Author's response to reviews

Title: Cancer Patient Perceptions on Biobanking Research

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Author's response to reviews: see over
Response Letter *BMC Medical Genomics* for article titled “Cancer Patient Perceptions on Biobanking Research” by Master *et al*.

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We would like to take the opportunity and thank the two reviewers for their most helpful feedback and we have acknowledged them accordingly. Our responses to reviewer comments are in the order in which they were received.

**Reviewer 1**

**Major Compulsory Revisions**

**Comment 1:** A number of conclusions are drawn that are not sufficiently founded based on the analyses conducted or information provided. First, this study did not measure or directly investigate any factors that affected the responses to the 2nd questionnaire; the questionnaire included 9 questions inquiring about perspectives in biobanking and tissue sampling. It did not include a control sample of non-leukemia patients. Therefore, it is erroneous to state that a purpose is to ‘determine whether their experience of receiving treatment and interacting with the physicians and clinic staff might have influenced their views on various ethical and legal issues relative to biorepository research’. This confounds an association with causation. From the information provided conclusions about the reasons for differential responses between the original and follow-up questionnaire can not be substantiated.

**Response:** The reviewer has raised an important point. In the last paragraph of the Background section, we have revised the manuscript to avoid implications of causation (which, as the reviewer notes, we did not explore) explaining that the follow-up survey aimed to determine whether patient views on the ethical and legal issues related to biorepository research had changed.

**Comment 2:** Furthermore, a substantial portion of the sample did not complete the follow-up, but this is not addressed in the ‘limitations’ section which should provide more in depth information about the potential bias due to non-response. Such information may be informed by analyzing the differences between the responders and non-responders (to the follow-up) with regards to how they completed the original questionnaire.

**Response:** Again, this is a very helpful comment. This analysis was needed and improves the paper. To determine whether there was a potential bias due to non-response, we compared responses between patients who completed the follow-up survey and those who did not. Chi-square tests did not yield any significant differences in the responses of these two groups, and therefore, we do not suspect a response bias. This has now been written at the end of the Methods section.

**Comment 3:** In the discussion the authors state that this work ‘highlights key differences in the perception of cancer patients as compared to other populations surveyed’. I think this statement needs a cautionary note as they did not study other populations using this questionnaire.

**Response:** We have revised this sentence in the first paragraph of the Discussion section.
Comment 4: Very little background information is provided about the development of the questionnaire or how well it reflects the measures used in other studies. The manuscript explains that the questionnaire aimed ‘to explore the perspectives of patients undergoing leukemia treatment’ does that mean it was especially formulated for leukemia patients? It does not seem to be. How was the survey developed, is it based on other surveys that have been published? Some questions are poorly worded and not completely relevant to the actual issues that must be addressed in biobanking to inform policy. For example, the question about withdrawing consent asks about withdrawing consent and samples in a single question. This has limited relevance and usability because once samples have been sent to analysis or shared (as they often are) in consortia then residual samples can be withdrawn but certain data can not. Consents have been widely modified to reflect this difference. Thus, it would be more informative to know if participants would still consider donating samples knowing that once their samples are sent to analyses that withdrawal of the data generated from those samples is not always possible. The research questions under investigation here are highly embedded in contextual issues so it is critical to describe more about the basis upon which cross-study comparisons can be made.

Response: Under the Survey Design and Analysis subsection of the Methods, we have now included an explanation of how the survey was designed. The survey we developed was meant to cover a general list of topics on biobanking and aimed to capture a range of Canadian stakeholders including the public, patients, and various scholars and professionals (legal scholars, bioethicists, government privacy commissioners and their staff, and scientists). It was developed in consultation with and piloted by the University of Alberta’s Population Research Laboratory. A survey of this sort is the first of its kind to be conducted in Canada where we will compare the opinions of these different groups. For comparison purposes, the surveys disseminated to different groups were nearly identical and written in non-technical language. The survey also meant to capture a general list of topics in order to compare and contrast responses of different groups and our aim here was not to capture any one topic in great depth. Results of these surveys will help inform questions for subsequent qualitative analysis through interviews which are meant to capture the reasons and rationales behind many of the responses found in the quantitative surveys. We are well aware of the practical and legal challenges associated with withdrawal in the context of tissue and biobanking. The goal of this question is simply to explore how, if given the choice, the public feels about the right of withdrawal.

