original report

Deleterious Germline Mutations Are a Risk Factor for Neoplastic Progression Among High-Risk Individuals Undergoing Pancreatic Surveillance

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abstract

PURPOSE To compare the risk of neoplastic progression by germline mutation status versus family history without a known germline mutation (familial risk) among individuals with an increased risk for pancreatic cancer who are undergoing surveillance.

METHODS Of 464 high-risk individuals in the Cancer of the Pancreas Screening program at Johns Hopkins Hospital who were undergoing pancreatic surveillance, 119 had a known deleterious germline mutation in a pancreatic cancer susceptibility gene; 345 met family history criteria for pancreatic surveillance but were not known to harbor a germline mutation. We used next-generation sequencing to identify previously unrecognized germline mutations among these 345 individuals. We compared the development of pancreatic cancer, high-grade dysplasia, or clinically worrisome features, adjusting for competing mortality, among all germline mutation carriers with the risk of progression in a cohort without a known germline mutation.

RESULTS Fifteen (4.3%) of 345 individuals classified as having familial risk had a previously unrecognized pancreatic cancer susceptibility gene mutation (nine that involved *ATM*, two *BRCA2*, one *BRCA1*, one *PALB2*, one *TP53*, and one *CPA1*). The cumulative incidence of pancreatic cancer, high-grade dysplasia, or worrisome features on pancreatic imaging was significantly higher in the germline mutation risk group (n = 134) than in the familial risk group (n = 330 [for pancreatic cancer, hazard ratio, 2.85; 95% CI, 1.0 to 8.18; P = .05]).

CONCLUSION The cumulative incidence of pancreatic cancer is significantly higher among individuals with an identifiable deleterious germline mutation in a pancreatic cancer susceptibility gene than it is among individuals with a strong family history but no identified mutation. Gene testing of individuals who meet criteria for pancreatic surveillance on the basis of their family history may better define those most at risk for neoplastic progression.

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INTRODUCTION

Pancreatic ductal adenocarcinoma is the third most common cause of cancer death in the United States, with a 5-year survival of only approximately 8%.[1] Most patients with pancreatic cancer are diagnosed at an advanced stage, and patients diagnosed with advanced disease have a 5-year survival rate of less than 5% and a median survival of less than 12 months.[2] Early detection of pancreatic cancer and its precursors may be the most effective way of reducing mortality as a result of the disease.[3,4] The International Cancer of the Pancreas Screening (CAPS) Consortium[5] recommends selective screening for high-risk individuals (HRIs) with an estimated 5% or higher lifetime risk of developing pancreatic cancer. Some patients are candidates for pancreatic surveillance because they carry a deleterious germline mutation in a known familial pancreatic cancer susceptibility gene (including *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *STK11*, *PRSS1*, and *TP53*).[6-14] Two additional genes that encode for pancreatic enzymes, *CPA1* (a known pancreatitis susceptibility gene) and *CPB1*, also have been implicated as pancreatic cancer susceptibility genes.[15] Of these genes, the lifetime risk of developing pancreatic cancer is highest among individuals who carry germline mutations in *PRSS1*,[13] *STK11*,[10] and *CDKN2A*.[16] Despite our improved understanding of the genetic basis for the aggregation of pancreatic cancer in families, inherited gene mutations explain only a small portion (less than 20%) of the familial clustering of pancreatic cancer.[17]

Most individuals in the CAPS program undergo pancreatic screening on the basis of their strong family history of pancreatic cancer. The estimated risk of developing pancreatic cancer among individuals with a family history increases with the number of affected first-degree relatives (FDRs).[18] On the basis of these risks, pancreatic surveillance is recommended for those with at least one FDR and one second-degree relative (SDR) with pancreatic cancer.[5]

ASSOCIATED CONTENT

Appendix

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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In many programs, surveillance commences at age 50 years for these germline mutation carriers (excluding *STK11*, *CDKN2A*, and *PRSS1*) and at age 55 years for those whose risk is solely on the basis of their family cancer history.[18] Knowledge of an individual's gene mutation status may help to better estimate pancreatic cancer risk. For example, a European study of 411 HRIs detected pancreatic cancer in 13 (7.3%) of 178 *CDKN2A* mutation carriers compared with three (1.4%) of 214 individuals at risk on the sole basis of their family history.[3] This study did not routinely gene test patients in the family history group, so some may have been misclassified.

We and others have reported that deleterious germline mutations in pancreatic cancer susceptibility genes are commonly (5% to 10%) identified in patients with pancreatic cancer.[14,19-21] Patients with a family history of pancreatic cancer are approximately twice as likely to have such a germline mutation as those without a family history, although most germline mutation carriers who develop pancreatic cancer do not report a family history of pancreatic cancer and do not have family histories that suggest an inherited cancer syndrome.[14,19] Some patients who undergo pancreatic surveillance because of their family history may carry a germline mutation in a pancreatic cancer susceptibility gene. The purpose of the current study was to determine whether individuals with a deleterious germline mutation are at greater risk of progression than individuals with a strong family history of pancreatic cancer but no known germline mutation.

METHODS

Study Design and Patients

This study included 464 HRIs who were prospectively enrolled in the CAPS studies[4,22-24] (ClinicalTrials.gov identifiers: NCT00438906, NCT00714701, and NCT02000089) between 1998 and 2017 (Data Supplement) who provided samples for germline DNA analysis. The current CAPS5 study enrolls individuals who meet recommended guidelines for pancreatic surveillance.[5] These guidelines recommend surveillance for individuals who meet familial risk criteria (ie, FDRs with pancreatic cancer) from familial pancreatic cancer kindred (ie, two FDRs with pancreatic cancer), in other words, someone who has at least one FDR and one SDR with pancreatic cancer who are at least 55 years old or 10 years younger than the youngest with pancreatic cancer in the family. The enrollment criteria for CAPS4 (2009 to 2013) was similar to CAPS5 (CAPS5 enrollment includes *ATM* mutation carriers). Earlier CAPS studies required a stronger family history of pancreatic cancer among familial risk individuals for enrollment (having either two FDRs or one FDR and two SDRs with pancreatic cancer), and the age eligibility was younger (40 years for CAPS1 [1998 to 2001] and 50 years for CAPS2 [2001 to 2004] and CAPS3 [2006 to 2009]). For individuals with a germline mutation in a familial pancreatic cancer susceptibility gene, pancreatic surveillance is recommended for those who are at least 30 years old who meet clinical criteria for Peutz-Jeghers syndrome and those with a germline mutation in *BRCA2*, *PALB2*, *CDKN2A*, *ATM*, *BRCA1*, *MLH1*, *MSH2*, and *MSH6* and who are at least 50 years old or 10 years younger than the youngest with pancreatic cancer in the family. Patients with *CDKN2A* mutations are recommended for pancreatic screening (typically starting at age 40 years) irrespective of family history, whereas for those with *BRCA2*, *ATM*, *PALB2*, and mismatch repair gene mutations, it is recommended if there is a family history of pancreatic cancer in a close blood relative (FDR or SDR). Pancreatic surveillance also is recommended for individuals with hereditary pancreatitis, who are at least 50 years old, or who are 20 years since their first attack of pancreatitis.

A detail description of follow-up and clinical management of HRIs has been published previously.[4] Pancreatic surveillance is up to date for most patients in the CAPS program. If pancreatic surveillance is not up to date, follow-up to determine status (alive or not) is determined from the medical record, CAPS study team communications, or updates provided by participation in the National Familial Pancreas Tumor Registry.[25] For patients who continued surveillance beyond their baseline visit, follow-up was up to date for 94%; status within the past 2 years was known for 96% (all but 20 patients). The characteristics of these 20 patients were similar to the overall study population (mean $\pm$ standard deviation age, 59 $\pm$ 10 years, 13 familial, seven germline, seven male). Patients not able to continue surveillance in CAPS are offered referral to a more local screening program. Two patients enrolled in CAPS were diagnosed with pancreatic cancer at their baseline evaluation; both had symptoms attributable to their pancreatic cancer, were not considered to have screen-detected cancer, and were not included in the incidence analysis. The final diagnoses were made by surgical pathology or cytology. All pathologic diagnoses were made by an expert pathologist (R.H.H.) using the WHO classification system,[26] including patients who underwent pancreatic resection at another institution. If the pathologic specimen had multiple pancreatic lesions, the highest pathologic grade present was used for end point analysis. Worrisome features found by pancreatic imaging (either main pancreatic duct dilation of 5 to 9 mm, pancreatic cyst size greater than or equal to 3 cm, cyst growth rate greater than or equal to 5 mm diameter/2 years, thickened enhanced cyst walls, nonenhanced mural nodules, abrupt change in main pancreatic duct caliber with distal pancreatic atrophy, or lymphadenopathy) were defined according to revisions of international consensus Fukuoka guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas.[27] This study was approved by the Johns Hopkins

TABLE 1. Identification of Previously Unrecognized Germline Mutations in Pancreatic Cancer Susceptibility Genes

Pt ID	Age†	Sex	Race	Gene	Chr Position	Amino Acid Change	Nucleotide Change	Function	Zygosity	Personal History of Cancer	FDR, No.	SDR, No.	Other Family History of Cancer
4*04	61	M	White	*BRCA2*	Chr13: 32914438	p.S1982Rfs	c.5946delT	Frameshift	Hetero	Prostate, thyroid	1	1	Stomach
2*82	45	M	White	*BRCA2*	Chr13: 32914438	p.S1982Rfs	c.5946delT	Frameshift	Hetero	Melanoma	1	2	NA
4*22	63	M	White	*BRCA1*	Chr17: 41276047-8	p.E23fs*17	c.68_69delAG	Frameshift	Hetero	None	2	0	None
1*38	65	M	White	*PALB2*	Chr16: 23619279	p.R1086X	c.3256C>T	Nonsense	Hetero	None	3	0	Breast, colon, endometrial, esophageal, gallbladder, stomach, liver, lung, uterine
3*87	51	F	White	*ATM*	Chr11: 108196143	p.R2227C	c.6679C>T	Missense	Hetero	None	1	1	Colon, prostate
3*12	58	F	White	*ATM*	Chr11: 108214103-6	Splice	c.*5_*8delGTGA	Noncoding	Hetero	None	1	3	Bladder, prostate
3*89	65	M	White	*ATM*	Chr11: 108236086	p.R3008C	c.9022C>T	Missense	Hetero	None	2	0	Colon, breast, stomach
4*55	50	F	White	*ATM*	Chr11: 108139228-9	p.A911delinsRLfs	c.2730_2731insAG	Frameshift	Hetero	None	1	1	None
3*68	60	F	White	*ATM*	Chr11: 108206686	p.K2756X	c.8266A>T	Nonsense	Hetero	None	2	3	Breast, colon, lung, stomach
1*02	59	M	White	*ATM*	Chr11: 108206686	p.K2756X	c.8266A>T	Nonsense	Hetero	None	2	2	Breast, colon, lung, lymphoma, prostate, stomach
1*66	70	M	White	*ATM*	Chr11: 108196143	p.R2227C	c.6679C>T	Missense	Hetero	Prostate	2	0	Brain, colon, lung, prostate, uterine
2*16	55	F	White	*ATM*	Chr11: 108284282	p.V1268Xfs	c.3802delG	Frameshift	Hetero	None	2	0	Breast, colon, stomach
1*10	60	M	White	*ATM*	Chr11: 108117816-9	p.E343Ifs	c.1027_1030delGAAA	Frameshift	Hetero	Melanoma	1	3	Breast, melanoma
2*48	60	F	White	*CPA1*	Chr7:130023579	p.D214Y	c.640G>T	Missense	Hetero	None	2	1	Ovarian
2*66	77	M	White	*TP53*	Chr17: 7577091	p.R283C	c.847C>T	Missense	Hetero	None	2	1	None

Abbreviations: Chr, chromosome; FDR, first-degree relative; Hetero, heterozygous; NA, not available; Pt ID, patient identifier; SDR, second-degree relative.
†In years at most recent follow-up.

