VOLUME 35 · NUMBER 30 · OCTOBER 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma

Koji Shindo, Jun Yu, Masaya Suenaga, Shahriar Fesharakizadeh, Christy Cho, Anne Macgregor-Das, Abdulrehman Siddiqui, P. Dane Witmer, Koji Tamura, Tae Jun Song, Jose Alejandro Navarro Almario, Aaron Brant, Michael Borges, Madeline Ford, Thomas Barkley, Jin He, Matthew J. Weiss, Christopher L. Wolfgang, Nicholas J. Roberts, Ralph H. Hruban, Alison P. Klein, and Michael Goggins

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

Published at jco.org on August 2, 2017.

Processed as a Rapid Communication manuscript.

K.S. and J.Y. contributed equally to this work.

Corresponding author: Michael Goggins, MD, Department of Pathology, Johns Hopkins Medical Institutions, 1550 Orleans St, Baltimore, MD 21231; e-mail: mgoggins@jhmi.edu.

0732-183X/17/3530w-3382w/$20.00

ABSTRACT

Purpose
Deleterious germline mutations contribute to pancreatic cancer susceptibility and are well documented in families in which multiple members have had pancreatic cancer.

Methods
To define the prevalence of these germline mutations in patients with apparently sporadic pancreatic cancer, we sequenced 32 genes, including known pancreatic cancer susceptibility genes, in DNA prepared from normal tissue obtained from 854 patients with pancreatic ductal adenocarcinoma, 288 patients with other pancreatic and periampullary neoplasms, and 51 patients with non-neoplastic diseases who underwent pancreatic resection at Johns Hopkins Hospital between 2000 and 2015.

Results
Thirty-three (3.9%; 95% CI, 3.0% to 5.8%) of 854 patients with pancreatic cancer had a deleterious germline mutation, 31 (3.5%) of which affected known familial pancreatic cancer susceptibility genes: *BRCA2* (12 patients), *ATM* (10 patients), *BRCA1* (3 patients), *PALB2* (2 patients), *MLH1* (2 patients), *CDKN2A* (1 patient), and *TP53* (1 patient). Patients with these germline mutations were younger than those without (mean ± SD, 60.8 ± 10.6 *v* 65.1 ± 10.5 years; $P = .03$). Deleterious germline mutations were also found in *BUB1B* (1) and *BUB3* (1). Only three of these 33 patients had reported a family history of pancreatic cancer, and most did not have a cancer family history to suggest an inherited cancer syndrome. Five (1.7%) of 288 patients with other periampullary neoplasms also had a deleterious germline mutation.

Conclusion
Germline mutations in pancreatic cancer susceptibility genes are commonly identified in patients with pancreatic cancer without a significant family history of cancer. These deleterious pancreatic cancer susceptibility gene mutations, some of which are therapeutically targetable, will be missed if current family history guidelines are the main criteria used to determine the appropriateness of gene testing.

J Clin Oncol 35:3382-3390. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic cancer is expected to be the second leading cause of cancer death in the United States by the year 2030.[1] Inherited gene mutations are known to contribute to pancreatic cancer in patients with familial pancreatic cancer (defined by the presence of two first-degree relatives with the disease),[2] but the extent to which deleterious gene mutations contribute to pancreatic cancer risk in individuals without a family history of pancreatic cancer is not well defined. Identifying inherited susceptibility gene mutations in an individual improves assessment and decisions regarding cancer screening for family members and can guide treatment of patients with pancreatic cancer.

The established familial pancreatic cancer susceptibility genes include the *BRCA2*, *ATM*, *PALB2*, *CDKN2A*, *PRSS1*, *STK11*, *MLH1*, and *MSH2*[3] genes.[4-8] The results of whole-genome sequencing of more than 600 individuals with familial pancreatic cancer were recently reported, with analysis focused on the role of low-frequency truncating mutations.[2] Deleterious germline

ASSOCIATED CONTENT

See accompanying Editorial on page 3375

Appendix

DOI: https://doi.org/10.1200/JCO.2017.72.3502

mutations in the *BRCA2* gene account for the biggest fraction of known familial pancreatic cancer genes (found in approximately 5% to 10% of familial pancreatic cancer families[7,9-12]), followed by *ATM* (deleterious mutations found in approximately 2% to 3%).[2,4] Deleterious germline mutations involving other genes are less common (each found in approximately ≤ 1% of affected individuals from familial pancreatic cancer kindred). These genes include *CDKN2A* (deleterious mutations cause familial atypical melanoma mole syndrome),[13-17] *PALB2* (DNA mismatch–repair genes that cause Lynch syndrome),[3] *STK11* (Peutz-Jeghers syndrome), and *PRSS1* (hereditary recurrent acute pancreatitis).[8,18-21] Germline *BRCA1* mutations increase the overall risk of developing pancreatic cancer by approximately two- to -four-fold.[2,7,22,23] The role of other genes in pancreatic cancer susceptibility is still being evaluated.

The prevalence of germline mutations in individual pancreatic cancer susceptibility genes in patients with apparently sporadic forms of the disease (ie, without a family history of pancreatic cancer) has also been studied.[24-27] These studies have primarily focused on *BRCA* genes. For example, germline *BRCA2* mutations are found in a small percentage of patients with apparently sporadic pancreatic cancer,[28] with a higher prevalence found in populations with many individuals of Ashkenazi Jewish heritage because of the common 6174delT *BRCA2* founder mutation in that population.[27,29-33] In one study, germline *BRCA* mutations were identified in 4.6% of an unselected series of 306 patients with pancreatic cancer from a single center.[24]

The absence of a significant family history in patients with an established deleterious germline mutation is probably primarily as the result of incomplete penetrance, rather than de novo mutation in the germline. For example, the average lifetime risk of developing pancreatic cancer among *BRCA2* gene mutation carriers is estimated to be approximately 5% to 10%.[34-36] Notably, these estimates have been determined primarily in families ascertained for breast and/or ovarian cancer and therefore may be an underestimate.

There is considerable potential clinical utility to identifying a germline susceptibility gene in a patient with pancreatic cancer. Mutation carriers with pancreatic cancer may have more options for personalized medicine directed against the genetic drivers of their cancer,[37] and their family members may benefit from cancer screening and cancer prevention strategies for pancreatic and extrapancreatic cancers.[38-42] Relatives of patients with apparently sporadic pancreatic cancer are at increased risk of mortality from other cancers.[43]

In this study, we determined the prevalence of germline mutations in known and candidate pancreatic cancer susceptibility genes in a large hospital-based series of patients unselected for their family history of pancreatic cancer. We compared the prevalence of deleterious mutations in these patients with the prevalence in patients who underwent surgery for other periampullary cancers and diseases.

METHODS

Patients and Specimens

This study included 854 patients with pancreatic ductal adenocarcinoma who were evaluated and treated at the Johns Hopkins Hospital between 2000 and 2015. Patients were enrolled in the study during their preoperative evaluation or during their multidisciplinary clinic visit. Personal and family history information was obtained from the medical record and from the National Familial Pancreas Tumor Registry. To estimate the prevalence of deleterious germline mutations in patients with other periampullary/pancreatic diseases referred to the same clinical services, we included 339 patients who had undergone pancreatic resection for periampullary/biliary pathology other than pancreatic cancer, including 108 with other cancers (duodenal, biliary, gall bladder), 113 with other neoplasms (pancreatic neuroendocrine tumors, GI stromal tumors, carcinoid), 25 with precancerous neoplasms (duodenal, ampullary adenoma), 25 with serous cystadenoma, and 51 with non-neoplastic conditions including 37 with pancreatitis (Table 1); patient demographic data are listed in Table 2.

All elements of this study were approved by the Johns Hopkins Institutional Review Board, and written informed consent was obtained from all patients.

DNA Extraction

Genomic DNA was extracted from either frozen normal tissue from pancreatic resection specimens (duodenum, spleen, or pancreas) or peripheral blood mononuclear cells using QIAamp DNA Micro Kit (QIAGEN, Hilden, Germany), according to the manufacturer's instructions. DNA samples were quantified using Quantifiler (Thermo Fisher Scientific, Waltham, MA).

DNA Sequencing

Thirty-two genes (Appendix Table A1 [online only]) were sequenced using an AmpliSeq Custom Panel. Next-generation sequencing was performed using the Ion Proton system (Life Technologies [Life-Tech], Carlsbad, CA), according to the manufacturer's protocols and as previously described.[44] These genes were either known pancreatic cancer susceptibility genes (*BRCA2*, *ATM*, *PALB2*, *BRCA1*, *CDKN2A*, *MLH1*, *MSH2*, *PRSS1*, *STK11*, and *TP53*), known cancer susceptibility genes (*MSH6*, *PMS2*, *CDH1*, *RAD51C*, *RAD51D*, *BUB1B*, and *FANCJ*), or candidate pancreatic cancer susceptibility genes (*FANCA*, *FANCC*, *FANCG*, *FANCL*, *ARID1A*, *RECQL4*, *XRCC2*, *XRCC3*, *ERCC4*, *TERT*, *BAP1*, *BUB1*, *BUB3*, and *RNF43*). Thus, 20 ng of DNA (10 ng per primer pool) were used for AmpliSeq polymerase chain reaction. After FuPa digestion, P1 adaptor/Xpress barcode ligation, and library clean up (Agencourt AMPure XP Reagent; Beckman Coulter, Brea, CA), libraries were eluted into low Tris-EDTA and quantified (Ion Quantitation Kit; Life-Tech).

Table 1. Pathology and Indications for Pancreatic Resection

Diagnosis	No.
Pancreatic ductal adenocarcinoma	854
Other diagnostic groups	339
Pancreatitis (AIP, CP, groove pancreatitis)	37
Ampullary adenoma	13
Cholangiocarcinoma (lower CBD)	47
Carcinoid, GIST, neuroendocrine tumor	109
Duodenal adenocarcinoma	54
Duodenal adenoma	12
Gallbladder adenocarcinoma	7
Lymphoepithelial cyst	1
Serous cystadenoma	25
Solid pseudopapillary neoplasm	4
Other malignancy*	17
Other†	13

Abbreviations: AIP, autoimmune pancreatitis; CBD, common bile duct; CP, chronic pancreatitis; GIST, GI stromal tumor.
*Nonpancreatic malignancies.
†Nonmalignant diseases with normal pancreas.

Table 2. Patient Characteristics

Classification	Pancreatic Cancer, No. (%)	Other Diseases, No. (%)
Total no. of patients	854	339
Mean age in years ± SD	65.0 ± 10.9	60.1 ± 14.1
< 51	81 (9)	79 (23)
51-60	199 (23)	80 (24)
61-70	297 (35)	95 (28)
71-80	220 (26)	69 (20)
≥ 80	57 (7)	16 (5)
Sex		
Male	455 (53)	181 (53)
Female	399 (47)	158 (47)
Race		
White	756 (89)	280 (83)
African American	52 (6)	31 (9)
Other	46 (5)	28 (8)
Family history of pancreatic cancer	109 (12.7)	15 (4)
First-degree relative with pancreatic cancer	77 (9.0)	

Libraries underwent emulsion polymerase chain reaction in an Ion OneTouch2 (Life-Tech) for 5 hours; Ion Sphere Particles were then cleaned and enriched in the OneTouch ES (Life-Tech). Enriched Ion Sphere Particles were loaded into P1v3 chips for sequencing (Ion Proton; Life-Tech). The postsequencing raw FASTQ files were launched in NextGENe (version 2.41; SoftGenetics, Chicago, IL) software for alignment to the hg19 human reference genome and single-nucleotide variant calling. Alignments were visually verified using Integrative Genomics Viewer (version 2.3; Broad Institute, Cambridge, MA) and NextGENe Viewer. The functional significance of variants was determined by interrogating ClinVar and PubMed. Variants of unknown significance are listed in Appendix Table A2 (online only). Variants identified as truncating (nonsense, frameshift, splice intervening sequence ± 1 or 2) and deleterious missense variants were validated by Sanger sequencing performed at The Johns Hopkins Synthesis & Sequencing Facility (Applied Biosystems DNA sequencers; Sanger validation primer sequences are listed in Appendix Table A3 [online only]). Deleterious variants were identified in several candidate pancreatic cancer susceptibility genes. To further evaluate these variants, primary pancreatic cancer tissue from three patients was laser-capture microdissected[44] and sequenced to evaluate for biallelic inactivation (tumor was not available from the patients with the *RAD51D* or *BUB1B* mutation). For genes with deleterious truncating variants (Table 3), we provide the truncating variant data in control subjects from the ExAC database (Broad Institute; Table 4).

Statistical Analysis

The mean age of carriers of a deleterious germline variant was compared with noncarriers using the *t* test. SPSS software was used (version 22; IBM, Armonk, NY). A two-tailed $P < .05$ was considered statistically significant.

RESULTS

Characteristics of the study population are listed in Table 1 and Table 2. Thirty-three (3.9%) of the 854 patients with pancreatic ductal adenocarcinoma had an identifiable deleterious germline mutation, of which 28 were truncating (Table 3). Thirty-one (3.5%) of these patients had a deleterious mutation in a known pancreatic cancer susceptibility gene. This included 12 patients with deleterious germline *BRCA2* mutations, five of whom carried the Ashkenazi Jewish founder *BRCA2* mutation (6174delT); ten with *ATM*; three with *BRCA1*; two with *PALB2*; two with *MLH1*; and one each with a *CDKN2A* and *TP53* mutation. Two patients had a mutation in a candidate pancreatic cancer susceptibility gene (*BUB1B* and *BUB3*). Patients with deleterious *BUB1B* mutations are prone to aneuploidy, chromosomal alterations, and cancer,[45] and *BUB1B* has been identified as a candidate pancreatic cancer susceptibility gene.[2] Evidence regarding the role of *BUB3* as a cancer susceptibility gene is less clear[46,47]; both *BUB1B* and *BUB3* regulate mitotic checkpoints and, in mouse models, *BUB3* heterozygotes are similarly prone to premature aging and chromosomal instability.[48] We sequenced the pancreatic cancer DNA from the patient with the deleterious germline *BUB3* variant but did not find evidence of biallelic inactivation.

In addition to the 33 patients with a deleterious mutation in a known or suspected pancreatic cancer susceptibility gene, three patients carried a deleterious mutation in another cancer susceptibility gene (one each involving *CDH1*, *RAD51D*, and *RAD51B*). The significance of these variants for pancreatic cancer susceptibility is not certain (they are listed in Appendix Table A2). *RAD51D* and *RAD51C* are ovarian cancer susceptibility genes.[49,50] Common variants in *RAD51B* are associated with increased breast cancer risk.[51] Germline *CDH1* mutations predispose to hereditary gastric cancer and lobular breast cancer. The *CDH1* P373L mutation identified in one patient has been described in a hereditary gastric cancer family.[52] We sequenced microdissected pancreatic cancer DNA from the patients with the germline *RAD51B* and *CDH1* mutation, but we did not find evidence of biallelic inactivation of their germline mutated gene in their pancreatic cancer. Overall, there is not sufficient evidence to indicate that *RAD51B* and *CDH1* germline mutations contribute to pancreatic cancer development.

Numerous variants of unknown significance were also identified (listed in Appendix Table A2). In addition to the 33 patients with deleterious mutations, two patients with pancreatic ductal adenocarcinoma carried the *BRCA2* polymorphic stop variant p.K3326X. This variant was initially not thought to confer a cancer risk, but is now considered a modifier allele with evidence that carriers have a small increased risk of breast, pancreatic, and other cancers.[53-55]

The majority (82%) of patients with deleterious germline mutations had a family history of other cancers, but only five mutation carriers (15%) had cancer family histories that suggested a familial cancer syndrome (Table 3). Eighteen of the 33 mutation carriers had a family history of breast cancer reported in a first- or second-degree relative, six had a family history of prostate cancer, and three had a family history of ovarian cancer. Only three (9%) of the 33 individuals with a germline deleterious mutation had a family history of pancreatic cancer. In comparison, among the 818 patients with pancreatic ductal adenocarcinoma without a germline mutation, 117 (14.3%) had a family history of pancreatic cancer identified; for 86 of these patients, it was in a first-degree relative.

