Author’s response to reviews

Title: German National Case Collection for Familial Pancreatic Cancer (FaPaCa) - Acceptance and psychological aspects of a pancreatic cancer screening program

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Manuscript HCCP-D-18-00003 „German National Case Collection for Familial Pancreatic Cancer (FaPaCa) - Acceptance and psychological aspects of a pancreatic cancer screening program“

Dear Professor Lubinski,

We are happy that you might consider our revised manuscript entitled “German National Case Collection for Familial Pancreatic Cancer (FaPaCa) - Acceptance and psychological aspects of a pancreatic cancer screening program“ for publication in your journal Hereditary Cancer in Clinical Practice. The comments of the reviewers were very constructive and have improved the manuscript. We revised the manuscript as outlined below. Changes in the text have been marked in yellow and appear in bold text.

We would be happy, if you could now accept our manuscript for publication.

Thank you very much for all your efforts,

Yours sincerely,

Frederike Franke
Reviewer:1

1. On page 4 line 24 you state only 4 studies have so far analyzed the psychological effects of PDAC screening. Please could you address in the methods how this was determined (systematic review, search terms?)

Response: Those four studies have been found using systematic literature search. As suggested we added this information in the methods section as follows: “A systematic literature search was conducted using PubMed to obtain an overview of the current state of research. Medical subject headings were [Pancreatic Cancer] AND [Screening] AND [Distress] AND [psychological impact / burden]”

2. In line 29 you state PDAC screening differs greatly from other cancer screening programs given poor prognosis, lack of reliable screening and relatively high morbidity of surgery. This differs from many screening programs but something like ovarian cancer screening would have the same first two issues. I think the second sentence in this paragraph has a typo (‘outmost’ should be ‘utmost’, line 34). Also, it doesn't directly seem to follow on from your first sentence, so perhaps adding one more explanatory sentence would be helpful in this paragraph.

Response: as suggested we changed the paragraph as follows: “PDAC screening differs greatly from other cancer screening programs such as those for breast cancer or colorectal cancer with respect to the poor prognosis of PDAC, the lack of reliable screening methods and the relatively high morbidity of potentially preventive or curative surgery [34]. Considering these facts it is of utmost importance to evaluate the acceptance and the psychological effects of a standardized PDAC screening program in a large cohort of IAR.”

3. On page 7 line 41 you refer to a questionnaire and quote two papers (number 29 and 39). Please could you explain how the questionnaire was taken from these papers/adapted. Has it been validated?

Response: we used the validated 16 item questionnaire used by Stigglebout et al. (29) and Harinck et al. (39), but we modified the wording of questions. As suggested this information was now added on page 7, 3rd paragraph.

4. On page 13 line 20 you refer to the level of cancer worries being acceptable. Could you clarify what threshold/benchmark is used to determine acceptability?
Response: we used no clear-cut benchmark. Since in our cohort 63% of IAR in group 1, 90% of IAR in group 2 and 70% of IAR in group 3 experienced thoughts of a possible PDAC not as a burden (Table 3), we hypothesized that the level of cancer worries appears to be acceptable. As suggested this was now added in the discussion section on page 13, 2nd paragraph.

5. On page 14 line 5 there is an inconsistent use of referencing (numbered elsewhere but here refers to name, journal and date).

Response: as suggested this has been corrected.

6. In line 7 you refer to fear of examination not being a major reason, but almost a quarter (21%) of participants who discontinued screening gave this as a reason. It seems this was an issue for a reasonable number in this group, so might be worth thinking about a little further for future education/support of potential participants in this area.

Response: the reviewer is correct that fear of the examination is one of the 3 most common reasons to discontinue the screening. Therefore, we modified the sentence on page 14, first paragraph as follows: “Fear of the examination was one of the three main reasons in our cohort, since 21% of participants who discontinued screening and 17% of non-participants gave fear of the diagnostic procedures as the reason (data not shown). Thus, it worth thinking about more education and support of potential participants.”

7. On page 15, line 11 you refer to cancer worries and psychological stress being 'acceptable'. Could you comment on the benchmark for being considered acceptable?

Response: please see response to point 4. In addition, we now changed “is” to “appear”

8. On page 16, line 40 there is a typo ('writing oft he manuscript').

Response: as suggested this has been corrected.

9. References: 7 and 13 have 4 named authors whereas elsewhere you have limited to 3 names and then et al.

Response: this has been revised as suggested.
Reviewer #2: Overall Comments:

This is an important study that will add to the body of literature describing the psychological outcomes of pancreas cancer screening in high risk patients. Overall, this cross sectional study was well done within the context of the cohort of subjects available. As the authors discuss, cross sectional studies of this nature are not as ideal as a longitudinal study, but the methods seemed sufficient and the response rate was high enough to give significant validity to this data obtained. Well US studies are able to collect more demographic data that this study team reported they were able to acquire, this does not detract much from the data. Of note, numerous grammatical errors were present in the paper that have not been noted in this review. Thorough editing is recommended. Lastly, it is promising that this study itself motivated additional at-risk individuals who hadn't been adhering to surveillance recommendations to pursue screening, and this finding supports the authors' recommendation for physicians whom patient have established trust become more educated on PDAC screening and that they discuss this with these at-risk patients. Thank you for your work.

