melanoma/pancreatic cancer	OR = 12.3 (12) OR = 36.0 (13)	Yes (5,14–16)[b]
MLH1	Lynch	6.2% (17) OR = 6.7 (12)	Yes (5,14,15,18)[b]
MSH2/EPCAM	Lynch	0.5%-1.6% (17) OR = 7.1 (13)	Yes (5,14,15,18)[b]
MSH6	Lynch	1.4%-1.6% (17) OR = 7.8 (13)	Yes (5,14,15,18)[b]
PMS2	Lynch	OR = 0.7 (12) ≤1%-1.6% (17)	Yes (18)[b]
PALB2	*PALB2*-associated cancer risk	RR = 2-3 (19) OR = 14.8 (13)	Yes (5,14,15)[b]
BMPR1A	Juvenile polyposis	Elevated risk (18,20,21)	No
SMAD4		Elevated risk (18,20,21)	No
STK11	Peutz-Jeghers	11.0% (17) 36% (22)	Yes (5,14–16,18)[c]
TP53	Li-Fraumeni	OR = 6.7 (12) OR = 7.2 (13)	Yes (5)[b]

[a]All other risk estimates are provided as cumulative risk. OR = odds ratio; RR = relative risk;
[b]Recommendations based on if a first-degree or second-degree relative had a PDAC diagnosis;
[c]Recommendations based on presence of pathogenic variant regardless of family history.

family history. For the PDAC patient, identification of PVs in certain genes may provide an opportunity to utilize targeted therapies, such as PARP inhibitors (9). For relatives, it provides an opportunity to utilize genetic testing to determine their own PV status and whether they are candidates for risk-reduction strategies targeted to PDAC and other cancers.

Table 1 provides an overview of the genes with the best evidence to date supporting an association with PDAC risk, along with the associated syndromes, risk estimates, and management recommendations from professional societies. Because of limited sample sizes, risk estimates for most genes vary statistically significantly between studies, with wide confidence intervals.

This study estimates the PDAC risk associated with PVs in hereditary cancer genes based on data from multigene panel testing of 676 667 individuals, 2445 of whom had a personal diagnosis of PDAC. Multivariable logistic regression models (MLRM) were used to estimate risk within a clinical testing population adjusted for variables that influence ascertainment and/or eligibility for hereditary cancer testing. It has been shown previously that this methodology generates risk estimates similar to those from population-based studies, representing the magnitude of risk attributable to the genetic findings independent of other risk factors that impact ascertainment (23). This is especially important considering that PVs associated with an increased risk for PDAC are frequently identified in individuals tested for reasons other than a personal or family history of PDAC, such as a personal and/or family history of other cancers, or as incidental findings from testing performed for other reasons. These improved PDAC risk estimates will hopefully contribute to the development of management recommendations better tailored to genetic findings. We also present data supporting current recommendations for germline testing in all PDAC patients based on a high prevalence of clinically significant PVs regardless of additional personal and/or family history variables.

Methods

Testing Population

Between September 2013 and May 2020, 676 667 individuals underwent clinical genetic testing for suspicion of hereditary cancer risk, performed by Myriad Genetic Laboratories, Inc (Salt Lake City, UT, USA), a national Clinical Laboratory Improvement Amendments and College of American Pathology certified facility. Clinical information and self-reported ancestry were obtained from provider-completed test request forms. All individuals provided consent for clinical testing. Testing data were de-identified for analysis. A waiver of consent for research was obtained from Advarra institutional review board (Pro00036775).

Patients were excluded from analysis if they were aged younger than 18 years at the time of testing, had prior genetic testing for familial or founder mutations, or were from states that disallow the use of de-identified genetic data for research. Patients were included in the PDAC cohort if a personal history of PDAC was indicated on the test request form.

