Original research

Polygenic and multifactorial scores for pancreatic ductal adenocarcinoma risk prediction

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ABSTRACT

Background Most cases of pancreatic ductal adenocarcinoma (PDAC) are asymptomatic in early stages, and the disease is typically diagnosed in advanced phases, resulting in very high mortality. Tools to identify individuals at high risk of developing PDAC would be useful to improve chances of early detection.

Objective We generated a polygenic risk score (PRS) for PDAC risk prediction, combining the effect of known risk SNPs, and carried out an exploratory analysis of a multifactorial score.

Methods We tested the associations of the individual known risk SNPs on up to 2851 PDAC cases and 4810 controls of European origin from the PANcreatic Disease ReseArch (PANDoRA) consortium. Thirty risk SNPs were included in a PRS, which was computed on the subset of subjects that had 100% call rate, consisting of 839 cases and 2040 controls in PANDoRA and 6420 cases and 4889 controls from the previously published Pancreatic Cancer Cohort Consortium I–III and Pancreatic Cancer Case-Control Consortium genome-wide association studies. Additional exploratory multifactorial scores were constructed by complementing the genetic score with smoking and diabetes.

Results The scores were associated with increased PDAC risk and reached high statistical significance (OR=2.70, 95% CI 1.99 to 3.68, $p=2.54\times10^{-10}$ highest vs lowest quintile of the weighted PRS, and OR=14.37, 95% CI 5.57 to 37.09, $p=3.64\times10^{-8}$, highest vs lowest quintile of the weighted multifactorial score).

Conclusion We found a highly significant association between a PRS and PDAC risk, which explains more than individual SNPs and is a step forward in the direction of the construction of a tool for risk stratification in the population.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and represents about 85% of total cases.[1] Due to the lack of early symptoms for most patients,[2] the lack of reliable biomarkers and the difficulty in imaging its initial development,[3] PDAC is typically detected in advanced stages,[1] when there is a shortage of effective therapies. Surgical removal is considered the most effective treatment for localised disease.[3]

Pancreatic cancer shows a multifactorial aetiology[4] and the main epidemiological risk factors are tobacco smoking, heavy alcohol consumption, type 2 diabetes mellitus, obesity and chronic pancreatitis.[5] Family history of pancreatic cancer is another risk factor, with about 5%–10% of patients reporting affected first-degree relatives, suggesting a contribution of inherited genetic variation in risk.[6] As for other complex diseases, PDAC is affected both by rare highly penetrant mutations associated with high risk and common low-penetrance variants. Both genome-wide association studies (GWAS) and candidate gene studies have identified several SNPs associated with the risk of developing PDAC.[7–17] Several SNPs with a genome-wide level of statistical significance ($p<5\times10^{-8}$) have been

identified and many others are considered potentially interesting since they are very close to this threshold.

Moreover, many studies showed a connection between blood groups and the risk of several malignancies including pancreatic cancer, in particular increased risk for non-O blood group subjects.[18–22]

A viable approach to reduce PDAC mortality would be to implement early detection. The overall incidence of the disease is relatively low, thus screening is not suggested for the general population. It would therefore be useful to have tools to stratify the general population and to identify a subgroup at higher risk among whom a regular screening could bring benefits. Genetic variants can be useful for such risk stratification. Common variants, taken individually, are associated with a small increase in risk and therefore are not applicable for risk prediction. However, the combination of different SNPs increases the cumulative effect on risk. Thus, the establishment of a multigenic score could lead to a better estimation of individual risk. This approach has already been successfully attempted for other cancers such as prostate,[23] breast[24–27] and endometrial.[28] For pancreatic cancer a first attempt has been made, however it was based on a very small number of SNPs.[29] The aim of this work was to generate a polygenic risk score (PRS) for PDAC risk prediction combining the effects of known risk SNPs, including the *ABO* alleles. In addition, as an exploratory analysis, we have included two well-known risk factors, smoking and diabetes, to construct a multifactorial score.

MATERIALS AND METHODS

Study population

The study was conducted on 3619 patients with PDAC and 5790 controls from nine European countries within the PANcreatic Disease ReseArch (PANDoRA) consortium.[30] Cases were defined by an established diagnosis of PDAC and controls were individuals of the general population without a pancreatic disease at recruitment, individuals that were hospitalised for non-tumour related causes, or blood donors. For each subject, information on country of origin, sex and age (age at diagnosis for cases and age at recruitment for controls) was also available. In addition, for a subset of individuals, smoking (expressed as ever (current+former)/never smokers) and diagnosis of type 2 diabetes (before the diagnosis of PDAC for the cases) were retrospectively collected. In accordance with the Declaration of Helsinki, written informed consent was obtained from each participant. Finally, we also used as a validation step genotyping data of 8769 PDAC cases and 7055 controls downloaded from the database of Genotypes and Phenotypes (dbGaP, https://www.ncbi.nlm.nih.gov/gap/) (study accession numbers phs000206.v5.p3 and phs000648.v1.p1; project reference number 12644). The genotyping data were obtained from previously published GWAS on PDAC risk: the Pancreatic Cancer Cohort Consortium (PanScan I–III)[7–9] and the Pancreatic Cancer Case-Control Consortium (PanC4).[10]

SNP selection

In order to generate a PRS, we selected polymorphisms belonging to the chromosomal regions identified through previous studies to be associated with PDAC risk at genome-wide significance level ($p<5\times10^{-8}$, 18 SNPs) or close to that threshold ($p<10^{-7}$, 11 SNPs). In regions with multiple risk-associated SNPs, only SNPs not in high LD ($r^2<0.7$) were selected. The selection was made based on the lowest p value with PDAC risk reported in the original study.

Table 1 Description of the PANDoRA study population

Country	Cases	Controls	Total
Czech Republic	386	450	836
Germany	1375	1791	3166
Greece	239	192	431
Hungary	260	353	613
Italy	968	1681	2649
Lithuania	56	185	241
The Netherlands	117	164	281
Poland	107	333	440
UK	111	311	422
Total	3619	5460	9079
Sex (%)			
Male	56.6	53.1	54.5
Female	43.4	46.9	45.5
Median age	64.3	56.0	59.6

PANDoRA, PANcreatic Disease ReseArch.

We also included SNPs necessary to infer the ABO blood groups from genotypes, in order to use the blood groups in the computation of the score. Namely, we selected rs505922, which discriminates O from non-O and rs8176746 that distinguishes between *ABO* A and B alleles.[18 21 22] The combination of these two SNPs allows to reconstruct ABO blood groups. The final selection resulted in 30 SNPs as described in online supplementary table I.

Genotyping

Genotyping of the PANDoRA cases and controls was performed at German Cancer Research Center in Heidelberg, Germany, using TaqMan or KASP (Kompetitive Allele-Specific PCR) technology, according to the manufacturer protocol, in 384-well plates. In addition to the samples, no-template controls and duplicated samples (8%), used for quality control purposes, were included on each plate and genotyped under the same conditions. The endpoint fluorescence reading of the plates and the assignment of the genotype were performed using a ViiA 7 Real-Time PCR System (Thermo Fisher Applied Biosystems, Waltham, MA, USA).

Data filtering, statistical analysis and score computation

For PANDoRA we started from a total of 9409 subjects (3619 cases and 5790 controls). Pearson χ^2 test was used to verify that the genotype frequencies of the controls were in Hardy-Weinberg equilibrium (HWE). We eliminated one genotyping plate filled with 330 controls because it systematically showed a deviation from HWE, leaving 5460 controls. The breakdown of cases and controls by countries is shown in table 1.

After exclusion of subjects with missing covariates and genotypes we used up to 2851 cases and 4810 controls to test whether the associations of the single risk variants replicated. The samples used had an average call rate of 97.6%, and a concordance rate between duplicated samples higher than 99%.

Considering only samples with call rate of 100%, 2879 subjects (839 cases and 2040 controls) remained for the PRS in PANDoRA, consisting of the 30 variants (28 loci each identified by an individual SNP and two SNPs for the ABO locus, see below).

