Dear editor and reviewers:

On behalf of all authors, I am here to answering all you concern regarding our manuscript titled 'Single-Nucleotide Polymorphisms based Genetic Risk Score in the Prediction of Pancreatic Cancer Risk'. Thank you all for spending your precious time reviewing this work, and providing valuable suggestion to perfect this paper.

Xiaoyi Wang

To the Editors:

We thank the editors for giving us the opportunity to resubmit the figures. We have re-prepared them using PowerPoint in the "figures.ppt" file. Please do not hesitate to contact us if you have any question.

To Reviewer 05128707:

Thank you for comments.

Your first question, the inclusion criteria for SNPs was stated in the first part of 'Materials and Methods'. All 21 SNPs were pancreatic adenocarcinoma (PDAC) risk associated loci reported in previous GWAS or pathway analysis studies[1-6]. We included those 21 SNPs in our previous study 'An evaluation study of reported pancreatic adenocarcinoma risk associated SNPs from genome-wide association studies in Chinese population'[7]. In that study, we verified those 21 SNPs' relationship with PDAC in our Chinese Han population (n=254), which is the same population as this study.

The answer to your second question is also related to our previous study. The results of our verification study showed that three loci were associated with PDAC risk after Bonferroni correction, which, to our surprise, were from Japanese population (rs7779540 at 7q36.2, OR=2.59, p=3.89E-06, 95%CI: 1.73-3.87), and European population (rs10919791 at 1q32.1, OR=1.52, p=6.07E-5, 95%CI: 1.24-1.86; rs401681 at 5p15.33, OR=1.42, p=5.15E-04, 95%CI: 1.17-1.72).

We discussed the possible reason why we couldn't replicate the results of loci from Chinese population in our previous study. This result reveal that different population may share come common variations related to PDAC. Therefore, we decided to include all loci we verified in the construction of genetic risk score (GRS). As stated in the manuscript, 18 of the 21 loci were included in the final calculation (page 6, **Materials and Methods:** *GRS calculation and statistical analysis*). We did perform a sensitivity analysis with only loci reported from Chinese population. However, the result was not better than current one, thus we chose not to report that.

As for question three, I calculated the actual power of our study, using the actual data we got from our study. Since our GRS data first underwent log transformation to achieve normality, I used 'proc power procedure' for two sample means to calculate the actual power. As listed below, when the means of two group were 1.96 and 1.09, with a weight of 1:4, and a total sample size of 1200, which is roughly the case of the actual number of our study, the actual power is 0.88 for the group with the standard deviation of 3.84 (cases), and >0.999 for the group with standard deviation of 0.94 (controls).

The POWER Procedure
Two-Sample t Test for Mean Difference

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Group 1 Mean	1.96
Group 2 Mean	1.09
Group 1 Weight	1
Group 2 Weight	4
Total Sample Size	1200
Number of Sides	2
Null Difference	0
Alpha	0.05

Computed Power		
Index	Std Dev	Power
1	3.84	0.880
2	0.94	>.999

Thus, we believe our sample size could provide enough power for the research purpose of this study.

We appreciate your comments in the question 4 to 6, the manuscript had been adjusted accordingly.

To reviewer 00183086:

Thank you very much for your precise suggestions, the manuscript has been modified accordingly.

To reviewer 00069827:

We appreciate your valuable comments. The discussion session has been revised accordingly.

As for the prevalence of different SNPs included in the GWA panel among PDAC patients in Chinese and international populations, we presented this

part of the data in our previous work[7], which is already published. Thus, we don't want to present duplicate information in this paper. I added one sentence in the results part to indicate this reference.

Table 2
Genotype frequency of 21 selected SNPs in different population groups and Hardy-Weinberg equilibrium (HWE) in the control subjects.

