JAMA Network Open

Original Investigation | Gastroenterology and Hepatology

Presumed Intraductal Papillary Mucinous Neoplasms in Individuals at High Risk for Pancreatic Cancer

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Abstract

IMPORTANCE Pancreatic cystic lesions are common during surveillance of individuals at hereditary risk for pancreatic cancer, but whether their incidence and progression differ across genetic risk groups remains uncertain.

OBJECTIVE To compare the incidence, morphologic characteristics, and progression of presumed intraductal papillary mucinous neoplasms (IPMNs) in individuals at high risk of PC across hereditary risk groups.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cohort study was conducted from January 2016 to December 2025 at 25 centers participating in the Italian Registry of Families at Risk of Pancreatic Cancer. Participants were individuals undergoing pancreatic surveillance with magnetic resonance imaging with cholangiopancreatography and/or endoscopic ultrasonography.

EXPOSURE Familial pancreatic cancer without pathogenic germline variants vs pathogenic germline variant (PGV) carrier status, further grouped into 3 predefined categories: PGV1 (Peutz-Jeghers syndrome or *CDKN2A* sequence variant carriers), PGV2 (*BRCA2* or *ATM* variant carriers), and PGV3 (Lynch syndrome–associated genes or *BRCA1* or *PALB2* variant carriers).

MAIN OUTCOMES AND MEASURES Cumulative incidence of presumed IPMNs, longitudinal changes in index cyst diameter and main pancreatic duct diameter, and progression to worrisome features or high-risk stigmata. Multivariable Cox proportional hazards regression was used to estimate hazard ratios (HRs) for incident IPMNs, adjusted for hereditary risk, age, sex, body mass index, tobacco smoking status, and diabetes.

RESULTS Among 1688 high-risk individuals (median age, 56 years [IQR, 50-64 years]; 1055 women [62.5%]), 496 (29.4%) had a presumed IPMN. Median follow-up from enrollment was 17 months (IQR, 0-36 months). A total of 1298 participants (76.9%) did not have a presumed pancreatic cyst at baseline, and 124 (9.6%) of these participants developed an incident lesion during follow-up. In the complete-case multivariable analysis of 1245 participants and 123 events, PGV1 (adjusted HR [AHR], 1.82; 95% CI, 0.97-3.43), PGV2 (AHR, 0.81; 95% CI, 0.45-1.45), and PGV3 (AHR, 0.70; 95% CI, 0.34-1.44) were not associated with incident cyst development compared with FPC, whereas older age was associated with higher incidence (AHR per year, 1.04; 95% CI, 1.02-1.05). Longitudinal trajectories of cyst growth (time × group interaction: $\chi^2 = 14.4$; $df = 15$; $P = .49$) and main pancreatic duct diameter (time × group interaction: $\chi^2 = 4.35$; $df = 15$; $P > .99$) did not differ significantly across

(continued)

Key Points

Question Do the incidence and short-term progression of presumed intraductal papillary mucinous neoplasms (IPMNs) differ across individuals grouped by hereditary pancreatic cancer (PC) risk factors who are undergoing surveillance?

Findings In this cohort study of 1688 individuals at high risk of PC undergoing pancreatic surveillance, cumulative incidence of new presumed IPMNs, cyst growth trajectories, and progression to worrisome features or high-risk stigmata did not differ significantly across hereditary risk groups.

Meaning These findings suggest that surveillance of presumed pancreatic cystic precursor lesions may be guided primarily by imaging phenotype and interval change rather than germline subgroup alone.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

groups, and progression to worrisome features or high-risk stigmata was infrequent (13 patients [2.6%]).

CONCLUSIONS AND RELEVANCE In this multicenter cohort study of individuals at high risk of PC who were undergoing pancreatic surveillance, the incidence and short-term progression of presumed IPMNs did not differ significantly across hereditary risk groups, whereas older age was associated with incident cyst development. Longer follow-up appears to be needed to assess potential gene-specific differences.

JAMA Network Open. 2026;9(9):e2635610. doi:10.1001/jamanetworkopen.2026.35610

Introduction

Pancreatic cancer (PC) remains one of the deadliest cancers worldwide,[1] and its poor prognosis is largely attributable to late diagnosis. Surveillance of individuals at increased familial or genetic risk has therefore emerged as a promising strategy to detect either early-stage PC or precursor lesions at a potentially curable stage.[2-7] Within surveillance programs, pancreatic cystic lesions, most commonly presumed branch-duct intraductal papillary mucinous neoplasms (IPMNs), represent the most frequent abnormal finding.[8,9]

In both the general population and surveillance settings, pancreatic cysts are often incidentally detected and usually follow an indolent course.[10,11] However, in high-risk individuals, including members of familial pancreatic cancer (FPC) kindreds and carriers of pathogenic germline variants (PGVs) in PC susceptibility genes, cyst prevalence appears substantially higher.[9,12,13] Whether this reflects a true biological predisposition, a surveillance-related phenomenon, or both remains uncertain. Moreover, the natural history and malignant potential of these lesions in genetically predisposed individuals are still not fully understood, and current guideline-based management may not fully capture clinically relevant progression in this context.[14,15]

Previous studies have yielded partly conflicting results. Some reports suggest that individuals from FPC kindreds are more likely to harbor larger cysts, whereas PGV carriers may show faster cyst growth or higher rates of neoplastic progression.[9] Other data indicate that even relatively small cystic lesions may carry a nonnegligible risk in high-risk individuals, questioning the applicability of conventional size-based thresholds derived from sporadic populations.[8,13] Collectively, these findings support the hypothesis that pancreatic cysts arising in high-risk individuals may differ according to the underlying genetic background,[16,17] but comparative data from structured surveillance programs remain limited. We therefore investigated whether the incidence, morphologic characteristics, and short-term progression of presumed IPMNs differed across hereditary risk groups in individuals undergoing PC surveillance within the Italian Registry of Families at Risk of Pancreatic Cancer (IRFARPC), hypothesizing that these outcomes would vary according to the underlying familial or genetic risk.

