Author’s response to reviews

Title: Return of Genetic and Genomic Research Findings: Experience of a Pediatric Biorepository

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Author’s response to reviews:

July 04, 2019
Dear Y-H. Taguchi,

We appreciate your review and comments on the submission of “Return of Genetic and Genomic Research Findings: Experience of a Pediatric Biorepository” and are delighted that the journal is willing to consider a revised version. We have provided detailed responses below to all of the first reviewer’s comments as suggested by you. All changes are highlighted in red in a copy of the resubmission.

Please note that at the time of submission, there were several research results in the process of return or disclosure and the outcome of the process is now known. The return numbers have therefore been updated in the revised manuscript.

Response to Reviewer 1:

Major comments

1. The use of the term "return". At various points the authors interchangeably use the term "return" to refer to the return of results from the biobank to the counselor or physician, and from the counselor or physician to the participant. This creates confusion as a reader. The authors should, at each instance of the use of the word "return", ensure it is clear to the reader to whom the finding is being returned (ie, at which step in the pipeline this is occurring). This includes Figure 2. Perhaps using the word "disclosure" for return at the point of the participant, and "return" for return at the point of the biobank team to the care provider, would improve clarity. Or using "communicated to…” as is done in Figure 2 for this later step, and save "return" to refer to the entire process.

Response: The following modifications have been made throughout the manuscript to make a distinction between the actions being carried out. “Return” has been used to refer to the act of the biobank providing results to either the physician or the research genetic counselor for communication to the patient/participant. The term “disclosure” has been used to reflect the act of communicating the research finding to the patient/participant by the physician or counselor. This modification should provide further clarity to the reader as suggested.

2. Where genetic counselors (GC) are used, and the associated costs. Where the cost finding largely hinges on the use of GCs (funded by research), where genetic counselors are used in the return pipeline needs to be clarified as it is often somewhat confusing. In cases where a research genetic counselor was not used, it was likely that a clinical genetic counselor was involved—the distinction needs to be made throughout. This should also be clarified in Figure 1—as it stands, at some points the figure appears to depict the process when results were returned through a GC and at some points it depicts both through a GC and physician. The figure should depict both entirely or clearly depict the final process (and explain this). With respect to cost, it would be helpful to estimate the
potential clinical cost associated with these results. Where the authors argue it costs more to include a genetic counselor in the return process, without the inclusion of a GC the cost born by the health care system is likely greater (as there may be greater physician or clinical GC burden). So, it's not as simple as one costing more than the other, but where those costs are covered from. With that being said, the primary aims here are research, so the result is still valuable without the clinical estimate, however this limitation should be addressed and the research nature of the GC in this result should be clearly outlined.

Response: The section on “process of return and disclosure of research results” (page 9-10) and its related figure 1 have been modified to detail the role of the genetic counselor as front line research staff in the process of disclosure of findings. Where research findings were disclosed by the participant’s physician, a clinical genetic counselor was involved later in the process if desired by the patient/participant. Estimation of costs incurred once the participant opted for clinical genetic testing or clinical genetic counseling was beyond the scope of our research project and this has been added to the limitations section on page 16, lines 338-340.

3. Secondary findings (SF). Throughout the methods it is unclear/inconsistent as to how SF are handled in the RRR process. At first mention (line 153) it seems that SF in the ACMG59 are reportable. Then in the results section (line 215) it is unclear as to whether you are only returning child onset disorders or child onset disorders AND findings ACMG59 genes. Finally, in the discussion (line 265) it says that SF associated with adult onset disorders were not returned due to ethical concerns. At each of these three instances it is important to clarify how SF are being managed. If it is the case that more SF were given to the RRR committee (ie broader inclusion criteria) and then the narrowed the scope, such as to only adult onset conditions, that needs to be clear. I agree with the authors' handling of these findings, it is just important to clarify for readers who may seek to replicate the process themselves.

Response: Only secondary findings in genes on the ACMG 59 gene list that were associated with childhood disorders were eligible for return. This has been clarified in methods on page 9, lines 174-175.

