ARTICLE

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Genetics and Genomics

A risk prediction tool for individuals with a family history of breast, ovarian, or pancreatic cancer: BRCAPANCPRO

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INTRODUCTION: Identifying families with an underlying inherited cancer predisposition is a major goal of cancer prevention efforts. Mendelian risk models have been developed to better predict the risk associated with a pathogenic variant of developing breast/ovarian cancer (with BRCAPRO) and the risk of developing pancreatic cancer (PANCPRO). Given that pathogenic variants involving *BRCA2* and *BRCA1* predispose to all three of these cancers, we developed a joint risk model to capture shared susceptibility.
METHODS: We expanded the existing framework for PANCPRO and BRCAPRO to jointly model risk of pancreatic, breast, and ovarian cancer and validated this new model, BRCAPANCPRO on three data sets each reflecting the common target populations.
RESULTS: BRCAPANCPRO outperformed the prior BRCAPRO and PANCPRO models and yielded good discrimination for differentiating *BRCA1* and *BRCA2* carriers from non-carriers (AUCs 0.79, 95% CI: 0.73–0.84 and 0.70, 95% CI: 0.60–0.80) in families seen in high-risk clinics and pancreatic cancer family registries, respectively. In addition, BRCAPANCPRO was reasonably well calibrated for predicting future risk of pancreatic cancer (observed-to-expected (O/E) ratio = 0.81 [0.69, 0.94]).
DISCUSSION: The BRCAPANCPRO model provides improved risk assessment over our previous risk models, particularly for pedigrees with a co-occurrence of pancreatic cancer and breast and/or ovarian cancer.

British Journal of Cancer (2021) 125:1712–1717; https://doi.org/10.1038/s41416-021-01580-x

INTRODUCTION

Cancer family history is an established predictor of an individual's personal cancer risk and whether he or she carries a cancer predisposition gene. Mendelian risk models have been shown to provide clinically useful, accurate individual-level risk assessment for the management of patients with hereditary cancer syndromes [1–4]. We have previously developed models for hereditary breast and ovarian cancer (BRCAPRO [1, 2]) and for hereditary pancreatic cancer (PANCPRO [3]). The BRCAPRO model provides individual estimates for the probability of carrying a deleterious mutation in *BRCA1* and/or *BRCA2*, based on an individual's family history of breast and/or ovarian cancer. Parameters for this model include the population carrier frequency for pathogenic variants in these genes as well as the associated penetrance. Based on the framework developed for BRCAPRO, we developed the PANCPRO risk model for familial pancreatic cancer that is based on segregation modelling for pancreatic cancer [3, 5]. Because the segregation model combines the effect of multiple dominant moderate-penetrance susceptibility loci into a single high-risk "locus", the individual effects of pathogenic variants in *BRCA1* or *BRCA2*, which increase the risk of pancreatic cancer in addition to breast and ovarian cancer, are not individually modelled. To overcome this limitation, we integrated our existing BRCAPRO and PANCPRO models into a single risk model for families with breast, ovarian, and pancreatic cancers. This integrated model, BRCAPANCPRO, was then validated in three independent data sets: two data sets based on ascertainment through a pancreatic cancer proband and one data set from a high-risk breast cancer clinic.

METHODS

Model development

The BRCAPANCPRO model was derived from the pre-existing BRCAPRO [1, 2] and PANCPRO [3] models, which were each built under a general Mendelian risk prediction approach and have been described and validated previously [3, 6–8]. Both BRCAPRO and PANCPRO are available in the BayesMendel R package [9]. Briefly, BRCAPRO takes information on family history of breast and/or ovarian cancers and provides the probability that an individual carries a pathogenic variant in the *BRCA1* or *BRCA2* genes and, if unaffected with cancer,