For the PanScan I–III and PanC4 data sets obtained from dbGaP, genotyping procedures, genotyping quality control checks and data collection were thoroughly reported in the

Table 2 Association between the selected SNPs and PDAC risk in PANDoRA

			Codominant model					Allelic model	
			M/M versus M/m		M/M versus m/m			M versus m	
SNP	Nearest gene(s)	Alleles (M/m)	OR (95% CI)	P value	OR (95% CI)	P value	P trend	OR (95% CI)	P value
rs13303010	*NOC2L*	A/G	1.34 (1.18 to 1.53)	**1.3×10^{-5}**	1.95 (1.32 to 2.90)	**0.001**	**5.7×10^{-8}**	1.42 (1.26 to 1.59)	**7.8×10^{-9}**
rs351365	*WNT2B*	G/A	0.97 (0.87 to 1.08)	0.523	0.83 (0.66 to 1.04)	0.099	0.072	0.92 (0.84 to 1.00)	0.056
rs2816938	*NR5A2*	T/A	1.11 (0.99 to 1.24)	0.077	1.08 (0.86 to 1.36)	0.515	0.151	1.09 (0.99 to 1.19)	0.076
rs3790844	*NR5A2*	T/C	0.93 (0.83 to 1.05)	0.226	0.94 (0.74 to 1.19)	0.607	**0.049**	0.93 (0.84 to 1.02)	0.1
rs1486134	*ETAA1*	T/G	1.10 (0.99 to 1.21)	0.080	1.11 (0.92 to 1.33)	0.291	0.058	1.06 (0.98 to 1.15)	0.124
rs9854771	*TP63*	G/A	0.88 (0.80 to 0.98)	**0.019**	0.81 (0.69 to 0.95)	**0.010**	**0.003**	0.91 (0.85 to 0.98)	**0.016**
rs2736100	*CLPTM1L TERT*	G/T	0.97 (0.86 to 1.09)	0.614	1.21 (1.05 to 1.39)	**0.008**	**0.012**	1.09 (1.01 to 1.17)	**0.018**
rs2853677	*CLPTM1L TERT*	A/G	0.78 (0.69 to 0.87)	**2.47×10^{-5}**	0.77 (0.66 to 0.89)	**6.3×10^{-4}**	**2.5×10^{-4}**	0.85 (0.79 to 0.92)	**9.1×10^{-5}**
rs2736098	*CLPTM1L TERT*	G/A	0.90 (0.81 to 1.00)	**0.050**	0.85 (0.69 to 1.05)	0.123	**0.004**	0.85 (0.78 to 0.93)	**3.6×10^{-4}**
rs35226131	*CLPTM1L TERT*	G/A	0.81 (0.64 to 1.03)	0.085	0.41 (0.12 to 1.34)	0.139	**0.012**	0.89 (0.71 to 1.11)	0.296
rs401681	*CLPTM1L TERT*	C/T	1.20 (1.07 to 1.35)	**0.002**	1.31 (1.14 to 1.50)	**1.3×10^{-4}**	**5.1×10^{-6}**	1.14 (1.07 to 1.23)	**1.7×10^{-4}**
rs17688601	*SUGCT*	C/A	0.97 (0.88 to 1.08)	0.628	0.73 (0.60 to 0.90)	**0.003**	0.051	0.91 (0.84 to 0.99)	**0.028**
rs73328514	*TNS3*	A/T	1.11 (0.97 to 1.26)	0.142	0.52 (0.31 to 0.89)	**0.016**	0.690	1.00 (0.88 to 1.13)	0.962
rs6971499	*LINC-PINT*	A/G	0.86 (0.76 to 0.97)	**0.012**	0.71 (0.49 to 1.04)	0.079	**0.001**	0.84 (0.75 to 0.93)	**0.002**
rs172310	*SHH*	C/A	1.02 (0.92 to 1.14)	0.636	0.94 (0.78 to 1.12)	0.462	0.964	1.01 (0.93 to 1.09)	0.848
rs2941471	*HNF4G*	A/G	0.95 (0.84 to 1.07)	0.396	0.79 (0.68 to 0.92)	**0.003**	**0.013**	0.89 (0.82 to 0.96)	**0.004**
rs10094872	*MYC*	A/T	1.16 (1.03 to 1.29)	**0.011**	1.40 (1.20 to 1.64)	**2.6×10^{-5}**	**2.9×10^{-5}**	1.18 (1.09 to 1.28)	**2.4×10^{-5}**
rs1561927	*MIR1208*	T/C	0.83 (0.75 to 0.93)	**0.001**	0.81 (0.66 to 1.00)	**0.044**	**3.4×10^{-4}**	0.86 (0.79 to 0.94)	**0.001**
rs8176746	*ABO*	C/A	1.10 (0.96 to 1.26)	0.171	1.11 (0.68 to 1.80)	0.674	0.235	1.04 (0.92 to 1.17)	0.546
rs505922	*ABO*	T/C	1.39 (1.24 to 1.55)	**7.2×10^{-9}**	1.39 (1.20 to 1.61)	**1.6×10^{-5}**	**1.4×10^{-7}**	1.19 (1.10 to 1.28)	**4.0×10^{-6}**
rs10991043	*SMC2*	T/C	1.05 (0.94 to 1.17)	0.403	1.02 (0.87 to 1.19)	0.793	0.353	1.01 (0.94 to 1.09)	0.709
rs7310409	*HNF1A*	G/A	1.02 (0.91 to 1.14)	0.709	1.21 (1.05 to 1.40)	**0.010**	0.051	1.08 (1.01 to 1.16)	**0.033**
rs9581943	*PDX1*	G/A	0.95 (0.85 to 1.07)	0.431	1.17 (1.01 to 1.36)	**0.043**	0.052	1.07 (0.99 to 1.16)	0.092
rs9543325	13q22.1	T/C	1.18 (1.05 to 1.32)	**0.005**	1.43 (1.23 to 1.66)	**3.2×10^{-6}**	**4.1×10^{-6}**	1.18 (1.10 to 1.28)	**1.3×10^{-5}**
rs8028529	15q14	T/C	1.00 (0.90 to 1.11)	0.966	1.15 (0.92 to 1.45)	0.229	0.907	1.05 (0.96 to 1.15)	0.291
rs7190458	*BCAR1*	C/T	1.26 (1.04 to 1.53)	**0.017**	1.67 (0.56 to 4.94)	0.355	**0.025**	1.20 (0.99 to 1.45)	0.068
rs4795218	*HNF1B*	G/A	0.93 (0.84 to 1.04)	0.211	0.77 (0.60 to 0.98)	**0.037**	**0.018**	0.091 (0.83 to 0.99)	**0.036**
rs11655237	*LINC00673*	C/T	1.25 (1.10 to 1.41)	**2.6×10^{-4}**	1.60 (1.08 to 2.39)	**0.021**	**2.9×10^{-5}**	1.24 (1.12 to 1.39)	**8.0×10^{-5}**
rs1517037	*GRP*	C/T	0.88 (0.79 to 0.99)	**0.026**	0.64 (0.48 to 0.86)	**0.002**	**0.001**	0.84 (0.77 to 0.93)	**3.6×10^{-4}**
rs16986825	*ZNRF3*	C/T	1.11 (1.00 to 1.25)	0.057	1.28 (0.97 to 1.68)	0.080	**0.004**	1.19 (1.08 to 1.31)	**3.7×10^{-4}**

All analyses were adjusted for age, sex and geographic region of origin.
Text in bold indicates associations with p≤0.05.
m, minor allele; M, major allele; PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.

original publications.[7–10] We removed individuals with gender mismatches, call rate <0.9, minimal or excessive heterozygosity (>3 SDs from the mean) or cryptic relatedness (PI_HAT >0.2). We performed imputation using IMPUTE4[31] and the 1000 Genomes version 3 reference panel.[32] The different GWAS data sets were each imputed separately. We discarded SNPs with a minor allele frequency <0.5%, completion rate <90%, evidence for violations of HWE ($p<10^{-6}$) or low-quality imputation score (INFO score <0.7). The number of SNPs available in the final data set was 7 509 345. Principal component analysis was carried out including genotypes from all the populations of phase 3 of the 1000 Genomes Project (http://www.internationalgenome.org/). Individuals not clustering with the 1000 Genomes subjects of European descent were excluded from further analysis.

Unconditional logistic regression was used to validate the associations between the individual SNPs and PDAC risk. ORs, 95% CIs and p values were calculated. The SNPs were analysed according to the codominant and allelic inheritance models,

Table 3 Association between the ABO blood groups and PDAC risk in 2361 PDAC cases and 4418 controls from PANDoRA

Cases	Controls	rs505922	rs8176746	Blood group	OR (95% CI)	P value
780	1785	T/T	Any	OO	Reference	–
885	1474	T/C	C/C	AO	1.40 (1.24 to 1.59)	**6.41×10^{-8}**
242	370	C/C	C/C	AA	1.53 (1.27 to 1.85)	**1.09×10^{-5}**
281	481	T/C	A/A	BO	1.40 (1.18 to 1.67)	**1.70×10^{-4}**
27	52	C/C	A/A	BB	1.34 (0.82 to 2.20)	0.245
146	256	T/C or C/C	C/A	AB	1.27 (0.82 to 2.20)	**0.042**

All analyses were adjusted for age, sex and geographic region of origin.
Text in bold indicates associations with p≤0.05.
PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.