TABLE 2. Characteristics of Cancer of the Pancreas Screening Participants at Baseline According to Germline Mutation Status

Characteristic	Risk Group		P
	Family History Only (n = 330)	Germline Mutation (n = 134)	
Age, years			
Mean ± SD	57.83 ± 10.18	53.98 ± 10.64	< .001
Median (range)	57.83 (22.38-83.49)	54.07 (26.77-76.27)	< .001
Race			.075
Asian	6 (1.8)	0 (0)	
Black	8 (2.4)	0 (0)	
Hispanic	1 (0.3)	0 (0)	
White	315 (95.5)	134 (100)	
Sex			.123
Female	172 (52.1)	81 (60.4)	
Male	158 (47.9)	53 (39.6)	
BMI, kg/m^2, mean (range)	26.7 (14.9-55.6)	26.55 (17.5-40.9)	.667
Smoker			.829
No	217 (65.8)	90 (67.2)	
Yes	113 (34.2)	44 (32.8)	
Diabetes			.496
No	295 (89.4)	123 (91.8)	
Yes	35 (10.6)	11 (8.2)	
Pancreatitis			.182
No	320 (97)	126 (94)	
Yes	10 (3)	8 (6)	
Alcohol use			.473
None or occasional	154 (46.7)	68 (50.7)	
Regular or heavy	176 (53.3)	66 (49.3)	
Worrisome features at baseline			.182
No	320 (97)	126 (94)	
Yes	10 (3)	8 (6)	
No. of FDRs			< .001
0	0 (0)	35 (26.1)	
1	180 (54.5)	72 (53.7)	
≥ 2	150 (45.5)	27 (20.1)	

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: BMI, body mass index; FDR, first-degree relative; SD, standard deviation.

institutional review board, and written informed consent was provided from all enrolled patients.

DNA Extraction

Genomic DNA was extracted from either peripheral blood mononuclear cells or frozen normal tissue from pancreatic resection specimens (duodenum, spleen, or pancreas) as previously described.[19]

Next-Generation Sequencing

Known pancreatic cancer susceptibility genes (BRCA2, ATM, PALB2, BRCA1, CDKN2A, MLH1, MSH2, PRSS1, STK11, TP53, CPA1, and CPB1), the cancer susceptibility genes MSH6 and BUB1B (Appendix Table A1, online only), and two candidate genes *CEL* and *CTRB2*[15] were sequenced using an AmpliSeq (Thermo Fisher Scientific, Waltham, MA) custom panel. Next-generation sequencing was performed with 540 chips (Ion S5 System; Thermo Fisher Scientific) or with P1v3 chips (Ion Proton; Thermo Fisher Scientific), according to manufacturer's protocols as previously described.[28,29] Eighteen DNA samples yielded very low read coverage and were excluded as uninformative.

All candidate potentially deleterious variants were validated by Sanger sequencing, (primers listed in Appendix Table A2, online only), which was performed at the Johns Hopkins Genetic Resources Core Facility. Variant prevalence information was obtained from public databases, including ExAC Browser by the Exome Aggregation Consortium[30] and Exome Variant Server by the National Heart, Lung, and Blood Institute Exome Sequencing Project.[31] ClinVar was used to classify the variants and rare nonsynonymous variants. Variants of uncertain significance (VUSs) in *CPA1* and *CPB1* were evaluated functionally as previously described[15] (Data Supplement).

Statistical Analysis

The characteristics of CAPS participants at baseline were summarized and compared between those with and without germline mutations. Differences between groups were evaluated using Fisher's exact test for categorical variables and *t* tests for continuous measures. Time to pancreatic cancer diagnosis; pancreatic cancer or high-grade dysplasia diagnosis; detection of worrisome features; and a composite outcome of first occurrence of pancreatic cancer, high-grade dysplasia, or worrisome features were calculated as time from CAPS enrollment to diagnosis/detection date. Those without the outcome were censored at the date of last follow-up. Patients with worrisome features or pancreatic cancer at baseline were excluded from the respective time-to-event analyses. Cumulative incidence of time-to-event outcomes were estimated using Fine and Gray's method, which accounted for death as a competing event.[32] Differences in time-to-event outcomes between those with and without a germline mutation were estimated using proportional subdistribution hazards models that adjusted for age at baseline CAPS enrollment and sex. Competing mortality was calculated using the date of last contact or date and cause of death. The cumulative probabilities of a diagnosis of pancreatic cancer, pancreatic cancer or high-grade dysplasia, and detection of worrisome features on pancreatic imaging at ages 60, 65, 70, 75, and 80 years were calculated using age of diagnosis or age at

TABLE 3. Estimates of Time to PDAC, PDAC or HGD, and Detection of Worrisome Features According to Germline Mutation Status

Mutation Status	No. of Patients	No. of Events	Cumulative Incidence (range) 5 Years	10 Years	15 Years	HR (95% CI)	*P*
Time to PDAC							
Family history–only risk	329	7	0.01 (0-0.04)	0.05 (0.01-0.1)	0.12 (0.02-0.23)	1.0 (ref)	
Germline mutation risk	133	6	0.01 (0-0.03)	0.19 (0-0.42)	0.45 (0.09-0.81)	2.85 (1 to 8.18)	.05
Time to PDAC or HGD							
Family history–only risk	329	10	0.03 (0-0.06)	0.07 (0.02-0.11)	0.13 (0.03-0.24)	1.0 (ref)	
Germline mutation risk	133	9	0.05 (0-0.09)	0.22 (0-0.44)	0.47 (0.12-0.82)	2.81 (1.17 to 6.76)	.02
Time to PDAC, HGD, or worrisome features							
Family history–only risk	320	21	0.07 (0.03-0.1)	0.18 (0.08-0.28)	0.24 (0.12-0.36)	1.0 (ref)	
Germline mutation risk	126	21	0.17 (0.08-0.26)	0.46 (0.24-0.68)	0.57 (0.3-0.84)	3.27 (1.8 to 5.96)	< .001
Time to worrisome features only							
Family history–only risk	320	20	0.07 (0.03-0.1)	0.17 (0.07-0.26)	0.23 (0.11, 0.35)	1.0 (ref)	
Germline mutation risk	126	19	0.16 (0.07-0.25)	0.37 (0.21-0.54)	0.48 (0.23, 0.73)	3.06 (1.64 to 5.71)	< .001

NOTE. Values are cumulative incidence of the event at 5, 10, and 15 years after enrollment, adjusting for death as a competing event. HR is adjusted for age at enrollment and sex.

Abbreviations: HGD, high-grade dysplasia (pancreatic intraepithelial neoplasia grade 3 or intraductal papillary mucinous neoplasm); HR, hazard ratio; PDAC, pancreatic ductal adenocarcinoma; ref, reference.

last follow-up. All participants were included in these calculations. The *t* test (one-sided) was used to determine whether BiP levels were elevated in variant-transfected cells versus wild-type–transfected cells. Statistical analysis and graphic presentations were performed using R version 3.4.2 (www.R-project.org) and JMP 13 software (SAS Institute, Cary, NC). $P < .05$ were considered statistically significant.

RESULTS

Identification of Previously Unrecognized Germline Mutations in Pancreatic Cancer Susceptibility Genes

Of 345 HRIs under surveillance initially on the basis of their family history of pancreatic cancer, 15 (4.3%) were found to have a deleterious germline mutation in a known pancreatic cancer susceptibility gene by sequencing analysis

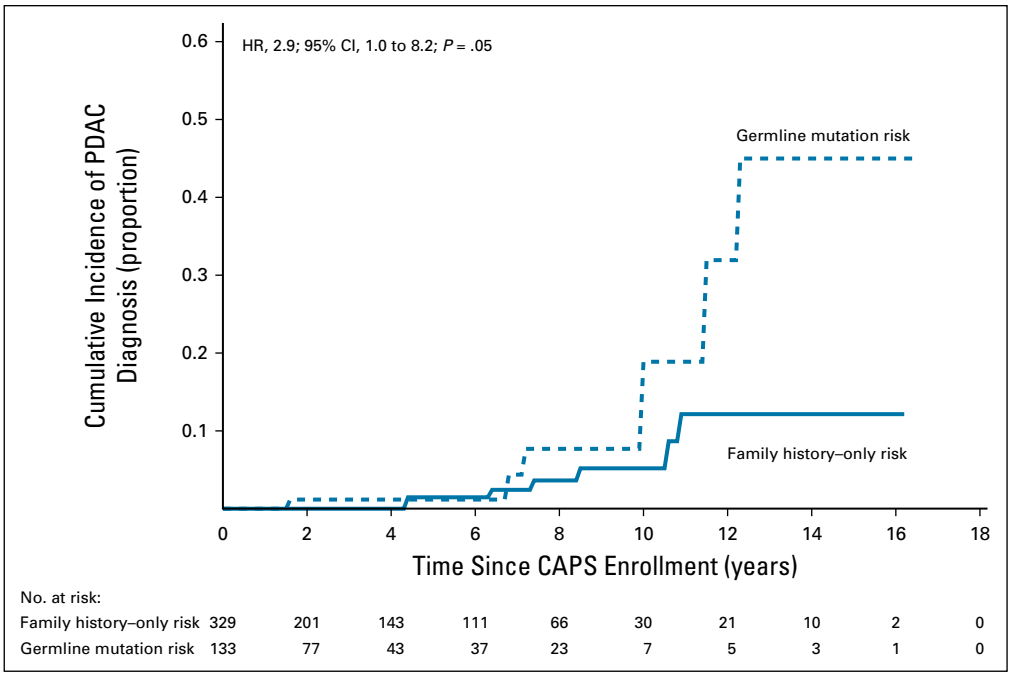

FIG 1. Estimates of time to pancreatic cancer diagnosis according to germline mutation status. CAPS, Cancer of the Pancreas Screening; HR, hazard ratio; PDAC, pancreatic ductal adenocarcinoma.