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Received: 19 May 2021 Revised: 7 September 2021 Accepted: 4 October 2021
Published online: 26 October 2021

their future risk of developing breast or ovarian cancer. Similarly, the PANCPRO model takes information on family history of pancreatic cancer and provides the probability an individual carries a deleterious mutation in a pancreatic cancer susceptibility gene, modelled from segregation analysis [5] and, if unaffected, their future risk of developing pancreatic cancer. This modelled gene, PANC, represents the combined effect of pathogenic variants in multiple genes with similar inheritance patterns and penetrance (i.e. dominant moderate-risk genes). Thus, the "PANC" locus represents the portion of pancreatic cancer due to dominant susceptibility genes, both those that have been localised and those that remain to be localised. For the BRCAPANCPRO model, we subtracted the carrier probability of *BRCA2* and *BRCA1* from the population allele frequency for PANC in the PANCPRO model. Carrier probabilities for *BRCA1* and *BRCA2* are obtained from BRCAPRO in the BayesMendel R package version 2.1-8. The penetrance (age-specific cancer risk) of pancreatic cancer for PANC carriers remained the same as in the original PANCPRO model. The penetrance of breast and ovarian cancer for PANC carriers was set to be equivalent to that of non-BRCA carriers in the BRCAPRO model. The penetrance of breast and ovarian cancer in *BRCA1* and *BRCA2* carriers remained the same as in BRCAPRO. The penetrance of pancreatic cancer among *BRCA1* and *BRCA2* carriers was estimated by increasing the age-specific probabilities of developing pancreatic cancer in Surveillance, Epidemiology, and End Results [10] by the odd ratio (OR) reported in the published literature, specifically for *BRCA1* carriers (OR: 2.58, 95% confidence interval (CI): 1.54, 4.05) and for *BRCA2* carriers (OR: 6.20, 95% CI: 4.62, 8.17) [11]. Sensitivity analysis was conducted using alternative estimates based on studies conducted in the Breast Cancer Family Registry; however, model performance was lower (results not shown) [12] BRCAPANCPRO also retains the fully functionality of BRCAPRO by allowing for input of breast and ovarian pathological markers oestrogen receptor (ER), progesterone receptor (PR), HER2, cytokeratin 14 (CK14), and CK5/6 and history of bilateral mastectomy or oophorectomy.

Validation of study populations

To validate BRCAPANCPRO, we used data from three complementary data sources as detailed below. The Johns Hopkins IRB approved this study. Cohort and registry data participants at Johns Hopkins and participating sites provided informed consent at the enrolling site. The study was performed in accordance with the Declaration of Helsinki.

Hereditary breast and ovarian cancer: Johns Hopkins High Risk Clinic Cohort (JHHRCC). Carrier probabilities were calculated in 319 families ascertained due to history of breast/ovarian cancer (286 had breast and/or ovarian cancer and 33 had breast/ovarian and a pancreatic cancer) using de-identified pedigree data and genetic testing results from patients undergoing genetic counselling at Johns Hopkins Hospital and data collected for clinial purposes. Data included cancer history (breast, ovarian, and pancreatic cancers, affection age) and current age. Of the 316 individuals who underwent testing, 34 were found to have pathogenic variants in *BRCA2*, 51 in *BRCA1*, and none in both genes. Individuals were included in the set to validate *BRCA1/2* carrier probability estimates if they underwent genetic testing.

High-risk pancreatic cancer patients with genetic testing: Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium cohort. Carrier probabilities were calculated in 554 families ascertained due to pancreatic cancer in the proband (280 had pancreatic cancer but no breast/ovarian cancer and 365 had breast/ovarian cancer and pancreatic cancer), recruited from 5 sites participating in the PACGENE Consortium who underwent testing for *BRCA1/2* as part of a previously published study [13, 14]. Of the 645 individuals who underwent testing, 22 were found to have pathogenic variants in *BRCA2*, 5 in *BRCA1*, and 1 in both genes. Individuals were included in the set to validate *BRCA1/2* carrier probability estimates if they underwent genetic testing.