Table 4 Associations between the genetic scores and PDAC risk

	PANDoRA				PanScan I–III+PanC4			
	Controls	Cases	OR (95% CI)	P value	Controls	Cases	OR (95% CI)	P value
Unweighted polygenic score								
First quintile	529	131	1.00 (reference)	–	1220	908	1.00 (reference)	–
Second quintile vs first quintile	395	148	1.60 (1.19 to 2.17)	2.13E-03	994	980	1.31 (1.16 to 1.49)	1.92E-05
Third quintile vs first quintile	437	185	1.94 (1.45 to 2.58)	**7.07E-06**	1025	1384	1.83 (1.62 to 2.06)	**1.24E-21**
Fourth quintile vs first quintile	355	176	2.19 (1.63 to 2.94)	**2.24E-07**	870	1291	2.00 (1.77 to 2.26)	**2.34E-26**
Fifth quintile vs first quintile	324	199	2.64 (1.97 to 3.54)	**8.76E-11**	780	1857	3.22 (2.86 to 3.64)	**1.20E-71**
95th vs 5th centile			3.81 (2.15 to 6.77)	**6.36E-06**			5.67 (4.50 to 7.14)	**9.72E-45**
95th vs 50th centile			1.76 (1.11 to 2.81)	1.67E-02			3.14 (2.72 to 3.64)	**1.33E-48**
Weighted polygenic score								
First quintile	410	94	1.00 (reference)	–	977	675	1.00 (reference)	–
Second quintile vs first quintile	408	145	1.66 (1.20 to 2.30)	2.48E-03	980	923	1.37 (1.2 to 1.57)	**1.91E-06**
Third quintile vs first quintile	408	155	1.79 (1.29 to 2.47)	4.24E-04	976	1240	1.86 (1.63 to 2.12)	**5.44E-14**
Fourth quintile vs first quintile	408	204	2.28 (1.67 to 3.12)	**2.50E-07**	977	1402	2.09 (1.84 to 2.38)	**2.32E-21**
Fifth quintile vs first quintile	406	241	2.70 (1.99 to 3.68)	**2.54E-10**	979	2180	3.24 (2.86 to 3.67)	**1.20E-63**
95th vs 5th centile			4.56 (2.50 to 8.35)	**1.19E-06**			4.63 (3.63 to 5.91)	**6.16E-32**
95th vs 50th centile			2.70 (1.72 to 4.22)	**1.76E-05**			3.15 (2.73 to 3.65)	**5.87E-49**

All analyses were adjusted for age, sex and geographic region of origin (PANDoRA) or the top eight principal components (PanScan I–III+PanC4).
Text in bold indicates associations with p≤0.05.
PanC4, Pancreatic Cancer Case-Control Consortium; PANDoRA, PANcreatic Disease ReseArch; PanScan, Pancreatic Cancer Cohort Consortium; PDAC, pancreatic ductal adenocarcinoma.

using the most common allele in controls as reference. The association between genotype-derived ABO blood groups and PDAC risk was also tested with unconditional logistic regression using the O group as the reference category. To validate the associations between the risk factors assessed as dichotomous variables and PDAC risk, logistic regression was used. All analyses were adjusted for: sex, age and country of origin (PANDoRA) or sex, age and the top eight principal components (PanScan and PanC4). Associations showing a p value less than 0.05 were considered significant since all these associations have been extensively studied and replicated elsewhere.

The genetic score was computed on the subset of subjects that had 100% call rate, consisting of 839 cases and 2040 controls in PANDoRA and 6420 cases and 4889 controls in PanScan I–III and PanC4, for a total of 14 188 subjects. Score quintiles were calculated based on their distribution in the controls. Details on score computation have been give elsewhere[14] and in the online supplementary material.

We built two types of PRS, a simple unweighted score and a weighted score. We generated the unweighted score for each subject by summing the total number of risk alleles (attributing the value of 1 to each risk allele) and adding the value associated with the ABO groups, with a value of 0 for the OO group, 1 for OA/OB and 2 for AB group. We generated the weighted score assigning to each genotype the relative OR, using the OR reported in the literature by GWAS on PDAC, and the same was done for the ABO groups. Subsequently, from the product of all the ORs, we obtained the weighted score of each individual. Online supplementary table II shows an example of how the scores were generated. The computed score was used as a categorical variable, calculating the quintiles based on the distribution in controls. We validated the genetic scores in 6420 PDAC cases and 4889 controls (subjects from PanScan I–III and PanC4 with 100% call rate) using the same statistical models used for the PANDoRA data set and adjusting for the top eight principal components to avoid confounding due to population stratification.

We also computed multifactorial scores (for PANDoRA only) complementing the genetic weighted score with variables for tobacco smoking and type 2 diabetes, using 101 PDAC cases and 250 controls. The computed scores were analysed for their association with PDAC risk with logistic regression, adjusting for sex, age and country of origin. Given the limited number of subjects in PANDoRA who had 100% call rate and complete data for the covariates, we also included in the multifactorial score subjects without all the genetic variants (call rate >80%, 243 cases and 511 controls) and normalised the scores of each subject, in order to make them comparable, by multiplying them for (total number of variables)/(number of available variables) obtaining a 'scaled' score.

Receiver operating characteristic curves were constructed and the related areas under the curve (AUC) were calculated, to determine the performance of scores in discriminating individuals with the disease from individuals without the disease.

RESULTS

Main effects of SNPs, ABO blood groups and epidemiological risk factors

Most of the associations between the GWAS-identified SNPs and ABO blood groups and PDAC risk were replicated in PANDoRA, using up to 2851 cases and 4810 controls (tables 2 and 3).

As expected, we observed statistically significant associations between smoking (with 1472 cases and 1865 controls), diabetes (with 1028 cases and 1906 controls) and PDAC risk (OR=2.66, 95% CI 2.20 to 3.21, $p=2\times10^{-22}$ for smoking, and OR=1.46, 95% CI 1.14 to 1.86, p=0.003 for diabetes) (online supplementary table III).

Risk scores

The PRS (which includes the genetically predicted ABO blood groups) showed very significant associations. For the highest versus lowest quintile of the unweighted score we observed in PANDoRA an OR=2.64 (95% CI 1.97 to 3.54, $p=8.76\times10^{-11}$)

Table 5 Associations between scores with genetic and non-genetic variables and PDAC risk in PANDoRA

Quintile	Controls	Cases	OR (95% CI)	P value
Unweighted multifactorial score				
First quintile	63	13	1.00 (reference)	–
Second quintile vs first quintile	50	12	1.09 (0.45 to 2.63)	8.53E-01
Third quintile vs first quintile	51	27	2.55 (1.19 to 5.47)	**1.60E-02**
Fourth quintile vs first quintile	47	17	1.70 (0.75 to 3.88)	2.05E-01
Fifth quintile vs first quintile	39	32	3.89 (1.81 to 8.37)	**5.05E-04**
Weighted multifactorial score				
First quintile	60	6	1.00 (reference)	
Second quintile vs first quintile	58	12	2.02 (0.71 to 5.75)	1.90E-01
Third quintile vs first quintile	51	13	2.54 (0.89 to 7.19)	8.00E-02
Fourth quintile vs first quintile	46	20	4.21 (1.55 to 11.4)	**4.71E-03**
Fifth quintile vs first quintile	35	50	14.37 (5.57 to 37.09)	**3.64E-08**

All analyses were adjusted for age, sex and geographic region of origin.
Text in bold indicates associations with p≤0.05.
PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.