Methods

Study Design and Setting

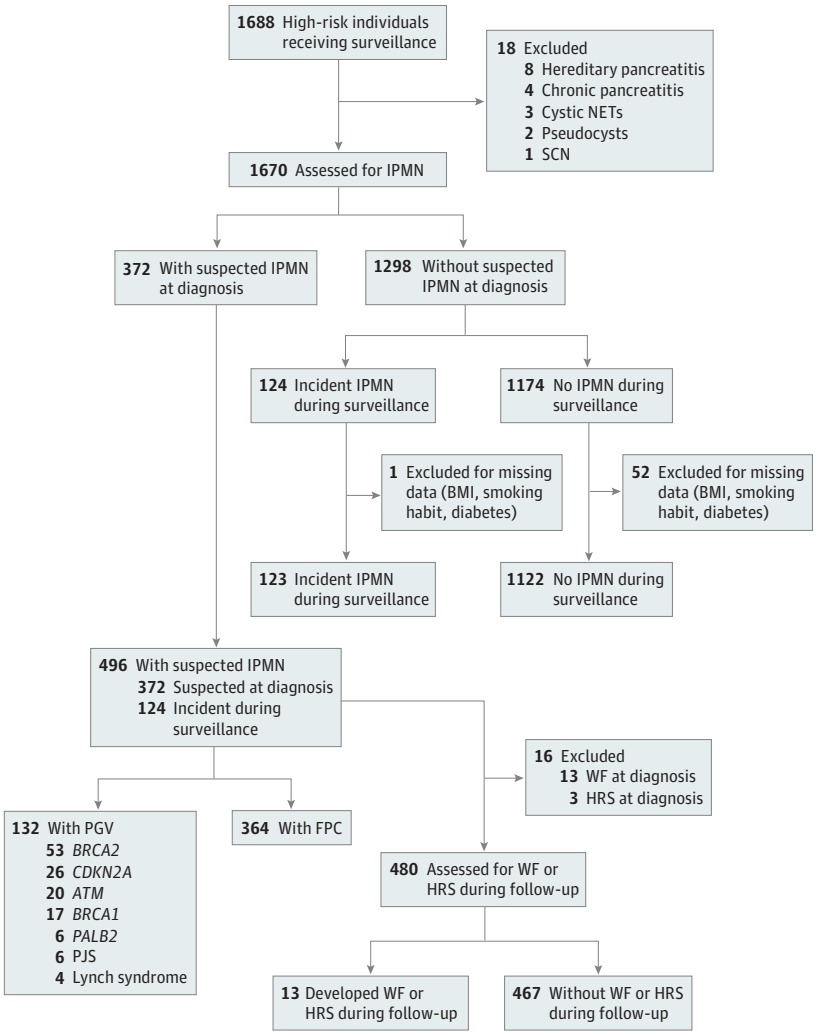
This multicenter cohort study was conducted from January 2016 through December 2025 within the IRFARPC registry, a prospective Italian surveillance program for individuals at increased familial and/or genetic risk of PC. The study was performed in accordance with the Declaration of Helsinki[18] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[19] The protocol was approved by the Ethics Committee for the Clinical Trial of Verona and

Rovigo provinces (462CESC) and the local ethics committees of the 25 participating centers, and all participants provided written informed consent before enrollment.

Study Population

Patient selection is detailed in the study flowchart (**Figure 1**). The organization, methods, and preliminary results of IRFARPC have been previously described.[7,20,21] In brief, the IRFARPC registry prospectively enrolls high-risk individuals with a family history of PC and/or a documented PGV. For this ancillary analysis, we restricted inclusion to individuals with FPC who had undergone germline testing either through the Familial Pancreatic Cancer Prophilation Program in Italy[22] or, in nonparticipating centers, through blood-based testing including at least the National Comprehensive Cancer Network–recommended PC susceptibility genes.[23] This approach ensured a homogenous comparison between genetically tested individuals with FPC and those who were PGV carriers. End point–specific analyses were restricted to participants with the clinical, radiologic, and follow-up data required for the relevant outcome; reasons for exclusion and analytic sample sizes are shown in Figure 1. Participants were categorized as follows: those with FPC, defined according to published IRFARPC[20] criteria as having at least 3 relatives with PC in the same lineage or at least 2 relatives in the same lineage (including ≥1 first-degree relative) with negative germline testing, and PGV carriers, defined as individuals who harbored pathogenic variants in PC susceptibility genes.

Figure 1. Study Flowchart and End Point–Specific Analytic Populations



The flowchart shows cohort derivation and the populations included in the cumulative incidence analysis, adjusted cumulative incidence analysis (multivariable Cox proportional hazards regression), longitudinal cyst and main pancreatic duct (MPD) growth analyses, and worrisome features (WF) or high-risk stigmata (HRS) development analysis. The distribution of specific pathogenic germline variants (PGVs) is reported among PGV carriers. BMI indicates body mass index; NET, neuroendocrine tumor; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; PJS, Peutz-Jeghers syndrome; SCN, serous cystic neoplasm.

For exploratory subgroup analyses, PGV carriers were grouped a priori into 3 study-defined categories reflecting differences in estimated PC lifetime risk and current surveillance frameworks[24-28]: PGV1 (patients with Peutz-Jeghers syndrome and *CDKN2A* sequence variant carriers), PGV2 (*BRCA2* or *ATM* sequence variant carriers), and PGV3 (Lynch syndrome–associated genes and *BRCA1* or *PALB2* sequence variant carriers). To reduce misclassification and confounding, cysts identified in individuals enrolled in the IRFARPC for genetic chronic pancreatitis were excluded because of the potential overlap between chronic pancreatitis–related ductal changes and IPMN-associated abnormalities, including main duct dilatation and branch duct ectasia or cystic lesions.

Surveillance Protocol

Surveillance consisted of magnetic resonance imaging with cholangiopancreatography and/or endoscopic ultrasonography (EUS), with modality selection left to the participating center's discretion according to local expertise and resources. EUS was generally used according to current guideline-based recommendations,[29] although 2 digestive endoscopy centers also used it routinely as a primary surveillance modality. When relevant progression or suspicious features emerged during follow-up, management decisions, including surgical resection, were discussed in a dedicated multidisciplinary setting.

Data Collection

For this analysis, demographic, clinical, genetic, radiologic, and follow-up variables were retrieved from the IRFARPC registry. Baseline clinical data included age, sex, body mass index (BMI), smoking status, alcohol consumption, diabetes, and history of pancreatitis and/or cancer. Pancreatic imaging data included the presence of pancreatic cystic lesions, their presumed nature, the number of lesions, their location within the pancreas, their maximal diameter, and the main pancreatic duct (MPD) diameter. For patients with cystic lesions, follow-up time was calculated from the date of registry enrollment and the date of cyst diagnosis. Longitudinal imaging data were used to assess changes in index cyst diameter and MPD diameter over time, radiologic progression, development of worrisome features or high-risk stigmata, and surgical resection with final pathology when available. Based on the available dataset, cyst burden was categorized by lesion count, and cyst growth was further described using predefined thresholds of 2.5 mm or more per year, 5 mm or more per year, and 10 mm or more per year.