Although there are no dedicated pancreatic cancer National Comprehensive Cancer Network (NCCN) guidelines for gene testing, the breast/ovarian cancer NCCN guidelines for gene testing[56] include recommendations for when to consider gene testing patients with

Table 3. Deleterious Mutations in Pancreatic Cancer Susceptibility Genes

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	Zygosity	Family History
PDAC patient cases											
Case_8*25	66	F	White	PDAC	*BRCA2*	13:32911298-9	p.K936Kfs	c.2808_2811delACAA	Frameshift	Heterozygous	Proband breast, prostate (father), breast (paternal aunt), breast (maternal aunt), stomach (paternal uncle), colon (paternal aunt), breast (paternal aunt)
Case_15*71	60	M	White	PDAC	*BRCA2*	13:32911298-9	p.K936Kfs	c.2808_2811delACAA	Frameshift	Heterozygous	Prostate (father)
Case_2*57	83	F	African American	PDAC	*BRCA2*	13:32911419	p.S976Sfs	c.2928delC	Frameshift	Heterozygous	None
Case_12*44	43	F	White	PDAC	*BRCA2*	13:32912036	p.F1182Xfs	c.3545_3546delTT	Frameshift	Heterozygous	Colon (father)
Case_13*16	72	F	White	PDAC	*BRCA2*	13:32914401	p.S1970X	c.5909C>AC	Nonsense	Heterozygous	Ovarian (mother), breast (maternal grandmother)
Case_5*32	63	F	White	PDAC	*BRCA2*	13:32914401	p.S1970X	c.5909C>AC	Nonsense	Heterozygous	None
Case_1*14	62	F	White	PDAC	*BRCA2*	13:32914438	p.S1982Rfs	c.5946delT	Frameshift	Heterozygous	Breast (mother)
Case_4*30	61	M	White	PDAC	*BRCA2*	13:32914438	p.S1982Rfs	c.5946delT	Frameshift	Heterozygous	NA
Case_10*72	57	F	White	PDAC	*BRCA2*	13:32914438	p.S1982Rfs	c.5946delT	Frameshift	Heterozygous	Breast with *BRCA2* gene positive (sister)
Case_14*33	42	F	White	PDAC	*BRCA2*	13:32914438	p.S1982Rfs	c.5946delT	Frameshift	Heterozygous	Lung (mother), lymphoma (grandfather), prostate (paternal uncle), pancreatic (two paternal great aunts)
Case_14*43	60	M	White	PDAC	*BRCA2*	13:32914438	p.S1982Rfs	c.5946delT	Frameshift	Heterozygous	Breast (sister), colon (father), colon (paternal grandfather), unknown (mother), ovary (paternal aunt), breast (another paternal aunt)
Case_13*10	59	M	White	PDAC	*BRCA2*	13:32932067	Splice	c.7805+1G>A	Noncoding	Heterozygous	Breast (sister), colon (mother), gastric (mother)
Case_14*60	63	M	White	PDAC	*ATM*	11:108098354	p.M1I†	c.3G>A	Missense	Heterozygous	Pancreas (maternal aunt), colon (paternal aunt)
Case_7*77	74	M	White	PDAC	*ATM*	11:108098600	p.W57X	c.170G>A	Nonsense	Heterozygous	None
Case_3*88	62	M	White	PDAC	*ATM*	11:108121753	p.E522Ifs	c.1564_1565delGA	Frameshift	Heterozygous	Prostate (brother), breast (mom)
Case_5*18	56	F	White	PDAC	*ATM*	11:108173656	p.S1799Mfs	c.5396delG	Frameshift	Heterozygous	Pancreas (brother), esophagus (father), breast (paternal aunt), throat (paternal grandmother)

(continued on following page)

Table 3. Deleterious Mutations in Pancreatic Cancer Susceptibility Genes (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	Zygosity	Family History
Case_13*92	60	F	White	PDAC	*ATM*	11:108186742	p.R2034X	c.6100C>T	Nonsense	Heterozygous	Breast (mother, maternal aunt, grandmother)
Case_9*25	60	F	Other	PDAC	*ATM*	11:108188128	p.I2076Ifs	c.6228delT	Frameshift	Heterozygous	Breast (mother)
Case_7*16	74	F	Other	PDAC	*ATM*	11:108206605	p.Q2729X	c.8185C>T	Nonsense	Heterozygous	None
Case_1*69	35	M	White	PDAC	*ATM*	11:108214065	p.F2799Kfs	c.8395_8404delTTTCAGTGCC	Frameshift	Heterozygous	Melanoma (paternal uncle)
Case_14*57	55	F	White	PDAC	*ATM*	11:108214065	p.F2799Kfs	c.8395_8404delTTTCAGTGCC	Frameshift	Heterozygous	Breast (mother, maternal grandmother), basal cell carcinoma (mother), glioma (son)
Case_15*06	77	M	White	PDAC	*ATM*	11:108236086	p.R3008C†	c.9022C>T	Missense	Heterozygous	Prostate cancer
Case_4*67	50	F	White	PDAC	*BRCA1*	17:41243887	p.E1221X	c.3661C>A	Nonsense	Heterozygous	Breast (sister), lung (maternal uncle), thyroid (brother), colon (mother), breast (two paternal aunts), lymphoma (father)
Case_14*38	71	F	White	PDAC	*BRCA1*	17:41247941	Splice	c.594-2T>G	Noncoding	Heterozygous	Skin (sister)
Case_2*21	58	M	White	PDAC	*BRCA1*	17:41276034	fs	c.70_80delCAGATGGGACA	Frameshift	Heterozygous	Breast (mother, sister), ovarian (mother), brain (mother)
Case_10*64	75	M	White	PDAC	*CDKN2A*	9:21994234	p.E33delinsGVfs	c.97_98insC	Frameshift	Heterozygous	NA
Case_13*60	47	F	White	PDAC	*MLH1*	3:37092123	p.Y750X	c.2250C>G	Nonsense	Heterozygous	Colon (father)
Case_12*10	62	F	White	PDAC	*MLH1*	3:37038184	p.N64S†	c.191A>G	Missense	Heterozygous	Breast (paternal aunt)
Case_5*38	54	M	White	PDAC	*PALB2*	16:23647028	p.N280Tfs	c.839delT	Frameshift	Heterozygous	Breast and uterine (sister)
Case_13*27	65	M	White	PDAC	*PALB2*	16:23641089	p.G796X	c.2386C>A	Nonsense	Heterozygous	Breast (paternal aunt)
Case_13*71	59	M	White	PDAC	*TP53*	17:7578388	p.R181H†	c.542C>T	Missense	Heterozygous	Prostate (father), lymphoma (son)
Case_15*64	81	M	White	PDAC	*BUB1B*	15:40509781	p.Q921H†	c.2763G>C	Missense	Heterozygous	Breast (daughter)
Case_8*23	69	M	White	PDAC	*BUB3*	10:124920082	Splice	c.576+1G>A	Noncoding	Heterozygous	Breast (mother), prostate (father)
Non-PDAC patient cases											
Case_5*83	38	M	White	Duodenal ulcer after XRT for lymphoma	*BRCA2*	13:32913795	p.L1768Rfs	c.5303_5304delTT	Frameshift	Heterozygous	None
Case_9*27	60	M	White	RCC (pancreas met)	*ATM*	11:108186742	p.R2034X	c.6100C>T	Nonsense	Heterozygous	Prostate (father), breast (mother)
Case_8*12	75	F	White	Cholangioca	*ATM*	11:108206605	p.Q2729X	c.8185C>T	Nonsense	Heterozygous	Breast (sister)
Case_9*13	70	F	White	Cholangioca	*BRIP1*	17:59821794	fs	c.2255_2256delTT	Frameshift	Heterozygous	Colorectal (mother), lung (father)
Case_6*66	54	F	White	GIST	*RAD51C*	17:56811508	p.S353Hfs	c.1057_1066delTCTGCATGTT	Frameshift	Heterozygous	None

NOTE. All candidates were validated by Sanger sequencing.

Abbreviations: Cholangioca, cholangiocarcinoma; F, female; GIST, GI stromal tumor; M, male; met, metastases; NA, not applicable; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; XRT, radiotherapy.

†Pathogenic missense.

pancreatic cancer. Candidates for gene testing include individuals 1with a close relative with pancreatic cancer, 2who are of Ashkenazi Jewish descent with pancreatic cancer, and 3with a close blood relative with ovarian cancer or young-onset breast cancer. On the basis of these criteria, five pancreatic cancer cases with the Ashkenazi *BRCA2* founder mutation would be eligible for gene testing, as would nine others with a significant cancer family history (first-degree relative with pancreatic cancer, a close blood relative with ovarian cancer or young-onset breast cancer, or multiple close relatives with breast cancer).

The average age ± SD at diagnosis of patients with pancreatic ductal adenocarcinoma identified as having a germline mutation in a known (*BRCA2*, *ATM*, *CDKN2A*, *PALB2*, *MLH1*, *BRCA1*, and *TP53*) pancreatic cancer susceptibility gene was 60.8 ± 10.6 years, significantly lower than the average age of the patients without an identifiable susceptibility gene mutation (65.1 ± 10.1 years; $P = .03$).

A significantly smaller percentage (five of 339 patients [1.5%]; $P = .02$) of patients with diagnoses other than pancreatic ductal adenocarcinoma had an identifiable deleterious germline mutation. All of the nonpancreatic cancer cases with a deleterious germline mutation had another malignancy (five of 238 patients [2.1%]). These included two of the 47 patients with cholangiocarcinoma (one with an *ATM* mutation and another with a *BRIP1* [*FANCJ*] mutation), one patient who had a renal cell carcinoma with pancreatic metastasis (*ATM* mutation), one patient with a duodenal GI stromal tumor (*RAD51C* mutation), and one patient who underwent pancreaticoduodenectomy for a recurrent bleeding duodenal ulcer after radiation therapy for lymphoma (*BRCA2* mutation). The significance of the *BRIP1* mutation is not clear. Evidence from large studies indicates that carriers of germline *BRIP1* mutations are at moderately increased risk of developing ovarian cancer but not breast cancer.[57,58]

No deleterious mutations were identified in any of the other disease control cases. Pancreatic cancer cases were more likely than disease controls without a malignant neoplasm to have a deleterious mutation ($P = .035$). We also compared the prevalence of truncating deleterious variants for each pancreatic cancer susceptibility gene in our pancreatic cancer cases with their prevalence in controls in the ExAC database. Germline truncating mutations involving *BRCA2* and *ATM* were significantly more common in pancreatic cancer cases than in ExAC controls (Table 4).

DISCUSSION

We found a significant yield of deleterious germline mutations in pancreatic cancer susceptibility genes in patients with pancreatic cancer without a pancreatic cancer family history. These patients with apparently sporadic pancreatic cancer also often do not have an extensive family history of pancreatic or other cancers that would trigger consideration for germline gene testing. The prevalence of deleterious germline mutations in patients with apparently sporadic pancreatic cancer is approximately half of that reported to date in patients with familial forms of pancreatic cancer.[7,27]

Family history remains one of the best predictors of future pancreatic cancer risk.[59-61] For common cancers such as breast/ovarian and colorectal cancer (where risk assessment, genetic counseling, and gene testing are well established), current guidelines recommend using family history to risk stratify family members to identify those individuals most likely to benefit from gene testing.[62] In contrast, our results for pancreatic cancer highlight the limitations of relying solely on current NCCN family history guidelines to determine which patients are most likely to carry a deleterious pancreatic cancer susceptibility gene. Indeed, most deleterious germline mutations found in patients with pancreatic cancer are in those who do not meet the familial criteria for gene testing.

Although the evidence is mostly anecdotal in the context of pancreatic cancer, not only can affected relatives have the opportunity to undertake cancer screening and prevention strategies, but it also would have an impact on the patient's treatment. Identifying *BRCA* mutations in patients with pancreatic cancer would provide the opportunity to have personalized therapy with poly (ADP-ribose) polymerase inhibitors or platinums,[63] and Lynch syndrome carriers with pancreatic cancer would have the potential to benefit from immunotherapy.[64] It is suspected that patients with *ATM* germline mutations would benefit from radiotherapy to control local disease (assuming that the gene is biallelically inactivated in their cancer)[65] and may also be more sensitive to certain chemotherapeutics.

Although a large gene panel was evaluated for this study, our results indicate that gene testing patients with pancreatic cancer should be limited to established pancreatic cancer susceptibility genes (*BRCA2*, *ATM*, *PALB2*, *CDKN2A*, and *BRCA1*, and mismatch-repair genes), with testing for *PRSS1* and *STK11* mutations for families suspected of having the corresponding clinical syndromes. Although using large gene panels to identify cancer susceptibility genes as part of research studies can be informative, early experience with using large gene panels to perform germline gene testing in clinical settings has shown that such panels pose challenges.[66] Because of the greater chance of identifying variants of unknown significance, many patients receive inconclusive results, and the potential for misunderstanding and anxiety is significant.

The potential to benefit the few individuals with actionable gene mutations would seem to justify the effort to routinely offer gene testing to all patients with pancreatic ductal adenocarcinoma to identify such cases.[39,67] However, offering widespread genetic testing for patients with pancreatic cancer has significant challenges, not the least being that patients should undergo genetic counseling before and after such testing to provide understanding and reassurance and to avoid harm.[68] Unfortunately, there are not enough genetic counselors to provide this service. This shortage of genetic counselors applies to other cancers and, as a result, most patients, even those who undergo gene testing for *BRCA* mutations, do so without genetic counseling.[69] The demand for *BRCA* gene testing has led to alternative approaches. One approach taken in some centers that are sequencing cancer samples is to provide an opt-out option for patients who do not want to know about germline information. Another approach in situations where there is considerable demand, such as for patients with ovarian cancer, is to provide genetic counseling where clinicians (including nurses trained in genetic counseling) provide the service.[70] Because of the potential for adverse events when gene testing is performed without adequate genetic counseling, most experts recommend

Table 4. Prevalence of Truncating Variants in Pancreatic Cancer Susceptibility Genes: ExAC Controls Versus PDAC Patient Cases

	ExAC Database (frameshift/stop)				PDAC Patient Cases, Present Study		Truncating Only*	
Gene	Truncating Allele, No.	Total Allele, Average	Total Genotypes	Truncating Variant Frequency, %	Truncating Variant, No.	PDAC, No.	Truncating Variant Frequency, %	*P*
BRCA2	251	117,864	58,932	0.43	12	854	1.41	< .0001
ATM	129	115,856	57,928	0.22	8	854	0.94	< .0001
BRCA1	134	111,384	55,692	0.24	3	854	0.35	.7625
CDKN2A	13	96,030	48,015	0.03	1	854	0.12	.1237
MLH1	36	116,544	58,272	0.06	1	854	0.12	.5218
PALB2	81	116,899	58,449.5	0.14	2	854	0.23	.4602

NOTE: Truncating mutations only were considered because the functional significance of many missense mutations is not known. *TP53* is not included in this list because most deleterious mutations in *TP53* are missense.
Abbreviation: PDAC, pancreatic ductal adenocarcinoma.
*All of them are heterozygous.

that appropriate counseling[71] and testing should only be undertaken by those with the expertise.[72] Genetic counseling for patients with pancreatic cancer poses additional challenges. Because pancreatic cancer often progresses rapidly, patients can greatly benefit from optimal selection of their first-line therapy; thus, ideally, counseling and testing would be incorporated into routine patient care so that it can be performed rapidly. Relatives of patients with pancreatic cancer who are also mutation carriers can also benefit from gene testing. Here, the need for genetic counseling is perhaps more important, because the lifetime estimates of developing pancreatic and other cancers for carriers of deleterious mutations need to be better defined, and the benefits of pancreatic screening are still being established.[38,41] Because cancer genetics risk assessment is not a routine component of pancreatic cancer care, it would be valuable to undertake studies to determine the benefits and challenges of incorporating risk assessment and gene testing into routine pancreatic cancer practice. Additional studies are also needed to determine how cancer family history and other risk factor information can help refine pancreatic cancer risk in mutation carriers. Furthermore, the pancreatic cancer risk associated with mutations in some pancreatic cancer susceptibility genes (such as *ATM* and *PALB2*) is not well defined, and the effectiveness of screening these mutation carriers is not established.

There are some limitations to our study. First, this was a retrospective study where we relied on self-reported family history of pancreatic and other cancers obtained from the medical record, and patient reporting of their familial cancer history is often incomplete. We were also not able to determine if detecting these mutations resulted in clinical benefit to the patients or their families.