Table 6 Associations between scores scaled (call rate >80%) with genetic and non-genetic variables and PDAC risk in PANDoRA

Quintile	Controls	Cases	OR (95% CI)	P value
Unweighted multifactorial score				
First quintile	113	29	1.00 (reference)	–
Second quintile vs first quintile	116	41	1.17 (0.65 to 2.11)	5.91E-01
Third quintile vs first quintile	116	62	2.17 (1.25 to 3.76)	**5.96E-03**
Fourth quintile vs first quintile	79	29	1.34 (0.71 to 2.54)	3.63E-01
Fifth quintile vs first quintile	87	82	3.66 (2.11 to 6.33)	**3.62E-06**
Weighted multifactorial score				
First quintile	116	38	1.00 (reference)	–
Second quintile vs first quintile	121	35	0.83 (0.46 to 1.50)	5.43E-01
Third quintile vs first quintile	98	48	1.75 (0.99 to 3.10)	5.40E-02
Fourth quintile vs first quintile	100	35	1.10 (0.61 to 2.00)	7.50E-01
Fifth quintile vs first quintile	76	87	6.01 (3.48 to 10.39)	**1.28E-10**

Scaled scores obtained by multiplying the score for (total number of variables)/(number of available variables), in subjects with call rate >80%. All analyses were adjusted for age, sex and geographic region of origin.
Text in bold indicates associations with p≤0.05.
PANDoRA, PANcreatic Disease ReseArch; PDAC, pancreatic ductal adenocarcinoma.

and for the highest versus lowest quintile of the weighted score, OR=2.70 (95% CI 1.99 to 3.68, $p=2.54\times10^{-10}$), using 839 cases and 2040 controls. The results are shown in table 4. The validation analysis performed in the PanScan and PanC4 data sets, using 6420 cases and 4889 controls, showed similar results. For the unweighted score, we observed an OR=3.22 (95% CI 2.86 to 3.64, $p=1.20\times10^{-71}$) for the highest versus lowest quintile and OR=3.24 (95% CI 2.86 to 3.67, $p=1.20\times10^{-63}$) for the weighted score comparing the highest versus lowest quintile. When we restricted the analyses to the extreme tails of the distribution, we observed substantially larger risks, with good agreement between PANDoRA and the PanScan+PanC4 data set. Namely, when we compared the top versus the bottom 5% of the distributions. We observed OR=4.56 (95% CI 2.50 to 8.35. $p=1.19\times10^{-6}$) in PANDoRA and OR=4.63 (95% CI 3.63 to 5.91, $p=6.16\times10^{-32}$) in PanScan+PanC4. The results are shown in table 4.

The exploratory analysis of different multifactorial risk scores, using 101 PDAC cases and 250 controls, showed significant associations as well. The results are summarised in table 5. The weighted score complemented with smoking and diabetes showed OR=14.37 (95% CI 5.57 to 37.09, $p=3.64\times10^{-8}$) for the highest versus lowest quintile. Similar statistically significant results were observed with the scaled score (OR=6.01, 95% CI 3.48 to 10.39, $p=1.28\times10^{-10}$), which includes a larger number of individuals (243 cases and 511 controls). The results of the scaled score are reported in table 6.

Evaluation of prediction performance results

The AUC value for the unweighted PRS is 0.59 (95% CI 0.57 to 0.61) in PANDoRA and 0.61 (95% CI 0.60 to 0.63) in the PanScan I–III and PanC4 combined data set. The highest AUC value for the multifactorial scores is 0.63 (95% CI 0.59 to 0.67).

DISCUSSION

A promising way to decrease PDAC mortality is to improve early detection, which can be achieved by identifying subjects at high risk of developing the disease. The International Cancer of the Pancreas Screening consortium recommends regular screening for subjects with at least a fivefold increased risk.[33] This level of risk determination can be obtained by integrating genetic and epidemiological risk factors. In recent years a number of SNPs convincingly associated with PDAC risk have been reported.[7–13] They generally show a small effect on risk (OR <1.5), therefore individually are not very useful in risk prediction. Yet, combining them in a PRS may lead to a significant improvement in risk prediction,[34 35] as already demonstrated for other diseases.[36–38]

The PRS reached high statistical significance both when unweighted and weighted, with similar ORs in PANDoRA and in the combined PanScan I–III+PanC4 data set, with an approximately threefold increase in risk for the 20% of subjects with the highest score values if compared with the subjects with the 20% lowest. The level of risk becomes more pronounced when looking only at the extremes of the distribution, with approximately fivefold differences in risk between the top and the bottom 5%. This level of risk is in the same order of magnitude as reported for rare, highly penetrant mutations in familial pancreatic cancer syndromes (eg, for mutations in *BRCA1*, *BRCA2* or *ATM*).[4] The substantial concordance between PANDoRA and the combined PanScan I–III+PanC4 data set, based on data of about 7000 PDAC cases and 7000 controls, makes us confident in the stability of these predictions.

In spite of the clear discrimination of risk level and the strong statistical significance, the values of the AUC based on the SNPs alone (ranging from 0.59 to 0.61) are not satisfactory. However, theoretical predictions[39] and previous studies on cancer types for which a much larger number of risk SNPs are known[23 24 36 37] have shown that the addition of risk variants increases the predictive power of PRS, to the point of envisaging their implementation in screening of the general population.[25] Thus, it is foreseeable that continued efforts for discovery of novel pancreatic cancer

risk SNPs will enable us in the middle/long term to build scores with a much larger number of genetic variants, which will lead to much improved risk prediction.

Furthermore, it is useful to combine the genetic score with non-genetic risk factors obtaining a multifactorial score. This has already been done for other cancers and has shown slightly better prediction performances.[23 37 40] The idea is to build a score that includes all known genetic variants associated with risk and all known epidemiological risk factors. The exploratory results we observed in our data set are encouraging because they showed a large increase in the ORs. It should, however, be noted that the data of the covariates in PANDoRA are largely incomplete and currently this prevents us from including all known non-genetic risk factors in the score. Moreover, as retrospective data, they may be subjected to recall bias. Data available from dbGaP for PanScan I–III and PanC4 do not include any variable about known risk factors; thus we could not evaluate the multifactorial score in the replication data set. For these reasons, we need to use caution in interpreting the results, but the combination of genotypes and data on risk factors seems a suitable way for the construction of a score that leads to the identification of a subgroup of subjects with very high risk. Indeed, subjects in the highest quintile of the multifactorial score including both smoking and diabetes reached an OR=14.37, which is comparable to effect of rare high-penetrance disease causing mutations.

Strengths of this study are the sample size, since it is the largest study of this type conducted on PDAC to date, and the number of polymorphisms included in the computation of the genetic score, since all the known *loci* have been included in the score, unlike what was previously done. In addition, another clear advantage of this study is the external validation of the score using PanScan and PanC4 data. The limitations are the possible bias deriving from the inclusion of subjects that come from different countries and the fact that in PANDoRA the information on epidemiological and lifestyle factors is limited. In addition, it is possible that the OR that we observe in the multifactorial risk score is inflated, given the relatively small sample size (101 cases and 250 controls) that we could use for running that exploratory analysis.

In conclusion, in this study, we found a highly significant association between a PRS and the risk of PDAC onset, which explains more than individual SNPs and is a step forward in the direction of the construction of a tool for risk stratification. Furthermore, the exploratory analysis of a multifactorial score was encouraging. In perspective, the implementation of the score with new genetic risk variants, which are continuously discovered, and with complete data on epidemiological risk factors can lead to the achievement of a tool for risk stratification of clinical utility. Such an instrument, if perfected, could be conceived as a tool for risk stratification in the population, which in turn can contribute to improved early diagnosis. A test with relatively low predictive power as the score could be used to define groups of subjects at increased risk on which to apply screening tools and, lastly, the expensive and invasive imaging on the subjects that are positive.