Definitions

Pancreatic cystic lesions detected during surveillance were considered to be presumed pancreatic precursor lesions on imaging, most commonly consistent with presumed branch-duct IPMNs in the appropriate clinical and radiologic context. For longitudinal analyses, the index cyst was defined as the dominant or most clinically relevant cystic lesion documented at baseline and subsequently followed up over time. Worrisome features and high-risk stigmata were defined according to the Kyoto guidelines for pancreatic cystic neoplasms.[29] Specifically, worrisome features included cyst diameter of 30 mm or greater, thickened or contrast-enhancing cyst wall, contrast-enhancing mural nodule less than 5 mm in diameter, MPD diameter of 5 to 9 mm, abrupt change in MPD caliber with distal pancreatic atrophy, lymphadenopathy, increased serum cancer antigen 19-9 level, and cyst growth rate of 2.5 mm or more per year. Acute pancreatitis judged to be related to the cyst and new-onset diabetes were also considered to be worrisome features. High-risk stigmata included obstructive jaundice related to a cystic lesion in the pancreatic head, a contrast-enhancing mural nodule with a diameter of 5 mm or more, and an MPD diameter of 10 mm or more. In this study, worrisome features or high-risk stigmata events were recorded according to the findings documented during surveillance imaging and summarized at baseline and during follow-up.

Statistical Analysis

Continuous variables were summarized as medians and IQRs and categorical variables as counts and percentages. Between-group comparisons were performed using the Wilcoxon rank sum test for continuous variables and the χ^2 or Fisher exact test for categorical variables, as appropriate. Time-to-event analyses for incident presumed IPMN and first worrisome features or high-risk stigmata events were performed using the Kaplan-Meier method, with curves representing 1 minus the Kaplan-Meier estimator and groups compared using the log-rank test. Incident presumed IPMN analyses included only participants without IPMN at baseline and considered the first lesion detected during surveillance as the event; participants with baseline lesions remained eligible for the other end point–specific analyses. Multivariable Cox proportional hazards regression was used to estimate hazard ratios (HRs) for incident presumed IPMN, adjusting for hereditary-risk group, age, sex, BMI, tobacco smoking status, and diabetes. Missingness was summarized by hereditary risk group; descriptive analyses used available cases, the Cox proportional hazards regression model used complete cases, and no values were imputed (eTable 4 in Supplement 1). Longitudinal trajectories of index cyst diameter and MPD diameter were modeled using mixed-effects models with natural cubic splines for time since cyst onset, including patient-specific random intercepts and slopes. Follow-up for longitudinal analyses was truncated at 60 months to improve model stability.

All statistical analyses were performed using R, version 4.4.1 (R Project for Statistical Computing). Two-sided $P < .05$ was considered significant.

Results

Study Population and Baseline Characteristics of Individuals With Presumed IPMNs

From January 2016 through December 2025, 1688 high-risk individuals undergoing surveillance were identified (median age, 56 years [IQR, 50-64 years]; 633 men [37.5%] and 1055 women [62.5%]), of whom 514 (30.5%) had at least 1 pancreatic cyst at baseline or during follow-up; 1174 (69.5%) remained cyst free. After exclusion of 18 patients with non-IPMN cysts (1 serous cystic neoplasm, 2 pseudocysts, 4 cases of chronic pancreatitis, 8 cases of hereditary pancreatitis, and 3 cystic neuroendocrine tumors), 496 (29.4%) had a presumed IPMN (171 men [34.5%], 325 women [65.5%]; median age, 61 years [IQR, 54-69 years]), of whom 364 (73.4%) had FPC and 132 (26.6%) were PGV carriers. Figure 1 summarizes cohort derivation and end point–specific analytic populations and reports the distribution of specific PGVs.

Among the 496 individuals with presumed IPMN, baseline demographic and clinical characteristics were broadly similar between the FPC and PGV groups (**Table**). Age, sex distribution, diabetes, smoking exposure, alcohol use, BMI, number of cysts, cyst location, and cyst growth categories did not significantly differ between groups. By contrast, a history of cancer was more frequent among PGV carriers than FPC individuals (64 of 130 [49.2%] vs 46 of 361 [12.7%]; $P < .001$), as was EUS use during surveillance (61 of 132 [46.2%] vs 121 of 364 [33.2%]; $P = .01$). In addition, the median follow-up from enrollment (overall, 17 months [IQR, 0-36 months]; FPC, 18 months [IQR, 0-40 months]; PGV, 14 months [IQR, 0-31 months]; $P = .03$) and from cyst diagnosis (overall, 13 months [IQR, 0-28 months]; FPC, 14 months [IQR, 0-31 months]; PGV, 11 months [IQR, 0-24 months]; $P = .050$) differed modestly between groups. Overall, the baseline morphologic phenotype of cysts appeared largely comparable between the 2 groups.

Sequence variant–specific baseline comparisons vs FPC are reported in eTable 1 in Supplement 1. While no differences were found in cyst number, location, growth, or distribution of worrisome features or high-risk stigmata across individual sequence variant subgroups, some heterogeneity was observed in selected clinical characteristics. For example, a history of cancer was more frequent in several sequence variant–defined groups, and differences in EUS utilization or follow-up duration were noted in some subgroups.