TABLE 4. Estimates of Cumulative Incidence of PDAC, PDAC or HGD, and Detection of Worrisome Features by Age, According to Germline Mutation Status

	Cumulative Incidence (range)				
Mutation Status	**60 Years**	**65 Years**	**70 Years**	**75 Years**	**80 Years**
Time to PDAC					
Family history–only risk	0 (0-0.01)	0 (0-0.01)	0.02 (0-0.04)	0.09 (0.01-0.16)	0.16 (0-0.32)
Germline mutation risk	0.03 (0-0.07)	0.08 (0.01-0.15)	0.08 (0.01-0.15)	0.15 (0-0.29)	*
Time to PDAC or HGD					
Family history–only risk	0.01 (0-0.02)	0.01 (0-0.02)	0.03 (0-0.06)	0.1 (0.02-0.17)	0.2 (0.04-0.37)
Germline mutation risk	0.05 (0.01-0.1)	0.1 (0.02-0.17)	0.13 (0.03-0.23)	0.19 (0.04-0.34)	*
Time to PDAC, HGD, or worrisome features					
Family history–only risk	0.02 (0-0.04)	0.05 (0.02-0.08)	0.09 (0.04-0.14)	0.23 (0.13-0.33)	0.5 (0.3-0.7)
Germline mutation risk	0.13 (0.06-0.2)	0.26 (0.15-0.37)	0.34 (0.21-0.48)	0.5 (0.3-0.7)	*

Abbreviations: HGD, high-grade dysplasia (pancreatic intraepithelial neoplasia grade 3 or intraductal papillary mucinous neoplasm with high-grade dysplasia); PDAC, pancreatic ductal adenocarcinoma.

*Could not estimate because no germline mutation carriers reached age 80 years.

(Table 1). These 15 patients included two with the Ashkenazi Jewish founder *BRCA2* mutation (C.5946delT), one with the Ashkenazi Jewish founder *BRCA1* mutation (C.68_69delAG), two with *PALB2* mutations, nine with an *ATM* mutation, and one with a *TP53* mutation. Sixty-six VUSs also were identified (Appendix Table A3, online only). Only definitively deleterious germline changes were considered significant in this study.

After gene testing the cohort, individuals were reclassified into those with a known deleterious germline mutation and those without (Data Supplement). Overall, 330 individuals were classified as having risk on the sole basis of their family history (familial risk group), and 134 were classified as having a deleterious germline mutation (Appendix Table A4, online only). Characteristics of both groups are listed in Table 2, and more detailed information about each mutation carrier is listed in Appendix Table A5 (online only). At the time of their baseline screening, individuals with a germline mutation were significantly younger than those in the familial risk group (mean ± standard deviation, 54.0 ± 10.6 *v* 57.9 ± 10.2 years of age, respectively; $P < .001$). The median follow-up period of pancreas surveillance in the germline mutation group and the familial risk group was similar (2.4 *v* 3.2 years, respectively; $P = .21$). The familial risk group was more likely than the germline mutation group to have multiple FDRs with pancreatic cancer (46% *v* 20% with two or more FDRs; $P < .001$). There were other no significant differences in the characteristics of the two groups.

Neoplastic Progression in the Familial Risk and Germline Mutation Groups

Estimates of time to a pancreatic cancer diagnosis, time to a diagnosis of pancreatic cancer or high-grade dysplasia, and time to the detection of worrisome features on imaging stratified by germline mutation status are listed in Table 3. The cumulative incidence of pancreatic cancer in the germline mutation group was higher than in the familial risk group, adjusted for age and sex and accounting for death as a competing event (hazard ratio [HR], 2.85; 95% CI, 1.0 to 8.18; $P = .05$; Fig 1). The likelihood of developing pancreatic cancer or high-grade dysplasia was also significantly higher in the germline mutation group than in the familial risk group (HR, 2.81; 95% CI, 1.17 to 6.76; $P = .02$; Data Supplement). Similar results also were found when the presence of clinically worrisome features in the pancreas was included as an end point (HR, 3.13; 95% CI, 1.71 to 5.6; $P < .001$; Data Supplement). Within the germline mutation group, *BRCA2* mutation carriers were significantly more likely than familial risk individuals to have neoplastic progression (to worrisome features, high-grade dysplasia, or pancreatic [HR, 2.44; $P = .05$]), as were *BRCA1* mutation carriers (HR, 7.49; $P < .001$) but not *PALB2* or *ATM* mutation carriers (Appendix Table A6, online only), although with the small number of carriers of these latter mutations, the power to detect any differences was limited. Estimates of the cumulative incidence of being diagnosed with pancreatic cancer, high-grade dysplasia, and worrisome features by ages 60, 65, 70, 75, and 80 years are listed in Table 4.

Characteristics of HRIs who developed pancreatic cancer or high-grade dysplasia are listed in Table 5. Four of six individuals in the germline mutation group who developed pancreatic cancer during surveillance had unresectable disease at diagnosis, and in three of these individuals, the germline mutation was identified after their pancreatic cancer diagnosis. One individual of particular interest was a 60-year-old female with two FDRs with pancreatic cancer who had a missense variant (c.640G>T; p.D214Y) in *CPA1* that was classified as deleterious after functional analysis. When expressed in HEK293 cells, this variant produced a protein with impaired secretion that induced endoplasmic

TABLE 5. Characteristics of High-Risk Individuals With PDAC or HGD

Pt No.	Age*	Sex	Risk Group	Gene Test Context	Time to Diagnosis (years)	Diagnosis	Management	TNM Stage	Personal History of Cancer	FDR, No.	SDR, No.	Other Family History of Cancer
1	70	M	Family history only	NA	10.7	PDAC	Total pancreatectomy	T1N0M0	None	1	3	None
2	56	M	Family history only	NA	9.7	PDAC	Distal pancreatectomy	T3N0M0	None	1	2	Ovarian
3	74	M	Family history only	NA	6.4	PDAC	Whipple	T3N1M0	None	3	0	Breast, colon, esophageal, melanoma
4	79	F	Family history only	NA	4.4	PDAC	Whipple	T3N1M0	None	4	3	Ovarian, lung
5	72	F	Family history only	NA	0†	PDAC	Unresectable	T4NxM1	None	2	2	Colon, ovarian, prostate, *BRCA2* (c.6174delT)
6	69	F	Family history only	NA	8.6	PDAC	Whipple	T2N1M0	None	2	0	None
7	73	F	Family history only	NA	4.3	PDAC	Whipple	T3N0M0	None	2	0	None
8	83	F	Family history only	NA	7.3‡	PDAC	NA	TxNxMx	None	3	0	Breast, colon, ovarian, rectal, stomach, uterine
9	58	F	Family history only	NA	3.6	IPMN-HGD, PanIN-3	Whipple	NA	None	1	2	NA
10	67	F	Family history only	NA	1.5	IPMN-HGD	Distal pancreatectomy	NA	None	1	2	Carcinoid, leukemia, lymphoma, sarcoma, skin
11	76	F	Family history only	N/A	0.4	PanIN-3	Whipple	NA	Breast	2	1	Breast
12	77	F	*BRCA2*	After diagnosis of PDAC	1.6	PDAC	Unresectable	T4NxM1	Breast, ovarian	1	4	None
13	51	F	*BRCA2*	Before study enrollment	6.8	PDAC	Distal pancreatectomy	T2N1M0	None	2	0	Breast
14	70	M	*BRCA1*	After diagnosis of PDAC	0†	PDAC	Unresectable	T4NxM1	None	2	2	Ovarian, prostate
15	63	F	*PALB2*	After diagnosis of PDAC	7.2	PDAC	Unresectable	TxNxMx	None	1	2	Breast, leukemia

(continued on following page)

TABLE 5. Characteristics of High-Risk Individuals With PDAC or HGD (continued)

Pt No.	Age*	Sex	Risk Group	Gene Test Context	Time to Diagnosis (years)	Diagnosis	Management	TNM Stage	Personal History of Cancer	FDR, No.	SDR, No.	Other Family History of Cancer
16	59	M	*ATM*	This study	7.0	PDAC	NAC, total pancreatectomy	T2N1M0	None	2	2	Breast, colon, lung, lymphoma, prostate, stomach
17	45	F	*ATM*	Before study enrollment	0.6	PDAC	Whipple	T2N1M0	Breast, stomach	1	4	Breast
18	53	F	FAMMM	Before study enrollment	10.0‡	PDAC	NA	TxNxMx	Melanoma	2	4	Bladder, melanoma
19	46	F	PJS	Before study enrollment	0.3	IPMN-HGD	Whipple	NA	None	0	0	Brain, breast, lung
20	66	F	PJS	Before study enrollment	2.6	IPMN-HGD	Distal pancreatectomy	NA	Breast	0	0	Duodenum
21	53	F	*BRCA1*	Before study enrollment	0.7	PanIN-3	Total pancreatectomy	NA	None	1	0	Breast, lymphoma, ovarian

Abbreviations: FDR, first-degree relative (with pancreatic cancer); HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; NA, not available; NAC, neoadjuvant chemotherapy; PanIN-3, pancreatic intraepithelial neoplasia grade 3; PDAC, pancreatic ductal adenocarcinoma; PJS, Peutz-Jeghers syndrome; SDR, second-degree relative (with pancreatic cancer).

*In years at diagnosis.

†Baseline visit.

‡Time to death.

reticulum stress[15] (Appendix Table A7, online only; Data Supplement). This patient did not have a clinical history of pancreatitis, but her endoscopic ultrasound showed many features of chronic pancreatitis (seven of nine endoscopic ultrasound features). She also had other features suggestive of pancreatitis, including a 4.7-mm main pancreatic duct dilation in the neck of her pancreas and a 10-mm cyst in the tail (Data Supplement). Four other patients had a VUS in *CPA1* or *CPB1* (one in *CPA1* and three in *CPB1*). These variants were tested as previously described[15] for their effect on secretion of their protein product and endoplasmic reticulum stress); all four variants produced normal function and so were classified as benign (Appendix Table A7).

DISCUSSION

We find that the risk of neoplastic progression within the pancreas is higher among individuals with a known deleterious germline mutation than in individuals with a strong family history alone. Furthermore, the five patients diagnosed with pancreatic cancer or a precursor lesion with high-grade dysplasia before the age of 55 years were all germline mutation carriers. These latter results support the recommendations of the International CAPS Consortium consensus that pancreatic surveillance of individuals who carry a deleterious germline mutation should start at an earlier age than those under surveillance for their pancreatic cancer family history.[5] The earlier age of enrollment for germline mutation carriers than for familial risk individuals would not be expected to create a bias in the determination of outcome between the two groups because recommendations for ongoing follow-up were the same for both groups, each individual's surveillance intervals are determined by the nature of any abnormalities detected during surveillance.