Response: we are grateful for this generous comment. As suggested the manuscript was overworked by a native speaker (EPS) and the grammatical errors have been corrected.

Specific comments:

1. Page 3, lines 24-27: I question why the authors decided to group the hereditary cancer syndromes with a high risk of pancreas cancer together with a condition such as FAP, which hasn't been shown to greatly elevate the risk for pancreas cancer as compared to other conditions. Since this paragraph seems to focus on high risk settings for pancreas cancer, perhaps removing moderate risk conditions from this section could be considered especially since the summary of these settings states that the lifetime risk for PDAC is >10% in these settings, which has not been shown in FAP (greatest RR reported is 4.5), Lynch (up to 4% risk) or HBOC (7% risk). Perhaps the hereditary conditions could be listed in both high- and moderate-risk groups, the statement about these settings leading to a 10-40% risk could be modified, or a statement could be added about family history playing a role in not just FPC families but also in families with hereditary conditions. The author may have meant that in lines 41-44, but it isn't clear whether those statements pertain to just FPC families or all settings discussed previously in the paragraph.

Response: as suggested we changed the paragraph as follows: “An increased PDAC risk occurs in hereditary syndromes such as Peutz-Jeghers-Syndrome (PJS) and familial atypical multiple mole melanoma (FAMMM), in hereditary pancreatitis and cystic fibrosis and in the setting of the familial pancreatic cancer (FPC) syndrome. FPC accounts for approximately 3%-5% of all PDAC cases [5, 6] and 80% of hereditary PDAC cases (11). Families with at least two first-degree relatives (FDR) with PDAC not fulfilling the criteria of another hereditary tumor
syndrome are defined as FPC. The lifetime risk of developing PDAC in FPC ranges between 10-40% depending on the number of affected first-degree relatives [4].

2. Page 4, line 27: Key article not cited by authors is cited below. The authors are recommended to review this article and incorporate information as necessary into the background section.

Response: as suggested we now cited the article of Hart et al. as reference number 33. In addition, we mentioned this study in the discussion section (page 13, 2nd paragraph) as follows: “Younger individuals showed a significant decrease in cancer-related intrusive thoughts, cancer-related avoidant thoughts, and cancer worry.”

3. Page 5, line 52: FDR is already defined as first degree relative in Page 5, line 15. Perhaps this inclusion of "close blood relative… or children" should move to that location in the paper.

Response: This has been revised as suggested.

4. Page 9, line 29: If 22 of the individuals in group 3 did not have accurate addresses, the response rate for this group would be 23 of 71 (32.4%). This number may be worth reporting instead of the return rate.

Response: as suggested we now added the response rate in group 3 as follows: “Therefore, the actual response rate in this group was 32% (23 of 71), but still much lower than in groups 1 and 2.

5. Page 12, lines 32-37: While the second half of this statement is accurate that this "study is the first to evaluate … the reasons for not participating in…” the first half of the statement is not accurate that this "study is the first to evaluate the participation rate of comprehensively counseled IAR".

Response: as suggested this sentenced was changed as follows: ”The present study is the first to evaluate the reasons for not participating in a recommended board-approved PDAC screening program besides evaluating the participation rate of comprehensively counseled IAR.”

6. Page 13, lines 56-59: I believe the authors intended to say that quitting cigarette smoking could dramatically reduce risk rather than engaging in the activity. The statement "In addition, no single factor - other than cigarette smoking -is known that can dramatically
reduce risk, nor is there any proven chemopreventive strategy" could be changed to "In addition, no single factor - other than quitting cigarette smoking - is known that can dramatically reduce risk, nor is there any proven chemopreventive strategy."

Response: the sentence was revised as suggested.

7. Page 14, line 31: The authors reported "return rate" not response rate in the data. While response rate for group 3 is not reported, the reviewer has calculated this number and agrees that there remains a difference in response rate.

Response: please see answer to point 4.

8. Page 14, lines 38-41: Since the IAR reported the FPC or syndromic status with their questionnaires, can the authors separate these cohorts within the data on comprehension and see if indeed there is a difference?

Response: we are grateful for this suggestion. However, since only 23 IAR had syndromic germline mutations such as BRCA1/2 or CDKN2a (Table 1), there would be not enough statistical power to come-up with a reliable result. Therefore, we decided not to perform such a comparison.

9. Page 16, line 9: an e needs to be added to syndrome.

Response: as suggested this has been corrected