Table. Baseline Characteristics of the Study Population

Characteristic	Participants[a]			*P* value[b]
	With FPC (n = 364)	With PGV (n = 132)	Total (N = 496)	
Age, median (IQR), y	61 (55-69)	60 (52-69)	61 (54-69)	.26
Sex				
Female	231 (63.5)	94 (71.2)	325 (65.5)	.11
Male	133 (36.5)	38 (28.8)	171 (34.5)	
Diabetes				
No	330/361 (91.4)	123/130 (94.6)	453/491 (91.3)	.36
Yes	31/361 (8.6)	7/130 (5.4)	38/491 (7.7)	
History of pancreatitis				
No	357/361 (98.1)	129/130 (99.2)	486/491 (99.0)	.85
Yes	4/361 (1.1)	1/130 (0.8)	5/491 (1.0)	
History of any cancer				
No	315/361 (87.3)	66/130 (50.8)	381/491 (77.6)	<.001
Yes	46/361 (12.7)	64/130 (49.2)	110/491 (22.4)	
Smoker				
Former	58/361 (16.1)	21/130 (16.2)	79/491 (16.1)	.87
Never	272/361 (75.3)	99/130 (76.2)	371/491 (75.6)	
Current	31/361 (8.6)	10/130 (7.7)	41/491 (8.4)	
Alcohol use				
No	270/361 (74.8)	92/130 (70.8)	362/491 (73.7)	.65
Yes[c]				
<21 Units/wk	85/361 (23.5)	36/130 (27.7)	121/491 (24.6)	
>21 Units/wk	6/361 (1.7)	2/130 (1.5)	8/491 (1.6)	
BMI, median (IQR)	24.0 (21.9-26.8)	24.2 (22.3-27.2)	24.1 (21.9-26.9)	.42
EUS performed	121 (33.2)	61 (46.2)	182 (36.7)	.01
Follow-up, median (IQR), mo				
From enrollment	18 (0-40)	14 (0-31)	17 (0-36)	.03
Since cyst diagnosis	14 (0-31)	11 (0-24)	13 (0-28)	.05
Cysts, No.				
1	219 (60.2)	87 (65.9)	306 (61.7)	.43
2-5	100 (27.5)	34 (25.8)	134 (27.0)	
>5	16 (4.4)	2 (1.5)	18 (3.6)	
Missing data	29 (8.0)	9 (6.8)	38 (7.7)	
Worrisome features or high-risk stigmata				
Acute pancreatitis	1/21 (4.8)	0	1/28 (3.6)	.95
Cyst growth rate ≥2.5 mm/y	2/21 (9.5)	1/7 (14.3)	3/28 (10.7)	
MPD diameter, mm				
5-9	7/21 (33.3)	4/7 (57.1)	11/28 (39.3)	
≥10	2/21 (9.5)	1/7 (14.3)	3/28 (10.7)	
Cyst size, mm				
≥30	4/21 (19.0)	0	4/28 (14.3)	
≥30 + MPD diameter 5-9 mm	1/21 (4.8)	0	1/28 (3.6)	
Solid component	1/21 (4.8)	0	1/28 (3.6)	
Thick walls	3/21 (14.3)	1/7 (14.3)	4/28 (14.3)	
None	343 (94.2)	125 (94.7)	468 (94.4)	

(continued)

Table. Baseline Characteristics of the Study Population (continued)

Characteristic	Participants[a]			*P* value[b]
	With FPC (n = 364)	With PGV (n = 132)	Total (N = 496)	
Cyst location				
Tail	60 (16.5)	17 (12.9)	77 (15.5)	.14
Body	84 (23.1)	44 (33.3)	128 (25.8)	
Head	115 (31.6)	37 (28.0)	152 (30.6)	
Missing data	105 (28.8)	34 (25.8)	139 (28.0)	
Cyst growth, mm/y				
≥2.5				
No	352 (96.7)	126 (95.5)	478 (96.4)	.59
Yes	12 (3.3)	6 (4.5)	18 (3.6)	
≥5				
No	354 (97.3)	127 (96.2)	481 (97.0)	.56
Yes	10 (2.7)	5 (3.8)	15 (3.0)	
≥10				
No	363 (99.7)	132 (100)	495 (99.8)	>.99
Yes	1 (0.3)	0	1 (0.2)	

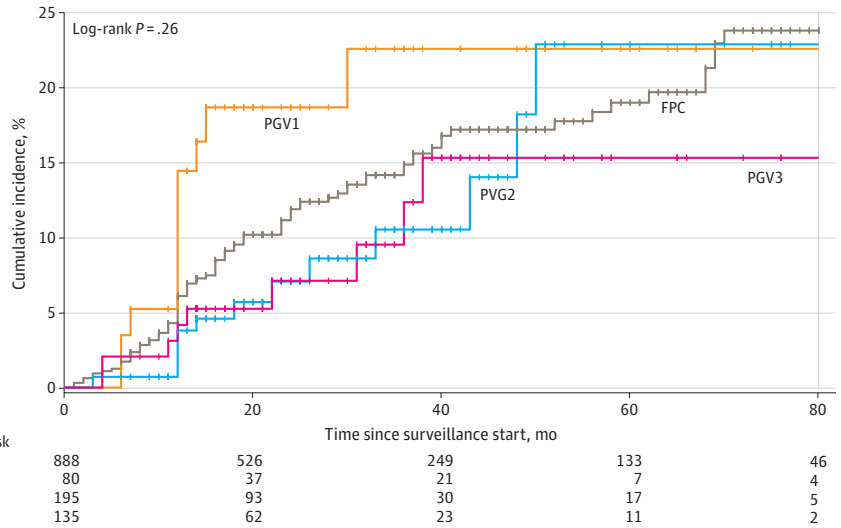
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EUS, endoscopic ultrasonography; FPC, familial pancreatic cancer; MPD, main pancreatic duct; PGV, pathogenic germline variant.

[a] Values are presented as number (percentage) or number/total number (percentage) of participants unless otherwise indicated.

[b] *P* values from Wilcoxon rank sum test (continuous variables) and χ^2 or Fisher exact tests (categorical variables).

[c] One unit of alcohol is defined as 10 g of pure ethanol, corresponding to approximately 1 standard drink (eg, 125 mL of wine, 330 mL of beer, or 25 mL of spirits).

Figure 2. Kaplan-Meier Curves Showing Cumulative Incidence of Incident Suspected Intraductal Papillary Mucinous Neoplasm (IPMN) Development According to Genetic Risk Category



No. at risk					
FPC	888	526	249	133	46
PGV1	80	37	21	7	4
PGV2	195	93	30	17	5
PGV3	135	62	23	11	2

Analysis was performed in the overall surveillance cohort of 1688 individuals after excluding 18 with non-IPMN cystic or pancreatic conditions and 372 with suspected IPMN already present at baseline. Curves represent 1 minus the Kaplan-Meier survival function among the remaining 1298 individuals free of suspected IPMN at study entry. Group differences were assessed using the log-rank test. FPC indicates familial pancreatic cancer; PGV1, pathogenic germline variant 1 (Peutz-Jeghers syndrome or *CDKN2A* sequence variant); PGV2, pathogenic germline variant 2 (*BRCA2* or *ATM* sequence variant); PGV3, pathogenic germline variant 3 (Lynch syndrome–associated genes or *BRCA1* or *PALB2* sequence variant).