Our results indicate that germline mutation status can be used to help to predict the risk of neoplastic progression and raise the question of whether patients eligible for pancreatic surveillance on the basis of current clinical guidelines should all undergo germline gene testing. National Comprehensive Cancer Network guidelines for gene testing patients with newly diagnosed pancreatic cancer have been revised recently on the basis of recent studies that found the prevalence of germline mutations in patients with pancreatic cancer to be significant (5% or higher) and that family history of pancreatic or other cancers is not a reliable indicator of which individuals harbor these mutations.[33] Furthermore, relatives of patients with pancreatic cancer can be identified as having a germline mutation after cascade testing of close blood relatives of these germline mutation carriers, and these individuals in turn may benefit from early detection screening. Our results give some guidance to health care providers who are considering offering panel gene testing to their patients with a family history of pancreatic cancer who meet family history criteria for pancreatic surveillance.

Although our results indicate that germline mutation carriers have a higher risk of neoplastic progression than those with familial risk alone, the risk of neoplastic progression was still significant among those with familial risk alone (approximately 16% of individuals in the familial risk group had progressed to pancreatic cancer by age 80 years; Table 4). Thus, we would recommend that individuals who meet family history criteria who do not have an identifiable germline mutation after gene testing still undergo pancreatic surveillance.

The study has some limitations. First, although overall pancreatic cancer risk may be higher among germline mutation carriers than among those with familial risk, this risk is not similarly elevated for all germline mutation carriers; some genes confer a higher risk when mutated than others, and some mutations are more deleterious than others, and variants in other genes can modify disease risk. Although pancreatic cancer risk associated with germline mutation has been estimated for several genes, larger cohorts of mutation carriers are needed to better determine this risk. Second, our study population may not be representative of all populations who meet eligibility criteria for pancreatic screening. As gene testing becomes more widespread, more individuals are expected to be identified as having deleterious germline variants associated with pancreatic cancer risk. Pancreatic cancer risk may not necessarily be as high in the wider population of patients who harbor relevant germline alterations without a significant family history of pancreatic cancer.

In conclusion, among a cohort of individuals undergoing pancreatic surveillance, the cumulative incidence of pancreatic cancer and high-grade dysplasia is significantly higher in individuals who carry a deleterious germline mutation than in individuals with a strong family history but without an identifiable germline mutation. The findings provide better risk stratification and improved clinical decision making with regard to recommendations for pancreatic and other cancer surveillance.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Deleterious Germline Mutations Are a Risk Factor for Neoplastic Progression Among High-Risk Individuals Undergoing Pancreatic Surveillance

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Target Regions of the 16 Genes

Chr	Chr_Start	Chr_End	Gene
Chr2	47630325	47630546	*MSH2*
Chr2	47630523	47630546	*MSH2*
Chr2	47635534	47635699	*MSH2*
Chr2	47637227	47637516	*MSH2*
Chr2	47639547	47639704	*MSH2*
Chr2	47641402	47641562	*MSH2*
Chr2	47643429	47643573	*MSH2*
Chr2	47656875	47657085	*MSH2*
Chr2	47672681	47672801	*MSH2*
Chr2	47690164	47690298	*MSH2*
Chr2	47693791	47693952	*MSH2*
Chr2	47698098	47698206	*MSH2*
Chr2	47702158	47702414	*MSH2*
Chr2	47703500	47703715	*MSH2*
Chr2	47705405	47705663	*MSH2*
Chr2	47707829	47708015	*MSH2*
Chr2	47709912	47710093	*MSH2*
Chr2	48010367	48010614	*MSH6*
Chr2	48010367	48010637	*MSH6*
Chr2	48018060	48018267	*MSH6*
Chr2	48023027	48023207	*MSH6*
Chr2	48025744	48028299	*MSH6*
Chr2	48026023	48028299	*MSH6*
Chr2	48030553	48030829	*MSH6*
Chr2	48032043	48032171	*MSH6*
Chr2	48032751	48032851	*MSH6*
Chr2	48033337	48033502	*MSH6*
Chr2	48033585	48033795	*MSH6*
Chr2	48033912	48034004	*MSH6*
Chr3	37035033	37035159	*MLH1*
Chr3	37038104	37038205	*MLH1*
Chr3	37042440	37042549	*MLH1*
Chr3	37042522	37042544	*MLH1*
Chr3	37045886	37045970	*MLH1*
Chr3	37048476	37048559	*MLH1*
Chr3	37050299	37050401	*MLH1*
Chr3	37053305	37053358	*MLH1*
Chr3	37053496	37053595	*MLH1*
Chr3	37055917	37056040	*MLH1*
Chr3	37055963	37056040	*MLH1*

(continued in next column)

TABLE A1. Target Regions of the 16 Genes (continued)

Chr	Chr_Start	Chr_End	Gene
Chr3	37058991	37059095	*MLH1*
Chr3	37061795	37061959	*MLH1*
Chr3	37067122	37067503	*MLH1*
Chr3	37070269	37070428	*MLH1*
Chr3	37081671	37081790	*MLH1*
Chr3	37083753	37083827	*MLH1*
Chr3	37089004	37089179	*MLH1*
Chr3	37090002	37090105	*MLH1*
Chr3	37090389	37090513	*MLH1*
Chr3	37091971	37092149	*MLH1*
Chr3	148545605	148545686	*CPB1*
Chr3	148545783	148545869	*CPB1*
Chr3	148552279	148552414	*CPB1*
Chr3	148558467	148558577	*CPB1*
Chr3	148558655	148558767	*CPB1*
Chr3	148559604	148559716	*CPB1*
Chr3	148562259	148562380	*CPB1*
Chr3	148562458	148562559	*CPB1*
Chr3	148563205	148563418	*CPB1*
Chr3	148575238	148575333	*CPB1*
Chr3	148577596	148577794	*CPB1*
Chr7	130020356	130020431	*CPA1*
Chr7	130020933	130021025	*CPA1*
Chr7	130021465	130021709	*CPA1*
Chr7	130021943	130022055	*CPA1*
Chr7	130023226	130023338	*CPA1*
Chr7	130023519	130023640	*CPA1*
Chr7	130024371	130024472	*CPA1*
Chr7	130024981	130025191	*CPA1*
Chr7	130025674	130025769	*CPA1*
Chr7	130027659	130027857	*CPA1*
Chr7	142457330	142457380	*PRSS1*
Chr7	142458400	142458570	*PRSS1*
Chr7	142459619	142459883	*PRSS1*
Chr7	142460276	142460423	*PRSS1*
Chr7	142460713	142460876	*PRSS1*
Chr9	21968222	21968246	*p16*
Chr9	21968718	21968775	*p16*
Chr9	21970895	21971212	*p16*
Chr9	21970996	21971212	*p16*

(continued on following page)

TABLE A1. Target Regions of the 16 Genes (continued)

Chr	Chr_Start	Chr_End	Gene
Chr9	21974470	21974831	*p16*
Chr9	21974671	21974831	*p16*
Chr9	21994132	21994335	*p16*
Chr9	135937375	135937460	*CEL*
Chr9	135939785	135939946	*CEL*
Chr9	135940021	135940154	*CEL*
Chr9	135940421	135940629	*CEL*
Chr9	135941911	135942052	*CEL*
Chr9	135942219	135942337	*CEL*
Chr9	135942469	135942597	*CEL*
Chr9	135944053	135944250	*CEL*
Chr9	135944437	135944651	*CEL*
Chr9	135945842	135946050	*CEL*
Chr9	135946368	135947156	*CEL*
Chr11	108098346	108098428	*ATM*
Chr11	108098497	108098620	*ATM*
Chr11	108099899	108100055	*ATM*
Chr11	108106391	108106566	*ATM*
Chr11	108114674	108114850	*ATM*
Chr11	108115509	108115758	*ATM*
Chr11	108117685	108117859	*ATM*
Chr11	108119654	108119834	*ATM*
Chr11	108121422	108121804	*ATM*
Chr11	108122558	108122763	*ATM*
Chr11	108123538	108123644	*ATM*
Chr11	108124535	108124771	*ATM*
Chr11	108126936	108127072	*ATM*
Chr11	108128202	108128338	*ATM*
Chr11	108129707	108129807	*ATM*
Chr11	108137892	108138074	*ATM*
Chr11	108139131	108139341	*ATM*
Chr11	108141785	108141878	*ATM*
Chr11	108141972	108142138	*ATM*
Chr11	108143253	108143339	*ATM*
Chr11	108143443	108143584	*ATM*
Chr11	108150212	108150340	*ATM*
Chr11	108151716	108151900	*ATM*
Chr11	108153431	108153611	*ATM*
Chr11	108154948	108155205	*ATM*
Chr11	108158321	108158447	*ATM*
Chr11	108159698	108159835	*ATM*
Chr11	108160323	108160533	*ATM*
Chr11	108163340	108163525	*ATM*

(continued in next column)

TABLE A1. Target Regions of the 16 Genes (continued)

Chr	Chr_Start	Chr_End	Gene
Chr11	108164034	108164209	*ATM*
Chr11	108165648	108165791	*ATM*
Chr11	108168008	108168114	*ATM*
Chr11	108170435	108170617	*ATM*
Chr11	108172369	108172521	*ATM*
Chr11	108173574	108173761	*ATM*
Chr11	108175396	108175584	*ATM*
Chr11	108178618	108178716	*ATM*
Chr11	108180881	108181047	*ATM*
Chr11	108183132	108183230	*ATM*
Chr11	108186544	108186643	*ATM*
Chr11	108186732	108186845	*ATM*
Chr11	108188094	108188253	*ATM*
Chr11	108190675	108190790	*ATM*
Chr11	108192022	108192152	*ATM*
Chr11	108196031	108196276	*ATM*
Chr11	108196779	108196957	*ATM*
Chr11	108198366	108198490	*ATM*
Chr11	108199742	108199970	*ATM*
Chr11	108200935	108201153	*ATM*
Chr11	108202165	108202289	*ATM*
Chr11	108202600	108202769	*ATM*
Chr11	108203483	108203632	*ATM*
Chr11	108204607	108204700	*ATM*
Chr11	108205690	108205841	*ATM*
Chr11	108206566	108206693	*ATM*
Chr11	108213943	108214103	*ATM*
Chr11	108216464	108216640	*ATM*
Chr11	108218000	108218097	*ATM*
Chr11	108224487	108224612	*ATM*
Chr11	108225532	108225606	*ATM*
Chr11	108235803	108235950	*ATM*
Chr11	108236046	108236240	*ATM*
Chr13	32890592	32890669	*BRCA2*
Chr13	32893208	32893467	*BRCA2*
Chr13	32899207	32899326	*BRCA2*
Chr13	32900232	32900292	*BRCA2*
Chr13	32900373	32900424	*BRCA2*
Chr13	32900630	32900755	*BRCA2*
Chr13	32903574	32903634	*BRCA2*
Chr13	32905050	32905172	*BRCA2*
Chr13	32906403	32907529	*BRCA2*
Chr13	32910396	32915338	*BRCA2*