Validation of future pancreatic cancer risk: National Familial Pancreas Tumor Registry (NFPTR). The NFPTR as Johns Hopkins is a registry of patients with pancreatic cancer and their family members. Families are ascertained through a patient undergoing care for their pancreatic cancer at Johns Hopkins Medicine or referred to the registry due to a history of pancreatic cancer. At enrollment, information on age, vital status, and cancer history is obtained for all first and selected (grandparent/avuncular) second-degree relatives of the pancreatic cancer patients. Families are contacted annually for updated health status as described in Wang et al. [3]. The observed incidence of pancreatic cancer in 26,329 pancreatic cancer-free individuals in 5095 families enrolled in NFPTR [15, 16] was compared to model-predicted risk of pancreatic cancer using the baseline family history for each individual during the follow-up period. Follow-up for each individual was from the date of enrollment in the registry, date of death, or date of last family health update or December 31, 2017. Individuals were included in the validation set if they met the following inclusion criteria: at least 1 pancreatic cancer in the family at baseline; aged 20–93 years; prospective follow-up data available. Of these individuals, 15,289 (58%) had family history of pancreatic cancer but no breast/ovarian cancer and 11,040 (42%) had family history breast/ovarian cancer and pancreatic cancer. These data were independent of the retrospective data on 287 families used in the segregation modelling, which provided the priors used for PANC in our model.

Validation of study design

BRCAPANCPRO was validated in two ways. First, carrier probabilities for *BRCA1* and *BRCA2* were assessed for model calibration and discrimination using the study data with germline testing for the *BRCA1* and/or *BRCA2* genes using data from the JHHRCC and PACGENE cohorts. Model calibration was evaluated as the ratio of the number of observed mutation carriers to the expected number, defined as the sum of carrier probabilities over the cohort. Model discrimination was evaluated with receiver operating characteristic (ROC) analysis. Second, future risk of pancreatic cancer was validated for all individuals in the NFPTR cohort using the observed incident cases of pancreatic cancer. Calibration was estimated by the ratio of the observed-to-expected (O/E) number of incident cases, and Hosmer–Lemeshow test evaluated goodness-of-fit of the model estimates, where $P < 0.05$ would suggest poor fit. Discrimination was evaluated with ROC analysis using the model-estimated annual risk of pancreatic cancer. CIs for all validation measures were estimated with 95% coverage using a bootstrap resampling approach with 10,000 simulations. The calibration of BRCAPANCPRO was compared to BRCAPRO and PANCPRO through paired *t* tests of the bootstrapped replicates. Improvement frequency (IF) was calculated as the proportion of bootstrap replicates where BRCAPANCPRO yielded better performance over BRCAPRO or PANCPRO.

RESULTS

Clinical illustration

Table 1 illustrates how BRCAPANCPRO integrates information currently used in either BRCAPRO or PANCPRO to aid in clinical decision making. We show risk estimates for a hypothetical family and how the probability of carrying a pathogenic variant changes as different scenarios in the family history are applied (Fig. 1) for each of the three models: BRCAPRO, PANCPRO, and BRCAPANCPRO. As expected, the overall probability that the proband has a predisposition gene increases with the increasing number of family members and shifts to *BRCA1*/*BRCA2* with an increased number of breast and ovarian cancers in the family.

Carrier probability validation

The JHHRCC is a high-risk breast and ovarian cancer cohort included in the validation to ensure that BRCAPANCPRO performed relatively similar to the existing BRCAPRO and did not produce unexpected results. BRCAPANCPRO's overall discriminative ability calculated as the area under the corresponding ROC curve (AUC) for this cohort was 0.79 (95% CI: 0.73, 0.84) and BRCAPRO's was 0.77 (95% CI: 0.70, 0.82). The IF for BRCAPANCPRO compared to BRCAPRO was 1.0 and similar (0.99 and 0.95) for *BRCA1* and *BRCA2*, respectively. Other performance measures are in Table 2. The calibration for BRCAPANCPRO was O/E ratio 1.46 (95% CI: 1.22, 1.73) and for BRCAPRO was 1.42 (95% CI: 1.17, 1.70), $P < 0.001$. Carrier probabilities for individuals with a family history of breast/ovarian cancer had similar predictions in both the BRCAPRO and BRCAPANCPRO models, demonstrating that the addition of pancreatic cancer to the model did not compromise performance for these families (Supplementary eFig. 1A). However, individuals with a family history of *both* pancreatic cancer and breast/ovarian cancer had greater changes in the carrier probabilities.