In summary, we found that there is a significant yield of deleterious germline mutations in pancreatic cancer susceptibility genes in unselected patients with apparently sporadic pancreatic cancer. Routine gene testing of patients with newly diagnosed pancreatic cancer and their families may yield significant clinical benefits.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Jun Yu, Alison P. Klein, Michael Goggins
Collection and assembly of data: Koji Shindo, Jun Yu, Shahriar Fesharakizadeh, Christy Cho, Anne Macgregor-Das, Abdulrehman Siddiqui, P. Dane Witmer, Koji Tamura, Tae Jun Song, Jose Alejandro Navarro Almario, Aaron Brant, Michael Borges, Madeline Ford, Thomas Barkley, Jin He, Matthew J. Weiss, Christopher L. Wolfgang, Ralph H. Hruban, Alison P. Klein, Michael Goggins
Data analysis and interpretation: Koji Shindo, Jun Yu, Masaya Suenaga, Anne Macgregor-Das, Koji Tamura, Nicholas J. Roberts, Alison P. Klein, Michael Goggins
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Rahib L, Smith BD, Aizenberg R, et al: Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 74:2913-2921, 2014
2. Roberts NJ, Norris AL, Petersen GM, et al: Whole genome sequencing defines the genetic heterogeneity of familial pancreatic cancer. Cancer Discov 6:166-175, 2016
3. Kastrinos F, Mukherjee B, Tayob N, et al: Risk of pancreatic cancer in families with Lynch syndrome. JAMA 302:1790-1795, 2009
4. Roberts NJ, Jiao Y, Yu J, et al: ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov 2:41-46, 2012
5. Klein AP: Genetic susceptibility to pancreatic cancer. Mol Carcinog 51:14-24, 2012
6. Lowenfels AB, Maisonneuve P, DiMagno EP, et al: Hereditary pancreatitis and the risk of pancreatic cancer. J Natl Cancer Inst 89:442-446, 1997
7. Zhen DB, Rabe KG, Gallinger S, et al: BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: A PACGENE study. Genet Med 17:569-577, 2015 doi:10.1038/gim.2014.153
8. Jones S, Hruban RH, Kamiyama M, et al: Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science 324:217, 2009
9. Grant RC, Selander I, Connor AA, et al: Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology 148:556-564, 2015
10. Couch FJ, Johnson MR, Rabe KG, et al: The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev 16:342-346, 2007
11. Hahn SA, Greenhalf B, Ellis I, et al: BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 95:214-221, 2003

12. Murphy KM, Brune KA, Griffin C, et al: Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: Deleterious BRCA2 mutations in 17%. Cancer Res 62:3789-3793, 2002

13. Hussussian CJ, Struewing JP, Goldstein AM, et al: Germline p16 mutations in familial melanoma. Nat Genet 8:15-21, 1994

14. Kamb A, Shattuck-Eidens D, Eeles R, et al: Analysis of the p16 gene (CDKN2) as a candidate for the chromosome 9p melanoma susceptibility locus. Nat Genet 8:23-26, 1994

15. Goldstein AM, Chan M, Harland M, et al: Features associated with germline CDKN2A mutations: A GenoMEL study of melanoma-prone families from three continents. J Med Genet 44: 99-106, 2007

16. Lynch HT, Fusaro RM, Lynch JF, et al: Pancreatic cancer and the FAMMM syndrome. Fam Cancer 7:103-112, 2008

17. de Snoo FA, Bishop DT, Bergman W, et al: Increased risk of cancer other than melanoma in CDKN2A founder mutation (p16-Leiden)-positive melanoma families. Clin Cancer Res 14:7151-7157, 2008

18. Slater EP, Langer P, Niemczyk E, et al: PALB2 mutations in European familial pancreatic cancer families. Clin Genet 78:490-494, 2010

19. Tischkowitz MD, Sabbaghian N, Hamel N, et al: Analysis of the gene coding for the BRCA2-interacting protein PALB2 in familial and sporadic pancreatic cancer. Gastroenterology 137:1183-1186, 2009

20. Schneider R, Slater EP, Sina M, et al: German national case collection for familial pancreatic cancer (FaPaCa): Ten years experience. Fam Cancer 10: 323-330, 2011

21. Harinck F, Kluijt I, van Mil SE, et al: Routine testing for PALB2 mutations in familial pancreatic cancer families and breast cancer families with pancreatic cancer is not indicated. Eur J Hum Genet 20:577-579, 2012

22. Thompson D, Easton DF; Breast Cancer Linkage Consortium: Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 94:1358-1365, 2002

23. Mocci E, Milne RL, Méndez-Villamil EY, et al: Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. Cancer Epidemiol Biomarkers Prev 22:803-811, 2013

24. Holter S, Borgida A, Dodd A, et al: Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol 33:3124-3129, 2015

25. Hu C, Hart SN, Bamlet WR, et al: Prevalence of pathogenic mutations in cancer predisposition genes among pancreatic cancer patients. Cancer Epidemiol Biomarkers Prev 25:207-211, 2016

26. Lucas AL, Frado LE, Hwang C, et al: BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer 120:1960-1967, 2014

27. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al: Identification of germline genetic mutations in patients with pancreatic cancer. Cancer 121:4382-4388, 2015

28. Goggins M, Schutte M, Lu J, et al: Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res 56: 5360-5364, 1996

29. Couch FJ, Farid LM, DeShano ML, et al: BRCA2 germline mutations in male breast cancer cases and breast cancer families. Nat Genet 13: 123-125, 1996

30. Neuhausen S, Gilewski T, Norton L, et al: Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 13:126-128, 1996

31. Oddoux C, Struewing JP, Clayton CM, et al: The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nat Genet 14: 188-190, 1996

32. Figer A, Irmin L, Geva R, et al: The rate of the 6174delT founder Jewish mutation in BRCA2 in patients with non-colonic gastrointestinal tract tumours in Israel. Br J Cancer 84:478-481, 2001

33. Ozçelik H, Schmocker B, Di Nicola N, et al: Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. Nat Genet 16: 17-18, 1997

34. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al: Cancer risks in BRCA2 families: Estimates for sites other than breast and ovary. J Med Genet 42:711-719, 2005

35. Struewing JP, Abeliovich D, Peretz T, et al: The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nat Genet 11:198-200, 1995

36. Ferrone CR, Levine DA, Tang LH, et al: BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol 27:433-438, 2009

37. Knudsen ES, O'Reilly EM, Brody JR, et al: Genetic diversity of pancreatic ductal adenocarcinoma and opportunities for precision medicine. Gastroenterology 150:48-63, 2016

38. Vasen H, Ibrahim I, Ponce CG, et al: Benefit of surveillance for pancreatic cancer in high-risk individuals: Outcome of long-term prospective follow-up studies from three European expert centers. J Clin Oncol 34:2010-2019, 2016

39. Manchanda R, Loggenberg K, Sanderson S, et al: Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: A randomized controlled trial. J Natl Cancer Inst 107:379, 2014

40. Metcalfe K, Lynch HT, Foulkes WD, et al: Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. JAMA Oncol 1:306-313, 2015

41. Canto MI, Hruban RH, Fishman EK, et al: Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology 142: 796-804; quiz e14-e15, 2012

42. Stoffel EM, Mangu PB, Gruber SB, et al: Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol 33:209-217, 2015

43. Wang L, Brune KA, Visvanathan K, et al: Elevated cancer mortality in the relatives of patients with pancreatic cancer. Cancer Epidemiol Biomarkers Prev 18:2829-2834, 2009

44. Yu J, Sadakari Y, Shindo K, et al: Digital next-generation sequencing identifies low-abundance mutations in pancreatic juice samples collected from the duodenum of patients with pancreatic cancer and intraductal papillary mucinous neoplasms. Gut doi:10.1136/gutjnl-2015-311166 [epub ahead of print on July 18, 2016]

45. Hanks S, Coleman K, Reid S, et al: Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. Nat Genet 36: 1159-1161, 2004

46. de Voer RM, Geurts van Kessel A, Weren RD, et al: Germline mutations in the spindle assembly checkpoint genes BUB1 and BUB3 are risk factors for colorectal cancer. Gastroenterology 145:544-547, 2013

47. Broderick P, Dobbins SE, Chubb D, et al: Validation of recently proposed colorectal cancer susceptibility gene variants in an analysis of families and patients—A systematic review. Gastroenterology 152:75-77.e4, 2017

48. Kalitsis P, Fowler KJ, Griffiths B, et al: Increased chromosome instability but not cancer predisposition in haploinsufficient Bub3 mice. Genes Chromosomes Cancer 44:29-36, 2005

49. Song H, Dicks E, Ramus SJ, et al: Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. J Clin Oncol 33:2901-2907, 2015

50. Norquist BM, Harrell MI, Brady MF, et al: Inherited mutations in women with ovarian carcinoma. JAMA Oncol 2:482-490, 2016

51. Orr N, Lemnrau A, Cooke R, et al: Genome-wide association study identifies a common variant in RAD51B associated with male breast cancer risk. Nat Genet 44:1182-1184, 2012

52. Roviello F, Corso G, Pedrazzani C, et al: Hereditary diffuse gastric cancer and E-cadherin: Description of the first germline mutation in an Italian family. Eur J Surg Oncol 33:448-451, 2007

53. Martin ST, Matsubayashi H, Rogers CD, et al: Increased prevalence of the BRCA2 polymorphic stop codon K3326X among individuals with familial pancreatic cancer. Oncogene 24:3652-3656, 2005

54. Thompson ER, Gorringe KL, Rowley SM, et al: Reevaluation of the BRCA2 truncating allele c.9976A > T (p.Lys3326Ter) in a familial breast cancer context. Sci Rep 5:14800, 2015

55. Meeks HD, Song H, Michailidou K, et al: BRCA2 polymorphic stop codon K3326X and the risk of breast, prostate, and ovarian cancers. J Natl Cancer Inst 108:djv315, 2015 doi:10.1093/jnci/djv315

56. Provenzale D, Gupta S, Ahnen DJ, et al: Genetic/familial high-risk assessment: Colorectal version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 14:1010-1030, 2016

57. Ramus SJ, Song H, Dicks E, et al: Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. J Natl Cancer Inst 107:djv214, 2015

58. Easton DF, Lesueur F, Decker B, et al: No evidence that protein truncating variants in BRIP1 are associated with breast cancer risk: Implications for gene panel testing. J Med Genet 53:298-309, 2016

59. Klein AP: Identifying people at a high risk of developing pancreatic cancer. Nat Rev Cancer 13: 66-74, 2013

60. Klein AP, Brune KA, Petersen GM, et al: Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 64:2634-2638, 2004

61. Brune KA, Lau B, Palmisano E, et al: Importance of age of onset in pancreatic cancer kindreds. J Natl Cancer Inst 102:119-126, 2010

62. Nelson HD, Fu R, Goddard K, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews, Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Rockville, MD, Agency for Healthcare Research and Quality, 2013

63. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al: Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 33:244-250, 2015

64. Le DT, Uram JN, Wang H, et al: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509-2520, 2015

65. Ayars M, Eshleman J, Goggins M: Susceptibility of ATM-deficient pancreatic cancer cells to radiation. Cell Cycle 16:991-998, 2017

66. Tung N, Domchek SM, Stadler Z, et al: Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 13:581-588, 2016

67. Foulkes WD, Knoppers BM, Turnbull C: Population genetic testing for cancer susceptibility: Founder mutations to genomes. Nat Rev Clin Oncol 13:41-54, 2016

68. Wolf SM, Branum R, Koenig BA, et al: Returning a research participant's genomic results to relatives: Analysis and recommendations. J Law Med Ethics 43:440-463, 2015

69. Armstrong J, Toscano M, Kotchko N, et al: Utilization and outcomes of BRCA genetic testing and counseling in a national commercially insured population: The ABOUT study. JAMA Oncol 1: 1251-1260, 2015

70. Percival N, George A, Gyertson J, et al: The integration of BRCA testing into oncology clinics. Br J Nurs 25:690-694, 2016

71. Kinney AY, Butler KM, Schwartz MD, et al: Expanding access to BRCA1/2 genetic counseling with telephone delivery: A cluster randomized trial. J Natl Cancer Inst 106:dju328, 2014

72. Bonadies DC, Brierley KL, Barnett RE, et al: Adverse events in cancer genetic testing: The third case series. Cancer J 20:246-253, 2014

Affiliations

All authors: The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University, Baltimore, MD.

Support

Supported by National Institutes of Health grants CA62924, R01CA176828, U01 CA210170, R01CA15482, and K99CA190889 (N.J.R.), Susan Wojcicki and Dennis Troper, and the Rolfe Pancreatic Cancer Foundation.

STATEMENT OF OWNERSHIP MANAGEMENT AND CIRCULATION (Required by 39 U.S.C. 3685)

1. Publication title: JOURNAL OF CLINICAL ONCOLOGY.
2. Publication no.: 0732-183X.
3. Filing date: October 1, 2017.
4. Issue frequency: 36 times/year; 3 times/month.
5. No. of issues published annually: 36.
6. Annual subscription price: $607.00.
7. Complete mailing address of known office of publication: 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609.
8. Complete mailing address of the headquarters or general business offices of the publisher: 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609.
9. Full names and complete mailing addresses of publisher, editor, and managing editor: Publisher: David Sampson, Publisher, Journal of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609. Editor: Stephen A. Cannistra, MD, Editor-in-Chief, Journal of Clinical Oncology, Beth Israel Deaconess Medical Ctr., 330 Brookline Ave., Boston, MA 02215. Managing Editor: Kenneth G. Kornfield, Managing Editor, Journal of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314.
10. Owner: American Society of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609.
11. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages, or other securities: None.
12. Purpose, function, and nonprofit status: Has not changed during preceding 12 months.
13. Publication title: JOURNAL OF CLINICAL ONCOLOGY.
14. Issue date for circulation data: Volume 35, Issue 27 (September 20, 2017).
15. Extent and nature of circulation: Average number of copies each issue during preceding 12 months: (a) Total no. copies (net press run), 22,378. (b) Paid and/or requested circulation: (1) Paid/requested outside-county mail subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): 14,703; (2) Paid in-county subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): N/A; (3) Sales through dealers and carriers, street vendors, counter sales, and other non-USPS paid distribution: 6,832; (4) Other classes mailed through the USPS: N/A. (c) Total paid and/or requested circulation (sum of 15b (1), (2), (3), and (4)): 21,535. (d) Free distribution by mail (samples, complimentary, and other free): (1) Outside-county as stated on form 3541: 366; (2) In-county as stated on form 3541: N/A; (3) Other classes mailed through the USPS: N/A; (4) Free distribution outside the mail (carriers or other means): 228. (e) Total free distribution (sum of 15d (1), (2), (3), and (4)): 594. (f) Total distribution (sum of 15c and 15e): 22,129. (g) Copies not distributed: 248. (h) Total (sum of 15f and 15g): 22,378. (i) Percent paid and/or requested circulation (15c/15f x 100): 97.32%. Actual no. copies of single issue published nearest to filing date: (a) Total no. copies (net press run): 21,587. (b) Paid and/or requested circulation: (1) Paid/requested outside-county mail subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): 14,640; (2) Paid in-county subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): N/A; (3) Sales through dealers and carriers, street vendors, counter sales, and other non-USPS paid distribution: 6,356; (4) Other classes mailed through the USPS: N/A. (c) Total paid and/or requested circulation (sum of 15b (1), (2), (3), and (4)): 20,996. (d) Free distribution by mail (samples, complimentary, and other free copies): (1) Outside-county as stated on Form 3541: 354; (2) In-county as stated on Form 3541: N/A; (3) Other classes mailed through the USPS: N/A; (4) Free distribution outside the mail (carriers or other means): 228. (e) Total free distribution (sum of 15d (1), (2), (3), and (4)): 582. (f) Total distribution (sum of 15c and 15e): 21,578. (g) Copies not distributed: 9. (h) Total (sum of 15f and 15g): 21,587. (i) Percent paid and/or requested circulation (15c/15f x 100): 97.30%.
16. Total circulation includes electronic copies. Report circulation on PS Form 3526-X worksheet. N/A.
17. This Statement of Ownership will be printed in Volume 35, Issue 30 (October 20, 2017).
18. I certify that the statements made by me above are correct and complete.