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REFERENCES

1 Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, Neale RE, Tempero M, Tuveson DA, Hruban RH, Neoptolemos JP. Pancreatic cancer. *Nat Rev Dis Primers* 2016;2:16022.
2 Becker AE, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. *World J Gastroenterol* 2014;20:11182–98.
3 Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med* 2014;371:1039–49.
4 Amundadottir LT. Pancreatic cancer genetics. *Int J Biol Sci* 2016;12:314–25.
5 Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol* 2015;44:186–98.
6 Klein AP. Genetic susceptibility to pancreatic cancer. *Mol Carcinog* 2012;51:14–24.
7 Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, Bueno-de-Mesquita HB, Gross M, Helzlsouer K, Jacobs EJ, LaCroix A, Zheng W, Albanes D, Bamlet W, Berg CD, Berrino F, Bingham S, Buring JE, Bracci PM, Canzian F, Clavel-Chapelon F, Clipp S, Cotterchio M, de Andrade M, Duell EJ, Fox JW, Gallinger S, Gaziano JM, Giovannucci EL, Goggins M, González CA, Hallmans G, Hankinson SE, Hassan M, Holly EA, Hunter DJ, Hutchinson A, Jackson R, Jacobs KB, Jenab M, Kaaks R, Klein AP, Kooperberg C, Kurtz RC, Li D, Lynch SM, Mandelson M, McWilliams RR, Mendelsohn JB, Michaud DS, Olson SH, Overvad K, Patel AV, Peeters PHM, Rajkovic A, Riboli E, Risch HA, Shu X-O, Thomas G, Tobias GS, Trichopoulos D, Van Den Eeden SK, Virtamo J, Wactawski-Wende J, Wolpin BM, Yu H, Yu K, Zeleniuch-Jacquotte A, Chanock SJ, Hartge P, Hoover RN. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nat Genet* 2009;41:986–90.
8 Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, Arslan AA, Bueno-de-Mesquita HB, Gallinger S, Gross M, Helzlsouer K, Holly EA, Jacobs EJ, Klein AP, LaCroix A, Li D, Mandelson MT, Olson SH, Risch HA, Zheng W, Albanes D, Bamlet WR, Berg CD, Boutron-Ruault M-C, Buring JE, Bracci PM, Canzian F, Clipp S, Cotterchio M, de Andrade M, Duell EJ, Gaziano JM, Giovannucci EL, Goggins M, Hallmans G, Hankinson SE, Hassan M, Howard B, Hunter DJ, Hutchinson A, Jenab M, Kaaks R, Kooperberg C, Krogh V, Kurtz RC, Lynch SM, McWilliams RR, Mendelsohn JB, Michaud DS, Parikh H, Patel AV, Peeters PHM, Rajkovic A, Riboli E, Rodriguez L, Seminara D, Shu X-O, Thomas G, Tjønneland A, Tobias GS, Trichopoulos D, Van Den Eeden SK, Virtamo J, Wactawski-Wende J, Wang Z, Wolpin BM, Yu H, Yu K, Zeleniuch-Jacquotte A, Fraumeni JF, Hoover RN, Hartge P, Chanock SJ. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat Genet* 2010;42:224–8.
9 Wolpin BM, Rizzato C, Kraft P, Kooperberg C, Petersen GM, Wang Z, Arslan AA, Beane-Freeman L, Bracci PM, Buring J, Canzian F, Duell EJ, Gallinger S, Giles GG, Goodman GE, Goodman PJ, Jacobs EJ, Kamineni A, Klein AP, Kolonel LN, Kulke MH, Li D, Malats N, Olson SH, Risch HA, Sesso HD, Visvanathan K, White E, Zheng W, Abnet CC, Albanes D, Andreotti G, Austin MA, Barfield R, Basso D, Berndt SI, Boutron-Ruault M-C, Brotzman M, Büchler MW, Bueno-de-Mesquita HB, Bugert P, Burdette L, Campa D, Caporaso NE, Capurso G, Chung C, Cotterchio M, Costello E, Elena J, Funel N, Gaziano JM, Giese NA, Giovannucci EL, Goggins M, Gorman MJ, Gross M, Haiman CA, Hassan M, Helzlsouer KJ, Henderson BE, Holly EA, Hu N, Hunter DJ, Innocenti F, Jenab M, Kaaks R, Key TJ, Khaw K-T, Klein EA, Kogevinas M, Krogh V, Kupcinskas J, Kurtz RC, LaCroix A, Landi MT, Landi S, Le Marchand L, Mambrini A, Mannisto S, Milne RL, Nakamura Y, Oberg AL, Owzar K, Patel AV, Peeters PHM, Peters U, Pezzilli R, Piepoli A, Porta M, Real FX, Riboli E, Rothman N, Scarpa A, Shu X-O, Silverman DT, Soucek P, Sund M, Talar-Wojnarowska R, Taylor PR, Theodoropoulos GE, Thornquist M, Tjønneland A, Tobias GS, Trichopoulos D, Vodicka P, Wactawski-Wende J, Wentzensen N, Wu C, Yu H, Yu K, Zeleniuch-Jacquotte A, Hoover R, Hartge P, Fuchs C, Chanock SJ, Stolzenberg-Solomon RS, Amundadottir LT. Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer. *Nat Genet* 2014;46:994–1000.
10 Childs EJ, Mocci E, Campa D, Bracci PM, Gallinger S, Goggins M, Li D, Neale RE, Olson SH, Scelo G, Amundadottir LT, Bamlet WR, Bijlsma MF, Blackford A, Borges M, Brennan P, Brenner H, Bueno-de-Mesquita HB, Canzian F, Capurso G, Cavestro GM, Chaffee KG, Chanock SJ, Cleary SP, Cotterchio M, Foretova L, Fuchs C, Funel N, Gazouli M, Hassan M, Herman JM, Holcatova I, Holly EA, Hoover RN, Hung RJ, Janout V, Key TJ, Kupcinskas J, Kurtz RC, Landi S, Lu L, Malecka-Panas E, Mambrini A, Mohelnikova-Duchonova B, Neoptolemos JP, Oberg AL, Orlow I, Pasquali C, Pezzilli R, Rizzato C, Saldia A, Scarpa A, Stolzenberg-Solomon RZ, Strobel O, Tavano F, Vashist YK, Vodicka P, Wolpin BM, Yu H, Petersen GM, Risch HA, Klein AP. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. *Nat Genet* 2015;47:911–6.
11 Campa D, Rizzato C, Stolzenberg-Solomon R, Pacetti P, Vodicka P, Cleary SP, Capurso G, Bueno-de-Mesquita HBA, Werner J, Gazouli M, Butterbach K, Ivanauskas A, Giese N, Petersen GM, Fogar P, Wang Z, Bassi C, Ryska M, Theodoropoulos GE, Kooperberg C, Li D, Greenhalf W, Pasquali C, Hackert T, Fuchs CS, Mohelnikova-Duchonova B, Sperti C, Funel N, Dieffenbach AK, Wareham NJ, Buring J, Holcátová I, Costello E, Zambon C-F, Kupcinskas J, Risch HA, Kraft P, Bracci PM, Pezzilli R, Olson SH, Sesso HD, Hartge P, Strobel O, Małecka-Panas E, Visvanathan K, Arslan AA, Pedrazzoli S, Souček P, Gioffreda D, Key TJ, Talar-Wojnarowska R, Scarpa A, Mambrini A, Jacobs EJ, Jamroziak K, Klein A, Tavano F, Bambi F, Landi S, Austin MA, Vodickova L, Brenner H, Chanock SJ, Delle Fave G, Piepoli A, Cantore M, Zheng W, Wolpin BM, Amundadottir LT, Canzian F, Costello E, Zambon C-FF, Kupcinskas J, Risch HA, Kraft P, Bracci PM, Pezzilli R, Olson SH, Sesso HD, Hartge P, Strobel O, Visvanathan K, Arslan AA, Pedrazzoli S, Gioffreda D, Key TJ, Talar-Wojnarowska R, Scarpa A, Mambrini A, Jacobs EJ, Jamroziak K, Klein A, Tavano F, Bambi F, Landi S, Austin MA, Vodickova L, Brenner H, Chanock SJ, Delle Fave G, Piepoli A, Cantore M, Zheng W, Wolpin BM, Amundadottir LT, Canzian F. TERT gene harbors multiple variants associated with pancreatic cancer susceptibility. *Int J Cancer* 2015;137:2175–83.
12 Zhang M, Wang Z, Obazee O, Jia J, Childs EJ, Hoskins J, Figlioli G, Mocci E, Collins I, Chung CC, Hautman C, Arslan AA, Beane-Freeman L, Bracci PM, Buring J, Duell EJ, Gallinger S, Giles GG, Goodman GE, Goodman PJ, Kamineni A, Kolonel LN, Kulke MH, Malats N, Olson SH, Sesso HD, Visvanathan K, White E, Zheng W, Abnet CC, Albanes D, Andreotti G, Brais L, Bueno-de-Mesquita HB, Basso D, Berndt SI, Boutron-Ruault M-C, Bijlsma MF, Brenner H, Burdette L, Campa D, Caporaso NE, Capurso G, Cavestro GM, Cotterchio M, Costello E, Elena J, Boggi U, Gaziano JM, Gazouli M, Giovannucci EL, Goggins M, Gross M, Haiman CA, Hassan M, Helzlsouer KJ, Hu N, Hunter DJ, Iskierka-Jazdzewska E, Jenab M, Kaaks R, Key TJ, Khaw K-T, Klein EA, Kogevinas M, Krogh V, Kupcinskas J, Kurtz RC, Landi MT, Landi S, Le Marchand L, Mambrini A, Mannisto S, Milne RL, Neale RE, Oberg AL, Panico S, Patel AV, Peeters PHM, Peters U, Pezzilli R, Porta M, Purdue M, Quiros JR, Riboli E, Rothman N, Scarpa A, Scelo G, Shu X-O, Silverman DT, Soucek P, Strobel O, Sund M, Małecka-Panas E, Taylor PR, Tavano F, Travis RC, Thornquist M, Tjønneland A, Tobias GS, Trichopoulos D, Vashist Y, Vodicka P, Wactawski-Wende J, Wentzensen N, Yu H, Yu K, Zeleniuch-Jacquotte A, Kooperberg C, Risch HA, Jacobs EJ, Li D, Fuchs C, Hoover R, Hartge P, Chanock SJ, Petersen GM, Stolzenberg-Solomon RS, Wolpin BM, Kraft P, Klein AP, Canzian F, Amundadottir LT. Three new pancreatic cancer susceptibility signals identified on chromosomes 1q32.1, 5p15.33 and 8q24.21. *Oncotarget* 2016;7:66328–43.
13 Klein AP, Wolpin BM, Risch HA, Stolzenberg-Solomon RZ, Mocci E, Zhang M, Canzian F, Childs EJ, Hoskins JW, Jermusyk A, Zhong J, Chen F, Albanes D, Andreotti G, Arslan AA, Babic A, Bamlet WR, Beane-Freeman L, Berndt SI, Blackford A, Borges M, Borgida A, Bracci PM, Brais L, Brennan P, Brenner H, Bueno-de-Mesquita B, Buring J, Campa D, Capurso G, Cavestro GM, Chaffee KG, Chung CC, Cleary S, Cotterchio M, Dijk F, Duell EJ, Foretova L, Fuchs C, Funel N, Gallinger S, M Gaziano JM, Gazouli M, Giles GG, Giovannucci E, Goggins M, Goodman GE, Goodman PJ, Hackert T, Haiman C, Hartge P, Hasan M, Hegyi P, Helzlsouer KJ, Herman J, Holcatova I, Holly EA, Hoover R, Hung RJ, Jacobs EJ, Jamroziak K, Janout V, Kaaks R, Khaw K-T, Klein EA, Kogevinas M, Kooperberg C, Kulke MH, Kupcinskas J, Kurtz RJ, Laheru D, Landi S, Lawlor RT, Lee I-M, LeMarchand L, Lu L, Malats N, Mambrini A, Mannisto S, Milne RL, Mohelníková-Duchoňová B, Neale RE, Neoptolemos JP, Oberg AL, Olson SH, Orlow I, Pasquali C, Patel AV, Peters U, Pezzilli R, Porta M, Real FX, Rothman N, Scelo G, Sesso HD, Severi G, Shu X-O, Silverman D, Smith JP, Soucek P, Sund M, Talar-Wojnarowska R, Tavano F, Thornquist MD, Tobias GS, Van Den Eeden SK, Vashist Y, Visvanathan K, Vodicka P, Wactawski-Wende J, Wang Z, Wentzensen N, White E, Yu H, Yu K, Zeleniuch-Jacquotte A, Zheng W, Kraft P, Li D, Chanock S, Obazee O, Petersen GM, Amundadottir LT. Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. *Nat Commun* 2018;9:556.