In the PACGENE cohort, which was enriched for pancreatic cancer, discrimination was similar for BRCAPANCPRO AUC of 0.70 (95%: 0.60, 0.80) and BRCAPRO AUC of 0.71 (95% CI: 0.58, 0.82). The IF suggested that these models perform similarly (IF = 0.46 overall).

Table 1. Clinical illustration of BRCAPANCPRO for a hypothetical family shown in Fig. 1.

	Carrier probability (%)			Counselee's absolute risk of developing cancer (%)[a]					
				By age 65 years			By age 85 years		
	PANC	*BRCA2*	*BRCA1*	PC	BC	OC	PC	BC	OC
As shown (counselee's sister affected with breast cancer at 45 years and paternal grandfather with pancreatic cancer at 75 years)	1.6	0.42	0.14	0.33	3.1	0.28	1.9	11.1	0.94
As shown, and paternal aunt has pancreatic cancer at age 60 years	13.6	0.49	0.11	1.3	3.1	0.29	5.2	11.2	0.96
As shown, and paternal aunt has breast cancer at age 60 years	1.6	1.4	0.34	0.34	3.4	0.41	1.9	11.7	1.4
As shown, and paternal aunt has ovarian cancer at age 60 years	1.4	4.2	2.7	0.36	4.5	1.2	2.2	14.2	3.6
As shown, and paternal aunt has ovarian cancer at age 60 years and other paternal aunt has breast cancer at 55 years	0.98	10.7	5.7	0.41	6.5	2.5	2.6	19	7.4
As shown, and paternal aunt has pancreatic cancer at age 60 years and other paternal aunt has breast cancer at 55 years	12.9	2	0.33	1.3	3.5	0.48	5.2	12.1	1.6

Diagnoses of breast, pancreas, and ovarian cancer are varied to show model behaviour. Rows correspond to variations on the pedigree.
PC pancreatic cancer, *BC* breast cancer, *OC* ovarian cancer.
[a]Assuming counselee has not developed any of these cancers before age 55 years.