Multigene Hereditary Cancer Panel Testing

Testing was performed on DNA extracted from blood or saliva using previously described technologies (24,25). The next

generation sequencing hereditary pan-cancer panel test included 25-35 genes: *APC*, *AXIN2*, *ATM*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM*, *GALNT12*, *GREM1*, *HOXB13*, *MLH1*, *MSH2*, *MSH3*, *MSH6*, *MUTYH*, *NBN*, *NTHL1*, *PALB2*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RNF43*, *RPS20*, *SMAD4*, *STK11*, and *TP53*. Sequencing and large rearrangement analysis was performed for all genes on the panel except *HOXB13* (sequencing only), *POLD1* and *POLE* (sequencing only; limited to the exonuclease domains), *GREM1* (large rearrangement only), and *EPCAM* (large rearrangement only). *POLD1*, *POLE*, and *GREM1* were added to the panel in July 2016, *HOXB13* in October 2018, and *AXIN2*, *GALNT12*, *MSH3*, *NTHL1*, *RNF43*, and *RPS20* in February 2019.

Variant Classification

Variant classification was consistent with guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, as described previously (26–28). Variants with a laboratory classification of deleterious or suspected deleterious were considered PVs.

Statistical Analysis

MLRM were used to estimate PDAC risk associated with each gene for which there were at least 5 individuals with a personal history of PDAC also carrying a PV in that gene. Risk is expressed as odds ratios (OR) with 95% confidence intervals (CI), which estimate the relative risks conferred by mutations after accounting for other risk factors. It has been shown that these models generate unbiased risk estimates for breast and ovarian cancer, similar to results from population-based studies (23,29,30). All models were adjusted for age, ancestry, gender, and personal and/or family cancer histories. Two-sided *P* values less than .05 were considered statistically significant for the purposes of this study. Further details regarding coding of variables are provided in Supplementary Methods (available online). Analyses were conducted using SAS software (SAS Institute Inc, Cary, North Carolina, USA).

Results

Patient Characteristics

Among the 676 667 individuals included in the analysis, 2445 (0.4%) had a personal history of PDAC. Patient demographics are presented in Table 2. Most PDAC patients were female (57.1%) and 42.9% were male. Patients with a history of PDAC were mainly of Black or African (10.7%) or White or non-Hispanic (61.7%) ancestry. Providers indicated that most patients were tested for suspicion of hereditary breast and ovarian cancer (HBOC) (90.7%). The remaining (9.3%) patients were tested for suspicion of Lynch syndrome. Most (70.5%) patients were diagnosed with PDAC after age 50 years, with only 16.9% of patients diagnosed at or younger than age 50 years. Age of diagnosis was not known for 12.7% of patients.

Genetic Testing for Patients With PDAC

The overall PV-positive rate was 11.1% (271 of 2445) among patients with PDAC. The distribution of PVs is presented in Table 3. PVs were most common in *BRCA2*, *ATM*, *BRCA1*, and *PALB2* in our patient population (2.9%, 2.1%, 1.0%, and 0.9%, respectively). Ten (0.4%) patients with PDAC had a PV in more than 1 gene. These patients were not included in the risk estimate analysis. The median age at diagnosis of PDAC varied by gene, ranging from 46 to 76 years.

Table 2. Demographics of patients with pancreatic ductal carcinoma[a]

	Pancreatic ductal carcinoma patients		
	All	With PV	Without PV
Category	No. (%)	No. (%)	No. (%)
Total	2445 (100)	271 (100)	2174 (100)
Gender			
Female	1395 (57.1)	143 (52.8)	1252 (57.6)
Male	1050 (42.9)	128 (47.2)	922 (42.4)
Ancestry			
Ashkenazi Jewish	28 (1.1)	6 (2.2)	22 (1.0)
Asian	61 (2.5)	10 (3.7)	51 (2.3)
Black/African	261 (10.7)	28 (10.3)	233 (10.7)
Hispanic/Latino	178 (7.3)	15 (5.5)	163 (7.5)
Middle Eastern	13 (0.5)	1 (0.4)	12 (0.6)
Multiple ancestries indicated	118 (4.8)	11 (4.1)	107 (4.9)
Native American	15 (0.6)	1 (0.4)	14 (0.6)
None specified	253 (10.3)	23 (8.5)	230 (10.6)
Other	7 (0.3)	1 (0.4)	6 (0.3)
Pacific Islander	2 (<0.1)	1 (0.4)	1 (<0.1)
White/Non-Hispanic	1509 (61.7)	174 (64.2)	1335 (61.4)
Reason for testing			
Clinical suspicion of HBOC	2217 (90.7)	236 (87.1)	1981 (91.1)
Clinical suspicion of Lynch syndrome	228 (9.3)	35 (12.9)	193 (8.9)
Age at pancreatic ductal carcinoma diagnosis, y			
<50	412 (16.9)	47 (17.3)	365 (16.8)
>50	1723 (70.5)	191 (70.5)	1532 (70.5)
Missing	310 (12.7)	33 (12.2)	277 (12.7)

[a]HBOC = hereditary breast and ovarian cancer; PV = pathogenic variants.