(continued on following page)

TABLE A1. Target Regions of the 16 Genes (continued)

Chr	Chr_Start	Chr_End	Gene
Chr13	32918689	32918795	*BRCA2*
Chr13	32920958	32921038	*BRCA2*
Chr13	32928992	32929430	*BRCA2*
Chr13	32930559	32930751	*BRCA2*
Chr13	32931873	32932071	*BRCA2*
Chr13	32936654	32936835	*BRCA2*
Chr13	32937310	32937675	*BRCA2*
Chr13	32944533	32944699	*BRCA2*
Chr13	32945087	32945242	*BRCA2*
Chr13	32950801	32950933	*BRCA2*
Chr13	32953448	32953657	*BRCA2*
Chr13	32953881	32954055	*BRCA2*
Chr13	32954138	32954287	*BRCA2*
Chr13	32968820	32969075	*BRCA2*
Chr13	32971029	32971186	*BRCA2*
Chr13	32972293	32972912	*BRCA2*
Chr15	40453416	40453461	*BUB1B*
Chr15	40457248	40457402	*BUB1B*
Chr15	40462257	40462327	*BUB1B*
Chr15	40462732	40462887	*BUB1B*
Chr15	40468672	40468879	*BUB1B*
Chr15	40475909	40476089	*BUB1B*
Chr15	40477360	40477585	*BUB1B*
Chr15	40477746	40477848	*BUB1B*
Chr15	40488740	40488980	*BUB1B*
Chr15	40491810	40491933	*BUB1B*
Chr15	40492439	40492565	*BUB1B*
Chr15	40493126	40493186	*BUB1B*
Chr15	40494600	40494671	*BUB1B*
Chr15	40494784	40494900	*BUB1B*
Chr15	40498379	40498664	*BUB1B*
Chr15	40500832	40500976	*BUB1B*
Chr15	40501830	40501981	*BUB1B*
Chr15	40502305	40502416	*BUB1B*
Chr15	40504694	40504854	*BUB1B*
Chr15	40505527	40505680	*BUB1B*
Chr15	40509691	40509873	*BUB1B*
Chr15	40510651	40510768	*BUB1B*
Chr15	40512759	40512965	*BUB1B*
Chr16	23614774	23614995	*PALB2*
Chr16	23619179	23619338	*PALB2*
Chr16	23625319	23625417	*PALB2*
Chr16	23632677	23632804	*PALB2*

(continued in next column)

TABLE A1. Target Regions of the 16 Genes (continued)

Chr	Chr_Start	Chr_End	Gene
Chr16	23634284	23634456	*PALB2*
Chr16	23635324	23635420	*PALB2*
Chr16	23637551	23637723	*PALB2*
Chr16	23640519	23640601	*PALB2*
Chr16	23640955	23641795	*PALB2*
Chr16	23646177	23647660	*PALB2*
Chr16	23649165	23649278	*PALB2*
Chr16	23649385	23649455	*PALB2*
Chr16	23652425	23652483	*PALB2*
Chr16	75238053	75238225	*CTRB2*
Chr16	75238665	75238809	*CTRB2*
Chr16	75239225	75239416	*CTRB2*
Chr16	75239634	75239723	*CTRB2*
Chr16	75239805	75239895	*CTRB2*
Chr16	75239982	75240096	*CTRB2*
Chr16	75240982	75241044	*CTRB2*
Chr17	7572921	7573013	*TP53*
Chr17	7573921	7574038	*TP53*
Chr17	7576531	7576589	*TP53*
Chr17	7576619	7576662	*TP53*
Chr17	7576847	7576931	*TP53*
Chr17	7577013	7577160	*TP53*
Chr17	7577493	7577613	*TP53*
Chr17	7578171	7578294	*TP53*
Chr17	7578365	7578457	*TP53*
Chr17	7578365	7578538	*TP53*
Chr17	7578365	7578559	*TP53*
Chr17	7579306	7579574	*TP53*
Chr17	7579306	7579595	*TP53*
Chr17	7579694	7579726	*TP53*
Chr17	7579833	7579917	*TP53*
Chr17	41197689	41197824	*BRCA1*
Chr17	41197795	41197824	*BRCA1*
Chr17	41199654	41199725	*BRCA1*
Chr17	41201132	41201216	*BRCA1*
Chr17	41203074	41203139	*BRCA1*
Chr17	41209063	41209157	*BRCA1*
Chr17	41215344	41215395	*BRCA1*
Chr17	41215885	41215973	*BRCA1*
Chr17	41219619	41219717	*BRCA1*
Chr17	41222939	41223260	*BRCA1*
Chr17	41226342	41226543	*BRCA1*
Chr17	41228499	41228633	*BRCA1*

(continued on following page)

TABLE A1. Target Regions of the 16 Genes (continued)

Chr	Chr_Start	Chr_End	Gene
Chr17	41228499	41228636	*BRCA1*
Chr17	41231345	41231421	*BRCA1*
Chr17	41234415	41234597	*BRCA1*
Chr17	41242955	41243054	*BRCA1*
Chr17	41243446	41246882	*BRCA1*
Chr17	41246755	41246882	*BRCA1*
Chr17	41247857	41247944	*BRCA1*
Chr17	41249255	41249311	*BRCA1*
Chr17	41251786	41251902	*BRCA1*
Chr17	41256133	41256283	*BRCA1*
Chr17	41256879	41256978	*BRCA1*
Chr17	41258467	41258548	*BRCA1*
Chr17	41258467	41258555	*BRCA1*
Chr17	41267737	41267801	*BRCA1*
Chr17	41276028	41276118	*BRCA1*
Chr19	1206907	1207207	*STK11*
Chr19	1218410	1218504	*STK11*
Chr19	1219317	1219417	*STK11*
Chr19	1220366	1220509	*STK11*
Chr19	1220574	1220721	*STK11*
Chr19	1221206	1221344	*STK11*
Chr19	1221942	1222010	*STK11*
Chr19	1222978	1223176	*STK11*
Chr19	1226447	1226651	*STK11*

Abbreviation: Chr, chromosome.

TABLE A2. Oligonucleotides Used for Polymerase Chain Reaction Amplification for Sanger Sequencing

Gene	Chr Position	Amino Acid Change	Nucleotide Change	Forward Primer Sequence	Reverse Primer Sequence
ATM	Chr11: 108196143	p.R2227C	c.6679C>T	TCATTTCTCTTGCTTACATGAAC	TGTATTTACCTGAGTGTTCTTG
ATM	Chr11: 108214103-6	Splice	c.*5_*8delGTGA	TGATCATCAAATGCTCTTTAATG	TTACTTAGTATCTTTGACAATTAC
ATM	Chr11: 108236086	p.R3008C	c.9022C>T	GAATGCAGATGACCAAGAATG	CCTGCTGTATGAGCAAATTC
ATM	Chr11: 108139228-9	p.A911delinsRLfs	c.2730_2731insAG	GCCCTTCTCTTAGTGTTAATG	ACATGTCAACTCATTACATTTAG
ATM	Chr11: 108206686	p.K2756X	c.8266A>T	TGATGACCTGAGACAAGATG	CTCCCAAAGCATTATGAATATG
ATM	Chr11: 108284282	p.V1268Xfs	c.3802delG	ATAATCTGGATAAAGTATGATAC	TGTCTCTGGTACCCTCATAG
ATM	Chr11: 108117816-9	p.E343Ifs	c.1027_1030delGAAA	ATCTGCTAGTGAATGAGATAAG	CTAGAGACAATCATTTAAGAATG
BRCA1	Chr17: 41276047-8	p.E23fs*17	c.68_69delAG	GAACAGAAAGAAATGGATTTATC	GGACCACAGGATTTGTGTTG
BRCA2	Chr13: 32914438	p.S1982Rfs	c.5946delT	AGTGAAGAAATTTTACAACATAAC	CTTGTGAGCTGGTCTGAATG
CEL	Chr9:135944128	p.N325NS	c.974A>G	GGAAACTGGGAGGTACAAG	ACAGGAAGGTGTGTGCATAC
CPA1	Chr7:130023579	p.D214Y	c.640G>T	CAGTGACCACAGAGGACATG	ACTACTTGTGCAGCTTAGAAG
CPA1	Chr7:148577788	p.A259V	c.776C>T	CCCATTTCCTTCCTCAGAATC	GCCTTTTGCAGGCGAGTAAC
CPB1	Chr3:148545842	p.R42H	c.125G>A	ATTTCCAATTCTCTGTGCTTC	GAATCACAGTGCGATCTAAG
CPB1	Chr3:148552355	p.A73G	c.218C>G	ATAATGTGCTCGCAGATTATC	CTCAGATGAAAGCATGCATG
CPB1	Chr3:148575263	p.T334I	c.1001C>T	ATGAAAATGGGTCCTGAATAAG	GTTCTTTGCACAGTTCTGAAG
CTRB2	Chr16:75239832	p.T72TN	c.215C>A	GAGGAGGCTGGAGCATTAG	GTTGTGGGTGAGAGAACATG
PALB2	Chr16: 23619279	p.R1086X	c.3256C>T	CATACTCTTGACAGTCTATTTG	ACCCATAGAGTAGCAGTTATG
TP53	Chr17: 7577091	p.R283C	c.847C>T	TCCTGAGTAGTGGTAATCTAC	AAAAGTGAATCTGAGGCATAAC

Abbreviation: Chr, chromosome.