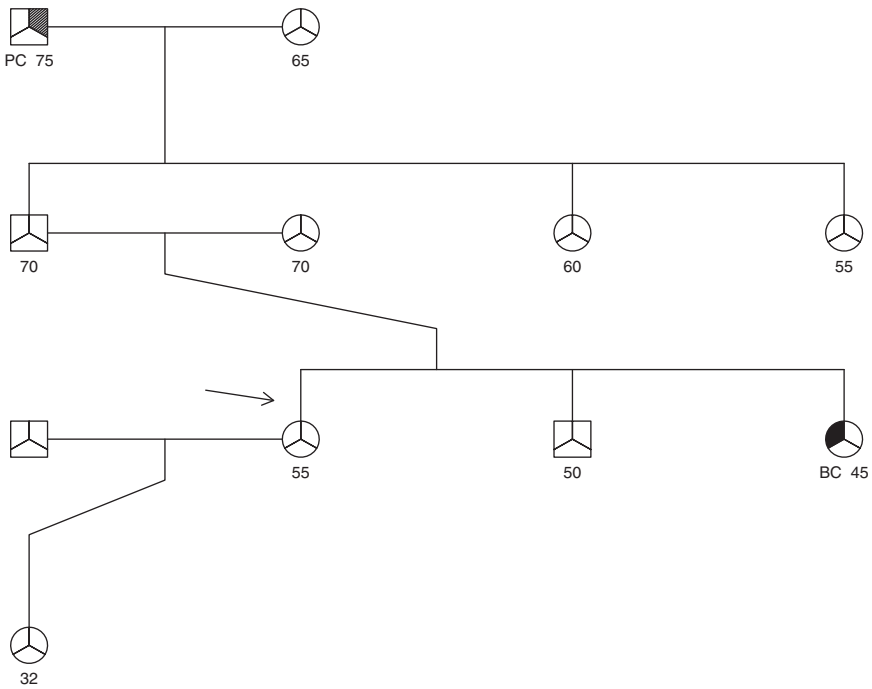

Fig. 1 Hypothetical family. Arrow indicates the counselee (female, age 55 years). PC pancreatic cancer, BC breast cancer.

However, BRCAPANCPRO yielded a markedly improved calibration (O/E = 1.94, 95% CI: 1.26, 3.08) compared to BRCAPRO (O/E = 3.07, 95% CI: 1.88, 5.46, IF = 1, $P < 0.001$). When we examined the individual-level carrier predictions (Supplementary eFig. 1B), individuals with a family history of both pancreatic cancer and breast/ovarian cancer had higher carrier probabilities in the BRCAPANCPRO model compared to BRCAPRO, further demonstrating the value of the combined model. Individuals with a family history of pancreatic cancer had similar predictions in both the PANCPRO and BRCAPANCPRO models, demonstrating that the addition of breast/ovarian cancer to the model did not compromise performance.

Future risk of pancreatic cancer

In the NFPTR cohort, the observed incidence of pancreatic cancer compared to model predictions (O/E ratio) yielded a calibration of 0.82 (95% CI: 0.69, 0.94) for BRCAPANCPRO, an improvement over the original PANCPRO model, O/E ratio 0.73 (95% CI: 0.61, 0.84, IF = 1.0, $P < 0.001$, Supplementary eFig. 2). Calibration did not vary according to degree of relation to the proband but did change across subgroups defined by type of ascertainment and family history (Table 3). BRCAPANCPRO was better calibrated in individuals where there was a family history of pancreatic cancer and either breast or ovarian cancer (O/E ratio 0.95 [0.75, 1.16]), compared to those with pancreatic cancer only (O/E ratio 0.69 [0.54, 0.86], $P < 0.001$). Model discrimination was similar between BRCAPANCPRO (AUC = 0.743 [0.707, 0.778] and PANCPRO (AUC = 0.738 [0.702, 0.773]).

Risk estimates were higher among individuals who developed pancreatic cancer during follow-up compared to individuals who remained disease free (Fig. 2, Kolmogorov–Smirnov $P < 0.001$). This difference held in each stratum ($P < 0.001$ for 0 to 1, 2, and 3 or more affected relatives at baseline).

Table 2. BRCAPANCPRO and BRCAPRO validation measures for carrier probability of *BRCA1/2* genes in JHHRCC and PACGENE families.

	BRCA1 or BRCA2 carriers (*N*)	Non-carriers (*N*)	AUC [95% CI]			O/E ratio *P*[a]
			Overall	*BRCA1*	*BRCA2*	
High-risk breast/ovarian cohort (JHHRCC)						
BRCAPANCPRO	85	234	0.79 [0.73, 0.84]	0.86 [0.81, 0.91]	0.64 [0.53, 0.74]	1.46 [1.22, 1.73]
						$P = 0.17$
BRCAPRO			0.77 [0.70, 0.82]	0.84 [0.78, 0.88]	0.62 [0.51, 0.73]	1.42 [1.17, 1.70]
						$P = 0.26$
High-risk pancreatic cancer cohort (PACGENE)						
BRCAPANCPRO	28	617	0.70 [0.60, 0.80]	0.82 [0.55, 0.98]	0.69 [0.55, 0.79]	1.94 [1.26, 3.08]
						$P = 0.55$
BRCAPRO			0.71 [0.58, 0.82]	0.79 [0.48, 0.99]	0.70 [0.58, 0.82]	3.07 [1.88, 5.46]
						$P = 0.10$

[a]*P* value for Hosmer–Lemeshow test for goodness of fit of the model prediction of carrier probability.