Comment 5: What is the basis for the conclusion on page 11 stating ‘What is interesting is that more patients indicated that they should have the right to withdraw from research when compared to other surveys and this could be partially explained by the high degree of trust they have in doctors, hospitals and university-based researchers and their views on the importance of biobanking research for leukemia’? Was this based on bivariate analyses between trust and the right to withdraw? If so, where is this presented? Also, several comparisons are being drawn in this one sentence which makes it difficult to interpret. Is this a between-survey difference or a statement about the relationship between trust and withdrawal in this survey?

Response: We have modified this sentence in the Conclusion section to reflect that we did not find this association and are speculating that patients may not desire having the right to withdraw because of their high degree of trust in doctors, hospitals and university-based researchers combined with their views on the importance of biobanking research for leukemia. We have also added a reference to
conceptual work that touches on the likely importance of trust to public participation in biobanking research.

**Minor Essential Revisions**

**Comment 6:** The title doesn’t seem to reflect what was actually studied, something like ‘...perceptions about ethical issues associated with biobanking research’ seems more accurate, because this study has not investigated perceptions of biobanking research per se.

**Response:** We have revised the title accordingly.

**Comment 7:** Abstract: What is the distinction between the perception of patients and the perception of the public?

**Response:** We have removed the words “and the public” from the Abstract.

**Comment 8:** Research Setting: The first sentence on page 4 indicates that the patients were randomly recruited, later on the authors explain that patients participant from the Princess Margaret Hospital Hematologica Malignancy Tissue Bank were invited as a convenience sample. Does this mean they were not randomly recruited?

**Response:** The word “randomly” has been deleted. Patients were recruited as they came in for routine treatment at the Princess Margaret Hospital.

**Comment 9:** There is considerable redundancy in the presentation of the results. Most of the findings could be conveyed in the figures and tables without repeating all percentages in the text.

**Response:** We feel that having percentages in both the text and the figures is not considerably redundant and it makes it easier for the reader to separately read the text or view the figures and fully understand and compare the data.

**Comment 10:** Some reorganization is needed. The Results section includes information that is either relevant for the methods or for the discussion. For example, on page 5, the information about why they limited consent models does not belong in the results, likewise, on page 6 the information defining anonymity and de-identification does not belong in Results.

**Response:** We have moved the information regarding limiting consent to three models to the Discussion section on consent. We feel that defining anonymity and de-identification should be in the Results section because these terms are not always clearly understood and are necessary to know in order to understand the data. As the explanation is not a method and placing them in the Discussion section would mean the reader would not know the explanation until the discussion, we have maintained their short description in the Results section.
Comment 11: The presentation of the sample numbers is a bit confusing. Apparently, 100 patients were recruited to the first survey but later it states that the recruited number is 78 and later it states that a response rate of 64.1% is equal to 100. Wouldn’t a response rate of 64% be 64 people? It is not clear who was recruited to the second survey, was it the initial sample or just responders to the 1st survey? Can the authors describe the sample in a more straightforward and clear manner.

Response: In the last paragraph of the subsection Research Setting under the Methods section we wrote: “Most of the 100 patients recruited (n=78) had already agreed for their samples to be deposited in the Princess Margaret Hospital Hematologic Malignancy Tissue Bank (REB 01-0573-C).” This sentence explains that 78 patients had agreed for their samples to be included in the biobank, but not everyone had their samples already deposited in the biobank upon the time the survey was delivered to them. This number has nothing to do with response rate. We have clarified several sentences in the revised manuscript.