David Sampson, Publisher

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Koji Shindo
No relationship to disclose

Jun Yu
No relationship to disclose

Masaya Suenaga
No relationship to disclose

Shahriar Fesharakizadeh
No relationship to disclose

Christy Cho
No relationship to disclose

Anne Macgregor-Das
No relationship to disclose

Abdulrehman Siddiqui
Stock or Other Ownership: 22nd Century Group

P. Dane Witmer
No relationship to disclose

Koji Tamura
No relationship to disclose

Tae Jun Song
No relationship to disclose

Jose Alejandro Navarro Almario
No relationship to disclose

Aaron Brant
No relationship to disclose

Michael Borges
No relationship to disclose

Madeline Ford
No relationship to disclose

Thomas Barkley
No relationship to disclose

Jin He
No relationship to disclose

Matthew J. Weiss
No relationship to disclose

Christopher L. Wolfgang
No relationship to disclose

Nicholas J. Roberts
No relationship to disclose

Ralph H. Hruban
Leadership: miDIAGNOSTICS
Patents, Royalties, Other Intellectual Property: Myriad Genetics

Alison P. Klein
Patents, Royalties, Other Intellectual Property: Myriad Genetics

Michael Goggins
Patents, Royalties, Other Intellectual Property: Myriad Genetics

Appendix

Table A1. Targeted Regions of the 32 Genes*

Chromosome	Chr Start	Chr_End	Gene
chr1	27022889	27024036	*ARID1A*
chr1	27056136	27056359	*ARID1A*
chr1	27057637	27058100	*ARID1A*
chr1	27059161	27059288	*ARID1A*
chr1	27087341	27087592	*ARID1A*
chr1	27087869	27087969	*ARID1A*
chr1	27088637	27088815	*ARID1A*
chr1	27089458	27089781	*ARID1A*
chr1	27092706	27092862	*ARID1A*
chr1	27092942	27093062	*ARID1A*
chr1	27094275	27094495	*ARID1A*
chr1	27097604	27097822	*ARID1A*
chr1	27098985	27099128	*ARID1A*
chr1	27099297	27099483	*ARID1A*
chr1	27099831	27099992	*ARID1A*
chr1	27100065	27100213	*ARID1A*
chr1	27100287	27100394	*ARID1A*
chr1	27100814	27101716	*ARID1A*
chr1	27101465	27101716	*ARID1A*
chr1	27102062	27102203	*ARID1A*
chr1	27105508	27107252	*ARID1A*
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*
chr2	58386894	58386940	*FANCL*
chr2	58387237	58387319	*FANCL*
chr2	58388651	58388778	*FANCL*
chr2	58389995	58390087	*FANCL*
chr2	58390158	58390214	*FANCL*
chr2	58390563	58390657	*FANCL*
chr2	58392853	58393014	*FANCL*
chr2	58425708	58425802	*FANCL*
chr2	58425723	58425802	*FANCL*
chr2	58431259	58431366	*FANCL*
chr2	58449071	58449182	*FANCL*
chr2	58453857	58453924	*FANCL*

(continued in next column)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	Chr Start	Chr_End	Gene
chr2	58456943	58457014	*FANCL*
chr2	58459183	58459252	*FANCL*
chr2	58468347	58468453	*FANCL*
chr2	111395535	111395741	*BUB1*
chr2	111397313	111397430	*BUB1*
chr2	111398605	111398774	*BUB1*
chr2	111398605	111398787	*BUB1*
chr2	111398878	111399046	*BUB1*
chr2	111399213	111399385	*BUB1*
chr2	111399690	111399816	*BUB1*
chr2	111406805	111406959	*BUB1*
chr2	111408117	111408366	*BUB1*
chr2	111411007	111411105	*BUB1*
chr2	111413310	111413498	*BUB1*
chr2	111414607	111414699	*BUB1*
chr2	111415117	111415227	*BUB1*
chr2	111415981	111416102	*BUB1*
chr2	111416185	111416324	*BUB1*
chr2	111417549	111417618	*BUB1*
chr2	111419153	111419423	*BUB1*
chr2	111423834	111423996	*BUB1*
chr2	111425092	111425287	*BUB1*
chr2	111425368	111425431	*BUB1*
chr2	111427024	111427135	*BUB1*
chr2	111428096	111428150	*BUB1*
chr2	111430232	111430439	*BUB1*
chr2	111431657	111431806	*BUB1*
chr2	111431877	111431947	*BUB1*
chr2	111435541	111435577	*BUB1*
chr3	37035033	37035159	*MLH1*
chr3	37038104	37038205	*MLH1*
chr3	37042522	37042544	*MLH1*
chr3	37042440	37042549	*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*
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	52436298	52436442	*BAP1*
chr3	52436612	52436695	*BAP1*
chr3	52436789	52436892	*BAP1*
chr3	52437148	52437319	*BAP1*
chr3	52437426	52437915	*BAP1*
chr3	52438463	52438607	*BAP1*
chr3	52439120	52439315	*BAP1*
chr3	52439775	52439933	*BAP1*
chr3	52440263	52440397	*BAP1*
chr3	52440839	52440928	*BAP1*
chr3	52441184	52441337	*BAP1*
chr3	52441409	52441481	*BAP1*
chr3	52441968	52442098	*BAP1*

(continued on following page)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	Chr Start	Chr_End	Gene
chr3	52442484	52442627	*BAP1*
chr3	52443564	52443629	*BAP1*
chr3	52443724	52443764	*BAP1*
chr3	52443852	52443899	*BAP1*
chr5	1253837	1253951	*TERT*
chr5	1254477	1254625	*TERT*
chr5	1255396	1255531	*TERT*
chr5	1258707	1258779	*TERT*
chr5	1260583	1260720	*TERT*
chr5	1264513	1264712	*TERT*
chr5	1266573	1266655	*TERT*
chr5	1268629	1268753	*TERT*
chr5	1271228	1271324	*TERT*
chr5	1272294	1272400	*TERT*
chr5	1278750	1278916	*TERT*
chr5	1279400	1279590	*TERT*
chr5	1280267	1280458	*TERT*
chr5	1282538	1282744	*TERT*
chr5	1293422	1294786	*TERT*
chr5	1294880	1295109	*TERT*
chr7	6013024	6013178	*PMS2*
chr7	6017213	6017393	*PMS2*
chr7	6018221	6018332	*PMS2*
chr7	6022449	6022627	*PMS2*
chr7	6026384	6027256	*PMS2*
chr7	6029425	6029591	*PMS2*
chr7	6031598	6031693	*PMS2*
chr7	6035159	6035269	*PMS2*
chr7	6036951	6037059	*PMS2*
chr7	6038733	6038911	*PMS2*
chr7	6042078	6042272	*PMS2*
chr7	6043315	6043428	*PMS2*
chr7	6043597	6043694	*PMS2*
chr7	6045517	6045667	*PMS2*
chr7	6048622	6048655	*PMS2*
chr7	152345721	152346453	*XRCC2*
chr7	152357780	152357872	*XRCC2*
chr7	152373120	152373169	*XRCC2*
chr8	145736808	145736943	*RECQL4*
chr8	145737058	145737177	*RECQL4*
chr8	145737288	145737455	*RECQL4*
chr8	145737521	145737712	*RECQL4*
chr8	145737769	145737949	*RECQL4*
chr8	145738019	145738159	*RECQL4*
chr8	145738224	145738526	*RECQL4*
chr8	145738595	145738772	*RECQL4*
chr8	145738763	145738869	*RECQL4*
chr8	145738949	145739101	*RECQL4*
chr8	145739306	145739496	*RECQL4*
chr8	145739567	145739751	*RECQL4*
chr8	145739820	145739914	*RECQL4*
chr8	145740314	145740461	*RECQL4*
chr8	145740528	145740631	*RECQL4*
chr8	145740704	145740846	*RECQL4*
chr8	145741142	145741279	*RECQL4*
chr8	145741366	145742153	*RECQL4*
chr8	145742428	145742579	*RECQL4*
chr8	145742792	145742897	*RECQL4*
chr8	145742980	145743024	*RECQL4*
chr8	145743079	145743173	*RECQL4*
chr9	21968222	21968246	*CDKN2A*
chr9	21968718	21968775	*CDKN2A*
chr9	21970996	21971212	*CDKN2A*
chr9	21970895	21971212	*CDKN2A*
chr9	21974671	21974831	*CDKN2A*
chr9	21974470	21974831	*CDKN2A*

(continued in next column)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	Chr Start	Chr_End	Gene
chr9	21994132	21994335	*CDKN2A*
chr9	35074099	35074218	*FANCG*
chr9	35074362	35074496	*FANCG*
chr9	35074918	35075084	*FANCG*
chr9	35075270	35075327	*FANCG*
chr9	35075456	35075756	*FANCG*
chr9	35075953	35076030	*FANCG*
chr9	35076423	35076585	*FANCG*
chr9	35076715	35076872	*FANCG*
chr9	35076962	35077103	*FANCG*
chr9	35077255	35077401	*FANCG*
chr9	35078132	35078345	*FANCG*
chr9	35078596	35078738	*FANCG*
chr9	35079142	35079243	*FANCG*
chr9	35079432	35079526	*FANCG*
chr9	97863983	97864137	*FANCC*
chr9	97869342	97869556	*FANCC*
chr9	97873472	97873632	*FANCC*
chr9	97873739	97873924	*FANCC*
chr9	97876905	97876997	*FANCC*
chr9	97879591	97879677	*FANCC*
chr9	97887362	97887472	*FANCC*
chr9	97888805	97888868	*FANCC*
chr9	97897622	97897789	*FANCC*
chr9	97912199	97912374	*FANCC*
chr9	97933355	97933430	*FANCC*
chr9	97934313	97934434	*FANCC*
chr9	98002925	98003030	*FANCC*
chr9	98009708	98009803	*FANCC*
chr9	98011403	98011578	*FANCC*
chr10	124914428	124914633	*BUB3*
chr10	124915168	124915248	*BUB3*
chr10	124917239	124917401	*BUB3*
chr10	124919917	124920086	*BUB3*
chr10	124921746	124921934	*BUB3*
chr10	124922122	124922349	*BUB3*
chr10	124923330	124923356	*BUB3*
chr10	124924557	124924577	*BUB3*
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 on following page)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	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*
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*
chr14	68290255	68290349	*RAD51B*
chr14	68292175	68292299	*RAD51B*
chr14	68301791	68301918	*RAD51B*
chr14	68331714	68331861	*RAD51B*
chr14	68352580	68352710	*RAD51B*
chr14	68353732	68353926	*RAD51B*
chr14	68758595	68758702	*RAD51B*
chr14	68878135	68878249	*RAD51B*

(continued in next column)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	Chr Start	Chr_End	Gene
chr14	68934883	68934972	*RAD51B*
chr14	68944359	68944386	*RAD51B*
chr14	68963835	68963862	*RAD51B*
chr14	69061196	69061325	*RAD51B*
chr14	104165129	104165359	*XRCC3*
chr14	104165464	104165521	*XRCC3*
chr14	104165695	104165918	*XRCC3*
chr14	104169504	104169669	*XRCC3*
chr14	104173334	104173557	*XRCC3*
chr14	104174853	104175001	*XRCC3*
chr14	104177364	104177429	*XRCC3*
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	14014017	14014234	*ERCC4*
chr16	14015882	14016073	*ERCC4*
chr16	14020412	14020618	*ERCC4*
chr16	14021879	14022097	*ERCC4*
chr16	14024561	14024752	*ERCC4*
chr16	14026008	14026147	*ERCC4*
chr16	14028043	14028164	*ERCC4*
chr16	14028997	14029605	*ERCC4*
chr16	14031617	14031720	*ERCC4*
chr16	14038574	14038697	*ERCC4*
chr16	14041465	14042209	*ERCC4*
chr16	23614774	23614995	*PALB2*
chr16	23619179	23619338	*PALB2*
chr16	23625319	23625417	*PALB2*
chr16	23632677	23632804	*PALB2*
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	68771313	68771371	*CDH1*
chr16	68772194	68772319	*CDH1*
chr16	68835567	68835801	*CDH1*
chr16	68842321	68842475	*CDH1*
chr16	68842590	68842756	*CDH1*
chr16	68844094	68844249	*CDH1*
chr16	68845581	68845767	*CDH1*
chr16	68846032	68846171	*CDH1*
chr16	68847210	68847403	*CDH1*

(continued on following page)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	Chr Start	Chr_End	Gene
chr16	68849412	68849667	*CDH1*
chr16	68853177	68853333	*CDH1*
chr16	68855898	68856133	*CDH1*
chr16	68857296	68857534	*CDH1*
chr16	68862071	68862212	*CDH1*
chr16	68863551	68863705	*CDH1*
chr16	68867187	68867407	*CDH1*
chr16	89805003	89805121	*FANCA*
chr16	89805100	89805121	*FANCA*
chr16	89805284	89805387	*FANCA*
chr16	89805535	89805702	*FANCA*
chr16	89805531	89805702	*FANCA*
chr16	89805880	89805966	*FANCA*
chr16	89806396	89806512	*FANCA*
chr16	89807206	89807279	*FANCA*
chr16	89809202	89809351	*FANCA*
chr16	89811361	89811484	*FANCA*
chr16	89812986	89813101	*FANCA*
chr16	89813233	89813303	*FANCA*
chr16	89815061	89815180	*FANCA*
chr16	89816132	89816315	*FANCA*
chr16	89818540	89818635	*FANCA*
chr16	89824979	89825118	*FANCA*
chr16	89828351	89828435	*FANCA*
chr16	89831292	89831479	*FANCA*
chr16	89833543	89833650	*FANCA*
chr16	89836239	89836437	*FANCA*
chr16	89836568	89836672	*FANCA*
chr16	89836966	89837047	*FANCA*
chr16	89838080	89838227	*FANCA*
chr16	89839673	89839797	*FANCA*
chr16	89842144	89842228	*FANCA*
chr16	89845203	89845263	*FANCA*
chr16	89845345	89845416	*FANCA*
chr16	89846271	89846370	*FANCA*
chr16	89849261	89849331	*FANCA*
chr16	89849409	89849515	*FANCA*
chr16	89851256	89851377	*FANCA*
chr16	89857805	89857949	*FANCA*
chr16	89858329	89858481	*FANCA*
chr16	89858873	89858960	*FANCA*
chr16	89862308	89862431	*FANCA*
chr16	89865481	89865492	*FANCA*
chr16	89865568	89865645	*FANCA*
chr16	89866007	89866051	*FANCA*
chr16	89869661	89869754	*FANCA*
chr16	89871682	89871805	*FANCA*
chr16	89874696	89874780	*FANCA*
chr16	89877109	89877215	*FANCA*
chr16	89877331	89877484	*FANCA*
chr16	89880922	89881026	*FANCA*
chr16	89882279	89882399	*FANCA*
chr16	89882939	89883028	*FANCA*
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*

(continued in next column)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	Chr Start	Chr_End	Gene
chr17	7579833	7579917	*TP53*
chr17	33427966	33428060	*RAD51D*
chr17	33428214	33428389	*RAD51D*
chr17	33430267	33430348	*RAD51D*
chr17	33430467	33430568	*RAD51D*
chr17	33433399	33433505	*RAD51D*
chr17	33434001	33434146	*RAD51D*
chr17	33434379	33434471	*RAD51D*
chr17	33443872	33444061	*RAD51D*
chr17	33445514	33445643	*RAD51D*
chr17	33446124	33446196	*RAD51D*
chr17	33446545	33446637	*RAD51D*
chr17	41197795	41197824	*BRCA1*
chr17	41197689	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*
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*
chr17	56432298	56432352	*RNF43*
chr17	56434823	56436189	*RNF43*
chr17	56437504	56437617	*RNF43*
chr17	56438138	56438310	*RNF43*
chr17	56439899	56440014	*RNF43*
chr17	56440630	56440772	*RNF43*
chr17	56440881	56440966	*RNF43*
chr17	56448266	56448399	*RNF43*
chr17	56492681	56492943	*RNF43*
chr17	56769999	56770154	*RAD51C*
chr17	56772286	56772555	*RAD51C*
chr17	56772286	56772559	*RAD51C*
chr17	56774048	56774225	*RAD51C*
chr17	56780551	56780695	*RAD51C*
chr17	56787214	56787356	*RAD51C*
chr17	56798101	56798178	*RAD51C*
chr17	56801395	56801466	*RAD51C*
chr17	56809839	56809910	*RAD51C*
chr17	56811473	56811588	*RAD51C*
chr17	59760651	59761506	*FANCJ*
chr17	59763191	59763531	*FANCJ*
chr17	59770785	59770878	*FANCJ*
chr17	59793306	59793429	*FANCJ*
chr17	59820368	59820500	*FANCJ*
chr17	59821787	59821957	*FANCJ*
chr17	59853756	59853928	*FANCJ*
chr17	59857616	59857767	*FANCJ*

(continued on following page)

Table A1. Targeted Regions of the 32 Genes* (continued)