Table 3. BRCAPANCPRO validation measures for future risk of pancreatic cancer in the NFPTR data.

	Incident cases (*N*)	Pancreatic cancer-free at follow-up (*N*)	O/E ratio [95% CI], *P*[c]	
			BRCAPANCPRO	Original PANCPRO
Relation to proband				
All first degree[a]	113	17,610	0.83 [0.67, 0.99], $P = 0.79$	0.73 [0.60, 0.88], $P = 0.06$
>first degree[b]	46	8560	0.78 [0.57, 1.01], $P = 0.84$	0.71 [0.50, 0.93], $P = 0.37$
Family history				
PC only	72	15,217	0.69 [0.54, 0.86], $P = 0.07$	0.61 [0.48, 0.76], $P < 0.001$
PC and BC/OC	87	10,953	0.95 [0.75, 1.16], $P = 0.99$	0.85 [0.68, 1.04], $P = 0.96$
Ascertainment method				
Clinic based	47	12,199	1.06 [0.79, 1.40], $P = 0.99$	0.93 [0.69, 1.21], $P = 0.99$
Referral	112	13,971	0.74 [0.48, 0.87], $P = 0.08$	0.66 [0.53, 0.78], $P < 0.001$
All individuals	159	26,170	0.81 [0.69, 0.94], P = 0.38	0.72 [0.61, 0.84], $P = 0.003$

O/E observed to expected, *CI* confidence interval, *N* number.
[a]First-degree relatives include parents, siblings, and offspring.
[b]Above first degree includes all second-degree relatives (grandparents, aunts, uncles, nieces, and nephews), third degree and above.
[c]*P* value for Hosmer–Lemeshow test for goodness of fit of the model prediction of future risk of pancreatic cancer.

DISCUSSION

Identification of families at an increased risk of developing a hereditary cancer is an important step in reducing the burden of cancer in these families. Risk models, including the BayesMendel R Package discussed here, BOADICEA (CanRisk), and the Gail (BCRAT), are widely used as part of risk assessment for families with breast/ovarian cancer or pancreatic cancer [9, 17–19]. However, the overlap in the genes underlying these models is substantial with 2.5–7% of all newly diagnosed pancreatic cancers carrying a pathogenic variant in *BRCA2* or *BRCA1* [11, 20–22]. Other susceptibility genes also confer risk for both pancreatic and women's cancers [23, 24]. The BOADICEA model implemented in (CanRisk) incorporates the effects of *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and *ATM* and other information to calculate risk of breast and ovarian cancer. The BRCAPANCPRO model provides risk estimates for pancreatic cancer in addition to breast/ovarian cancer and includes additional genetic effects on pancreatic cancer risk via *PANC*.

Our BRCAPANCPRO model was designed to address this need and demonstrates improved performance in families with breast/ovarian and pancreatic cancers without compromising performance when there is only breast/ovarian cancer (BRCAPRO) or pancreatic cancer (PANCPRO) in the family. The inclusion of pancreatic cancer family history in the BRCAPANCPRO model does not sacrifice discrimination of *BRCA1* or *BRCA2* carriers from non-carriers, and the validation suggests improved calibration compared to the original BRCAPRO for families with hereditary breast or ovarian cancer and PANCPRO for families with hereditary pancreatic cancer. However, while the O/E ratios for BRCAPANCPRO were in most cases closer to 1.0 than those of prior models, there remained some underprediction of *BRCA1* and *BRCA2* carrier status in these families that underwent genetic testing. This is likely attributable to overrepresentation of breast, ovarian, or pancreatic cancer in the PACGENE and Johns Hopkins High Risk Cohort as a result of the ascertainment mechanisms. In our future risk validation, for families ascertained due to high risk, all models overestimated pancreatic cancer risk (O/E ratio <1.0); however, the extent of this overestimation was less for BRCAPANCPRO compared to PANCPRO (Table 3). In families unselected for cancer history who were instead clinically ascertained for a single proband, BRCAPANCPRO performed well (O/E 1.06 (95% CI 0.79–1.40), Table 3) indicating that overprediction of pancreatic cancer risk may be related to case ascertainment. However, genetic testing data are not widely available in these data, and thus we cannot directly validate carrier status estimates in these same data. Furthermore, since PANC incorporates genetic risk due to yet unmapped loci, it cannot be validated by evaluation of genetic testing results but can be evaluated by assessing the accuracy of future cancer risk estimates. Further studies may reveal whether these calibration differences are due to