14 Campa D, Matarazzi M, Greenhalf W, Bijlsma M, Saum K-U, Pasquali C, van Laarhoven H, Szentesi A, Federici F, Vodicka P, Funel N, Pezzilli R, Bueno-de-Mesquita HB, Vodickova L, Basso D, Obazee O, Hackert T, Soucek P, Cuk K, Kaiser J, Sperti C, Lovecek M, Capurso G, Mohelnikova-Duchonova B, Khaw K-T, König A-K, Kupcinskas J, Kaaks R, Bambi F, Archibugi L, Mambrini A, Cavestro GM, Landi S, Hegyi P, Izbicki JR, Gioffreda D, Zambon CF, Tavano F, Talar-Wojnarowska R, Jamroziak K, Key TJ, Fave GD, Strobel O, Jonaitis L, Andriulli A, Lawlor RT, Pirozzi F, Katzke V, Valsuani C, Vashist YK, Brenner H, Canzian F. Genetic determinants of telomere length and risk of pancreatic cancer: a PANDoRA study. *Int J Cancer* 2019;144:1275–83.

15 Campa D, Pastore M, Gentiluomo M, Talar-Wojnarowska R, Kupcinskas J, Malecka-Panas E, Neoptolemos JP, Niesen W, Vodicka P, Fave GD, Bueno-de-Mesquita HB, Gazouli M, Pacetti P, Di Leo M, Ito H, Klüter H, Soucek P, Corbo V, Yamao K, Hosono S, Kaaks R, Vashist Y, Gioffreda D, Strobel O, Shimizu Y, Dijk F, Andriulli A, Ivanauskas A, Bugert P, Tavano F, Vodickova L, Zambon CF, Lovecek M, Landi S, Key TJ, Boggi U, Pezzilli R, Jamroziak K, Mohelnikova-Duchonova B, Mambrini A, Bambi F, Busch O, Pazienza V, Valente R, Theodoropoulos GE, Hackert T, Capurso G, Cavestro GM, Pasquali C, Basso D, Sperti C, Matsuo K, Büchler M, Khaw K-T, Izbicki J, Costello E, Katzke V, Michalski C, Stepien A, Rizzato C, Canzian F. Functional single nucleotide polymorphisms within the cyclin-dependent kinase inhibitor 2A/2B region affect pancreatic cancer risk. *Oncotarget* 2016;7:57011–20.

16 Gentiluomo M, Peduzzi G, Lu Y, Campa D, Canzian F. Genetic polymorphisms in inflammatory genes and pancreatic cancer risk: a two-phase study on more than 14 000 individuals. *Mutagenesis*;74.

17 Gentiluomo M, Lu Y, Canzian F, Campa D. Genetic variants in taste-related genes and risk of pancreatic cancer. *Mutagenesis* 2019;34:391–4.

18 Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, Giovannucci EL, Fuchs CS. ABO blood group and the risk of pancreatic cancer. *J Natl Cancer Inst* 2009;101:424–31.

19 Marcus DM. The ABO and Lewis blood-group system. Immunochemistry, genetics and relation to human disease. *N Engl J Med* 1969;280:994–1006.

20 Wolpin BM, Kraft P, Xu M, Steplowski E, Olsson ML, Arslan AA, Bueno-de-Mesquita HB, Gross M, Helzlsouer K, Jacobs EJ, LaCroix A, Petersen G, Stolzenberg-Solomon RZ, Zheng W, Albanes D, Allen NE, Amundadottir L, Austin MA, Boutron-Ruault M-C, Buring JE, Canzian F, Chanock SJ, Gaziano JM, Giovannucci EL, Hallmans G, Hankinson SE, Hoover RN, Hunter DJ, Hutchinson A, Jacobs KB, Kooperberg C, Mendelsohn JB, Michaud DS, Overvad K, Patel AV, Sanchéz M-J, Sansbury L, Shu X-O, Slimani N, Tobias GS, Trichopoulos D, Vineis P, Visvanathan K, Virtamo J, Wactawski-Wende J, Watters J, Yu K, Zeleniuch-Jacquotte A, Hartge P, Fuchs CS. Variant ABO blood group alleles, secretor status, and risk of pancreatic cancer: results from the pancreatic cancer cohort Consortium. *Cancer Epidemiol Biomarkers Prev* 2010;19:3140–9.

21 Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, Stolzenberg-Solomon RZ, Arslan AA, Jacobs EJ, Lacroix A, Petersen G, Zheng W, Albanes D, Allen NE, Amundadottir L, Anderson G, Boutron-Ruault M-C, Buring JE, Canzian F, Chanock SJ, Clipp S, Gaziano JM, Giovannucci EL, Hallmans G, Hankinson SE, Hoover RN, Hunter DJ, Hutchinson A, Jacobs K, Kooperberg C, Lynch SM, Mendelsohn JB, Michaud DS, Overvad K, Patel AV, Rajkovic A, Sanchéz M-J, Shu X-O, Slimani N, Thomas G, Tobias GS, Trichopoulos D, Vineis P, Virtamo J, Wactawski-Wende J, Yu K, Zeleniuch-Jacquotte A, Hartge P, Fuchs CS. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort Consortium. *Cancer Res* 2010;70:1015–23.

22 Rizzato C, Campa D, Pezzilli R, Soucek P, Greenhalf W, Capurso G, Talar-Wojnarowska R, Heller A, Jamroziak K, Khaw K-T, Key TJ, Bambi F, Landi S, Mohelnikova-Duchonova B, Vodickova L, Büchler MW, Bugert P, Vodicka P, Neoptolemos JP, Werner J, Hoheisel JD, Bauer AS, Giese N, Canzian F. ABO blood groups and pancreatic cancer risk and survival: results from the pancreatic disease research (PANDoRA) Consortium. *Oncol Rep* 2013;29:1637–44.