Chromosome	Chr Start	Chr_End	Gene
chr17	59858195	59858371	*FANCJ*
chr17	59861625	59861790	*FANCJ*
chr17	59870952	59871095	*FANCJ*
chr17	59876455	59876665	*FANCJ*
chr17	59878608	59878840	*FANCJ*
chr17	59885822	59886123	*FANCJ*
chr17	59924456	59924586	*FANCJ*
chr17	59926484	59926622	*FANCJ*
chr17	59934413	59934597	*FANCJ*
chr17	59937151	59937273	*FANCJ*
chr17	59938802	59938905	*FANCJ*
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*
chr7	142457330	142457380	*PRSS1*
chr7	142458400	142458570	*PRSS1*
chr7	142459619	142459883	*PRSS1*
chr7	142460276	142460423	*PRSS1*
chr7	142460713	142460876	*PRSS1*

Table A2. Variants of Uncertain Significance

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Deleterious variants of uncertain significance													
Case_4*12	63	M	White	PDAC	*RAD51B*	14:68292235	p.R47RX	c.139C>T	Nonsense	Deleterious	Yes	Heterozygous	None
Case_15*52	65	M	White	PDAC	*RAD51D*	17:33443903	p.R100X	c.298G>A	Nonsense	Deleterious	Yes	Heterozygous	None
Case_7*18	76	F	Other	PDAC	*CDH1*	16:68846147	p.P373L**	c.1118C>T	Missense	Deleterious	Yes	Heterozygous	Lung cancer (patient)
Variants thought to confer modest increased cancer risk													
Case_3*56	65	M	White	PDAC	*BRCA2*	13:32972626	p.K3326X	c.9976A>T	Nonsense	VUS	Yes	Heterozygous	None
Case_4*50	65	M	White	PDAC	*BRCA2*	13:32972626	p.K3326X	c.9976A>T	Nonsense	VUS	Yes	Heterozygous	NA
Variants of uncertain significance													
Case_1*77	58	M	White	PDAC	*BRCA2*	13:32911703	p.H1071Y	c.3211C>T	Missense	VUS	Yes	Heterozygous	Melanoma (mother)
Case_9*66	66	F	White	PDAC	*BRCA2*	13:32911794	p.H1101R	c.3302A>G	Missense	VUS	Yes	Heterozygous	N-reone
Case_14*39	73	F	White	PDAC	*BRCA2*	13:32911939	p.M1149I	c.3447G>A	Missense	VUS	Yes	Heterozygous	Lung (father), bladder (paternal aunt), breast (niece)
Case_4*44	54	M	White	PDAC	*BRCA2*	13:32912586	p.C1365Y	c.4094G>A	Missense	VUS	Yes	Heterozygous	NA
Case_15*63	56	F	White	PDAC	*BRCA2*	13:32915133	p.T2214I	c.6641C>T	Missense	VUS	Yes	Heterozygous	None
Case_5*27	49	M	White	PDAC	*BRCA2*	13:32931943	p.Q2561R	c.7682A>G	Missense	VUS	Yes	Heterozygous	Melanoma (mother), colon (father)
Case_7*25	76	M	White	PDAC	*BRCA2*	13:32893421	p.Q92R	c.275A>G	Missense	VUS	No	Heterozygous	Pancreas (sister), bladder (paternal grandfather), bladder (maternal grandfather)
Case_15*46	69	F	White	PDAC	*BRCA2*	13:32906456	p.D281N	c.841G>A	Missense	VUS	No	Heterozygous	Lung (mother)
Case_7*49	68	M	White	PDAC	*BRCA2*	13:32912190	p.A1233V	c.3698C>T	Missense	VUS	No	Heterozygous	Pancreas (father), lung (two brothers), lung (sister), colon (another sister)
Case_13*12	74	F	White	PDAC	*BRCA2*	13:32914022	p.F1844I	c.5530T>A	Missense	VUS	No	Heterozygous	None
Case_13*12	74	F	White	PDAC	*BRCA2*	13:32914028	p.I1846V	c.5536A>G	Missense	VUS	No	Heterozygous	None
Case_1*81	56	M	Other	PDAC	*BRCA2*	13:32915054	p.K2188E	c.6562A>G	Missense	VUS	No	Heterozygous	NA
Case_8*40	41	F	Other	Non-PDAC: Duodenal AC	*BRCA2*	13:32972471	p.L3274W	c.9821T>G	Missense	VUS	Yes	Heterozygous	Lung (paternal grandfather), lung (aunts), lung (uncles), breast (paternal grandmother), duodenal tumor (grandmother)
Case_7*45	66	F	White	Non-PDAC: RCC (with metastasis to pancreas)	*BRCA1*	17:41201181	p.G1809D	c.5426C>T	Missense	VUS	No	Heterozygous	Lymphoma (father)
Case_11*03	61	M	African American	PDAC	*BRCA1*	17:41245975	p.V525I	c.1573C>T	Missense	VUS	No	Heterozygous	Breast (two cousins)
Case_5*45	57	M	African American	PDAC	*BRCA1*	17:41245975	p.V525I	c.1573C>T	Missense	VUS	No	Heterozygous	None
Case_4*68	61	F	White	PDAC	*ATM*	11:108164137	p.V1570A	c.4709T>C	Missense	VUS	No	Heterozygous	Colon (father), lung (brother)
Case_8*43	60	F	White	PDAC	*ATM*	11:108164137	p.V1570A	c.4709T>C	Missense	VUS	No	Heterozygous	Breast (sister), breast (aunt)
Case_15*77	54	M	White	PDAC	*ATM*	11:108170506	p.S1691R	c.5071A>C	Missense	VUS	No	Heterozygous	Lung (mother), melanoma (father)
Case_5*37	70	M	White	PDAC	*ATM*	11:108170506	p.S1691R	c.5071A>C	Missense	VUS	No	Heterozygous	Pancreas (father)
Case_14*36	57	F	White	PDAC	*ATM*	11:108183194	p.K1992T	c.5975A>C	Missense	VUS	No	Heterozygous	Breast and cervical (maternal), cervical (daughter), cervical and colon (maternal aunt)
Case_3*32	82	F	White	PDAC	*ATM*	11:108183194	p.K1992T	c.5975A>C	Missense	VUS	No	Heterozygous	NA
Case_3*37	55	M	White	PDAC	*ATM*	11:108183194	p.K1992T	c.5975A>C	Missense	VUS	No	Heterozygous	None
Case_15*87	70	M	White	PDAC	*PALB2*	16:23634339	p.T983S	c.2947T>A	Missense	VUS	No	Heterozygous	Leukemia (mother)
Case_9*68	60	M	White	PDAC	*PALB2*	16:23634383	p.A968G	c.2903G>C	Missense	VUS	No	Heterozygous	Breast (two maternal aunts), lung (multiple uncles)
Case_15*06	77	M	White	PDAC	*PALB2*	16:23634446	p.L947S	c.2840A>G	Missense	VUS	No	Heterozygous	None
Case_3*95	63	M	White	PDAC	*PALB2*	16:23637686	p.S873R	c.2619A>C	Missense	VUS	No	Heterozygous	Breast (sister)
Case_14*08	83	M	White	PDAC	*PALB2*	16:23641275	p.T734S	c.2200T>A	Missense	VUS	No	Heterozygous	Colon (sister)
Case_4*74	78	F	White	PDAC	*PALB2*	16:23646376	p.N497K	c.1491A>C	Missense	VUS	No	Heterozygous	None
Case_3*86	70	F	White	PDAC	*PALB2*	16:23646857	p.L337S	c.1010A>G	Missense	VUS	No	Heterozygous	Leukemia (mother)

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_4*42	65	M	White	PDAC	*PALB2*	16:23646857	p.L337S	c.1010A>G	Missense	VUS	No	Heterozygous	Pancreas (brother)
Case_13*72	38	F	White	PDAC	*PALB2*	16:23646866	p.Y334C	c.1001T>C	Missense	VUS	No	Heterozygous	Prostate (paternal grandfather)
Case_14*33	42	F	White	PDAC	*PALB2*	16:23646866	p.Y334C	c.1001T>C	Missense	VUS	No	Heterozygous	Lung (mother), lymphoma (grandfather), prostate (paternal uncle)
Case_5*16	61	M	White	PDAC	*PALB2*	16:23647280	p.R196K	c.587C>T	Missense	VUS	No	Heterozygous	Prostate (father)
Case_12*36	65	M	African American	PDAC	*PALB2*	16:23647467	p.D134N	c.400C>T	Missense	VUS	No	Heterozygous	None
Case_2*48	54	F	White	PDAC	*PALB2*	16:23647569	p.L100F	c.298G>A	Missense	VUS	No	Heterozygous	NA
Case_8*68	21	M	White	Non-PDAC: Control (multifocal fibrosis in pancreas)	*PALB2*	16:23652442	p.E13K	c.37C>T	Missense	VUS	No	Heterozygous	None
Case_11*10	66	F	Other	Non-PDAC: Duodenal AC	*PALB2*	16:23646375	p.D498Y	c.1492C>A	Missense	VUS	No	Heterozygous	NA
Case_6*39	54	M	White	Non-PDAC: Tubulovillous adenoma in duodenum	*ARID1A*	1:27106106	p.R1906Q	c.5717G>A	Missense	VUS	No	Heterozygous	None
Case_3*91	60	M	White	Non-PDAC: Duodenal AC	*ARID1A*	1:27106106	p.R1906Q	c.5717G>A	Missense	VUS	No	Heterozygous	None
Case_13*37	63	F	White	Non-PDAC: Duodenal AC	*ARID1A*	1:27107046	p.Q2219H	c.6657G>T	Missense	VUS	No	Heterozygous	Leukemia (mother), gastric (paternal grandmother, paternal uncle)
Case_14*24	75	F	White	PDAC	*ARID1A*	1:27023634	p.A247V	c.740C>T	Missense	VUS	No	Heterozygous	None
Case_4*59	53	M	White	PDAC	*ARID1A*	1:27023951	p.A353P	c.1057G>C	Missense	VUS	No	Heterozygous	None
Case_6*82	57	F	White	PDAC	*ARID1A*	1:27056179	p.P392H	c.1175C>A	Missense	VUS	No	Heterozygous	Melanoma (mother), lung (sister), cervical (grandmother)
Case_14*44	64	F	White	PDAC	*ARID1A*	1:27056290	p.R429Q	c.1286G>A	Missense	VUS	No	Heterozygous	Lung (paternal uncle)
Case_2*35	80	F	White	PDAC	*ARID1A*	1:27059217	p.M618I	c.1854G>G	Missense	VUS	No	Heterozygous	NA
Case_5*16	61	M	White	PDAC	*ARID1A*	1:27087500	p.I692V	c.2074A>G	Missense	VUS	No	Heterozygous	Prostate (father)
Case_6*15	74	F	White	PDAC	*ARID1A*	1:27087500	p.I692V	c.2074A>G	Missense	VUS	No	Heterozygous	Breast (sister), prostate (brother)
Case_6*64	81	M	White	PDAC	*ARID1A*	1:27099423	p.M1220I	c.3660G>A	Missense	VUS	No	Heterozygous	None
Case_2*92	64	F	White	PDAC	*ARID1A*	1:27100168	p.S1322G	c.3964A>G	Missense	VUS	No	Heterozygous	NA
Case_11*21	55	F	White	PDAC	*ARID1A*	1:27101235	p.Y1506C	c.4517A>G	Missense	VUS	No	Heterozygous	None
Case_10*79	77	F	Other	PDAC	*ARID1A*	1:27101442	p.P1575Q	c.4724C>A	Missense	VUS	No	Heterozygous	NA
Case_3*66	87	M	White	PDAC	*ARID1A*	1:27105698	p.G1770V	c.5309G>T	Missense	VUS	No	Heterozygous	Breast (mother), prostate (brother), leukemia (brother)
Case_3*14	66	M	White	PDAC	*ARID1A*	1:27105725	p.E1779G	c.5336A>G	Missense	VUS	No	Heterozygous	?Lung (sister)
Case_12*21	54	M	Other	PDAC	*ARID1A*	1:27106036	p.T1883S	c.5647A>T	Missense	VUS	No	Heterozygous	Prostate (father)
Case_13*64	78	M	White	PDAC	*ARID1A*	1:27106106	p.R1906Q	c.5717G>A	Missense	VUS	No	Heterozygous	Prostate (brother), pancreas (brother), lung, liver (cousin)
Case_2*19	54	F	White	PDAC	*ARID1A*	1:27106106	p.R1906Q	c.5717G>A	Missense	VUS	No	Heterozygous	Pancreas (sister, paternal aunt), liver (maternal grandfather), thyroid (paternal grandfather), colon (daughter)
Case_4*23	64	F	White	PDAC	*ARID1A*	1:27106106	p.R1906Q	c.5717G>A	Missense	VUS	No	Heterozygous	Lymphoma (father)
Case_8*13	72	F	White	PDAC	*ARID1A*	1:27106106	p.R1906Q	c.5717G>A	Missense	VUS	No	Heterozygous	Breast (unknown)
Case_11*50	60	F	White	PDAC	*ARID1A*	1:27106168	p.A1927P	c.5779G>C	Missense	VUS	No	Heterozygous	Pancreas (maternal uncle), prostate (father), BCC (sister, niece), breast (multiple cousins)
Case_12*92	78	F	White	PDAC	*ARID1A*	1:27106333	p.V1982I	c.5944G>A	Missense	VUS	No	Heterozygous	Colon and RCC (father)
Case_4*04	68	M	White	PDAC	*BAP1*	3:52437807	p.L452F	c.1354G>A	Missense	VUS	No	Heterozygous	Liver (mother), breast (grandmother)
Case_11*84	63	M	White	Non-PDAC: pNET	*BAP1*	3:52437275	p.Q590L	c.1769T>A	Missense	VUS	No	Heterozygous	NA
Case_7*60	45	M	White	Non-PDAC: pNET	*BRIP1*	17:59761304	p.R1035C	c.3103G>G	Missense	VUS	No	Heterozygous	Prostate (father)
Case_3*13	62	F	White	Non-PDAC: pNET	*BRIP1*	17:59934481	p.R106H	c.317C>T	Missense	VUS	No	Heterozygous	Ocular (mother)
Case_8*57	41	M	White	Non-PDAC: Carcinoid tumor	*BRIP1*	17:59934460	p.T113I	c.338G>A	Missense	VUS	No	Heterozygous	NA
Case_14*25	56	F	White	PDAC	*BRIP1*	17:59934534	p.C88del	c.262_264delACA	In-Frame	VUS	Yes	Heterozygous	Pancreatitis (nephew)