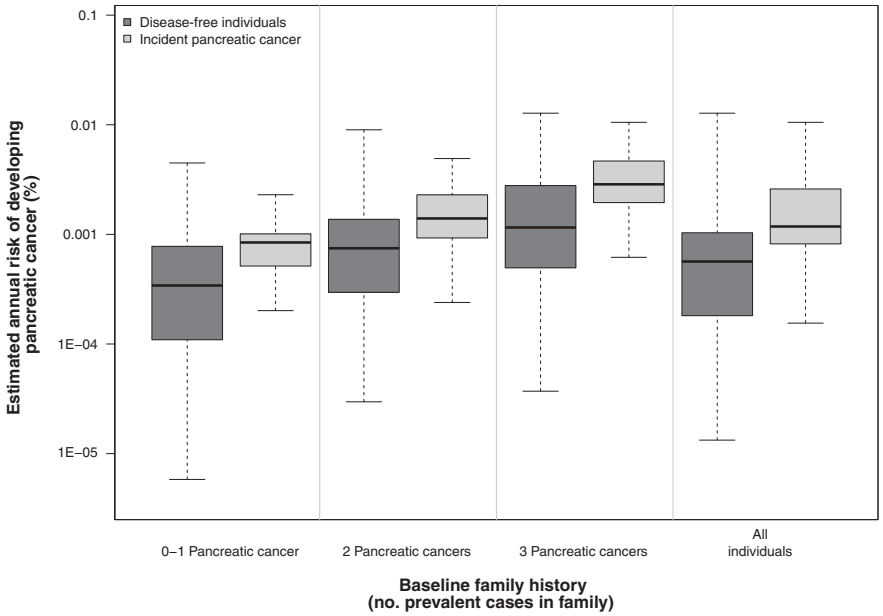

Fig. 2 Estimated risk of Pancreatic cancer. Distribution of estimated average annual risk of developing pancreatic cancer for incident pancreatic cancer patients and disease-free individuals in BRCAPANCPRO according to the number of pancreatic cancers in the family at baseline.

ascertainment efforts or inaccuracies in our choices for penetrance and prevalence.

A limitation of the new BRCAPANCPRO model is that it incorporates cancer risk estimates from the existing literature, which limits generalisability to different populations according to race and ethnicity. However, validation studies of previous versions of BRCAPRO in Black and Hispanic populations have shown performance similar to that in European populations [8, 25]. For pancreatic cancer, there are only a few studies describing the prevalence of *BRCA1* and *BRCA2* pathogenic variants in patients of Chinese and Japanese ancestry but the data are even more limited for those of other ancestries [26]. The segregation model used to develop PANCPRO was based on families of primarily European Ancestry. Studies are ongoing to address this critical need. In contrast, several studies have examined the prevalence and associated penetrance of pathogenic variants in *BRCA1* and *BRCA2* in the various ancestral populations. Our model not only allows a user to specify both penetrance and prevalence estimates tailored to the proband's race, ethnicity, and/or geographic region but also to the underlying rate in non-carriers. The underlying rate of cancer in the population can also impact model performance as shown in validation studies of BRCAPRO in Asian populations [27]. As cancer risk estimates improve, these can be readily incorporated into our model by replacing a user-specified input in the BayesMendel package. The BRCAPANPRO model is inherently limited by our imperfect knowledge of the genetic basis of pancreatic cancer as well as breast/ovarian cancer. While our combined BRCAPANCPRO model is a step forward by directly incorporating the effect of *BRCA1* and *BRCA2* on pancreatic cancer risk, additional pancreatic cancer susceptibility genes have been identified in the past several years, including *ATM* and *PALB2* [24, 28]. In the future, the framework demonstrated here can readily be expanded to incorporate these effects directly vs indirectly via *PANC*. Finally given the lack of histological data on breast cancer cases in our validation set, we were unable to validate the contribution of pathological markers ER, PR, HER2, CK14, and CK5/6, in the context of our BRCAPANPRO model, as we had done previously for BRCAPRO [29].