23 Lindström S, Schumacher FR, Cox D, Travis RC, Albanes D, Allen NE, Andriole G, Berndt SI, Boeing H, Bueno-de-Mesquita HB, Crawford ED, Diver WR, Gaziano JM, Giles GG, Giovannucci E, Gonzalez CA, Henderson B, Hunter DJ, Johansson M, Kolonel LN, Ma J, Le Marchand L, Pala V, Stampfer M, Stram DO, Thun MJ, Tjonneland A, Trichopoulos D, Virtamo J, Weinstein SJ, Willett WC, Yeager M, Hayes RB, Severi G, Haiman CA, Chanock SJ, Kraft P. Common genetic variants in prostate cancer risk prediction--results from the NCI Breast and Prostate Cancer Cohort Consortium (BPC3). *Cancer Epidemiol Biomarkers Prev* 2012;21:437–44.

24 Hüsing A, Canzian F, Beckmann L, Garcia-Closas M, Diver WR, Thun MJ, Berg CD, Hoover RN, Ziegler RG, Figueroa JD, Isaacs C, Olsen A, Viallon V, Boeing H, Masala G, Trichopoulos D, Peeters PHM, Lund E, Ardanaz E, Khaw K-T, Lenner P, Kolonel LN, Stram DO, Le Marchand L, McCarty CA, Buring JE, Lee I-M, Zhang S, Lindström S, Hankinson SE, Riboli E, Hunter DJ, Henderson BE, Chanock SJ, Haiman CA, Kraft P, Kaaks R, BPC3. Prediction of breast cancer risk by genetic risk factors, overall and by hormone receptor status. *J Med Genet* 2012;49:601–8.

25 Mavaddat N, Pharoah PDP, Michailidou K, Tyrer J, Brook MN, Bolla MK, Wang Q, Dennis J, Dunning AM, Shah M, Luben R, Brown J, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Czene K, Darabi H, Eriksson M, Peto J, Dos-Santos-Silva I, Dudbridge F, Johnson N, Schmidt MK, Broeks A, Verhoef S, Rutgers EJ, Swerdlow A, Ashworth A, Orr N, Schoemaker MJ, Figueroa J, Chanock SJ, Brinton L, Lissowska J, Couch FJ, Olson JE, Vachon C, Pankratz VS, Lambrechts D, Wildiers H, Van Ongeval C, van Limbergen E, Kristensen V, Grenaker Alnæs G, Nord S, Borresen-Dale A-L, Nevanlinna H, Muranen TA, Aittomäki K, Blomqvist C, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Burwinkel B, Marme F, Schneeweiss A, Sohn C, Trentham-Dietz A, Newcomb P, Titus L, Egan KM, Hunter DJ, Lindstrom S, Tamimi RM, Kraft P, Rahman N, Turnbull C, Renwick A, Seal S, Li J, Liu J, Humphreys K, Benitez J, Pilar Zamora M, Arias Perez JI, Menéndez P, Jakubowska A, Lubinski J, Jaworska-Bieniek K, Durda K, Bogdanova NV, Antonenkova NN, Dörk T, Anton-Culver H, Neuhausen SL, Ziogas A, Bernstein L, Devilee P, Tollenaar RAEM, Seynaeve C, van Asperen CJ, Cox A, Cross SS, Reed MWR, Khusnutdinova E, Bermisheva M, Prokofyeva D, Takhirova Z, Meindl A, Schmutzler RK, Sutter C, Yang R, Schürmann P, Bremer M, Christiansen H, Park-Simon T-W, Hillemanns P, Guénel P, Truong T, Menegaux F, Sanchez M, Radice P, Peterlongo P, Manoukian S, Pensotti V, Hopper JL, Tsimiklis H, Apicella C, Southey MC, Brauch H, Brüning T, Ko Y-D, Sigurdson AJ, Doody MM, Hamann U, Torres D, Ulmer H-U, Försti A, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Andrulis IL, Knight JA, Glendon G, Marie Mulligan A, Chenevix-Trench G, Balleine R, Giles GG, Milne RL, McLean C, Lindblom A, Margolin S, Haiman CA, Henderson BE, Schumacher F, Le Marchand L, Eilber U, Wang-Gohrke S, Hooning MJ, Hollestelle A, van den Ouweland AMW, Koppert LB, Carpenter J, Clarke C, Scott R, Mannermaa A, Kataja V, Kosma V-M, Hartikainen JM, Brenner H, Arndt V, Stegmaier C, Karina Dieffenbach A, Winqvist R, Pylkäs K, Jukkola-Vuorinen A, Grip M, Offit K, Vijai J, Robson M, Rau-Murthy R, Dwek M, Swann R, Annie Perkins K, Goldberg MS, Labrèche F, Dumont M, Eccles DM, Tapper WJ, Rafiq S, John EM, Whittemore AS, Slager S, Yannoukakos D, Toland AE, Yao S, Zheng W, Halverson SL, González-Neira A, Pita G, Rosario Alonso M, Álvarez N, Herrero D, Tessier DC, Vincent D, Bacot F, Luccarini C, Baynes C, Ahmed S, Maranian M, Healey CS, Simard J, Hall P, Easton DF, Garcia-Closas M. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst* 2015;107. doi:10.1093/jnci/djv036. [Epub ahead of print: 08 Apr 2015].

26 Maas P, Barrdahl M, Joshi AD, Auer PL, Gaudet MM, Milne RL, Schumacher FR, Anderson WF, Check D, Chattopadhyay S, Baglietto L, Berg CD, Chanock SJ, Cox DG, Figueroa JD, Gail MH, Graubard BI, Haiman CA, Hankinson SE, Hoover RN, Isaacs C, Kolonel LN, Le Marchand L, Lee I-M, Lindström S, Overvad K, Romieu I, Sanchez M-J, Southey MC, Stram DO, Tumino R, VanderWeele TJ, Willett WC, Zhang S, Buring JE, Canzian F, Gapstur SM, Henderson BE, Hunter DJ, Giles GG, Prentice RL, Ziegler RG, Kraft P, Garcia-Closas M, Chatterjee N. Breast cancer risk from modifiable and Nonmodifiable risk factors among white women in the United States. *JAMA Oncol* 2016;2:1295–302.

27 Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, Tyrer JP, Chen T-H, Wang Q, Bolla MK, Yang X, Adank MA, Ahearn T, Aittomäki K, Allen J, Andrulis IL, Anton-Culver H, Antonenkova NN, Arndt V, Aronson KJ, Auer PL, Auvinen P, Barrdahl M, Beane Freeman LE, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Bernstein L, Blomqvist C, Bogdanova NV, Bojesen SE, Bonanni B, Børresen-Dale A-L, Brauch H, Bremer M, Brenner H, Brentnall A, Brock IW, Brooks-Wilson A, Brucker SY, Brüning T, Burwinkel B, Campa D, Carter BD, Castelao JE, Chanock SJ, Chlebowski R, Christiansen H, Clarke CL, Collée JM, Cordina-Duverger E, Cornelissen S, Couch FJ, Cox A, Cross SS, Czene K, Daly MB, Devilee P, Dörk T, Dos-Santos-Silva I, Dumont M, Durcan L, Dwek M, Eccles DM, Ekici AB, Eliassen AH, Ellberg C, Engel C, Eriksson M, Evans DG, Fasching PA, Figueroa J, Fletcher O, Flyger H, Försti A, Fritschi L, Gabrielson M, Gago-Dominguez M, Gapstur SM, García-Sáenz JA, Gaudet MM, Georgoulias V, Giles GG, Gilyazova IR, Glendon G, Goldberg MS, Goldgar DE, González-Neira A, Grenaker Alnæs GI, Grip M, Gronwald J, Grundy A, Guénel P, Haeberle L, Hahnen E, Haiman CA, Håkansson N, Hamann U, Hankinson SE, Harkness EF, Hart SN, He W, Hein A, Heyworth J, Hillemanns P, Hollestelle A, Hooning MJ, Hoover RN, Hopper JL, Howell A, Huang G, Humphreys K, Hunter DJ, Jakimovska M, Jakubowska A, Janni W, John EM, Johnson N, Jones ME, Jukkola-Vuorinen A, Jung A, Kaaks R, Kaczmarek K, Kataja V, Keeman R, Kerin MJ, Khusnutdinova E, Kiiski JI, Knight JA, Ko Y-D, Kosma V-M, Koutros S, Kristensen VN, Krüger U, Kühl T, Lambrechts D, Le Marchand L, Lee E, Lejbkowicz F, Lilyquist J, Lindblom A, Lindström S, Lissowska J, Lo W-Y, Loibl S, Long J, Lubiński J, Lux MP, MacInnis RJ, Maishman T, Makalic E, Maleva Kostovska I, Mannermaa A, Manoukian S, Margolin S, Martens JWM, Martinez ME, Mavroudis D, McLean C, Meindl A, Menon U, Middha P, Miller N, Moreno F, Mulligan AM, Mulot C, Muñoz-Garzon VM, Neuhausen SL, Nevanlinna H, Neven P, Newman WG, Nielsen SF, Nordestgaard BG, Norman A, Offit K, Olson JE, Olsson H, Orr N, Pankratz VS, Park-Simon T-W, Perez JIA, Pérez-Barrios C, Peterlongo P, Peto J, Pinchev M, Plaseska-Karanfilska D, Polley EC, Prentice R, Presneau N, Prokofyeva D, Purrington K, Pylkäs K, Rack B, Radice P, Rau-Murthy R, Rennert G, Rennert HS, Rhenius V, Robson M, Romero A, Ruddy KJ, Ruebner M, Saloustros E, Sandler DP, Sawyer EJ, Schmidt DF, Schmutzler RK, Schneeweiss A, Schoemaker MJ, Schumacher F, Schürmann P, Schwentner L, Scott C, Scott RJ, Seynaeve C, Shah M, Sherman ME, Shrubsole MJ, Shu X-O, Slager S, Smeets A, Sohn C, Soucy P, Southey MC, Spinelli JJ, Stegmaier C, Stone J, Swerdlow AJ, Tamimi RM, Tapper WJ, Taylor JA, Terry MB, Thöne K, Tollenaar RAEM, Tomlinson I, Truong T, Tzardi M, Ulmer H-U, Untch M, Vachon CM, van Veen EM, Vijai J, Weinberg CR, Wendt C, Whittemore AS, Wildiers H, Willett W, Winqvist R, Wolk A, Yang XR, Yannoukakos D, Zhang Y, Zheng W, Ziogas A, Dunning AM, Thompson DJ, Chenevix-Trench G, Chang-Claude J, Schmidt MK, Hall P, Milne RL, Pharoah PDP, Antoniou AC, Chatterjee N, Kraft P, García-Closas M, Simard J, Easton DF, ABCTB Investigators, kConFab/AOCS Investigators, NBCS Collaborators. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am J Hum Genet* 2019;104:21–34.