TABLE A3. VUSs

Pt ID	Age†	Sex	Race	Gene	Chr Position	rsID	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Personal History of Cancer	FDR, No.	SDR, No.	Family History of Cancer
1*64	52	M	White	*ATM*	Chr11: 108119823	rs56128736	p.V410AV	c.1229T>C	Missense	B/VUS	No	Hetero	None	1	2	Breast
2*79	79	M	White	*ATM*	Chr11: 108119823	rs56128736	p.V410AV	c.1229T>C	Missense	B/VUS	No	Hetero	None	1	5	Prostate
3*13	70	F	White	*ATM*	Chr11: 108122659		p.R568RI	c.1703G>T	Missense	VUS	No	Hetero	None	2	0	NA
2*95	62	F	White	*ATM*	Chr11: 108141988	rs139552233	p.S978PS	c.2932T>C	Missense	B/VUS	No	Hetero	None	1	0	None
2*58	60	M	White	*ATM*	Chr11: 108100014	rs137882485	p.S99SG	c.295A>G	Missense	VUS	No	Hetero	None	2	1	None
3*74	63	M	White	*ATM*	Chr11: 108100014	rs137882485	p.S99SG	c.295A>G	Missense	VUS	No	Hetero	None	2	2	Colon, lung
2*59	67	M	White	*ATM*	Chr11: 108142070	rs146531614	p.N1005NS	c.3014A>G	Missense	VUS	No	Hetero	None	2	0	None
1*21	56	F	White	*ATM*	Chr11: 108160516	rs34640941	p.Y1475YC	c.4424A>G	Missense	B/VUS	No	Hetero	None	1	2	None
2*04	77	F	White	*ATM*	Chr11: 108186610	rs11212587	p.G2023RG	c.6067G>G	Missense	B/VUS	No	Hetero	None	2	0	Breast, colon, melanoma
2*25	44	M	White	*ATM*	Chr11: 108186610	rs11212587	p.G2023RG	c.6067G>G	Missense	B/VUS	No	Hetero	None	1	1	None
2*72	56	M	White	*ATM*	Chr11: 108202754		p.Q2593QR	c.7778A>G	Missense	VUS	No	Hetero	None	1	1	Breast, lung
2*89	74	F	White	*ATM*	Chr11: 108202754		p.Q2593QR	c.7778A>G	Missense	VUS	No	Hetero	Breast	1	1	None
2*96	65	M	White	*BRCA1*	Chr17: 41245574	rs55678461	p.M658MI	c.1974G>C	Missense	B/VUS	No	Hetero	None	1	1	None
3*80	78	F	White	*BRCA1*	Chr17: 41245574	rs55678461	p.M658MI	c.1974G>C	Missense	B/VUS	No	Hetero	None	1	1	Colon, lung
1*30	62	F	Black	*BRCA1*	Chr17: 41245393	rs80357147	p.K719EK	c.2155A>G	Missense	VUS	No	Hetero	None	2	1	None
1*42	61	M	Black	*BRCA1*	Chr17: 41245393	rs80357147	p.K719EK	c.2155A>G	Missense	VUS	No	Hetero	None	2	1	Breast, colon
3*49	59	M	White	*BRCA1*	Chr17: 41245197	rs55914168	p.S784LS	c.2351C>T	Missense	B/VUS	No	Hetero	None	2	1	Colon, prostate
2*66	77	M	White	*BRCA2*	Chr13: 32912031	rs28897720	p.K1180KR	c.3539A>G	Missense	VUS	No	Hetero	None	2	1	None
1*53	48	F	White	*BRCA2*	Chr13: 32913473	rs80359476	p.Y1661HY	c.4981T>C	Missense	VUS	No	Hetero	None	1	2	NA
1*55	42	M	White	*BRCA2*	Chr13: 32913473	rs80359476	p.Y1661HY	c.4981T>C	Missense	VUS	No	Hetero	None	1	2	None
2*02	47	M	White	*BRCA2*	Chr13: 32900658	rs80359511	p.I180TI	c.539T>C	Missense	VUS	No	Hetero	None	1	2	None
2*36	54	M	White	*BRCA2*	Chr13: 32915015		p.E2175QE	c.6523G>C	Missense	VUS	No	Hetero	None	2	0	None
4*28	72	F	White	*BRCA2*	Chr13: 32915061		p.V2190AV	c.6569T>C	Missense	VUS	No	Hetero	None	1	1	Breast, cervical, leukemia, lymphoma, melanoma, uterine
2*61	71	M	White	*BRCA2*	Chr13: 32971146		p.A3205L	c.9613_9614delGCinsCT	Missense	VUS	No	Hetero	None	2	0	None
2*76	75	M	White	*BRCA2*	Chr13: 32971146		p.A3205L	c.9613_9614delGCinsCT	Missense	VUS	No	Hetero	None	2	0	Colon, prostate
4*02	52	F	White	*BUB1B*	Chr15: 40498541		p.L631IL	c.1891C>A	Missense	VUS	No	Hetero	None	1	1	None
3*44	55	F	White	*BUB1B*	Chr15: 40477447		p.N278NS	c.833A>G	Missense	VUS	No	Hetero	None	1	2	Skin, renal
1*65	60	M	White	*CEL*	Chr9: 135942575		p.P296PL	c.887C>T	Missense	VUS	No	Hetero	None	2	1	Bladder, brain, colon, lung
3*15	63	M	Black	*CEL*	Chr9: 135944128		p.N325NS	c.974A>G	Missense	VUS	Yes	Hetero	None	2	0	Breast, lung
1*95	59	F	White	*CTRB2*	Chr16: 75241024	rs147238447	p.L6VL	c.16C>G	Missense	VUS	No	Hetero	None	2	1	Colon
1*96	76	M	White	*CTRB2*	Chr16: 75241024	rs147238447	p.L6VL	c.16C>G	Missense	VUS	No	Hetero	None	2	1	Colon
3*22	53	F	White	*CTRB2*	Chr16: 75239832		p.T72TN	c.215C>A	Missense	VUS	Yes	Hetero	Breast	1	1	None
1*23	70	M	White	*MLH1*	Chr3: 37089130	rs35001569	p.K618A	c.1852A>G	Missense	VUS	No	Hetero	None	1	3	None
2*13	62	F	White	*MLH1*	Chr3: 37089130	rs35001569	p.K618A	c.1852A>G	Missense	VUS	No	Hetero	None	1	3	Colon, endometrial, uterine
2*39	65	M	White	*MLH1*	Chr3: 37092047		p.R725HR	c.2174G>A	Missense	VUS	No	Hetero	None	1	2	None

(continued on following page)

TABLE A3. VUSs (continued)

Pt ID	Age†	Sex	Race	Gene	Chr Position	rsID	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Personal History of Cancer	FDR, No.	SDR, No.	Family History of Cancer
3*16	49	F	White	*MLH1*	Chr3: 37092047		p.R725HR	c.2174G>A	Missense	VUS	No	Hetero	None	1	3	Colon
3*41	66	F	White	*MLH1*	Chr3: 37092047		p.R725HR	c.2174G>A	Missense	VUS	No	Hetero	None	1	1	None
3*83	69	M	Asian	*MSH2*	Chr2: 47672788	rs575905950	p.M460MV	c.1378A>G	Missense	VUS	No	Hetero	None	2	0	None
3*20	60	F	White	*MSH2*	Chr2: 47690244	rs35107951	p.D487DE	c.1461C>G	Missense	VUS	No	Hetero	None	1	1	Breast, uterine
3*02	75	F	White	*MSH2*	Chr2: 47641470	rs759242666	p.N285NK	c.855C>G	Missense	VUS	No	Hetero	Skin	2	0	None
1*09	65	F	White	*MSH6*	Chr2: 48033792		Splice	c.*12_*15delACTA	Noncoding	VUS	No	Hetero	None	1	2	NA
2*62	45	F	White	*MSH6*	Chr2: 48026486	rs200938360	p.N455NT	c.1364A>C	Missense	VUS	No	Hetero	None	2	1	None
4*29	77	M	White	*MSH6*	Chr2: 48026603		p.A494AV	c.1481C>T	Missense	VUS	No	Hetero	None	1	3	None
2*80	66	F	White	*MSH6*	Chr2: 48010542		p.P57PR	c.170C>G	Missense	VUS	No	Hetero	None	1	2	Breast, prostate, skin
2*68	77	M	White	*MSH6*	Chr2: 48010560	rs587779920	p.S63SC	c.188C>G	Missense	VUS	No	Hetero	None	3	0	Breast, ovarian
1*67	53	F	White	*MSH6*	Chr2: 48030603	rs142254875	p.P1073PS	c.3217C>T	Missense	VUS	No	Hetero	None	1	2	Breast, colon
3*54	54	M	White	*MSH6*	Chr2: 48030603	rs142254875	p.P1073PS	c.3217C>T	Missense	VUS	No	Hetero	None	1	3	NA
3*94	48	M	White	*MSH6*	Chr2: 48030603	rs142254875	p.P1073PS	c.3217C>T	Missense	VUS	No	Hetero	None	1	2	None
1*76	57	M	White	*MSH6*	Chr2: 48033621		p.P1278TP	c.3832C>A	Missense	B/VUS	No	Hetero	None	1	2	Leukemia, lung, lymphoma, prostate, stomach
4*03	66	M	White	*MSH6*	Chr2: 48025785	rs41557217	p.E221ED	c.663A>C	Missense	VUS	No	Hetero	None	3	0	None
4*21	56	F	White	*MSH6*	Chr2: 48025785	rs41557217	p.E221ED	c.663A>C	Missense	VUS	No	Hetero	None	1	1	None
4*53	56	M	White	*MSH6*	Chr2: 48025785	rs41557217	p.E221ED	c.663A>C	Missense	VUS	No	Hetero	Prostate, leukemia	1	1	None
3*19	60	F	White	*PALB2*	Chr16: 23635412		p.P918SP	c.2752C>T	Missense	VUS	No	Hetero	None	2	0	Breast
2*63	64	F	Asian	*PALB2*	Chr16: 23632742	rs183489969	p.E1018ED	c.3054G>C	Missense	B/VUS	No	Hetero	None	1	1	NA
4*49	47	M	White	*PALB2*	Chr16: 23619239	rs142132127	p.T1099RT	c.3296C>G	Missense	VUS	Yes	Hetero	Colon, bladder	2	0	Colon
2*77	62	F	White	*PALB2*	Chr16: 23614851		p.W1164WR	c.3490T>C	Missense	VUS	No	Hetero	None	2	0	None
3*33	69	M	White	*PALB2*	Chr16: 23614851		p.W1164WR	c.3490T>C	Missense	VUS	No	Hetero	None	2	0	NA
3*88	76	F	White	*STK11*	Chr19: 1223090		p.D343ND	c.1027G>A	Missense	VUS	No	Hetero	None	2	1	None
1*75	56	F	White	*STK11*	Chr19: 1223125	rs59912467	p.F354FL	c.1062C>G	Missense	B/VUS	No	Hetero	None	1	2	Breast, skin
1*77	54	F	White	*STK11*	Chr19: 1223125	rs59912467	p.F354FL	c.1062C>G	Missense	B/VUS	No	Hetero	None	1	2	Breast
2*70	44	F	Asian	*STK11*	Chr19: 1223125	rs59912467	p.F354FL	c.1062C>G	Missense	B/VUS	No	Hetero	None	1	1	Colon
2*83	78	M	White	*STK11*	Chr19: 1223125	rs59912467	p.F354FL	c.1062C>G	Missense	B/VUS	No	Hetero	None	2	0	None
3*14	72	M	White	*STK11*	Chr19: 1223125	rs59912467	p.F354FL	c.1062C>G	Missense	B/VUS	No	Hetero	None	2	0	None

Abbreviations: B, benign; Chr, chromosome; FDR, first-degree relative; Hetero, heterozygous; ID, identifier; NA, not available; Pt, patient; SDR, second-degree relative; VUS, variant of uncertain significance.

†In years (latest).