Genetic testing guidelines have changed considerably over the past several years in part due to the decreasing cost of germline genetic testing, together with the improved therapeutic options for cancer patients with specific alterations. These include poly (ADP-ribose) polymerase inhibitors for BRCA-deficient breast, ovarian, and pancreatic cancers or checkpoint inhibitors for mismatch repair-deficient tumours [30–32]. While the United States has recently recommended that germline genetic testing be offered to all patients with pancreatic cancer, ovarian cancer, and young-onset breast cancer patients (<50 years) regardless of ancestry or family history, as well as breast cancer patients meeting certain family history criteria [33, 34], universal testing is not wide-spread in the rest of the world and risk models such as BRCAPANCPRO are widely used as a guide to help identify individuals who may benefit from germline genetic testing. Furthermore, patients, including >80% of those with a family history of pancreatic cancer [35], who undergo gene testing will not have a susceptibility gene mutation identified. Decision support tools such as risk models can help individuals with a familial history of cancer understand their future risk of cancer. Risk models can provide guidance on risk of pancreatic cancer among their relatives, which in turn could have an impact upon early detection screening decisions. BRCAPANCPRO is part of the R package BayesMendel and freely available for research use. Physician-facing interfaces are also available commercially.

The new BRCAPANCPRO model is an improved tool for families with a history of breast, ovarian, and/or pancreatic cancer as it leverages the overlap in risk for carriers of *BRCA1, BRCA2*, and the pancreatic cancer susceptibility gene to improve specification of cancer risk and subsequent personalisation of appropriate screening and follow-up for early detection.

DATA AVAILABILITY

Data are available, through a collaborative agreement, upon request. BRCAPANCPRO is part of the R package BayesMendel and freely available for research use.

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ACKNOWLEDGEMENTS

Deepest gratitude to the patients and families who participated in research studies contributing to this work.

AUTHOR CONTRIBUTIONS

ALB—study design, statistical analysis, drafting and revision of manuscript. EJC—statistical analysis, revision of manuscript. NP—data collection, statistical analysis, revision of manuscript. GMP, KGR, SG, AB, SS, MLC, AGS, MGG, RHH—data collection, revision of manuscript. GP—study design, supervision of data analysis, data collection, revision of manuscript, APK—study design, supervision of data analysis, data collection, provision of funding, drafting and revision of manuscript.

FUNDING

This work was supported by the Lustgarten Foundation and NCI RO1CA154823 (to APK), U01CA247283 (to APK), NCI P50 CA62924 (to APK), P30CA006973 (to Nelson), P30CA006516 (to Glimcher), R01 CA132829 (to SS), R01CA097075 (to GMP), Rolfe Pancreatic Cancer Foundation (to GMP), and the Sol Goldman Pancreatic Cancer Research Center.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Johns Hopkins IRB approved this study. Cohort and registry data participants at Johns Hopkins and participating sites provided informed consent at the enrolling site. The study was performed in accordance with the Declaration of Helsinki.

CONSENT TO PUBLISH

Not applicable as no individual-level information is shared.

COMPETING INTERESTS

APK has previously consulted for MERCK and SS has consulted for Myriad Genetics.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41416-021-01580-x.

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