The July 2018 NCCN guideline update recommending germline testing for all patients with PDAC was correlated with an increase in the proportion of patients with PDAC within the tested population, suggesting a positive association between guideline recommendations and patients receiving germline testing. The PV rate declined after 2018 but remained close to 10% annually (Figure 1).

Among patients with a history of PDAC, 29.8% (728 of 2445) had a personal history of additional cancer(s). The PV rate among patients with PDAC and additional cancer(s) was 14.4% compared with a PV rate of 9.7% among those with no history of additional cancers (Table 4). Most patients with a PDAC diagnosis had a family history of cancer (84.5%; 2066 of 2445). The PV rate among patients with PDAC and a family history of cancer was 11.6% compared with a rate of 8.4% in patients with PDAC and no reported family history (Table 5).

Risk Estimates (OR) for PDAC

Risk estimates derived from the logistic regression analysis are presented in Table 6. PVs in *CDKN2A* (p16INK4a), *ATM*, *MSH2*, *PALB2*, *BRCA2*, and *BRCA1* were associated with a statistically significantly higher risk of PDAC compared with PV-negative individuals after accounting for age, gender, personal and/or

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Table 3. Pathogenic variant gene distribution

Genes	No.	% of patients with PVs	Median age of PDAC diagnosis, y
BRCA2	71	2.9	59
ATM	52	2.1	62
BRCA1	25	1	57
PALB2	23	0.9	54
CHEK2	20	0.8	64
CDKN2A (p16INK4a)	13	0.5	63
BRIP1	12	0.5	63
MSH2	12	0.5	52
MSH6	8	0.3	60
NBN	6	0.2	55
PMS2	4	0.2	51
BARD1	3	0.1	62
MLH1	3	0.1	46
RAD51C	3	0.1	76
APC	2	0.1	55
RAD51D	2	0.1	49
CDH1	1	<0.1	61
TP53	1	<0.1	49
Multiple genes[a]	10	0.4	69
Any	271	11.1	60

[a]The following combinations were observed among individuals with PVs in multiple genes: *ATM*/*BRCA2* (n = 3), *ATM*/*CHEK2* (n = 2), *ATM*/*BRIP1* (n = 1), *ATM*/*CDKN2A* (p16INK4a) (n = 1), *ATM*/*PMS2* (n = 1), *BRCA2*/*CDKN2A* (p16INK4a) (n = 1), *BRIP1*/*PALB2* (n = 1). PDAC = pancreatic ductal adenocarcinoma; PV =pathogenic variant.

family cancer history, and ancestry ($P < .05$). The highest risk of PDAC was associated with PVs in *CDK2NA* (p16INK4a) (OR = 8.69, 95% CI = 4.69 to 16.12; $P < .0001$).

Discussion

Several cancer predisposition genes have a well-established association with PDAC risk, but published gene-specific risk estimates vary widely and may not apply to carriers of PVs detected in individuals without a family history of the disease or other risk factors for PDAC. The estimates presented here are based on the results of multigene panel testing in 676 667 individuals, including 2445 PDAC patients. Overall, 11.1% of the PDAC patients were found to carry at least 1 PV in a hereditary cancer predisposition gene. We were able to calculate statistically significant PDAC risk for 6 genes, including *CDKN2A*, *ATM*, *MSH2*, *PALB2*, *BRCA2*, and *BRCA1*. The odds ratios for these genes are lower than those that have been reported previously. This is because, in part, these estimates having been adjusted for clinical and demographic characteristics that may be associated with cancer risk, including age, personal cancer history, family cancer history, and ancestry yielding odds ratios attributable specifically to having a PV in each of the studied genes. This methodology was originally applied by Kurian et al. (23) to evaluate gene-specific breast and ovarian cancer risks. Although the risks reported by Kurian et al. (23) were lower than previously reported for many genes, the findings align with recent reports from large cohorts in unselected populations, reinforcing the importance of adjusting for additional confounding risk factors (29,30).