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_15*52	65	M	White	PDAC	*BRIP1*	17:59934534	p.C88del	c.262_264delACA	In-Frame	VUS	Yes	Heterozygous	None
Case_7*80	65	F	Other	PDAC	*BRIP1*	17:59760836	p.I1191V	c.3571T>C	Missense	VUS	No	Heterozygous	None
Case_7*88	63	M	White	PDAC	*BRIP1*	17:59761493	p.V972I	c.2914C>T	Missense	VUS	No	Heterozygous	Melanoma (unknown)
Case_14*03	58	M	White	PDAC	*BRIP1*	17:59763397	p.I902T	c.2705A>G	Missense	VUS	No	Heterozygous	Breast (sister)
Case_7*48	67	F	White	PDAC	*BRIP1*	17:59793335	p.R823S	c.2469C>A	Missense	VUS	No	Heterozygous	Ovary (niece), lymphoma (niece), testicular (son), lymphoma (mother)
Case_4*48	72	M	White	PDAC	*BRIP1*	17:59820409	p.I782V	c.2344T>C	Missense	VUS	No	Heterozygous	Prostate, brain cancer (details unknown)
Case_5*91	68	F	Other	PDAC	*BRIP1*	17:59820409	p.I782V	c.2344T>C	Missense	VUS	No	Heterozygous	Breast (cousin), prostate (unknown)
Case_3*14	66	M	White	PDAC	*BRIP1*	17:59821830	p.Q740H	c.2220C>A	Missense	VUS	No	Heterozygous	?Lung (sister)
Case_13*50	50	M	African American	PDAC	*BRIP1*	17:59858260	p.R579C	c.1735G>A	Missense	VUS	No	Heterozygous	Skin (paternal grandmother)
Case_13*03	64	F	White	PDAC	*BRIP1*	17:59858352	p.Y548C	c.1643T>C	Missense	VUS	No	Heterozygous	Rectal (mother), prostate (father), rectal (two maternal uncles)
Case_3*83	65	F	White	PDAC	*BRIP1*	17:59870990	p.G481C	c.1441C>A	Missense	VUS	No	Heterozygous	NA
Case_3*63	57	M	White	PDAC	*BRIP1*	17:59876546	p.R419W	c.1255G>A	Missense	VUS	No	Heterozygous	Colon (grandfather)
Case_2*42	73	M	White	PDAC	*BRIP1*	17:59885961	p.E262A	c.785T>G	Missense	VUS	No	Heterozygous	NA
Case_10*91	55	M	White	PDAC	*BRIP1*	17:59937223	p.P47A	c.139G>C	Missense	VUS	No	Heterozygous	NA
Case_3*67	21	F	White	Non-PDAC: SPN	*BUB1*	2:111416232	p.K455R	c.1364T>C	Missense	VUS	No	Heterozygous	Breast (maternal aunt, maternal grandmother, cousin, other relative), colon (paternal grandfather, other relative)
Case_6*63	78	F	African American	Non-PDAC: Focal chronic pancreatitis with PanIN1A	*BUB1*	2:111430268	p.E131G	c.392T>C	Missense	VUS	No	Heterozygous	None
Case_1*32	84	M	White	PDAC	*BUB1*	2:111395554	p.R1082H	c.3245C>T	Missense	VUS	No	Heterozygous	None
Case_1*24	62	F	White	PDAC	*BUB1*	2:111399025	p.Y881F	c.2642T>A	Missense	VUS	No	Heterozygous	Breast (maternal cousin), thyroid (maternal cousin)
Case_10*15	53	F	Other	PDAC	*BUB1*	2:111399752	p.E803K	c.2407C>T	Missense	VUS	No	Heterozygous	Breast (sister), liver (father)
Case_3*25	74	F	Other	PDAC	*BUB1*	2:111399752	p.E803K	c.2407C>T	Missense	VUS	No	Heterozygous	None
Case_6*15	74	F	White	PDAC	*BUB1*	2:111415192	p.V516G	c.1547A>C	Missense	VUS	No	Heterozygous	Breast (sister), prostate (brother)
Case_15*56	68	M	White	PDAC	*BUB1*	2:111419369	p.R336T	c.1007C>G	Missense	VUS	No	Heterozygous	Brain (father), breast (sister), genital (mother, sister), colon (maternal grandfather)
Case_10*71	76	M	Other	PDAC	*BUB1*	2:111425226	p.A226V	c.677G>A	Missense	VUS	No	Heterozygous	NA
Case_11*07	83	F	White	PDAC	*BUB1*	2:111425226	p.A226V	c.677G>A	Missense	VUS	No	Heterozygous	None
Case_15*49	85	F	White	PDAC	*BUB1*	2:111425226	p.A226V	c.677G>A	Missense	VUS	No	Heterozygous	Colon (father), lung (brother)
Case_2*33	66	M	White	PDAC	*BUB1*	2:111425226	p.A226V	c.677G>A	Missense	VUS	No	Heterozygous	NA
Case_2*36	61	F	White	PDAC	*BUB1*	2:111425226	p.A226V	c.677G>A	Missense	VUS	No	Heterozygous	Pancreas (mother, father), unknown cancer (sister)
Case_7*38	57	F	White	Non-PDAC: pNET	*BUB1B*	15:40512901	p.N1032H	c.3094A>C	Missense	VUS	No	Heterozygous	None
Case_11*35	38	M	African American	PDAC	*BUB1B*	15:40457337	p.T40M	c.119C>T	VUS	VUS	Yes	Heterozygous	Colon (father)
Case_12*15	59	M	African American	PDAC	*BUB1B*	15:40457337	p.T40M	c.119C>T	VUS	VUS	Yes	Heterozygous	Breast (mother), pancreas (brother), lung (father)
Case_12*36	65	M	African American	PDAC	*BUB1B*	15:40457337	p.T40M	c.119C>T	VUS	VUS	Yes	Heterozygous	None
Case_15*07	55	M	White	PDAC	*BUB1B*	15:40457337	p.T40M	c.119C>T	VUS	VUS	Yes	Heterozygous	Liver (maternal grandmother), leukemia (son), Hodgkin lymphoma (paternal grandfather), prostate (father)
Case_1*68	62	F	White	PDAC	*BUB1B*	15:40512901	p.N1032H	c.3094A>C	Missense	VUS	No	Heterozygous	NA
Case_1*72	73	F	White	PDAC	*BUB1B*	15:40512901	p.N1032H	c.3094A>C	Missense	VUS	No	Heterozygous	NA
Case_10*80	51	M	White	PDAC	*BUB1B*	15:40512901	p.N1032H	c.3094A>C	Missense	VUS	No	Heterozygous	NA
Case_11*48	62	M	White	PDAC	*BUB1B*	15:40512901	p.N1032H	c.3094A>C	Missense	VUS	No	Heterozygous	NA
Case_14*54	86	M	Other	PDAC	*BUB1B*	15:40512901	p.N1032H	c.3094A>C	Missense	VUS	No	Heterozygous	Lung (sister, cousin, aunt, uncle)
Case_15*65	70	F	White	PDAC	*BUB3*	10:124914608	p.V59I	c.175G>A	Missense	VUS	No	Heterozygous	None
Case_6*51	56	F	White	Non-PDAC: pNET	*CDH1*	16:68867265	p.S838G	c.2512A>G	Missense	VUS	Yes	Heterozygous	MEN1A (mother and four aunts)
Case_9*19	66	F	White	Non-PDAC: Duodenal AC	*CDH1*	16:68863674	p.D805N	c.2413G>A	Missense	VUS	No	Heterozygous	None

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_7*22	52	F	Other	Non-PDAC: Chronic pancreatitis	*CDH1*	16:68867247	p.V832M	c.2494G>A	Missense	VUS	No	Heterozygous	None
Case_3*86	70	F	White	PDAC	*CDH1*	16:68845646	p.A298T	c.892G>A	Missense	VUS	No	Heterozygous	Leukemia (mother)
Case_4*91	70	M	White	PDAC	*CDH1*	16:68845646	p.A298T	c.892G>A	Missense	VUS	No	Heterozygous	None
Case_7*19	44	M	White	PDAC	*CDH1*	16:68857353	p.Y663C	c.1988A>G	Missense	VUS	No	Heterozygous	Lymphoma (uncle), brain (another uncle)
Case_12*12	81	M	White	PDAC	*CDH1*	16:68863674	p.D805N	c.2413G>A	Missense	VUS	No	Heterozygous	Unknown
Case_1*44	52	M	Other	PDAC	*CDH1*	16:68867247	p.V832M	c.2494G>A	Missense	VUS	No	Heterozygous	None
Case_2*47	73	F	African American	PDAC	*CDKN2A*	9:21971060	p.A100S	c.298C>A	Missense	VUS	No	Heterozygous	NA
Case_6*70	57	M	Other	PDAC	*ERCC4*	16:14014052	p.I10M	c.30T>G	Missense	VUS	No	Heterozygous	None
Case_13*59	46	F	White	PDAC	*ERCC4*	16:14016064	p.I128M	c.384T>G	Missense	VUS	No	Heterozygous	None
Case_5*06	58	M	White	PDAC	*ERCC4*	16:14020561	p.V178L	c.532G>T	Missense	VUS	No	Heterozygous	Lymphoma (mother), brain cancer (paternal uncle), lymphoma (maternal aunt)
Case_1*40	73	F	White	PDAC	*ERCC4*	16:14028081	p.P379S	c.1135C>T	Missense	VUS	No	Heterozygous	None
Case_12*13	66	M	White	PDAC	*ERCC4*	16:14028081	p.P379S	c.1135C>T	Missense	VUS	No	Heterozygous	Lung (father)
Case_12*33	56	F	White	PDAC	*ERCC4*	16:14028081	p.P379S	c.1135C>T	Missense	VUS	No	Heterozygous	None
Case_15*35	68	M	White	PDAC	*ERCC4*	16:14028081	p.P379S	c.1135C>T	Missense	VUS	No	Heterozygous	Colon (father), thyroid (mother), breast (sister)
Case_5*32	63	F	White	PDAC	*ERCC4*	16:14028081	p.P379S	c.1135C>T	Missense	VUS	No	Heterozygous	None
Case_8*09	90	M	White	PDAC	*ERCC4*	16:14028081	p.P379S	c.1135C>T	Missense	VUS	No	Heterozygous	None
Case_13*68	42	F	White	PDAC	*ERCC4*	16:14028147	p.L401F	c.1201C>T	Missense	VUS	No	Heterozygous	Pancreas (maternal uncle), breast (maternal aunt)
Case_2*76	72	M	White	PDAC	*ERCC4*	16:14028147	p.L401F	c.1201C>T	Missense	VUS	No	Heterozygous	Gastric (mother), lung (paternal aunt), breast (sister)
Case_12*02	38	F	Other	PDAC	*ERCC4*	16:14028156	p.P404S	c.1210C>T	Missense	VUS	No	Heterozygous	Lung (paternal grandmother)
Case_6*67	61	M	White	PDAC	*ERCC4*	16:14029422	p.G545R	c.1633G>C	Missense	VUS	No	Heterozygous	None
Case_12*15	59	M	African American	PDAC	*ERCC4*	16:14029515	p.R576G	c.1726A>G	Missense	VUS	No	Heterozygous	Breast (mother), pancreas (brother), lung (father)
Case_1*12	75	F	White	PDAC	*ERCC4*	16:14029516	p.R576T	c.1727G>C	Missense	VUS	No	Heterozygous	None
Case_13*16	72	F	White	PDAC	*ERCC4*	16:14029516	p.R576T	c.1727G>C	Missense	VUS	No	Heterozygous	Ovarian (mother), breast (maternal grandmother)
Case_13*72	38	F	White	PDAC	*ERCC4*	16:14029516	p.R576T	c.1727G>C	Missense	VUS	No	Heterozygous	Prostate (paternal grandfather)
Case_15*58	61	M	White	PDAC	*ERCC4*	16:14029535	p.D582E	c.1746C>G	Missense	VUS	No	Heterozygous	None
Case_8*03	63	M	White	PDAC	*ERCC4*	16:14041476	p.Q675K	c.2023C>A	Missense	VUS	No	Heterozygous	None
Case_11*24	55	F	White	PDAC	*ERCC4*	16:14041570	p.I706T	c.2117T>C	Missense	VUS	No	Heterozygous	Pancreas (mother)
Case_4*04	68	M	White	PDAC	*ERCC4*	16:14041570	p.I706T	c.2117T>C	Missense	VUS	No	Heterozygous	Liver (mother), breast (grandmother)
Case_12*40	78	M	White	PDAC	*ERCC4*	16:14041609	p.T719N	c.2156C>A	Missense	VUS	No	Heterozygous	None
Case_12*91	31	F	White	PDAC	*ERCC4*	16:14041672	p.R740H	c.2219G>A	Missense	VUS	No	Heterozygous	Lung cancer and brain tumor (great aunt), biliary tract cancer (uncle)
Case_1*61	73	F	White	PDAC	*ERCC4*	16:14041848	p.R799W	c.2395C>T	Missense	VUS	No	Heterozygous	NA
Case_13*47	64	M	White	PDAC	*ERCC4*	16:14041918	p.Q822R	c.2465A>G	Missense	VUS	No	Heterozygous	None
Case_8*48	62	M	White	PDAC	*ERCC4*	16:14042026	p.V858A	c.2573T>C	Missense	VUS	No	Heterozygous	Gastric (father)
Case_4*22	72	F	African American	PDAC	*ERCC4*	16:14042070	p.I873V	c.2617A>G	Missense	VUS	No	Heterozygous	None
Case_2*38	76	M	White	PDAC	*ERCC4*	16:14042100	p.E883K	c.2647G>A	Missense	VUS	No	Heterozygous	None
Case_4*73	48	M	African American	Non-PDAC: SCN	*ERCC4*	16:14016005	p.A109T	c.325G>A	Missense	VUS	No	Heterozygous	Colon (father), breast (maternal grandmother)
Case_9*37	42	F	White	Non-PDAC: SCN	*ERCC4*	16:14029517	p.R576S	c.1728A>T	Missense	VUS	No	Heterozygous	None
Case_8*56	62	M	Other	Non-PDAC: Duodenal AC	*ERCC4*	16:14031656	p.E615D	c.1845G>C	Missense	VUS	No	Heterozygous	Uterine (sister), liver (brother)
Case_7*69	77	F	White	Non-PDAC: pNET	*FANCA*	16:89805603	p.V1369M	c.4105C>C	Missense	VUS	No	Heterozygous	Esophagus (brother)
Case_5*66	80	M	White	Non-PDAC: pNET	*FANCA*	16:89805946	p.R1317Q	c.3950C>T	Missense	VUS	No	Heterozygous	NA
Case_8*78	37	F	Other	Non-PDAC: SCN, PanIN2	*FANCA*	16:89816196	p.S1061G	c.3181T>C	Missense	VUS	No	Heterozygous	Lung (father)
Case_3*50	71	M	White	Non-PDAC: Duodenal carcinoid	*FANCA*	16:89836270	p.R827G	c.2479T>C	Missense	VUS	No	Heterozygous	None

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_2*20	64	M	White	Non-PDAC: Duodenal AC	*FANCA*	16:89857891	p.M427V	c.1279T>C	Missense	VUS	No	Heterozygous	None
Case_9*08	68	F	African American	Non-PDAC: Gallbladder AC	*FANCA*	16:89865610	p.Q286R	c.857T>C	Missense	VUS	No	Heterozygous	Unknown primary cancer (uncle)
Case_7*56	57	F	White	Non-PDAC: GIST	*FANCA*	16:89874721	p.L193V	c.577G>C	Missense	VUS	No	Heterozygous	None
Case_11*61	57	M	White	Non-PDAC: Duodenal AC	*FANCA*	16:89805360	p.T1397R	c.4190G>C	Missense	VUS	No	Heterozygous	Colon (grandmother and mother), lymphoma (father)
Case_14*01	53	F	White	PDAC	*FANCA*	16:89805103	p.R1425H	c.4274C>T	Missense	VUS	No	Heterozygous	Esophagus (maternal grandfather), gastric (paternal grandfather), bladder (paternal uncle)
Case_14*53	51	F	White	PDAC	*FANCA*	16:89805934	p.R1321H	c.3962C>T	Missense	VUS	No	Heterozygous	None
Case_14*12	47	M	White	PDAC	*FANCA*	16:89806446	p.K1297R	c.3890T>C	Missense	VUS	No	Heterozygous	Liver (father), breast (mother)
Case_2*19	54	F	White	PDAC	*FANCA*	16:89809308	p.P1222L	c.3665G>A	Missense	VUS	No	Heterozygous	Pancreas (sister, paternal aunt), liver (maternal grandfather), thyroid (paternal grandfather), colon (daughter)
Case_7*10	54	F	White	PDAC	*FANCA*	16:89838208	p.V677M	c.2029C>T	Missense	VUS	No	Heterozygous	Melanoma (sister)
Case_15*85	66	M	White	PDAC	*FANCA*	16:89865610	p.Q286R	c.857T>C	Missense	VUS	No	Heterozygous	Larynx (paternal uncle)
Case_3*07	63	M	White	PDAC	*FANCA*	16:89874721	p.L193V	c.577G>C	Missense	VUS	No	Heterozygous	NA
Case_12*41	71	M	White	PDAC	*FANCA*	16:89877386	p.T126R	c.377G>C	Missense	VUS	No	Heterozygous	Lung (father), brain, lung, and rectal (paternal uncles)
Case_5*62	62	M	White	PDAC	*FANCA*	16:89877419	p.G115E	c.344C>T	Missense	VUS	No	Heterozygous	None
Case_12*40	78	M	White	PDAC	*FANCA*	16:89881011	p.P67Q	c.200G>T	Missense	VUS	No	Heterozygous	None
Case_12*12	81	M	White	PDAC	*FANCC*	9:97864063	p.R535C	c.1603G>A	Missense	VUS	No	Heterozygous	Unknown
Case_14*09	67	M	White	PDAC	*FANCC*	9:97869467	p.G472R	c.1414C>T	Missense	VUS	No	Heterozygous	None
Case_15*72	65	M	White	PDAC	*FANCC*	9:97873792	p.F428V	c.1282A>C	Missense	VUS	No	Heterozygous	None
Case_3*25	74	F	Other	PDAC	*FANCC*	9:97887391	p.A325T	c.973C>T	Missense	VUS	No	Heterozygous	None
Case_12*48	75	F	White	PDAC	*FANCC*	9:97887430	p.I312V	c.934T>C	Missense	VUS	No	Heterozygous	None
Case_5*38	54	M	White	PDAC	*FANCC*	9:97897704	p.H256R	c.767T>C	Missense	VUS	No	Heterozygous	Breast and uterine (sister), multiple sclerosis (father)
Case_9*01	51	F	White	Non-PDAC: SCN	*FANCC*	9:97912271	p.H207L	c.620T>A	Missense	VUS	No	Heterozygous	NA
Case_7*24	50	M	White	Non-PDAC: Duodenal AC	*FANCC*	9:97912337	p.R185Q	c.554C>T	Missense	VUS	No	Heterozygous	None
Case_12*29	56	F	White	PDAC	*FANCC*	9:98011545	p.C10Y	c.29C>T	Missense	VUS	No	Heterozygous	None
Case_1*16	81	F	Other	PDAC	*FANCG*	9:35074426	p.T568A	c.1702T>C	Missense	VUS	No	Heterozygous	None
Case_10*78	62	M	White	PDAC	*FANCG*	9:35078282	p.W122C	c.366C>G	Missense	VUS	No	Heterozygous	None
Case_12*56	53	M	White	PDAC	*FANCG*	9:35078282	p.W122C	c.366C>G	Missense	VUS	No	Heterozygous	Breast (aunt), bone (cousin)
Case_3*14	66	M	White	PDAC	*FANCG*	9:35078310	p.R113K	c.338C>T	Missense	VUS	No	Heterozygous	?Lung (sister)
Case_5*66	80	M	White	Non-PDAC: pNET	*FANCL*	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	VUS	Yes	Heterozygous	NA
Case_7*20	62	M	White	Non-PDAC: Duodenal AC (with mucinous feature)	*FANCL*	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	VUS	Yes	Heterozygous	Uterine cancer and melanoma (mother)
Case_10*08	55	M	White	PDAC	*FANCL*	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	VUS	Yes	Heterozygous	None
Case_12*61	50	M	White	PDAC	*FANCL*	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	VUS	Yes	Heterozygous	None
Case_14*20	82	F	White	PDAC	*FANCL*	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	VUS	Yes	Heterozygous	Thyroid (son)
Case_15*40	43	M	White	PDAC	*FANCL*	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	VUS	Yes	Heterozygous	Pancreas (father), ? stomach CA (paternal grandmother)
Case_2*40	78	F	White	PDAC	*FANCL*	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	VUS	Yes	Heterozygous	NA
Case_12*36	65	M	African American	PDAC	*FANCL*	2:58456957	p.V70I	c.208C>T	Missense	VUS	No	Heterozygous	None
Case_1*14	62	F	White	PDAC	*FANCL*	2:58456962	p.R68P	c.203C>G	Missense	VUS	No	Heterozygous	Breast (mother)
Case_12*54	53	F	White	PDAC	*FANCL*	2:58456962	p.R68P	c.203C>G	Missense	VUS	No	Heterozygous	Liver (father), breast (mother), breast (maternal aunts [three]), breast (maternal cousin)
Case_15*57	83	F	White	PDAC	*MLH1*	3:37050390	p.V180G	c.539T>G	Missense	VUS	No	Heterozygous	Colon (uncle)
Case_2*53	54	F	White	PDAC	*MLH1*	3:37061929	p.N338S	c.1013A>G	Missense	VUS	No	Heterozygous	Breast (great aunt), prostate (father, paternal uncle), oral (maternal great aunt)