Cumulative Incidence of Presumed Incident IPMN Development

For the analysis of presumed incident IPMN development, we considered the overall surveillance cohort after excluding the 18 individuals with non-IPMN cystic or pancreatic conditions and further excluding 372 patients who already had a presumed IPMN at baseline. The resulting at-risk cohort, therefore, comprised 1298 individuals free of presumed IPMNs at study baseline (76.9% of the total cohort), of whom 124 (9.6%) developed a suspected IPMN during surveillance. The resulting cumulative incidence of new presumed IPMNs increased progressively over time across all genetic risk categories (**Figure 2**), without significant differences between subgroups at univariable analysis. The complete-case multivariable analysis included 1245 participants and 123 incident events. Compared with FPC, hereditary risk group was not associated with incident presumed IPMN

development; the adjusted HR for PGV1 was 1.82 (95% CI, 0.97-3.43); for PGV2, 0.81 (95% CI, 0.45-1.45); and for PGV3, 0.70 (95% CI, 0.34-1.44). Older age was associated with higher incidence of IPMN (adjusted HR per year, 1.04; 95% CI, 1.02-1.05), whereas sex, BMI, smoking status, and diabetes were not associated with incident IPMN development (eFigure 1 in Supplement 1).

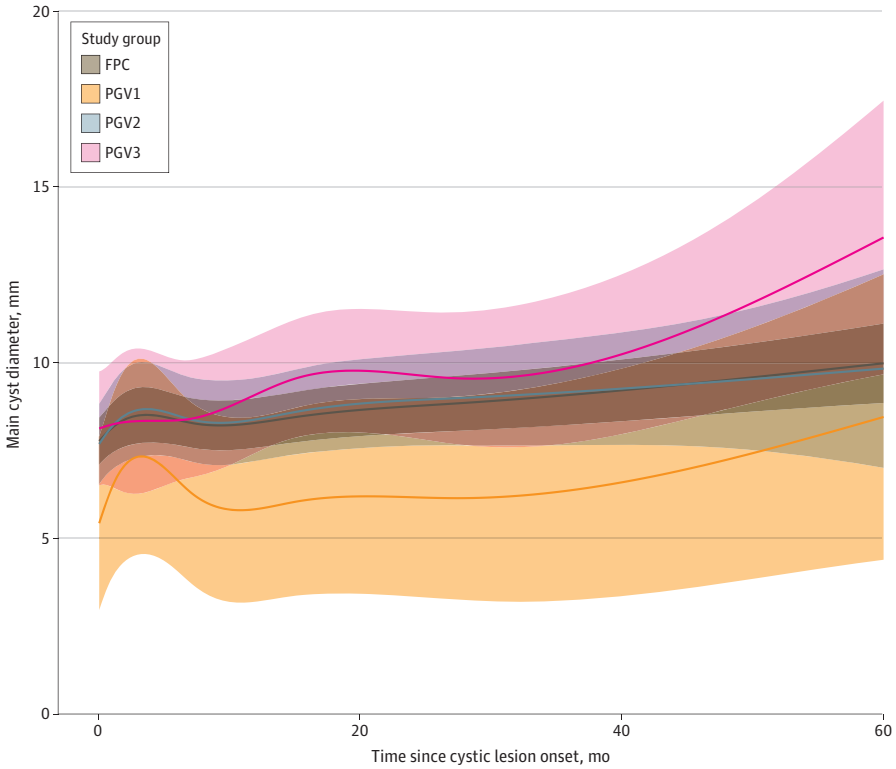
Longitudinal Evolution of Index Cyst and MPD Diameter

Across all study groups, the model-estimated diameter of the index cyst increased over time (eTable 2 in Supplement 1). However, longitudinal mixed-effects modeling did not reveal differences in cyst growth trajectories between FPC and PGV categories during the first 60 months of follow-up (time × group interaction: $\chi^2 = 14.4$; $df = 15$; $P = .49$). The 95% CIs broadly overlapped across groups at all evaluated time points (**Figure 3**). At 60 months, the model-estimated mean cyst diameter was 9.95 mm (95% CI, 8.81-11.08 mm) in the FPC group and 8.41 mm (95% CI, 4.33-12.49 mm) in the PGV1, 9.79 mm (95% CI, 6.95-12.63 mm) in the PGV2, and 13.54 mm (95% CI, 9.63-17.46 mm) in the PGV3 groups. Although PGV3 showed numerically larger estimates at later time points, uncertainty was substantial and no between-group difference emerged. By contrast, the MPD diameter remained stable overall during follow-up (**Figure 4**), with no evidence of differential longitudinal evolution among FPC and PGV categories (time × group interaction: $\chi^2 = 4.35$; $df = 15$; $P > .99$). Model-estimated MPD values were similar across all groups, and 95% CIs overlapped throughout the observation period, supporting a largely comparable morphologic course across genetic risk categories (eTable 3 in Supplement 1).

Progression to Worrisome Features or High-Risk Stigmata

At baseline, of the 496 patients with suspected IPMNs, 16 (3.2%) already met criteria for worrisome features (13 [2.6%]) or high-risk stigmata (3 [0.6%]), and 13 additional patients (2.6%) developed at least 1 worrisome feature or high-risk stigmata event during follow-up. The cumulative incidence of

Figure 3. Line Graph Showing Longitudinal Growth of Pancreatic Cystic Lesions by Study Group



Model-estimated trajectories of the index cyst diameter over time are shown for the groups with familial pancreatic cancer (FPC), pathogenic germline variant 1 (PGV1 [Peutz-Jeghers syndrome or *CDKN2A* sequence variant]), PGV2 (*BRCA2* or *ATM* sequence variant), and PGV3 (Lynch syndrome–associated genes or *BRCA1* or *PALB2* sequence variant). Estimates were obtained from a linear mixed-effects model with natural cubic splines for months since cyst onset, including patient-specific random intercepts and slopes. Shading represents 95% CIs. Follow-up was truncated at 60 months to improve model stability.

worrisome features or high-risk stigmata during surveillance did not differ significantly across patient categories. Although early visual differences between PGV subgroups were observed, interpretation of late follow-up curves was limited by the small number of individuals remaining at risk in some subgroups (eFigure 2 in Supplement 1).