At the time of recruitment for the initial survey, patients were also asked if they would agree to participate in a follow-up survey six months later. Of the 72 patients who provided consent to complete a follow-up survey, only 45 patients actually completed and returned the follow-up survey giving a response rate of 62.5%. This has also been clarified in the revised paper.

Comment 12: Page 5 refers to 45 participants who completed both initial and follow-up surveys while Table 1 indicates 43 participants who completed both, and on page 6 it states that 44 participants completed the follow up. The authors should correct or explain, these discrepancies.

Response: Under the Statistical Analysis subsection of the Methods, we have clarified that in order to maintain statistical accuracy, those individuals that made errors and chose more than one response or who left the answer blank were not included in the sample when performing the statistical analysis.

Comment 13: Unanswered questions or multiply answered questions were not counted in the final sample. How much data was lost to this and what is the potential bias? Did particular questions tend to be unanswered?

Response: Incorrectly/unanswered questions tended to be those with multiple parts (i.e., a, b, c, etc.) with each part requiring a single Likert scale response. We suspect that participants misinterpreted the instructions because they only completed one part instead of answering a single response to each part. We have indicated this as a potential source of bias in the Limitations subsection of the Discussion although not many made these types of errors.

Comment 14: The authors indicate that for their comparative analyses that ‘if a question was left unanswered in the follow-up survey, we considered this as a change in response’. What does this mean and how was it scored?

Response: This sentence has been removed.
**Discretionary Revisions**

**Comment 15:** Abstract: The last sentence of the ‘Results’ and ‘Conclusions’ in the Abstract are nearly fully redundant, consider shortening the results.

**Response:** We have shortened the sentence in the Results section of the Abstract.

**Comment 16:** Page 3, the word ‘tenet’ is misused, a tenet is a principle, the collection of biological materials plus other data is not a principle.

**Response:** We have revised this sentence.

**Comment 17:** References 1 and 2 don’t fully capture the substantial investments made, authors should also refer to the pan-European BBMRI.

**Response:** We have added the pan-European BBMRI website as a reference.

**Comment 18:** Page 3, statement that ‘many studies evaluating public and patient perspectives on biobanking’ should be referenced.

**Response:** We have clearly referenced throughout the discussion many of public and patient perspective studies and there are too many to reference in the above sentence where the point is to illustrate that only a few perceptions studies have captured the views of Canadians.

**Reviewer 2**

**Discretionary Revisions**

**Copyediting issues**

**Comment 1:** Generally speaking, when reporting on survey data the term “felt” should not be used. A person feels hot or cold. I would replace the word “felt” with reported, explained, stated, etc. but I will leave this modification to the discretion of the authors.

**Response:** We have removed the word “felt” throughout the text.

**Comment 2:** In some cases you have a comma after the last item in a list and in some cases you do not. Make sure you are consistent.

**Response:** We have corrected this.
Comment 3: Copyediting error “Of the those patients...” in the results: Trust section.

Response: We have corrected this.

Comment 4: Abstract
It is easier to read and understand data if it is presented in order- from high to low or from low to high. The results in your abstract would be easier to understand if you presented them as follows: 59.6%, 30.3%, 10.1%

Response: We have corrected this.

Comment 5: Abstract
When you state the following: “The majority of patients (62.2%) felt they had a right to withdraw their consent, but many changed their mind in the follow-up survey explaining that they should not have the right to withdraw consent.” It would be useful for the reader to know exactly how many changed their minds.

Response: This result is explained within the Results and Discussions sections and we don’t feel it is necessary to also explain in the Abstract.

Comment 6: Abstract
Why are the numbers (percentages) left out of the conclusions paragraph in the abstract?

Response: We didn’t see the need to repeat the exact values again in the Conclusion.

Comment 7: Background
You could also mention Canadian biobanks in your list that appears at the end of the first para since your case study is located in Canada (see for example: http://www.statcan.gc.ca/surveyenquete/household-menages/5071u-eng.htm)

Response: We have indicated this in the Background section and added the reference.

Comment 8: Background
It is very interesting that you surveyed patients twice, once after initial visit and then again after 6 months. Why did you choose the 6 month mark and not a year later for example? Your readers would like to know, especially those who might wish to conduct similar studies in the future.