Chr[a]	SNP	Chinese Population of "1000 Genomes Project"		Studied subjects of this study		HWE[c] in controls
		Minor allele	MAF[b]	MAF[b] (case)	MAF[b] (control)	P
1	rs10919791	G	0.29	0.37	0.28	0.56
5	rs2736098[d]	T	0.42	–	–	–
5	rs401681	T	0.28	0.38	0.30	1.00
5	rs2255280	C	0.36	0.37	0.32	0.84
6	rs2317900	C	0.38	0.35	0.37	0.09
7	rs6971499	C	0.04	0.04	0.05	0.77
7	rs7779540	A	0.02	0.06	0.02	0.27
7	rs167020	A	0.01	0.01	0.01	1.00
8	rs1561927	C	0.04	0.03	0.04	0.01
9	rs2073828	A	0.37	0.28	0.32	0.60
9	rs505922	C	0.38	0.47	0.44	0.48
10	rs12413624	A	0.37	0.40	0.39	0.95
12	rs792864	A	0.44	0.42	0.44	0.11
13	rs9581943	A	0.39	0.38	0.34	0.80
13	rs4885093	G	0.42	0.48	0.44	0.15
13	rs9543325	C	0.43	0.49	0.44	0.20
16	rs7190458	A	0.03	0.02	0.02	1.00
21	rs372883	C	0.43	0.45	0.43	0.64
21	rs1547374	G	0.41	0.42	0.44	0.00
22	rs16986825	T	0.36	0.43	0.41	0.77
22	rs5768709	G	0.22	0.22	0.25	0.27

[a] Chromosome.
[b] Minor allele frequency.
[c] Hardy-Weinberg equilibrium.
[d] Control group missing rate 0.26, didn't include in the final analysis.

Reference:

1. Wu, C., et al., *Genome-wide association study identifies five loci associated with susceptibility to pancreatic cancer in Chinese populations.* Nat Genet, 2011. **44**(1): p. 62-6.
2. Low, S.K., et al., *Genome-wide association study of pancreatic cancer in Japanese population.* PLoS One, 2010. **5**(7): p. e11824.
3. Amundadottir, L., et al., *Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer.* Nat Genet, 2009. **41**(9): p. 986-90.
4. Petersen, G.M., et al., *A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33.* Nat Genet, 2010. **42**(3): p. 224-8.
5. Wolpin, B.M., et al., *Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer.* Nat Genet, 2014. **46**(9): p. 994-1000.
6. Li, D., et al., *Pathway analysis of genome-wide association study data highlights pancreatic development genes as susceptibility factors for pancreatic cancer.* Carcinogenesis, 2012. **33**(7): p. 1384-90.
7. Wang, X., et al., *An evaluation study of reported pancreatic adenocarcinoma risk-associated SNPs from genome-wide association studies in Chinese population.* Pancreatology, 2017. **17**(6): p. 931-935.

Round 2

Dear editor and respected reviewer:

Thank you again for your time spending reviewing and editing our manuscript titled “Single-Nucleotide Polymorphisms based Genetic Risk Score in the Prediction of Pancreatic Cancer Risk”. Your comments are crucial for us to improve our current work and future related study. We hope that the revision is acceptable and are looking forward to your response. Below we provide a point-by-point response to the comments.

We highly appreciate the reviewer’s constructive comments and thanks very much for his/her efforts on our manuscript.

1. The comments of second-round review: Overall, an interesting article and innovative approach opening new possibilities for pancreatic cancer screening and early cancer detection. However, I am not convinced that the genetic test serves the purpose the authors claim it should do. In my opinion the authors successfully proved that cancer patients have a higher presence of of certain types of SNPs. In order to prove the concept, the test should be employed in large cohort of patients being investigated for various pancreatic tumours and/or long-term prospective cohort of healthy individuals with know genetic profile to check the PDAC development rates. Please revise your manuscript according to the reviewer's comments.
Response: We highly appreciate the reviewer's concerns. Pancreatic adenocarcinoma (PDAC) is a type of cancer with extreme poor prognosis. In this study, we proposed single nucleotide polymorphisms based genetic risk score to be a novel method to indicate PDAC risk. Our study results reveal that subjects with a higher GRS score showed a higher probability for PDAC.
We totally agree with reviewer’s comment that the PDAC risk predicting value of GRS should be validated in a well-designed cohort with large population, as we mentioned in the discussion session. Model-building and validation would be a nice full loop to testify our hypothesis. However, real world research is restricted by many factors. If we could get further funding, we would very much like to validate our research results in a cohort study. The publish of our current work would set a good foundation for our future grant application. Furthermore, currently follow-up genomic research after national GWAS is scarce, we humbly hope that our research would inspire authors of previous PDAC GWAS to look into this interesting and promising topic. Finally, we would like to express our sincere gratitude to your precious comment one more time. We would every much like to verify our study results in a cohort study, if possible.

2 Please fill out the STROBE form with page numbers.
Response: The STROBE form has been updated.

Sincerely yours,

Prof. Deliang Fu