TABLE A4. Known Germline Mutations in Pancreatic Cancer Susceptibility Genes

Pt No.	Age†	Sex	Race	Gene	Nucleotide Change	Amino Acid Change	Function	Personal History of Cancer	FDR, No.	SDR, No.	Family History of Cancer	Diagnosis
1	57	F	White	*BRCA2*	c.1813dupA	p.Ile605Asnfs	Frameshift	Endometrial	0	1	Breast	Worrisome features
2	52	M	White	*BRCA2*	c.1888dupA	p.Thr630Asnfs	Frameshift	None	1	0	Bile duct, brain, breast, colon, ovarian	
3	56	M	White	*BRCA2*	c.1889delC	p.Ser617Ter	Nonsense	None	2	1	Breast, esophagus, liver	
4	74	M	White	*BRCA2*	c.1755_1759delGAAAA	p.Lys585Asnfs	Frameshift	None	1	2	Breast	
5	38	F	White	*BRCA2*	c.1755_1759delGAAAA	p.Lys585Asnfs	Frameshift	None	0	2	Breast, ovarian	
6	49	F	White	*BRCA2*	c.2330dupA	p.Asp777Glufs	Frameshift	None	1	2	Breast, uterine	
7	62	F	White	*BRCA2*	c.7806-2A>G		Splice	Breast	1	2	Breast, ovarian, prostate, stomach	Worrisome features
8	53	M	White	*BRCA2*	c.3353_3355delTAG	p.Leu1118_Lys1453delinsTer	Inframe	None	1	2	Breast	
9	61	F	White	*BRCA2*	c.3554_3555delCA	p.Thr1185Serfs	Frameshift	Uterine	1	2	Breast, lymphoma, prostate	
10	56	F	White	*BRCA2*	c.4478_4481delAAAG	p.Glu1493Valfs	Frameshift	None	1	1	Breast, prostate	
11	54	F	White	*BRCA2*	c.4478_4481delAAAG	p.Glu1493Valfs	Frameshift	None	1	1	Breast, colon	
12	51	F	White	*BRCA2*	c.4478_4481delAAAG	p.Glu1493Valfs	Frameshift	None	1	1	Breast, colon	
13	56	F	White	*BRCA2*	c.5350_5351delAA	p.Asn1784Hisfs	Frameshift	Breast	1	0	Breast, lung	
14	61	F	White	*BRCA2*	c.5351delA	p.Asn1784Thrfs	Frameshift	Breast, parotid gland	0	3	Breast	
15	60	M	White	*BRCA2*	c.5909C>A	p.Ser1970Ter	Nonsense	Breast	2	2	Breast, ovarian	
16	58	M	White	*BRCA2*	c.5909C>A	p.Ser1970Ter	Nonsense	None	2	2	Breast, ovarian	
17	58	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	2	Colon	Worrisome features
18	51	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	1	Bile duct, breast, colon, kidney, ovarian	
19	53	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	3	Bile duct, breast, colon, gallbladder	
20	77	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Breast, ovarian	1	4	None	PDAC, worrisome features
21	65	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	2	0	Breast	Worrisome features
22	55	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	1	Breast	
23	62	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	1	Breast, colon	
24	62	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	0	Colon	
25	65	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	0	Breast, ovarian	
26	49	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	0	1	Breast, ovarian	
27	68	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	0	Breast	Worrisome features
28	69	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	0	Breast	
29	66	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	0	1	Breast, ovarian, prostate	
30	67	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	2	1	Breast	
31	67	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	0	1	Prostate	
32	67	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Breast	1	0	Breast	

(continued on following page)

TABLE A4. Known Germline Mutations in Pancreatic Cancer Susceptibility Genes (continued)

Pt No.	Age†	Sex	Race	Gene	Nucleotide Change	Amino Acid Change	Function	Personal History of Cancer	FDR, No.	SDR, No.	Family History of Cancer	Diagnosis
33	72	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	0	Breast, ovarian, stomach, uterine	
34	65	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	2	6	Breast	
35	75	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Breast	1	2	Breast	Worrisome features
36	62	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	0	1	Melanoma	
37	54	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Breast	1	0	Melanoma	
38	62	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	0	3	Prostate	
39	50	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	1	Ampullary, stomach	
40	72	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Breast	0	1	Ovarian	
41	61	F	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Breast	1	1	Breast	
42	47	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	0	2	Breast	
43	35	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	None	1	2	NA	
44	69	F	White	*BRCA2*	c.6275_6276delTT	p.Leu2092Profs	Frameshift	Breast, ovarian	2	2	Breast	
45	42	F	White	*BRCA2*	c.6275_6276delTT	p.Leu2092Profs	Frameshift	Breast	0	2	Breast	
46	67	M	White	*BRCA2*	c.6486_6489delACAA	p.Lys2162Asnfs	Frameshift	None	1	0	Breast	
47	60	M	White	*BRCA2*	c.6814delA	p.Arg2272Glufs	Frameshift	None	1	0	Breast	
48	59	F	White	*BRCA2*	c.7230delT	p.Phe2410Leufs	Frameshift	Breast, skin	0	1	Breast	
49	56	M	White	*BRCA2*	c.7762_7764delATAinsTT	p.Ile2588Phefs	Frameshift	None	1	0	Breast, kidney	
50	49	M	White	*BRCA2*	c.8364G>A	p.Trp2788Ter	Nonsense	None	1	0	Breast, colon, ovarian	
51	65	M	White	*BRCA2*	c.8364G>A	p.Trp2788Ter	Nonsense	None	0	1	Breast, colon, ovarian	
52	69	F	White	*BRCA2*	c.8364G>A	p.Trp2788Ter	Nonsense	Breast	1	0	Breast, ovarian	
53	51	F	White	*BRCA2*	c.8364G>A	p.Trp2788Ter	Nonsense	None	2	0	Breast	PDAC, worrisome features
54	42	F	White	*BRCA2*	MR			None	1	1	Breast	
55	79	F	White	*BRCA2*	MR			Colon	1	1	Breast	Worrisome features
56	47	F	White	*BRCA2*	MR			None	0	1	Breast	
57	62	F	White	*BRCA2*	MR			Breast, endometrial, uterine	1	0	Breast	
58	60	F	White	*BRCA2*	MR			Breast, ovarian	1	0	Breast, lung, lymphoma	
59	64	M	White	*BRCA2*	MR			None	1	0	Breast	
60	70	M	White	FAMMM	c.206A>G	p.Glu69Gly	Missense	Colon, melanoma	0	1	Breast, colon, melanoma, stomach	
61	39	F	White	FAMMM	c.249C>G	p.His83Gln	Missense	Melanoma	1	1	Melanoma	
62	64	F	White	FAMMM	c.377T>A	p.Val126Asp	Missense	Melanoma	1	2	Melanoma, prostate	
63	44	F	White	FAMMM	c.225del19		Nonsense	Breast, melanoma	1	1	Melanoma	
64	53	F	White	FAMMM	MR			Melanoma	2	4	Bladder, melanoma	PDAC
65	49	F	White	FAMMM	MR			Breast, melanoma	0	2	Melanoma	
66	79	M	White	FAMMM	MR			None	2	0	Melanoma	

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TABLE A4. Known Germline Mutations in Pancreatic Cancer Susceptibility Genes (continued)

Pt No.	Age†	Sex	Race	Gene	Nucleotide Change	Amino Acid Change	Function	Personal History of Cancer	FDR, No.	SDR, No.	Family History of Cancer	Diagnosis
67	49	F	White	FAMMM	MR			None	0	2	Breast, melanoma	
68	50	M	White	PJS	c.970delCCGAG		Frameshift	None	0	0	NA	
69	51	F	White	PJS	C.910C>T	p.Arg304Trp	Missense	Ovarian	0	0	Breast	Worrisome features
70	37	M	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	0	0	NA	Worrisome features
71	53	F	White	PJS	Clinical diagnosis	Clinical Diagnosis		Breast	0	0	Breast, colon	
72	55	F	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	0	0	NA	
73	46	F	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	0	0	Brain, breast, lung	HGD
74	45	M	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	0	0	Colon	Worrisome features
75	42	F	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	0	0	Cervical	
76	47	F	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	0	0	Breast, esophagus, stomach	
77	35	F	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	0	0	PJS	
78	64	M	White	PJS	Clinical diagnosis	Clinical Diagnosis		None	1	0	Lung, stomach	Worrisome features
79	66	F	White	PJS	Clinical diagnosis	Clinical Diagnosis		Breast	0	0	Duodenum	HGD, worrisome features
80	65	F	White	HNPCC	c.3261delC	p.Phe1088Serfs	Frameshift	Endometrial	1	0	Breast, cervical, thyroid, uterine	
81	77	M	White	HNPCC	c.184C>T	p.Gln62Ter	Nonsense	Colon	1	0	Colon, leukemia, melanoma, uterine	Worrisome features
82	55	F	White	*BRCA1*	c.1188delT	p.Asp396Glufs	Frameshift	Breast	1	0	Colon	
83	65	M	White	*BRCA1*	c.181T>G	p.Cys61Gly	Missense	Thyroid	1	2	Breast, bone, melanoma, ovarian, stomach	Worrisome features
84	70	M	White	*BRCA1*	c.427G>T	p.Glu143Ter	Frameshift	None	2	2	Ovarian, prostate	PDAC, worrisome features
85	60	F	White	*BRCA1*	c.4986+4A>T		Intron	Breast	1	1	Ovarian, prostate, stomach	
86	48	M	White	*BRCA1*	c.5251C>T	p.Arg1751Ter	Nonsense	Breast	1	0	Breast, ovarian	
87	63	F	White	*BRCA1*	c.5266dupC	p.Gln1756Profs	Frameshift	None	1	1	Breast, lung	
88	77	M	White	*BRCA1*	c.5266dupC	p.Gln1756Profs	Frameshift	None	2	0	Breast, leukemia	
89	64	F	White	*BRCA1*	c.68_69delAG	p.Glu23Valfs	Frameshift	None	0	1	Breast, ovarian	Worrisome features
90	62	F	White	*BRCA1*	c.68_69delAG	p.Glu23Valfs	Frameshift	None	1	0	Breast	
91	54	F	White	*BRCA1*	c.68_69delAG	p.Glu23Valfs	Frameshift	Breast, ovarian	1	0	Breast	
92	56	M	White	*BRCA1*	c.68_69delAG	p.Glu23Valfs	Frameshift	None	2	1	Breast	
93	42	F	White	*BRCA1*	c.68_69delAG	p.Glu23Valfs	Frameshift	None	0	1	Breast, ovarian, lung, lymphoma	Worrisome features
94	53	M	White	*BRCA1*	MR			None	1	0	Breast	Worrisome features
95	51	F	White	*BRCA1*	MR			Breast	1	0	Colon	
96	40	F	White	*BRCA1*	MR			Breast	1	1	None	
97	63	M	White	*BRCA1*	MR			None	2	0	Breast, ovarian	
98	42	M	White	*BRCA1*	MR			None	1	0	Breast	