Response: We felt that 6 months was sufficient time for patients to receive treatment and experience working with physicians that could influence their views on biobanking. We have now indicated this in the text.
**Comment 9: Methods: Research Setting**
You mention the gender ratio in your 2 surveys but what about the other demographics? Were they similar in the first and second surveys?

**Response:** As we had indicated in the limitations section, we didn’t report other demographics of participants in order to maintain patient confidentiality and prevent their identification.

**Comment 10: Methods: Research Setting**
Do you have any idea why some people decided not to participate in your survey? Do you suspect that those who did not participate in the biobank research were less likely overall to participate in all research including your surveys?

**Response:** We did not measure why some patients may have not decided to participate. We have no reason to believe that those that did not participate in our survey did not volunteer to have their samples and health information in the biobank.

**Comment 11: Results: Consent**
Again, it is easier for your reader to understand your data if you present it in order 59.6%, 30.3%, then 10.1%. I am not sure why you are presenting 10.1 before 30.3?

**Response:** We reported the data in order the questions appear in the actual survey. We have now reported them in decreasing order in the manuscript.

**Comment 12: Results: Consent**
When you say “*a significant number of responses changed*” I assume you mean statistically significant yes?

**Response:** Yes the term “significant” is used only to mean statistical significance.

**Comment 13: Results: Consent**
(a) I find the following sentence very hard to follow and would suggest rewording it: “Patients had diverse views with relatively similar numbers when asked whether they would feel bothered by reconsenting;”

(b) I also find this sentence very hard to follow and would suggest rewording: “Similarly, patients presented relatively diverse views, but were more likely to have greater trust in a study if they were allowed to re-consent with approximately 40% either agreeing or strongly agreeing, 26.7% disagreeing or strongly disagreeing, and approximately 33.7% indifferent (χ²=18.651, df=4, p=0.001).”

(c) This passage is also very hard to follow: “When comparing initial and follow-up responses, a slight but significant difference was seen in that a larger proportion of patients had less trust in the study (χ²=44.260, df=25, p=0.01) and fewer felt respected and involved (χ²=41.127, df=25, p=0.022) in follow-up responses (data not shown).”

**Response:** All of these sentences have been fixed.
Comment 14: Results: Withdrawal
Why did they change their views on withdraw in the second survey? How did they come to know about the various consequences associated with the decision to withdraw?

Response: We did not measure in the follow-up survey why participants’ views changed on withdrawal.

Comment 15: Results: Return of Results
In some cases I am finding it hard to figure out if you are referring to results from the first survey or the second survey in this section. Please clarify to help your reader.

Response: We have attempted to clarify this in the revised text. Generally all results focus on the initial survey and only when indicated that we are discussing the results of the follow-up do we mean the follow-up survey.

Comment 16: Results: Public Health Surveillance
Why did they change their minds in the second survey about retuning results?

Response: We did not measure what factors may have influenced patients to change their opinions.

Comment 17: Results: Ownership and Decision-Making
You should clarify in this section who actually owns samples and the role of data stewards.

Response: We are unclear what the reviewer means here. Our questionnaire did not attempt to provide additional detail beyond what is written to explain the role of data stewards or who actually owns samples. It is also unclear why such an explanation would be given in the Results section.

Comment 18: Results: Trust
For those that changed their views in the second survey, please state in the text if these changes are statistically significant for your reader.

Response: We have reported probability values in parentheses or used the word “significant” to denote statistical significance.

Comment 19: Discussion: Consent
When discussing the Netherlands study results, put the results in decreasing order 61%, 56%, 45%, to help your reader understand and follow the results.

Response: We have made this change.
**Comment 20: Discussion: Consent**
Also the results from the Netherland study reveal that 61% indicated that they would like to choose the type of future research, while in the Atlanta, Georgia study, 10% wanted to choose future research options using a checklist. These seem like very different results and not similar at all unless I am reading this incorrectly or missing something. How do these results support your findings? This is not clear to me at all. Please examine this portion of the manuscript again carefully.