Individual Trajectories and Surgical Outcomes

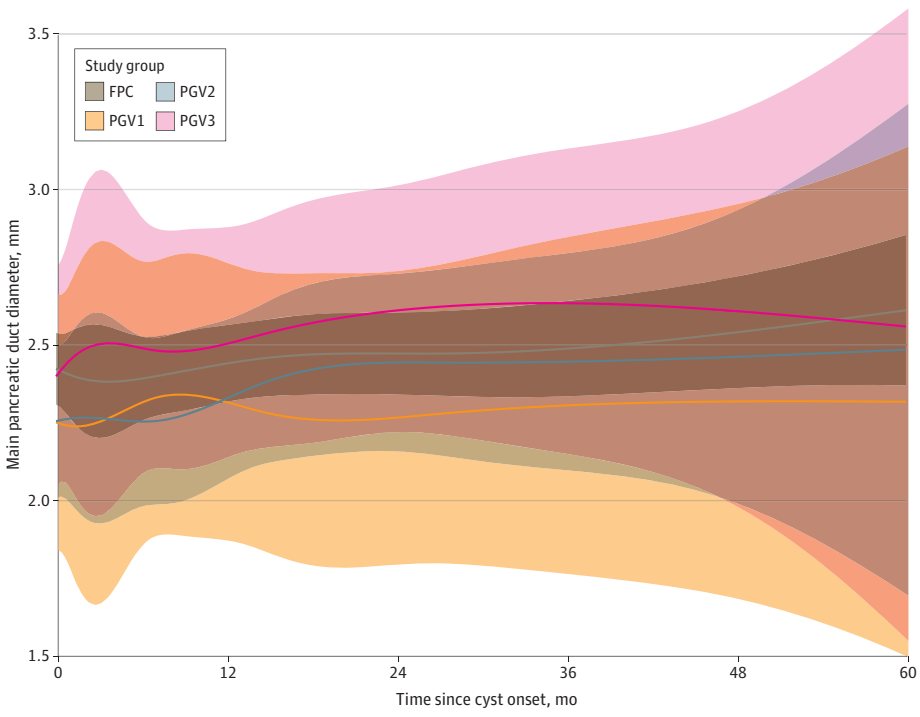
A swimming plot showed marked heterogeneity in disease evolution (eFigure 3 in Supplement 1). Worrisome features were more frequent than high-risk stigmata and generally occurred earlier during surveillance. EUS examinations were variably distributed over follow-up and were not consistently followed by surgery.

Only 2 patients (0.4%) underwent surgical resection. One patient (in the PGV1 group, with Peutz-Jeghers syndrome) had an invasive IPMN-associated carcinoma staged as pT1cN0 on final pathology, whereas the other (an FPC case) had a mixed-type IPMN with low-grade dysplasia.

Discussion

In this multicenter cohort study, presumed IPMNs showed broadly similar baseline features across genetically defined high-risk subgroups. Among individuals without a cyst at baseline, the cumulative onset of new incident lesions increased over time without significant between-subgroup differences, whereas age emerged as a more relevant factor associated with cyst development compared with genetics. Once detected, presumed IPMNs also had no differential short-term to midterm evolution according to genetic background, as neither cyst growth nor MPD evolution differed significantly across subgroups. Despite numerically higher incidence and smaller cyst and MPD diameter estimates in the PGV1 group, overlapping 95% CIs and the small subgroup size precluded a clear interpretation; routine EUS use at 2 of the centers did not appear to fully explain this pattern (eTable 5 in Supplement 1). Overall, imaging phenotype and interval changes appeared to be more

Figure 4. Line Graph Showing Longitudinal Changes in Main Pancreatic Duct Diameter by Study Group



Model-estimated trajectories of main pancreatic duct diameter over time are shown for the familial pancreatic cancer (FPC), pathogenic germline variant 1 (PGV1 [Peutz-Jeghers syndrome or *CDKN2A* sequence variant]), PGV2 (*BRCA2* or *ATM* sequence variant), and PGV3 (Lynch syndrome–associated genes or *BRCA1* or *PALB2* sequence variant) groups. Estimates were obtained from a linear mixed-effects model with natural cubic splines for months since cyst onset, including patient-specific random intercepts and slopes. Shading indicates 95% CIs. Follow-up was truncated at 60 months to improve model stability.

informative than genetic subgrouping alone in defining the early course of these lesions, although the absence of statistical significance does not imply biological equivalence.

These findings should be interpreted in the context of current literature, which consistently indicates that pancreatic cysts are common in individuals at high PC risk but remains inconclusive regarding whether their natural history truly differs across familial and sequence variant–defined subgroups. Konings et al[9] found that individuals with FPC were more likely to harbor cysts with a diameter of 10 mm or greater, whereas lesions in sequence variation carriers were more likely to progress. Overbeek et al[13] reported faster IPMN growth in high-risk individuals, particularly in those with PGVs. By contrast, our data do not support a clear separation in either incident lesion development or short-term to midterm morphologic evolution across the high-risk groups analyzed, supporting that a homogenous policy in terms of follow-up imaging once a presumed IPMN becomes detectable is likely to be adequate.

A similarly consistent message emerged from the longitudinal analyses. Neither index cyst diameter nor MPD diameter showed significantly different trajectories across groups during follow-up, and progression to worrisome features or high-risk stigmata was infrequent overall. Although individual heterogeneity was evident, few patients developed relevant radiologic progression and only 2 ultimately underwent surgery. The higher prevalence of IPMNs compared with many population-based estimates[30] may reflect both inherited susceptibility and repeated high-sensitivity imaging, whereas the few progressive events suggest that many detected lesions are indolent. Differences with results of prior series[8] likely reflect the heterogenous study population and methodologic variation, including baseline cyst size thresholds.

These findings should be interpreted cautiously. The study may have been underpowered to detect modest differences at later time points within smaller subgroups. This is especially relevant given the relatively short median follow-up, the limited number of patients contributing to the tail of the longitudinal models, and the biological heterogeneity within the PGV category, which in this cohort was largely attributable to *BRCA1-BRCA2* carriers.

Few studies have explored *BRCA* carriers' pancreatic imaging findings specifically; thus, available data remain limited.[31-33] Evidence is even more limited for carriers of other pathogenic variants, such as *CDKN2A*, *ATM*, or *PALB2*, for whom data on cyst behavior and malignant transformation remain sparse due to the rarity of these conditions.[34,35] Moreover, the higher prevalence of previous neoplastic disease among PGV carriers in the cohort in our study likely reflects the broader multiorgan penetrance of several susceptibility genes rather than a feature directly related to pancreatic cyst biology and reinforces the biological heterogeneity encompassed within the PGV category.

Our findings also support a broader conceptual point. In high-risk individuals, PC risk may not be fully captured by visible cyst progression alone. This is consistent with the observation that concomitant PC may more often arise from pancreatic intraepithelial neoplasias than from true IPMN-derived carcinoma in surveillance cohorts.[36] Accordingly, surveillance of the pancreatic parenchyma as a whole may be at least as important as lesion-centered monitoring of cyst size or growth.

A collateral implication of our findings is that the rate of low-yield surgery was low (2 of 496 patients [0.4%]), in line with previous reports of cohorts of high-risk individuals[37] and in surgical series of pancreatic cysts.[38] This may indicate that imaging-based management remains pragmatically applicable in the short term even in genetically enriched populations provided that decision-making continues to rely primarily on morphologic characteristics, interval evolution, and overall clinical context rather than on germline status alone.