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_14*55	68	M	White	PDAC	*MLH1*	3:37067357	p.R423K	c.1268G>A	Missense	VUS	No	Heterozygous	Breast (mother), skin (mother)
Case_5*54	66	M	African American	PDAC	*MLH1*	3:37083821	p.S577L	c.1730C>T	Missense	VUS	No	Heterozygous	Throat (brother), colon (paternal grandfather)
Case_9*42	43	M	Other	Non-PDAC: Myxoid liposarcoma metastasis to pancreas	*MLH1*	3:37053562	p.R217C	c.649C>T	Missense	VUS	No	Heterozygous	Breast (sister), lymphoma (father), breast (mother)
Case_7*10	54	F	White	PDAC	*MSH2*	2:47672711	p.A434V	c.1301C>T	Missense	VUS	No	Heterozygous	Melanoma (sister)
Case_6*64	81	M	White	PDAC	*MSH2*	2:47702331	p.E643K	c.1927G>A	Missense	VUS	No	Heterozygous	None
Case_12*19	51	M	White	PDAC	*MSH2*	2:47702367	p.V655I	c.1963G>A	Missense	VUS	No	Heterozygous	Ovary (mother), esophagus (paternal grandmother)
Case_1*39	70	F	White	PDAC	*MSH6*	2:48010445	p.A25S	c.73G>T	Missense	VUS	No	Heterozygous	Breast (mother), mycosis fungoides (mother)
Case_15*32	60	M	African American	PDAC	*MSH6*	2:48010466	p.G32C	c.94G>T	Missense	VUS	No	Heterozygous	Ovarian (mother, paternal aunt)
Case_1*62	75	M	White	PDAC	*MSH6*	2:48025785	p.E221D	c.663A>C	Missense	VUS	No	Heterozygous	NA
Case_12*51	65	M	White	PDAC	*MSH6*	2:48025785	p.E221D	c.663A>C	Missense	VUS	No	Heterozygous	NA
Case_9*73	78	F	White	PDAC	*MSH6*	2:48025988	p.G289D	c.866G>A	Missense	VUS	No	Heterozygous	None
Case_7*51	60	F	African American	PDAC	*MSH6*	2:48027054	p.R644S	c.1932G>C	Missense	VUS	No	Heterozygous	Lung (father), colon (sister)
Case_10*93	57	F	White	PDAC	*MSH6*	2:48027269	p.T716I	c.2147C>T	Missense	VUS	No	Heterozygous	NA
Case_1*81	56	M	Other	PDAC	*MSH6*	2:48027506	p.I795T	c.2384T>C	Missense	VUS	No	Heterozygous	NA
Case_13*88	66	M	Other	PDAC	*MSH6*	2:48027683	p.K854M	c.2561A>T	Missense	VUS	No	Heterozygous	Autoimmune pancreatitis (brother), unknown (father), bladder (sister)
Case_11*35	38	M	African American	PDAC	*MSH6*	2:48027789	p.Q889H	c.2667G>T	Missense	VUS	No	Heterozygous	Colon (father)
Case_12*88	55	M	White	PDAC	*MSH6*	2:48028160	p.K1013R	c.3038A>G	Missense	VUS	No	Heterozygous	None
Case_10*33	35	F	White	PDAC	*MSH6*	2:48030589	p.R1068Q	c.3203G>G	Missense	VUS	No	Heterozygous	None
Case_5*46	74	M	White	PDAC	*MSH6*	2:48030589	p.R1068Q	c.3203G>G	Missense	VUS	No	Heterozygous	None
Case_12*79	49	F	White	PDAC	*MSH6*	2:48030603	p.P1073S	c.3217C>T	Missense	VUS	No	Heterozygous	Breast and liver (mother), liver (aunt), stomach (grandmother)
Case_14*29	72	M	White	PDAC	*MSH6*	2:48030603	p.P1073S	c.3217C>T	Missense	VUS	No	Heterozygous	None
Case_2*56	64	F	White	PDAC	*MSH6*	2:48030613	p.R1076H	c.3227G>A	Missense	VUS	No	Heterozygous	Skin (sister)
Case_1*94	59	M	White	PDAC	*MSH6*	2:48030619	p.V1078A	c.3233T>C	Missense	VUS	No	Heterozygous	Prostate (father)
Case_3*15	57	F	White	Non-PDAC: pNET	*MSH6*	2:48026596	p.M492V	c.1474A>G	Missense	VUS	No	Heterozygous	Breast (mother, maternal grandmother), prostate (maternal grandfather)
Case_8*34	62	M	White	Non-PDAC: pNET	*MSH6*	2:48033947	p.T1344N	c.4031C>A	Missense	VUS	No	Heterozygous	None
Case_2*05	40	F	African American	Non-PDAC: Acute and chronic pancreatitis	*MSH6*	2:48027054	p.R644S	c.1932G>C	Missense	VUS	No	Heterozygous	None
Case_3*34	53	M	White	PDAC	*MSH6*	2:48033750	p.R1321G	c.3961A>G	Missense	VUS	No	Heterozygous	Gastric (father), breast (two aunts), leukemia (aunt), skin (mother), eight brothers and sisters with unknown cancer
Case_7*38	57	F	White	Non-PDAC: pNET	*PMS2*	7:6026561	p.N612S	c.1835T>C	Missense	VUS	No	Heterozygous	None
Case_5*17	68	F	White	PDAC	*PMS2*	7:6031660	p.H311R	c.767T>C	Missense	VUS	No	Heterozygous	None
Case_5*34	54	F	White	PDAC	*PMS2*	7:6031660	p.H311R	c.767T>C	Missense	VUS	No	Heterozygous	None
Case_5*41	78	F	White	PDAC	*PMS2*	7:6031660	p.H311R	c.767T>C	Missense	VUS	No	Heterozygous	Colon (mother), colon (brother)
Case_5*64	84	M	White	PDAC	*PMS2*	7:6031660	p.H311R	c.767T>C	Missense	VUS	No	Heterozygous	Lung and stomach (sister), lung (two brothers)
Case_3*10	75	M	White	PDAC	*PRSS1*	7:142459680	p.Q86X	c.156C>T	Nonsense	VUS	Yes	Heterozygous	NA
Case_11*04	58	F	White	PDAC	*PRSS1*	7:142460307	p.C160X	c.480C>A	Nonsense	VUS	Yes	Heterozygous	None
Case_4*65	45	F	White	PDAC	*PRSS1*	7:142459720	p.Y99C	c.296A>G	Missense	VUS	No	Heterozygous	None
Case_12*25	52	M	African American	PDAC	*RAD51B*	14:68290285	p.V9M	c.25G>A	Missense	VUS	No	Heterozygous	Pancreas (mother)
Case_1*39	70	F	White	PDAC	*RAD51B*	14:68290312	p.R18C	c.52C>T	Missense	VUS	No	Heterozygous	Breast (mother), mycosis fungoides (mother)
Case_12*8	64	F	White	PDAC	*RAD51B*	14:68331763	p.M120T	c.359T>C	Missense	VUS	No	Heterozygous	Multiple myeloma (brother)
Case_4*75	62	F	African American	PDAC	*RAD51B*	14:68352656	p.S175R	c.523A>C	Missense	VUS	No	Heterozygous	None

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_12*50	63	M	White	PDAC	*RAD51B*	14:68352672	p.Y180C	c.539A>G	Missense	VUS	No	Heterozygous	Colon (mother), prostate (father), prostate (grandfather, two uncles), renal cell cancer (aunts)
Case_12*09	63	M	White	PDAC	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	Pancreas (grandfather), pancreatitis (father)
Case_13*55	73	F	White	PDAC	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	None
Case_15*57	83	F	White	PDAC	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	Colon (uncle)
Case_5*43	63	M	White	PDAC	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	Ovary (mother), colon (father)
Case_5*88	78	F	White	PDAC	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	Colon (brother)
Case_6*92	51	M	Other	PDAC	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	Lung (mother), questionable unknown type of skin cancer (brother)
Case_7*49	68	M	White	PDAC	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	Pancreas (father), lung (two brothers), lung (sister), colon (another sister)
Case_1*03	47	F	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	Pancreas (father)
Case_1*77	58	M	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	Melanoma (mother)
Case_13*43	83	M	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	Breast (mother)
Case_14*56	40	F	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	None
Case_15*74	77	M	African American	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	None
Case_15*77	54	M	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	Lung (mother), melanoma (father)
Case_15*78	65	M	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	Breast (mother), lung (father)
Case_3*86	70	F	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	Leukemia (mother)
Case_5*17	68	F	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	None
Case_9*69	79	M	White	PDAC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	None
Case_13*87	63	F	African American	PDAC	*RAD51B*	14:68353913	p.S250A	c.748T>G	Missense	VUS	No	Heterozygous	Colon (maternal aunt)
Case_5*66	80	M	White	Non-PDAC: pNET	*RAD51B*	14:68352672	p.Y180C	c.539A>G	Missense	VUS	No	Heterozygous	NA
Case_6*07	41	F	White	Non-PDAC: SCN	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	None
Case_2*64	46	M	White	Non-PDAC: pNET	*RAD51B*	14:68353784	p.V207L	c.619G>T	Missense	VUS	No	Heterozygous	Esophagogastric (father)
Case_6*66	54	F	White	Non-PDAC: GIST	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	None
Case_4*17	64	M	White	Non-PDAC: Duodenal AC	*RAD51B*	14:68353893	p.K243R	c.728A>G	Missense	VUS	No	Heterozygous	Colonic polyp (mother, father), Hodgkin lymphoma (maternal cousin)
Case_6*60	75	F	African American	Non-PDAC: Gallbladder AC	*RAD51B*	14:68290285	p.V9M	c.25G>A	Missense	VUS	No	Heterozygous	None
Case_6*60	75	F	African American	Non-PDAC: Gallbladder AC	*RAD51C*	17:56798159	p.L297P	c.890T>C	Missense	VUS	No	Heterozygous	None
Case_2*48	54	F	White	PDAC	*RAD51C*	17:56774057	p.M136I	c.408G>A	Missense	VUS	No	Heterozygous	NA
Case_9*84	50	M	White	PDAC	*RAD51C*	17:56787298	p.L262V	c.784T>G	Missense	VUS	No	Heterozygous	Colon (sister), prostate (father), breast (paternal aunt), breast (son), colon (daughter), lymphoma (maternal grandmother), colon (paternal grandmother)
Case_10*93	57	F	White	PDAC	*RAD51D*	17:33434074	p.N158S	c.473T>C	Missense	VUS	No	Heterozygous	NA
Case_1*25	62	M	White	PDAC	*RAD51D*	17:33434132	p.C139R	c.415A>G	Missense	VUS	No	Heterozygous	Uterus (mother)
Case_14*12	47	M	White	PDAC	*RAD51D*	17:33434132	p.C139R	c.415A>G	Missense	VUS	No	Heterozygous	Liver (father), breast (mother)
Case_2*92	64	F	White	PDAC	*RAD51D*	17:33434415	p.^{125}IM	c.375A>C	Missense	VUS	No	Heterozygous	NA
Case_1*07	80	F	White	PDAC	*RAD51D*	17:33443893	p.A103V	c.308G>A	Missense	VUS	No	Heterozygous	None
Case_11*55	57	F	White	PDAC	*RECQL4*	8:145736832	p.P1204S	c.3610G>A	Missense	VUS	No	Heterozygous	None
Case_3*14	66	M	White	PDAC	*RECQL4*	8:145736832	p.P1204S	c.3610G>A	Missense	VUS	No	Heterozygous	?Lung (sister)
Case_5*49	79	M	White	PDAC	*RECQL4*	8:145736832	p.P1204S	c.3610G>A	Missense	VUS	No	Heterozygous	None
Case_13*71	59	M	White	PDAC	*RECQL4*	8:145737086	p.G1161S	c.3481C>T	Missense	VUS	No	Heterozygous	Prostate (father), lymphoma (son)
Case_10*73	76	F	White	PDAC	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	NA
Case_12*69	68	M	White	PDAC	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	None
Case_14*18	70	M	White	PDAC	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	Gastric (mother)
Case_14*66	77	F	White	PDAC	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	Uterine cancer (sister)
Case_4*83	71	F	White	PDAC	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	None
Case_4*88	71	F	White	PDAC	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	None
Case_11*53	50	F	White	PDAC	*RECQL4*	8:145738149	p.R921Q	c.2762C>T	Missense	VUS	No	Heterozygous	Colon (paternal grandmother)
Case_4*65	45	F	White	PDAC	*RECQL4*	8:145738405	p.A861T	c.2581C>T	Missense	VUS	No	Heterozygous	None