**Response:** We are reporting survey data that corroborates our findings and data that differs. We can only speculate why the findings are different. We have now indicated in the Discussion section that only “some” of the studies corroborate our findings and that it is unknown what factors may influence differences in opinions between surveys and that this may be due to the way the questions of surveys are worded.

**Comment 21: Discussion: Consent**
Can you reword this following passage to make it easier to follow? “To deepen our understanding of patient preferences on re-consent, we asked whether patients would feel that it was a waste of time and money, bothered, that they had greater control, that they had more trust in the study, or felt more respected and involved.”

**Response:** We have reworded this sentence.

**Comment 22: Discussion: Consent**
Regarding the last para of the consent discussion-Have you considered that the cancer patients who completed your survey and the Alberta sample are all Canadians and maybe their perceptions are similar because of the perceptions associated with their shared nationality?

Perhaps this explains the difference between their views and the views of U.S. participants? And you do not explain why Albertans have these views. Are they more likely than citizens of other provinces to trust the health care system? Why do the views of Albertans align with those of cancer patients? Unless the views are similar because they are all Canadian? I am not sure how supported your claims are in this section.

**Response:** Our revised manuscript includes a possible explanation to account for the similarities in some of the responses between patients and Albertans due to a shared nationality and trust in the healthcare system.

**Comment 23: Discussion: Withdrawal**
The complexities around the right to withdraw and the impacts that withdrawal would have on tailoring treatment regimens for example, would make an interesting future research study with a patient or lay citizen population.

**Response:** We have included a sentence to explain that additional studies are needed to study the complexities surrounding the right to withdraw.
Comment 24: Discussion: Return of Results
This sentence is hard to read: “Several studies indicate that many participants want to receive results where there are some treatment options and people have less of a desire to know results for either untreatable conditions or where the significance of the finding is not well understood [37-39].”

Response: We have fixed this sentence.

Comment 25: Discussion: Return of Results
I would change this sentence to read “...high desire to know...” instead of “Our results clearly show that cancer patients have a high desire of knowing the results of research.”

Response: We have fixed this sentence.

Comment 26: Discussion: Ownership and Decision Making
In the passage below you say that most participants believed but 29% is not most. I think you mean to say that this was the most common answer yes? “This explanation is supported by the observation that most patients (29.1%) believed that the hospital was the owner of the samples in another study [40].”

Response: Yes the reviewer is correct in our interpretation and we have fixed this sentence.

Comment 27: Discussion: Trust
The last portion of this sentence needs to be reworded: “Doctors, hospitals, and university researchers funded by government were trusted the most by patients and for-profit industry and insurance companies the least, with moderate trust in their provincial government.”

Response: We have fixed this sentence.

Comment 28: Discussion: Trust
You need a reference for the “other studies” mentioned in this comment: “…in general, cancer patients have similar high levels of trust in the organizations seen in other studies.”

Response: We have fixed this sentence and added references.

Comment 29: Limitations
I do not agree with the following statement: “…second limit to quantitative surveys is that deeper penetrating questions cannot be posed and thus we are limited to the information...”. This is not true of all quant research. Your statement is too broad. It is a limitation of this survey study but not all quant studies. Some quant methods do collect reasons.

Response: We have fixed this sentence.
Comment 30: Conclusions
I think you mean to say -with the results of other surveys- in this sentence- yes? “...similarities with other surveys”

Response: We have fixed this sentence.

Comment 31: Conclusions
Be clear about when you are talking about the results of the first survey or the second survey or both in the Conclusions section.

Response: We have fixed this sentence.

Comment 32: Tables and Figures
Table 4-were all these questions posed exactly the same in each survey? If not, that should be mentioned.

Response: Yes, we actually used this question from the other study in our surveys.

For the Tables and Figures, you will want to mention that not all the totals equal 100% due to rounding.

Response: We have indicated this comment in all tables and figures.