The only other PDAC risk estimates derived from multigene testing of comparably large samples are from the case-control analyses published by Hu et al., where PDAC cases tested at a commercial laboratory (13), or from a single cancer clinic (12), were compared with general population controls from the Genome Aggregation Database and the Exome Aggregation Database Consortium. This approach has become popular for investigating gene associations with cancer risks in samples for which large control groups are difficult to obtain. However, there are concerns about the reliability of genetic data available in these databases, especially for difficult to analyze regions of DNA. Additionally, previous studies have shown that the use of general population controls can artificially inflate the calculated relative risk, as the heterogeneity in sample ascertainment can lead to clinical cases enriched for PVs compared with general population cases (23,31).

Among PDAC patients, PVs were most common in *BRCA2* and *ATM*. This is consistent with other large studies, indicating that PVs in these genes are important contributors to inherited PDAC risk (7,12,32,33). The odds ratio for PDAC was 2.55 (95% CI = 1.99 to 3.27) for *BRCA2* and 3.44 (95% CI = 2.58 to 4.60) for *ATM*, which is less than half of what was previously reported in other large studies (12,13).

PVs in *PALB2* were relatively common in PDAC patients. The 3.09 odds ratio (95% CI = 2.02 to 4.74) calculated for *PALB2* is close to the 2.37 [relative risk estimated in a previous study of 534 families with known PVs in *PALB2* (5) but much lower than the 14.8 odds ratio (95% CI = 8.12 to 26.22) calculated elsewhere (12)].

CDK2NA (p16INK4a) is consistently found to be one of the highest risk genes for PDAC in the published literature, with reported risks ranging from a 12- to 36-fold increased risk in carriers (12,13). *CDKN2A* (p16INK4a) conferred the highest PDAC risk of the genes evaluated here (OR = 8.69, 95% CI = 4.69 to 16.12), although the confidence interval is wide because of the relatively small number of individuals identified with PVs in this gene. Additional studies may be needed to better refine the gene-specific risk, but the body of evidence consistently shows a high risk of PDAC in *CDKN2A* (p16INK4a) PV carriers, supporting recommendations for PDAC screening in unaffected carriers.

Individuals with Lynch syndrome are believed to have an increased risk for PDAC, and screening is currently recommended for carriers of PVs in *MLH1*, *MSH2*, and *MSH6* if they have a first- or second-degree relative with PDAC (5,14,18). However, risk estimates for these genes are inconsistent between studies. We calculated a 3.17 odds ratio (95% CI = 1.70 to 5.91) for *MSH2*, based on 12 PVs identified in PDAC patients. *MSH6* PVs were identified in 8 individuals with PDAC, but the odds ratio was not statistically significantly different from 1. No other Lynch gene had sufficient findings for analysis.

Previous studies report an 11- to 36-fold increased PDAC risk associated with PVs in *STK11* (17,22). We did not identify any *STK11* PVs in PDAC patients, which is consistent with other studies reporting on the outcomes of multigene panel testing in adults with PDAC (12,13). This is probably because individuals with PVs in this gene are often ascertained at a young age based on clinical manifestations of Peutz-Jeghers syndrome.

The odds ratio for PDAC associated with *CHEK2* was not statistically significant, although *CHEK2* PVs were found in 0.8% of the PDAC patients. *CHEK2* is not considered to be a PDAC risk gene, and PVs in *CHEK2* are relatively common in patients referred for hereditary cancer testing (12,34). *BRIP1* PVs were also relatively common, found in 0.5% of the PDAC patients. The 1.78 odds ratio (95% CI = 0.99 to 3.20) for *BRIP1* was approaching statistical significance, but a larger sample size could likely yield more definitive results.