(continued on following page)

TABLE A4. Known Germline Mutations in Pancreatic Cancer Susceptibility Genes (continued)

Pt No.	Age†	Sex	Race	Gene	Nucleotide Change	Amino Acid Change	Function	Personal History of Cancer	FDR, No.	SDR, No.	Family History of Cancer	Diagnosis
99	53	F	White	*BRCA1*	MR			None	1	0	Breast, ovarian, lymphoma	HGD, worrisome features
100	36	M	White	*PALB2*	c.172_175delTTGT	p.Gln60Argfs	Frameshift	None	1	1	Breast, melanoma, ovarian	
101	44	F	White	*PALB2*	c.172_175delTTGT	p.Gln60Argfs	Frameshift	None	1	2	Breast	
102	76	M	White	*PALB2*	c.2982dupT	p.Ala995Cysfs	Frameshift	Prostate	1	1	None	
103	72	F	White	*PALB2*	c.2982dupT	p.Ala995Cysfs	Frameshift	Breast	0	1	Breast	
104	69	F	White	*PALB2*	c.2982dupT	p.Ala995Cysfs	Frameshift	Breast	0	1	Breast	
105	63	F	White	*PALB2*	c.3456dupA	p.Pro1153Thrfs	Frameshift	None	1	2	None	PDAC, worrisome features
106	54	F	White	*PALB2*	c.3523C>T	p.Gln1175Ter	Nonsense	None	1	0	Colon	
107	35	F	White	*PALB2*	MR			None	1	1	Breast, melanoma	
108	52	F	White	*PALB2*	MR			Breast	0	1	Bone, breast	
109	58	F	White	*PALB2*	MR			Breast	2	2	Breast	
110	47	F	White	*PALB2*	MR			Breast	2	0	Breast	
111	29	F	White	Hereditary pancreatitis	c.101A>G	p.Asn34Ser	Frameshift	None	0	0	None	
112	63	F	White	Hereditary pancreatitis	c.101A>G	p.Asn34Ser	Frameshift	None	1	2	None	
113	59	F	White	Hereditary pancreatitis	MR			None	0	0	Colon	Worrisome features
114	57	F	White	*ATM*	c.3214G>T	p.Glu1072Ter	Missense	None	1	3	None	
115	56	F	White	*ATM*	c.3802delG	p.Val1268Terfs	Frameshift	Breast	1	1	Lung	
116	72	M	White	*ATM*	c.3802delG	p.Val1268Terfs	Frameshift	Prostate	2	0	Breast	
117	60	M	White	*ATM*	c.4987-1G>T		Splice	None	1	1	None	
118	45	F	White	*ATM*	c.8266A>T	p.Lys2756Ter	Nonsense	Breast, stomach	1	4	Breast	PDAC, worrisome features
119	70	F	White	*ATM*	c.8565_8566delTGinsAA	p.Ser2855_Val2856delinsArgIle	Missense	Skin	2	0	Bladder	Worrisome features
4*04	61	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Prostate, thyroid	1	1	Stomach	
2*82	45	M	White	*BRCA2*	c.5946delT	p.Ser1982Argfs	Frameshift	Melanoma	1	2	NA	
4*22	63	M	White	*BRCA1*	c.68_69delAG	p.Glu23Valfs	Frameshift	None	2	0	None	
1*38	65	M	White	*PALB2*	c.3256C>T	p.Arg1086Ter	Nonsense	None	3	0	Breast, colon, endometrial, esophageal, gallbladder, stomach, liver, lung, uterine	
3*87	51	F	White	*ATM*	c.6679C>T	p.Arg2227Cys	Missense	None	1	1	Colon, prostate	
3*12	58	F	White	*ATM*	c.*5_*8delGTGA		Splice	None	1	3	Bladder, prostate	
3*89	65	M	White	*ATM*	c.9022C>T	p.Arg3008Cys	Missense	None	2	0	Colon, breast, stomach	
4*55	50	F	White	*ATM*	c.2730_2731insAG	p.A911delinsRLfs	Frameshift	None	1	1	None	

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TABLE A4. Known Germline Mutations in Pancreatic Cancer Susceptibility Genes (continued)

Pt No.	Age†	Sex	Race	Gene	Nucleotide Change	Amino Acid Change	Function	Personal History of Cancer	FDR, No.	SDR, No.	Family History of Cancer	Diagnosis
3*68	60	F	White	*ATM*	c.8266A>T	p.Lys2756Ter	Nonsense	None	2	3	Breast, colon, lung, stomach	
1*02	59	M	White	*ATM*	c.8266A>T	p.Lys2756Ter	Nonsense	None	2	2	Breast, colon, lung, lymphoma, prostate, stomach	PDAC, worrisome features
1*66	70	M	White	*ATM*	c.6679C>T	p.Arg2227Cys	Missense	Prostate	2	0	Brain, colon, lung, prostate, uterine	
2*16	55	F	White	*ATM*	c.3802delG	p.Val1268Terfs	Frameshift	None	2	0	Breast, colon, stomach	
1*10	60	M	White	*ATM*	c.1027_1030delGAAA	p.Glu343Ilefs	Frameshift	Melanoma	1	3	Breast, melanoma	
2*48	60	F	White	*CPA1*	c.640G>T	p.Asp214Tyr	Missense	None	2	1	Ovarian	
2*66	77	M	White	*TP53*	c.847C>T	p.Arg283Cys	Missense	None	2	1	None	Worrisome features

Abbreviations: FAMMM, familial atypical multiple mole melanoma; FDR, first-degree relative; HGD, high-grade dysplasia (pancreatic intraepithelial neoplasia grade 3 or intraductal papillary mucinous neoplasm); HNPCC, hereditary nonpolyposis colorectal cancer; MR, medical record; NA, not available; PDAC, pancreatic ductal adenocarcinoma; PJS, Peutz-Jeghers syndrome; Pt, patient; SDR, second-degree relative.

†In years.

TABLE A5. Category of High-Risk Individuals for Pancreatic Ductal Adenocarcinoma

Category	No.
Familial pancreatic cancer risk group	330
More than two FDRs	150
One FDR, one SDR minimum	180
Germline mutation risk group	134
Peutz-Jeghers syndrome	12
BRCA2	61
PALB2	12
FAMMM	8
BRCA1	19
HNPCC	2
ATM	15
Hereditary pancreatitis	3
CPA1	1
TP53	1

Abbreviations: FAMMM, familial atypical multiple mole melanoma; FDR, first-degree relative; HNPCC, hereditary nonpolyposis colorectal cancer; SDR, second degree relative.

TABLE A6. Estimates of Time to PDAC, PDAC or HGD, or Detection of Worrisome Features According to Germline Mutation Status

Mutation Status	No. of Patients	No. of Events	Cumulative Incidence (range)			HR (95% CI)	*P*
			5 Years	10 Years	15 Years		
BRCA1	18	5	0.27 (0-0.55)	NA	NA	7.39 (3.11 to 17.56)	< .001
Other germline mutation risk (not *BRCA1*)	108	16	0.15 (0.06-0.25)	0.4 (0.16-0.63)	0.51 (0.22-0.81)	2.8 (1.46 to 5.38)	.002
Family history–only risk	320	21	0.07 (0.03-0.1)	0.18 (0.08-0.28)	0.24 (0.12-0.36)	1.0 (ref)	—
BRCA2	59	7	0.12 (0.02-0.21)	0.27 (0.05-0.49)	NA	2.42 (1 to 5.86)	.05
Other germline mutation risk (not *BRCA2*)	67	14	0.22 (0.08-0.36)	0.57 (0.26-0.88)	0.77 (0.34-1.2)	3.97 (2.05 to 7.7)	< .001
Family history–only risk	320	21	0.07 (0.03-0.1)	0.18 (0.08-0.28)	0.24 (0.12-0.36)	1.0 (ref)	—
ATM	14	2	0.14 (0-0.42)	0.14 (0-0.42)	0.57 (0-1.42)	1.5 (0.36 to 6.31)	.58
Other germline mutation risk (not *ATM*)	112	19	0.17 (0.08-0.26)	0.54 (0.27-0.8)	NA	3.75 (2.01 to 6.98)	< .001
Family history–only risk	320	21	0.07 (0.03-0.1)	0.18 (0.08-0.28)	0.24 (0.12-0.36)	1.0 (ref)	—
PALB2	12	1	0 (0-0)	0.5 (0-1.48)	NA	2.73 (0.37 to 20.27)	.33
Other germline mutation risk (not *PALB2*)	114	20	0.18 (0.09-0.27)	0.47 (0.22-0.72)	0.57 (0.29-0.85)	3.31 (1.8 to 6.07)	< .001
Family history–only risk	320	21	0.07 (0.03-0.1)	0.18 (0.08-0.28)	0.24 (0.12-0.36)	1.0 (ref)	—
BRCA2 or *PALB2*	71	8	0.11 (0.02-0.2)	0.31 (0.09-0.53)	NA	2.45 (1.06 to 5.68)	.04
Other germline mutation risk (not *BRCA2* nor *PALB2*)	55	13	0.24 (0.08-0.39)	0.6 (0.21-0.99)	0.79 (0.38-1.19)	4.12 (2.1 to 8.11)	< .001
Family history–only risk	320	21	0.07 (0.03-0.1)	0.18 (0.08-0.28)	0.24 (0.12-0.36)	1.0 (ref)	—

NOTE. Values are cumulative incidence of the event at 5, 10, and 15 years after enrollment adjusted for death as a competing event. HR adjusted for age at enrollment and sex.

Abbreviations: HGD, high-grade dysplasia (pancreatic intraepithelial neoplasia grade 3 or intraductal papillary mucinous neoplasm); HR, hazard ratio; NA, not applicable; PDAC, pancreatic ductal adenocarcinoma; ref, reference.

TABLE A7. *CPA1* and *CPB1* Variants

Gene	Chr Position	rsID	Amino Acid Change	Nucleotide Change	Function	Zygosity	Loss of Secretion	ER Stress Inducing	Classification
CPA1	Chr7: 130023579		p.D214Y	c.640G>T	Missense	Heterozygous	Yes	Yes	Deleterious
CPA1	Chr7:148577788		p.A259V	c.776C>T	Missense	Heterozygous	No	No	Defective
CPB1	Chr3:148545842	rs193238667	p.R42H	c.125G>A	Missense	Heterozygous	No	No	Defective
CPB1	Chr3:148552355		p.A73G	c.218C>G	Missense	Heterozygous	No	No	Defective
CPB1	Chr3:148575263		p.T334I	c.1001C>T	Missense	Heterozygous	No	No	Defective

Abbreviations: Chr, chromosome; ER, endoplasmic reticulum; ID, identifier.