Limitations

This study has several limitations. Surveillance strategies were not uniform across centers, and lesion classification was based on imaging, with histologic confirmation available only in resected cases. Different end points required partially overlapping analytic cohorts, and subgroup analyses were

constrained by small numbers, particularly at later follow-up. In addition, the short median follow-up time (17 months) and its modest asymmetry between groups may have obscured delayed or group-specific differences and precluded reliable assessment of malignant neoplasm progression; therefore, nonsignificant findings should not be interpreted as equivalence. The lack of an external nonhereditary comparator limits broader contextual interpretation. Accordingly, our findings apply primarily to the short-term to midterm phase of surveillance. While some previous studies suggest that the most relevant cyst changes may occur relatively early,[6,9,13] our data do not exclude the possibility that clinically meaningful divergence across genetic subgroups may emerge only after longer follow-up, over 5 to 10 years.

Conclusions

In this multicenter cohort study of individuals at high-risk of PC undergoing pancreatic surveillance, the incidence and short-term progression of presumed IPMNs did not differ significantly across hereditary risk groups, whereas older age was associated with incident cyst development. These findings suggest that imaging phenotype and interval change should remain central to surveillance, while gene-specific considerations and longer-term data remain important.

ARTICLE INFORMATION

Accepted for Publication: July 30, 2026.

Published: September 23, 2026. doi:10.1001/jamanetworkopen.2026.35610

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Conflict of Interest Disclosures: Dr Coluccio reported receiving personal fees from Boston Scientific, Olympus, and Fujifilm outside the submitted work. Dr De Marchi reported receiving personal fees from Zenas BioPharma outside the submitted work. Prof Panzuto reported receiving personal fees from Ipsen, Istituto Gentili, Novartis, and Mylan (Viatris) outside the submitted work. Dr Di Matteo reported receiving personal fees from Fujifilm for preceptorship, proctorship, and consulting and grants from Boston Scientific for preceptorship outside the submitted work. Prof Paiella reported receiving personal fees from Alpha Tau Medical, ClearNote Health, and Fresenius Kabi outside the submitted work. No other disclosures were reported.

Group Information: The Italian Registry of Families at Risk of Pancreatic Cancer (IRFARPC) Study Group members appear in Supplement 2.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the investigators and collaborators of the IRFARPC for their contribution to patient enrollment, data collection, and registry activities. No nonauthor contributors were compensated for this work.

Additional Information: ChatGPT 4 (OpenAI) was used on May 15, 2026, to assist with language editing and readability during manuscript preparation. It was not used for data analysis, interpretation, or generation of results, figures, tables, or references. All output was reviewed and edited by the authors, who take responsibility for the integrity of the content generated.

REFERENCES

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11):2913-2921. doi:10.1158/0008-5472.CAN-14-0155

2. Klatte DCF, Boekestijn B, Onnekink AM, et al; Dutch Pancreatic Cancer Group. Surveillance for pancreatic cancer in high-risk individuals leads to improved outcomes: a propensity score-matched analysis. *Gastroenterology*. 2023;164(7):1223-1231.e4. doi:10.1053/j.gastro.2023.02.032

3. Klatte DCF, Boekestijn B, Wasser MNJM, et al. Pancreatic cancer surveillance in carriers of a germline *CDKN2A* pathogenic variant: yield and outcomes of a 20-year prospective follow-up. *J Clin Oncol*. 2022;40(28):3267-3277. doi:10.1200/JCO.22.00194

4. Blackford AL, Canto MI, Dbouk M, et al. Pancreatic cancer surveillance and survival of high-risk individuals. *JAMA Oncol*. 2024;10(8):1087-1096. doi:10.1001/jamaoncol.2024.1930

5. Canto MI, Almario JA, Schulick RD, et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. *Gastroenterology*. 2018;155(3):740-751.e2. doi:10.1053/j.gastro.2018.05.035

6. Dbouk M, Katona BW, Brand RE, et al. The Multicenter Cancer of Pancreas Screening Study: impact on stage and survival. *J Clin Oncol*. 2022;40(28):3257-3266. doi:10.1200/JCO.22.00298

7. Paiella S, Capurso G, Carrara S, et al. Outcomes of a 3-year prospective surveillance in individuals at high risk of pancreatic cancer. *Am J Gastroenterol*. 2024;119(4):739-747. doi:10.14309/ajg.0000000000002546

8. Aijazi M, Fasanella KE, McGrath K, Smith LM, Singhi AD, Brand RE. Pancreatic cysts greater than 1 cm are associated with an increased risk for developing pancreatic cancer in individuals from pancreatic-cancer prone kindreds undergoing surveillance. *Pancreas*. 2024;53(4):e350-e356. doi:10.1097/MPA.0000000000002312

9. Konings IC, Harinck F, Poley JW, et al; Dutch Research Group on Pancreatic Cancer Surveillance in High-Risk Individuals. Prevalence and progression of pancreatic cystic precursor lesions differ between groups at high risk of developing pancreatic cancer. *Pancreas*. 2017;46(1):28-34. doi:10.1097/MPA.0000000000000725

10. Kromrey ML, Bülow R, Hübner J, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut*. 2018;67(1):138-145. doi:10.1136/gutjnl-2016-313127

11. Chang YR, Park JK, Jang JY, Kwon W, Yoon JH, Kim SW. Incidental pancreatic cystic neoplasms in an asymptomatic healthy population of 21 745 individuals: large-scale, single-center cohort study. *Medicine (Baltimore)*. 2016;95(51):e5535. doi:10.1097/MD.0000000000005535

12. Harinck F, Konings IC, Kluijt I, et al; Dutch Research Group on Pancreatic Cancer Surveillance in High-Risk Individuals. A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. *Gut*. 2016;65(9):1505-1513. doi:10.1136/gutjnl-2014-308008

13. Overbeek KA, Koopmann BDM, Levink IJM, et al; Dutch Familial Pancreatic Cancer Surveillance Study Work Group. Intraductal papillary mucinous neoplasms in high-risk individuals: incidence, growth rate, and malignancy risk. *Clin Gastroenterol Hepatol*. 2024;22(1):62-71.e7. doi:10.1016/j.cgh.2023.03.035

14. Dbouk M, Brewer Gutierrez OI, Lennon AM, et al. Guidelines on management of pancreatic cysts detected in high-risk individuals: an evaluation of the 2017 Fukuoka guidelines and the 2020 International Cancer of the Pancreas Screening (CAPS) Consortium statements. *Pancreatology*. 2021;21(3):613-621. doi:10.1016/j.pan.2021.01.017