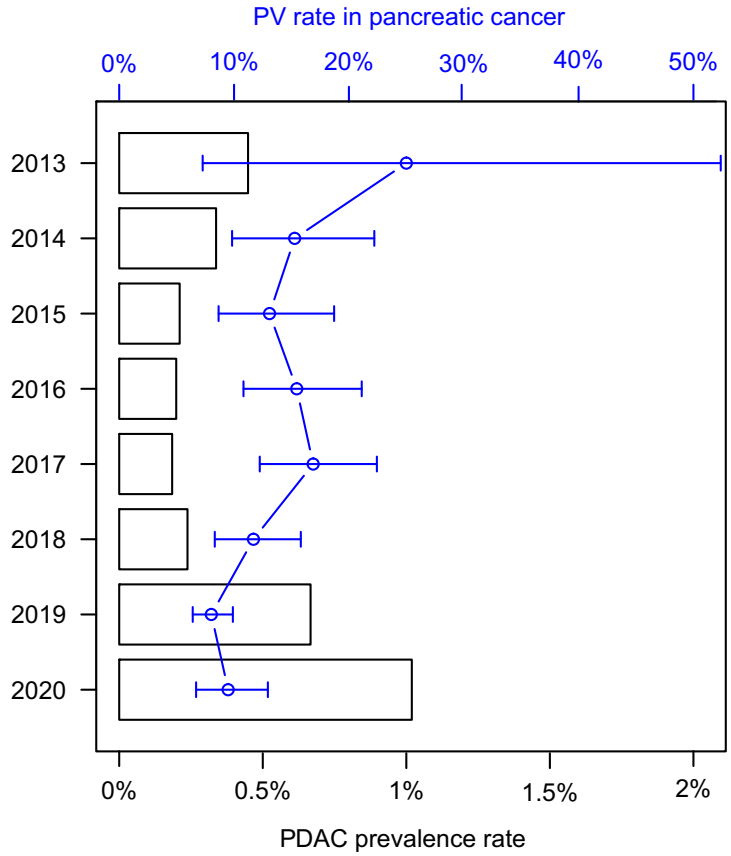

Figure 1. PV rate from 2013 to 2020 in patients with PDAC referred for genetic testing. 2013 only includes data from the last 4 months of 2013, the year that the Myriad myRisk hereditary cancer test was launched. PV = pathogenic variants; PDAC = pancreatic ductal adenocarcinoma.

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Table 4. Personal cancer history in patients with PDAC

Personal history of other cancers	No. tested	No. with a PV	% with a PV
No additional cancer	1717	166	9.7
Any additional cancer or polyps[a]	728	105	14.4
Breast	268	48	17.9
Colorectal	82	8	9.8
Ovarian	32	4	12.5
Endometrial	42	9	21.4
Prostate	68	7	10.3
Melanoma	38	9	23.7
Gastric	11	2	18.2
Other	240	38	15.8

[a]Patients may have 1 or more cancers. Patients with multiple additional cancers are counted for each cancer for which they have a personal history. Twenty-three patients were tested with colon polyps of which 6 (26.1%) patients had a PV. Patients included had more than 20 polyps to align with National Comprehensive Cancer Network guidelines for APC testing. PDAC = pancreatic ductal adenocarcinoma; PV = pathogenic variant.

Table 5. Family history of cancer in patients with PDAC

Family history of other cancers	No. tested	No. with a PV	% with a PV
No family history of other cancer	379	32	8.4
Family history of any other cancer or polyps[a]	2066	239	11.6
Breast	1017	153	15.0
PDAC	586	71	12.1
Colorectal	525	74	14.1
Ovarian	288	43	14.9
Endometrial	118	13	11.0
Prostate	425	53	12.5
Melanoma	139	19	13.7
Gastric	199	23	11.6
Other	1064	111	10.4

[a]Patients may have 1 or more cancers. Patients with multiple additional cancers are counted for each cancer for which they have a family history. Eight patients were tested with colon polyps of which 1 patient (12.5%) had a PV. Family members included had more than 20 polyps to align with National Comprehensive Cancer Network guidelines for APC testing. PDAC = pancreatic ductal carcinoma; PV = pathogenic variant.

Consistent with previous studies, our results support the 2018 NCCN guideline expansion recommending multigene hereditary cancer panel testing in patients diagnosed with PDAC at any age, without additional clinical history requirements (12,32,33). The number of PDAC patients referred for testing after the guideline expansion increased, with a drop in the positive rate, although it remained close to 10%. The positive rate was somewhat enriched in patients with a personal or family history of additional cancers but remained above 8% even among patients with no additional personal or family cancer history.