28 Hüsing A, Dossus L, Ferrari P, Tjønneland A, Hansen L, Fagherazzi G, Baglietto L, Schock H, Chang-Claude J, Boeing H, Steffen A, Trichopoulou A, Bamia C, Katsoulis M, Krogh V, Palli D, Panico S, Onland-Moret NC, Peeters PH, Bueno-de-Mesquita HB, Weiderpass E, Gram IT, Ardanaz E, Obón-Santacana M, Navarro C, Sánchez-Cantalejo E, Etxezarreta N, Allen NE, Khaw KT, Wareham N, Rinaldi S, Romieu I, Merritt MA, Gunter M, Riboli E, Kaaks R. An epidemiological model for prediction of endometrial cancer risk in Europe. *Eur J Epidemiol* 2016;31:51–60.
29 Klein AP, Lindström S, Mendelsohn JB, Steplowski E, Arslan AA, Bueno-de-Mesquita HB, Fuchs CS, Gallinger S, Gross M, Helzlsouer K, Holly EA, Jacobs EJ, Lacroix A, Li D, Mandelson MT, Olson SH, Petersen GM, Risch HA, Stolzenberg-Solomon RZ, Zheng W, Amundadottir L, Albanes D, Allen NE, Bamlet WR, Boutron-Ruault M-C, Buring JE, Bracci PM, Canzian F, Clipp S, Cotterchio M, Duell EJ, Elena J, Gaziano JM, Giovannucci EL, Goggins M, Hallmans G, Hassan M, Hutchinson A, Hunter DJ, Kooperberg C, Kurtz RC, Liu S, Overvad K, Palli D, Patel AV, Rabe KG, Shu X-O, Slimani N, Tobias GS, Trichopoulos D, Van Den Eeden SK, Vineis P, Virtamo J, Wactawski-Wende J, Wolpin BM, Yu H, Yu K, Zeleniuch-Jacquotte A, Chanock SJ, Hoover RN, Hartge P, Kraft P. An absolute risk model to identify individuals at elevated risk for pancreatic cancer in the general population. *PLoS One* 2013;8:e72311.
30 Campa D, Rizzato C, Capurso G, Giese N, Funel N, Greenhalf W, Soucek P, Gazouli M, Pezzilli R, Pasquali C, Talar-Wojnarowska R, Cantore M, Andriulli A, Scarpa A, Jamroziak K, Delle Fave G, Costello E, Khaw K-T, Heller A, Key TJ, Theodoropoulos G, Malecka-Panas E, Mambrini A, Bambi F, Landi S, Pedrazzoli S, Bassi C, Pacetti P, Piepoli A, Tavano F, di Sebastiano P, Vodickova L, Basso D, Plebani M, Fogar P, Büchler MW, Bugert P, Vodicka P, Boggi U, Neoptolemos JP, Werner J, Canzian F. Genetic susceptibility to pancreatic cancer and its functional characterisation: the pancreatic disease research (PANDoRA) Consortium. *Dig Liver Dis* 2013;45:95–9.
31 Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. *Nature* 2018;562:203–9.
32 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. A map of human genome variation from population-scale sequencing. *Nature* 2010;467:1061–73.
33 Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley J-W, Kamel I, Nio Y, Schulick RS, Bassi C, Kluijt I, Levy MJ, Chak A, Fockens P, Goggins M, Bruno M, International Cancer of Pancreas Screening (CAPS) Consortium. International cancer of the pancreas screening (CAPS) Consortium Summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 2013;62:339–47.
34 Janssens ACJW, Aulchenko YS, Elefante S, Borsboom GJJM, Steyerberg EW, van Duijn CM. Predictive testing for complex diseases using multiple genes: fact or fiction? *Genet Med* 2006;8:395–400.
35 Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Res* 2007;17:1520–8.
36 Pharoah PDP, Antoniou AC, Easton DF, Ponder BAJ. Polygenes, risk prediction, and targeted prevention of breast cancer. *N Engl J Med* 2008;358:2796–803.
37 Wacholder S, Hartge P, Prentice R, Garcia-Closas M, Feigelson HS, Diver WR, Thun MJ, Cox DG, Hankinson SE, Kraft P, Rosner B, Berg CD, Brinton LA, Lissowska J, Sherman ME, Chlebowski R, Kooperberg C, Jackson RD, Buckman DW, Hui P, Pfeiffer R, Jacobs KB, Thomas GD, Hoover RN, Gail MH, Chanock SJ, Hunter DJ. Performance of common genetic variants in breast-cancer risk models. *N Engl J Med* 2010;362:986–93.
38 Figlioli G, Chen B, Elisei R, Romei C, Campo C, Cipollini M, Cristaudo A, Bambi F, Paolicchi E, Hoffmann P, Herms S, Kalemba M, Kula D, Pastor S, Marcos R, Velázquez A, Jarząb B, Landi S, Hemminki K, Gemignani F, Försti A. Novel genetic variants in differentiated thyroid cancer and assessment of the cumulative risk. *Sci Rep* 2015;5:8922.
39 Gu W, Pepe MS. Estimating the capacity for improvement in risk prediction with a marker. *Biostatistics* 2009;10:172–86.
40 Pearce CL, Rossing MA, Lee AW, Ness RB, Webb PM, Chenevix-Trench G, Jordan SM, Stram DA, Chang-Claude J, Hein R, Nickels S, Lurie G, Thompson PJ, Carney ME, Goodman MT, Moysich K, Hogdall E, Jensen A, Goode EL, Fridley BL, Cunningham JM, Vierkant RA, Weber RP, Ziogas A, Anton-Culver H, Gayther SA, Gentry-Maharaj A, Menon U, Ramus SJ, Brinton L, Wentzensen N, Lissowska J, Garcia-Closas M, Massuger LFAG, Kiemeney LALM, Van Altena AM, Aben KKH, Berchuck A, Doherty JA, Iversen E, McGuire V, Moorman PG, Pharoah P, Pike MC, Risch H, Sieh W, Stram DO, Terry KL, Whittemore A, Wu AH, Schildkraut JM, Kjaer SK, for Australian Cancer Study (Ovarian Cancer), Australian Ovarian Cancer Study Group, Ovarian Cancer Association Consortium. Combined and interactive effects of environmental and GWAS-identified risk factors in ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2013;22:880–90.