15. Paiella S, Salvia R, De Pastena M, et al. Screening/surveillance programs for pancreatic cancer in familial high-risk individuals: a systematic review and proportion meta-analysis of screening results. *Pancreatology*. 2018;18(4):420-428. doi:10.1016/j.pan.2018.04.002

16. Diwan EA, Saba H, Blackford AL, et al. Mild dilatation of the main pancreatic duct is a risk factor for progression to pancreatic cancer in high-risk individuals. *Gastro Hep Adv*. 2025;4(10):100802. doi:10.1016/j.gastha.2025.100802

17. Pozzi Mucelli RM, Vujasinovic M, Farah-Mwais A, et al. Performance of MRI-based surveillance for high-risk individuals for pancreatic cancer. *Eur J Radiol*. 2025;191:112275. doi:10.1016/j.ejrad.2025.112275

18. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808. doi:10.1136/bmj.39335.541782.AD

20. Archibugi L, Casciani F, Carrara S, et al. The Italian Registry of Families at Risk for Pancreatic Cancer (IRFARPC): implementation and evolution of a national program for pancreatic cancer surveillance in high-risk individuals. *Fam Cancer*. 2024;23(3):373-382. doi:10.1007/s10689-024-00366-3

21. Paiella S, Capurso G, Cavestro GM, et al. Results of first-round of surveillance in individuals at high-risk of pancreatic cancer from the AISP (Italian Association for the Study of the Pancreas) Registry. *Am J Gastroenterol*. 2019;114(4):665-670. doi:10.1038/s41395-018-0414-z

22. Paiella S, Secchettin E, Archibugi L, et al. Discovering hereditary risk through surveillance: a prospective genetic analysis of individuals with familial pancreatic cancer. *United European Gastroenterol J*. 2026;14(1):e70187. doi:10.1002/ueg2.70187

23. Stoffel EM, McKernin SE, Brand R, et al. Evaluating susceptibility to pancreatic cancer: ASCO provisional clinical opinion. *J Clin Oncol*. 2019;37(2):153-164. doi:10.1200/JCO.18.01489

24. Calderwood AH, Sawhney MS, Thosani NC, et al. American Society for Gastrointestinal Endoscopy guideline on screening for pancreatic cancer in individuals with genetic susceptibility: methodology and review of evidence. *Gastrointest Endosc*. 2022;95(5):827-854.e3. doi:10.1016/j.gie.2021.12.002

25. Goggins M, Overbeek KA, Brand R, et al; International Cancer of the Pancreas Screening (CAPS) consortium. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020;69(1):7-17. doi:10.1136/gutjnl-2019-319352

26. Kasuga A, Okamoto T, Udagawa S, et al. Molecular features and clinical management of hereditary pancreatic cancer syndromes and familial pancreatic cancer. *Int J Mol Sci*. 2022;23(3):1205. doi:10.3390/ijms23031205

27. Solomon S, Das S, Brand R, Whitcomb DC. Inherited pancreatic cancer syndromes. *Cancer J*. 2012;18(6):485-491. doi:10.1097/PPO.0b013e318278c4a6

28. Klatte DCF, Wallace MB, Löhr M, Bruno MJ, van Leerdam ME. Hereditary pancreatic cancer. *Best Pract Res Clin Gastroenterol*. 2022;58-59:101783. doi:10.1016/j.bpg.2021.101783

29. Ohtsuka T, Fernandez-Del Castillo C, Furukawa T, et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. *Pancreatology*. 2024;24(2):255-270. doi:10.1016/j.pan.2023.12.009

30. Wong P, Pollini T, Hernandez S, et al. Prevalence and size-based risk categorization of pancreatic cysts among asymptomatic individuals with screening MRI. *JAMA Netw Open*. 2026;9(3):e260983. doi:10.1001/jamanetworkopen.2026.0983

31. Raitses-Gurevich M, Tau N, Moss Massasa EE, et al. Exploring pancreatic variability in *BRCA* carriers vs non-carriers: a diffusion tensor MRI study. *Eur J Radiol*. 2026;194:112483. doi:10.1016/j.ejrad.2025.112483

32. Cao CX, Sharib JM, Blanco AM, et al. Abdominal imaging of pancreatic cysts and cyst-associated pancreatic cancer in *BRCA1/2* mutation carriers: a retrospective cross-sectional study. *J Am Coll Surg*. 2020;230(1):53-63.e1. doi:10.1016/j.jamcollsurg.2019.09.019

33. Chahla E, Cheesman A, Mahon SM, et al. Frequency and significance of abnormal pancreatic imaging in patients with *BRCA1* and *BRCA2* genetic mutations. *Scientifica (Cairo)*. 2016;2016:5619358. doi:10.1155/2016/5619358

34. Hutchings D, Jiang Z, Skaro M, et al. Histomorphology of pancreatic cancer in patients with inherited ATM serine/threonine kinase pathogenic variants. *Mod Pathol*. 2019;32(12):1806-1813. doi:10.1038/s41379-019-0317-6

35. Skaro M, Nanda N, Gauthier C, et al. Prevalence of germline mutations associated with cancer risk in patients with intraductal papillary mucinous neoplasms. *Gastroenterology*. 2019;156(6):1905-1913. doi:10.1053/j.gastro.2019.01.254

36. Gonda TA, Cahen DL, Farrell JJ. Pancreatic cysts. *N Engl J Med*. 2024;391(9):832-843. doi:10.1056/NEJMra2309041

37. Paiella S, Secchettin E, Lionetto G, et al. Surveillance of individuals at high risk of developing pancreatic cancer: a prevalence meta-analysis to estimate the rate of low-yield surgery. *Ann Surg*. 2024;279(1):37-44. doi:10.1097/SLA.0000000000006094

38. Salvia R, Burelli A, Nepi A, et al. Pancreatic cystic neoplasms: still high rates of preoperative misdiagnosis in the guidelines and endoscopic ultrasound era. *Surgery*. 2023;174(6):1410-1415. doi:10.1016/j.surg.2023.07.016

SUPPLEMENT 1.

eTable 1. Clinical, Surveillance, and Cyst Characteristics According to Specific Pathogenic Germline Variant
eTable 2. Model-Estimated Index Cyst Diameter Over Follow-Up by Hereditary Risk Group
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SUPPLEMENT 2.

Italian Registry of Families at Risk of Pancreatic Cancer Study Group

SUPPLEMENT 3.

Data Sharing Statement