Our study has some limitations. Clinical information was obtained from provider-completed test requisition forms in conjunction with clinical testing and was not verified. It is

Table 6. Gene-specific risk of pancreatic ductal adenocarcinoma[a]

Gene	OR (95% CI)	*P*
CDKN2A (p16INK4a)	8.69 (4.69 to 16.12)	<.001
ATM	3.44 (2.58 to 4.60)	<.001
MSH2	3.17 (1.70 to 5.91)	<.001
PALB2	3.09 (2.02 to 4.74)	<.001
BRCA2	2.55 (1.99 to 3.27)	<.001
BRCA1	1.62 (1.07 to 2.43)	.02
BRIP1	1.78 (0.99 to 3.20)	.05
NBN	1.48 (0.65 to 3.36)	.35
MSH6	1.11 (0.55 to 2.25)	.78
CHEK2	1.04 (0.67 to 1.63)	.86

[a]CI = confidence interval; OR = odds ratio.

possible that some of the reported pancreatic cancers were endocrine tumors rather than exocrine PDAC. However, it is unlikely that testing would have been ordered for a patient with an endocrine pancreatic tumor, given that the testing criteria are specific to PDAC and the gene panel used for testing does not include any of the genes currently believed to be relevant to endocrine pancreatic tumors. We did not address other factors that may contribute to increased risk, such as environment or lifestyle. The majority of patients included in this study were referred for testing due to suspicion of HBOC or Lynch syndrome, which may impact the observed cancer histories (5). However, multigene panel testing is recommended for a variety of hereditary cancer syndromes beyond HBOC and Lynch, which we observed in our testing population. Additionally, although this study included one of the largest cohorts of patients with PDAC tested to date, there were still limited numbers of PVs in many genes, limiting ability to estimate the risk associated with those genes.

The lower risk estimates found in this study may have broader implications for gene-specific PDAC risk management in unaffected individuals, although the impact of additional clinical factors, such as family history and other PDAC risk factors will need further investigation. One area for future investigation is the average age of diagnosis, which varied within the group of genes for which there are statistically significant odds ratio, ranging from 63 for *CDKN2A* to 52 for *MSH2*. This could impact recommendations for the age at which to initiate screening. The MLRM methodology used for this study can in theory be applied to pooled datasets from multiple clinical laboratories, which would be a powerful strategy for obtaining the larger sample sizes required to better resolve these questions.

Findings from this study provide statistically significant gene-specific PDAC risk estimates for *CDKN2A* (p16INK4a), *ATM*, *MSH2*, *PALB2*, *BRCA1*, and *BRCA2*. These estimates are lower than those from previous studies, likely because of the use of a MLRM methodology. *CDK2NA* (p16INK4a) was associated with the highest PDAC risk, consistent with previous findings. Our data also validate current testing recommendations for all PDAC patients. Although positive rates have declined over time, as testing criteria have become broader, the proportion of individuals with PDAC positive for a PV in a clinically important hereditary cancer gene remains high regardless of personal or family cancer history. Genetic findings provide critical information that can be used to target screening and prevention options for PDAC and other cancers to unaffected individuals, as well as potentially informing therapeutic options for patients already diagnosed with this disease.

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Notes

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Author contributions: Anna Gardiner: Conceptualization, Methodology, Data Curation, Writing—Original Draft, Writing—Review and Editing, Visualization. John Kidd: Conceptualization, Validation, Formal Analysis, Data Curation, Writing—Review and Editing. Maria Elias: Conceptualization, Data Curation, Writing—Original Draft, Writing—Review and Editing. Kayla Young: Conceptualization, Data Curation, Writing—Original Draft, Writing—Review and Editing. Brent Mabey: Validation, Formal Analysis. Nassim Taherian: Conceptualization, Writing—Review and Editing. Shelly Cummings: Writing—Review and Editing. Mokenge Malafa: Writing—Review and Editing. Eric Rosenthal: Conceptualization, Formal Analysis, Writing—Original Draft, Writing—Review and Editing. Jennifer Permuth: Conceptualization, Formal Analysis, Writing—Original Draft, Writing—Review and Editing, Supervision.

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Data Availability

The data that support the findings of this study are available from Myriad upon reasonable request. Requests can be initiated by contacting the corresponding author by email. Data requests will be reviewed by Myriad and will be made available assuming the intent is to advance research, there are no patient privacy or safety concerns, and the data will not be made open access.

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