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_15*41	70	F	White	PDAC	*RECQL4*	8:145738441	p.R849C	c.2545G>A	Missense	VUS	No	Heterozygous	Breast (paternal grandmother, maternal grandmother, sister), lung CA (? relatives)
Case_15*18	64	M	White	PDAC	*RECQL4*	8:145738604	p.P821S	c.2461G>A	Missense	VUS	No	Heterozygous	Pancreas CA (paternal cousin), thyroid CA (mother), lung CA (brother)
Case_11*51	78	F	African American	PDAC	*RECQL4*	8:145738963	p.G731E	c.2192C>T	Missense	VUS	No	Heterozygous	Pancreas (brother), breast (mother)
Case_14*02	72	M	White	PDAC	*RECQL4*	8:145739583	p.R623H	c.1868C>T	Missense	VUS	No	Heterozygous	None
Case_14*37	69	F	White	PDAC	*RECQL4*	8:145739583	p.R623H	c.1868C>T	Missense	VUS	No	Heterozygous	Colon (mother)
Case_10*72	57	F	White	PDAC	*RECQL4*	8:145740364	p.L526F	c.1576G>A	Missense	VUS	No	Heterozygous	Bilateral breast (sister, *BRCA2* positive)
Case_2*04	79	M	White	PDAC	*RECQL4*	8:145740364	p.L526F	c.1576G>A	Missense	VUS	No	Heterozygous	NA
Case_5*42	75	M	White	PDAC	*RECQL4*	8:145740364	p.L526F	c.1576G>A	Missense	VUS	No	Heterozygous	None
Case_12*65	78	M	White	PDAC	*RECQL4*	8:145740375	p.R522H	c.1565C>T	Missense	VUS	No	Heterozygous	NA
Case_13*46	67	M	White	PDAC	*RECQL4*	8:145740375	p.R522H	c.1565C>T	Missense	VUS	No	Heterozygous	Colon (father), pheochromocytoma (brother)
Case_5*42	75	M	White	PDAC	*RECQL4*	8:145740375	p.R522H	c.1565C>T	Missense	VUS	No	Heterozygous	None
Case_14*90	74	F	White	PDAC	*RECQL4*	8:145740572	p.R482H	c.1445C>T	Missense	VUS	No	Heterozygous	Colon (mother), renal cell (brother), lung (brother)
Case_4*36	62	M	White	PDAC	*RECQL4*	8:145740752	p.V450M	c.1348C>T	Missense	VUS	No	Heterozygous	Colon (father)
Case_1*02	83	M	Other	PDAC	*RECQL4*	8:145741388	p.R372T	c.1115C>G	Missense	VUS	No	Heterozygous	None
Case_10*15	53	F	Other	PDAC	*RECQL4*	8:145741388	p.R372T	c.1115C>G	Missense	VUS	No	Heterozygous	Breast (sister), liver (father)
Case_11*24	55	F	White	PDAC	*RECQL4*	8:145741409	p.R365Q	c.1094C>T	Missense	VUS	No	Heterozygous	Pancreas (mother)
Case_9*53	59	F	White	PDAC	*RECQL4*	8:145741533	p.P324S	c.970G>A	Missense	VUS	No	Heterozygous	Lung (mother), lung (maternal aunt), throat (maternal grandfather), breast (paternal aunt), lung (another paternal aunt)
Case_7*89	48	M	White	PDAC	*RECQL4*	8:145741542	p.G321R	c.961C>T	Missense	VUS	No	Heterozygous	CLL (father), prostate (paternal uncle), pancreas (paternal uncle), breast (paternal aunt), melanoma with kidney and testicular cancer (paternal uncle), colon and basal cell skin (paternal grandfather)
Case_6*13	57	M	African American	PDAC	*RECQL4*	8:145741611	p.P298S	c.892G>A	Missense	VUS	No	Heterozygous	Bone, meta or primary (father)
Case_11*27	83	F	African American	PDAC	*RECQL4*	8:145741686	p.A273T	c.817C>T	Missense	VUS	No	Heterozygous	Colon (two brothers)
Case_1*93	46	M	White	PDAC	*RECQL4*	8:145742451	p.L113M	c.337G>T	Missense	VUS	No	Heterozygous	NA
Case_5*07	61	M	White	PDAC	*RECQL4*	8:145742451	p.L113M	c.337G>T	Missense	VUS	No	Heterozygous	None
Case_1*52	49	F	White	PDAC	*RECQL4*	8:145742480	p.P103L	c.308G>A	Missense	VUS	No	Heterozygous	Breast (paternal aunt), ?bile duct (mother)
Case_4*07	69	F	White	PDAC	*RECQL4*	8:145742480	p.P103L	c.308G>A	Missense	VUS	No	Heterozygous	Colon (mother)
Case_10*84	80	M	White	Non-PDAC: pNET	*RECQL4*	8:145736832	p.P1204S	c.3610G>A	Missense	VUS	No	Heterozygous	NA
Case_11*81	66	M	White	Non-PDAC: pNET	*RECQL4*	8:145736832	p.P1204S	c.3610G>A	Missense	VUS	No	Heterozygous	Liver (maternal uncle)
Case_3*15	57	F	White	Non-PDAC: pNET	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	Breast (mother, maternal grandmother), prostate (maternal grandfather)
Case_9*90	34	F	White	Non-PDAC: pNET	*RECQL4*	8:145738093	p.D940N	c.2818C>T	Missense	VUS	No	Heterozygous	Colorectal (mother)
Case_3*15	57	F	White	Non-PDAC: pNET	*RECQL4*	8:145739583	p.R623H	c.1868C>T	Missense	VUS	No	Heterozygous	Breast (mother, maternal grandmother), prostate (maternal grandfather)
Case_8*75	63	F	Other	Non-PDAC: Gallbladder AC	*RECQL4*	8:145739467	p.H635Y	c.1903G>A	Missense	VUS	No	Heterozygous	None
Case_2*20	64	M	White	Non-PDAC: Duodenal AC	*RECQL4*	8:145736819	p.P1208L	c.3623G>A	Missense	VUS	No	Heterozygous	None
Case_14*83	72	F	White	Non-PDAC: Duodenal AC	*RECQL4*	8:145738441	p.R849C	c.2545G>A	Missense	VUS	No	Heterozygous	Colon (paternal grandmother)
Case_9*42	43	M	Other	Non-PDAC: Myxoid liposarcoma metastasis to pancreas	*RNF43*	17:56436044	p.A365T	c.1093C>T	Missense	VUS	No	Heterozygous	Breast (sister), lymphoma (father), breast (mother)
Case_7*56	57	F	White	Non-PDAC: GIST	*RNF43*	17:56439952	p.L214V	c.640G>C	Missense	VUS	No	Heterozygous	None

(continued on following page)

Table A2. Variants of Uncertain Significance (continued)

Patient Case ID	Age, Years	Sex	Race	Disease Group	Gene	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	VUS	Sanger Validation	Zygosity	Family Cancer History
Case_9*45	39	M	White	Non-PDAC: Focal chronic pancreatitis, PanIN2	*RNF43*	17:56436127	p.R337Q	c.1010C>T	Missense	VUS	No	Heterozygous	Idiopathic pancreatitis (mother)
Case_3*77	63	F	White	Non-PDAC: Duodenal AC	*RNF43*	17:56439918	p.R225H	c.674C>T	Missense	VUS	No	Heterozygous	Breast (maternal cousin)
Case_11*10	66	F	Other	Non-PDAC: Duodenal AC	*RNF43*	17:56440710	p.E170K	c.508C>T	Missense	VUS	No	Heterozygous	NA
Case_4*25	71	M	White	PDAC	*RNF43*	17:56434843	p.L765P	c.2294A>G	Missense	VUS	No	Heterozygous	Lung (mother)
Case_12*30	63	F	White	PDAC	*RNF43*	17:56434876	p.G754A	c.2261C>G	Missense	VUS	No	Heterozygous	Prostate (paternal grandfather)
Case_14*23	68	M	White	PDAC	*RNF43*	17:56435312	p.R609W	c.1825G>A	Missense	VUS	No	Heterozygous	Head and neck (father), liposarcoma (son)
Case_12*02	38	F	Other	PDAC	*RNF43*	17:56436044	p.A365T	c.1093C>T	Missense	VUS	No	Heterozygous	Lung (paternal grandmother)
Case_14*33	42	F	White	PDAC	*RNF43*	17:56436127	p.R337Q	c.1010C>T	Missense	VUS	No	Heterozygous	Lung (mother), lymphoma (grandfather), prostate (paternal uncle)
Case_4*12	63	M	White	PDAC	*RNF43*	17:56436127	p.R337Q	c.1010C>T	Missense	VUS	No	Heterozygous	None
Case_5*47	57	M	White	PDAC	*RNF43*	17:56436127	p.R337Q	c.1010C>T	Missense	VUS	No	Heterozygous	Pancreas (mother, maternal aunt), brain (second-degree relative)
Case_6*37	60	F	White	PDAC	*RNF43*	17:56436127	p.R337Q	c.1010C>T	Missense	VUS	No	Heterozygous	Breast (mother), colon (maternal grandmother), gastric (father), lymphoma (father), colon (paternal grandmother)
Case_11*62	55	F	White	PDAC	*RNF43*	17:56439952	p.L214V	c.640G>C	Missense	VUS	No	Heterozygous	None
Case_9*29	63	F	White	PDAC	*RNF43*	17:56439952	p.L214V	c.640G>C	Missense	VUS	No	Heterozygous	Bladder (father)
Case_15*25	69	F	White	PDAC	*RNF43*	17:56440903	p.R145Q	c.434C>T	Missense	VUS	No	Heterozygous	None
Case_13*17	79	F	White	PDAC	*STK11*	19:1206955	p.G15S	c.43G>A	Missense	VUS	No	Heterozygous	None
Case_11*62	55	F	White	PDAC	*TERT*	5:1271291	p.G804V	c.2411C>A	Missense	VUS	No	Heterozygous	None
Case_8*53	78	F	White	PDAC	*XRCC2*	7:152345836	p.D245G	c.734T>C	Missense	VUS	No	Heterozygous	None
Case_6*76	56	F	White	PDAC	*XRCC2*	7:152345950	p.E207G	c.620T>C	Missense	VUS	No	Heterozygous	None
Case_15*60	70	F	White	PDAC	*XRCC2*	7:152346287	p.I95V	c.283T>C	Missense	VUS	No	Heterozygous	None
Case_7*22	52	F	Other	Non-PDAC: Chronic pancreatitis	*XRCC2*	7:152345974	p.M199T	c.596A>A	Missense	VUS	No	Heterozygous	None
Case_13*83	63	F	African American	PDAC	*XRCC3*	14:104165747	p.R243H	c.728C>T	Missense	VUS	No	Heterozygous	Prostate (father, brother), colon (brother), Hodgkin disease (brother), breast (maternal aunt)
Case_15*65	70	F	White	PDAC	*XRCC3*	14:104165747	p.R243H	c.728C>T	Missense	VUS	No	Heterozygous	None
Case_8*75	63	F	Other	Non-PDAC: Gallbladder AC	*XRCC3*	14:104165864	p.R204Q	c.611C>T	Missense	VUS	No	Heterozygous	None
Case_10*34	74	F	Other	Non-PDAC: Duodenal AC	*XRCC3*	14:104165864	p.R204Q	c.611C>T	Missense	VUS	No	Heterozygous	Pancreas (brother), uterine (daughter)
Case_2*25	42	F	African American	Non-PDAC: Ampullary NET	*XRCC3*	14:104169593	p.R160W	c.478G>A	Missense	VUS	No	Heterozygous	Lymphoma (mother)

Abbreviations: AC, adenocarcinoma; BCC, basal cell carcininoma; CA, cancer; CLL, chronic lymphocytic leukemia; F, female; GIST, GI stromal tumor; M, male; MEN1A, multiple endocrine neoplasia 1A; NA, not applicable; NET, neuroendocrine tumor; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; SCN, serous cystadenoma; SPN, solid pseudopapillary neoplasm; VUS; variants of undetermined significance.

Table A3. Sanger Sequencing Validation PrimersGene

	Chromosome Position	Amino Acid Change	Nucleotide Change	Function	Sanger Validated	Amplicon Size	Sanger Validation Forward Primer	Sanger Validation Reverse Primer
ATM	11:108098354	p.M1IM	c.3G>AG	Missense	Yes	537	agaatgtgcctctaattgtac	gtgtaagtcttaacatttatcttt
ATM	11:108121753	p.E522Ifs	c.1564_1565delGA	Frameshift	Yes	262	acgatgccttacggaagttg	acataatgcatgctgaacttac
ATM	11:108173656	p.S1799Mfs	c.5396delG	Frameshift	Yes	356	atttgttatactcattttgtgtag	gggtgatattatgtgaagatg
ATM	11:108186742	p.R2034RX	c.6100C>CT	Nonsense	Yes	274	tggtggagggaagatgttac	ctacactagtgatggctttac
ATM	11:108188128	p.I2076Ifs	c.6228delT	Frameshift	Yes	278	gggattttaaatgatattgtgaac	tacctgacggaagtgcaatg
ATM	11:108206605	p.Q2729QX	c.8185C>CT	Nonsense	Yes	291	acagatgctcagattggtttg	ccacttcacccaaccaaatg
ATM	11:108214065	p.F2799Kfs	c.8395_8404delTTTCAGTGCC	Frameshift	Yes	206	tcagcgaagtggtgttcttg	ctgacagctgtcagctttaat
ATM	11:108236086	p.R3008RC	c.9022C>CT	Missense	Yes	181	ccaaggcctttaaactgttc	cctgctgtatgagcaaattc
BRCA1	17:41243887	p.E1221XE	c.3661C>AC	Nonsense	Yes	147	cacatttggctcagggttac	tatgcctagtagactgagaag
BRCA1	17:41247941	Splice	c.594-2T>GT	Noncoding	Yes	180	atcttggtcatttgacagttc	tgcctgttaagttggcaaac
BRCA1	17:41276034	FS	c.70_80delCAGATGGGACA	Frameshift	Yes	191	atctgctcttcgcgttgaag	caatagcctaatcttactagac
BRCA2	13:32914401	p.S1970XS	c.5909C>AC	Nonsense	Yes	265	gtctggattggagaaagtttc	ctggtctgaatgttcgttac
BRCA2	13:32932067	Splice	c.7805+1G>AG	Noncoding	Yes	350	tatacgtatggcgtttctaaac	tttcaaaagacttctacagaatg
BRCA2	13:32972626	p.K3326KX	c.9976A>AT	Nonsense	Yes	303	acctgttagtcccatttgtac	agtctgagataatcttctgaac
BRCA2	13:32911298-9	p.K936Kfs	c.2808_2811delACAA	Frameshift	Yes	417	ccagactctgaagaacttttc	cttatttgaagctgttctgaag
BRCA2	13:32912036	p.F1182Xfs	c.3545_3546delTT	Frameshift	Yes	313	ccaagctacatattgcagaag	ctttttgcagagcttcagtag
BRCA2	13:32913795	p.L1768Rfs	c.5303_5304delTT	Frameshift	Yes	269	aatcatctctccgaaaaacaag	ggtgaagagctagtcacaag
BRIP1	17:59934534	p.C88del	c.262_264delACA	In-Frame	Yes	275	atcttaggaaacctcccaatc	ccttgacaagttgatgaagtg
BUB3	10:124920082	Splice	c.576+1G>AG	Noncoding	Yes	397	atgccatttttcaggcaagaag	gttaacgcacttcctgttaac
CDKN2A	9:21971060	p.A100SA	c.298C>AC	Missense	Yes	296	tctggcaggtcatgatgatg	atctatgcgggcatggttac
CDKN2A	9:21994234	p.E33delinsGVfs	c.97_98insC	Frameshift	Yes	373	gtcccagtctgcagttaag	acgaattatctgtttacgaaatc
FANCL	2:58386929	p.T372Nfs	c.1114_1115insTAAT	Frameshift	Yes	281	ctgaaacttcagaagtgttttc	atacctgtccttttgatgttag
FANCL	2:58388668	p.C342Afs	c.1024delA	Frameshift	Yes	146	tatgtacaacgaataagttagtg	cataagcatctggaataaactg
MLH1	3:37092123	p.Y750YX	c.2250C>CG	Nonsense	Yes	146	acacattctgcctcctaaac	atcggaatacagagaaagaag
PALB2	16:23641089	p.G796XG	c.2386C>AC	Nonsense	Yes	203	tgaaagactcagtctgtcttg	ctcctggcatgtgtttctac
PALB2	16:23647028	p.N280Tfs	c.839delT	Frameshift	Yes	310	aaggtgttgatacattcctaag	taggtgagttcatttagagaac
PRSS1	7:142459680	p.Q86QX	c.256C>CT	Nonsense	Yes	345	caacctctggagcagatag	gtgaggagagcttgattaac
PRSS1	7:142460307	p.C160XC	c.480C>AC	Nonsense	Yes	359	gtctcttgccaggacttatg	accacctttttgagttcaaatc
RAD51B	14:68292235	p.R47RX	c.139C>CT	Nonsense	Yes	264	gaaggtttccttttaactctag	gtgcctcatccctaaaaaaac
RAD51C	17:56811508	p.S353Hfs	c.1057_1066delTCTGCATGTT	Frameshift	Yes	278	gccctagaataaagtagctttc	caagtccacttgtacacattga
RAD51D	17:33443903	p.R100XR	c.298G>AG	Nonsense	Yes	387	gtgaacaggaagccgattg	ccaggacagtctcgatttc