4. Clinical confirmation vs clinical genetic testing. In the final line of the abstract, and in the paper, you state that "Research findings that were returned had 100% clinical confirmation and 89% participant opt-in for clinical genetic testing and counseling". The distinction between these two things, however, is unclear. Does clinical confirmation happen before or irrespective of the participant's decision to opt in? Is this the confirmation in the research lab? This should be clarified and justified. At some points in the paper it seems you refer to the opt-in clinical genetic testing as "clinical confirmation"—e.g. on Lines 232-233, you say that 89% of families opted for "clinical confirmatory testing", on lines 273 you say "confirmed in an accredited laboratory in patients who opted for confirmatory clinical testing". Furthermore, on Lines 267-268 you say that "all participants…chose to pursue clinical confirmation…". This seems inconsistent with your previous statement of 89%, but may be linked to the "100% clinical confirmation" claim, so could benefit from clarification.
Response: Clinical confirmation of findings happens after findings are disclosed and is dependent on whether a patient opts to pursue further investigation of this finding through clinical genetics which includes repeat testing through a clinically accredited lab. We understand that in certain instances in the manuscript, clinical confirmation rates were reported prior to opt-in rates for testing which might have led to confusion. This has been modified on page 3 (line 57-58), 12 (line 257), 13 (line 285) & 14 (line 293-94).

Minor comments:

1. Comment (Abstract): If unable to estimate clinical costs, final line of results should make sure to clarify that these are research costs and a research genetic counsellor (and don't reflect clinical costs). In the conclusion "returned" means to the participant or their care provider? The difference between clinical confirmation and clinical genetic testing is unclear, and important. This last line is also a result that should be in the results section, not a conclusion.

   Response: It has been clarified that these are costs incurred by the research program and does not include an estimate of clinical costs associated with return (lines 59-60). The term disclosed has been used (instead of return) to refer to findings going back to the participant (lines 50, 54-57, 59). The results have been removed from the conclusion and the distinction between clinical confirmation and testing has been clarified (line 57).

2. Comment (line 79): References somewhat outdated, perhaps look to Thorogood 2019 or other more recent literature to show that there is still a lack of guidance.

   Response: The Thorogood reference has been included as reference #14 on page 5, line 98.

3. Comment (line 86-87): Too many brackets

   Response: Brackets are fixed on page 5, line 105.

4. Comment (line 90): "if the participant was asked and consented to receive" (no obligation to ask, as you indicate)

   Response: This line has been modified to include “was asked” as suggested on page 6 line 108.

5. Comment (line 96): "In this study…” should start a new paragraph.

   Response: Modified as suggested on page 6, line 115.

6. Comment (line 102-103): Should be genetic and genomic results, as per title

   Response: Modified as suggested on page 6, line 121.

7. Comment (line 114-117): Break this into two sentences.
Response: Modified as suggested on page 6, line 135.

8. Comment (line 121-124): Break this into two sentences.

Response: Modified as suggested on page 6, line 142.

9. Comment (line 124, 126): The term "consent" is being used somewhat informally, but holds a lot of meaning in this space. Patients can consent to what they choose. "The consent form required" or "Enrollment required that participants consent to findings being returned…". In line 126, consent wasn't amended, but the consent form or process.

Response: Modified to clarify that the language in the consent form was revised to reflect this change in process on page 7, lines 144-145.

10. Comment (line 150): If findings are not concordant with available clinical phenotype were they not reportable? So does that mean no SF were reportable unless in a cardiac gene?

Response: Only secondary findings in genes included in the ACMG 59 gene list that were associated with childhood onset disorders were eligible for return. This is clarified further on page 9, lines 174-175.

11. Comment (line 151): "(i) the finding was a sequence or copy number variant classified as pathogenic or likely pathogenic…"

Response: Modified as suggested on page 8, line 171.

12. Comment (line 153): incidental ø secondary

Response: Changed “incidental” to “secondary” as suggested on page 8, line 173.

13. Comment (line 154): the 59 genes aren't reportable, but pathogenic or likely pathogenic findings in them

Response: Modified the statement to read “secondary finding in one or more of the 59 genes deemed reportable by the ACMG but only for those associated with a childhood onset disorder” on page 9, line 173-174.

14. Comment (line 155): do you mean confirmatory clinical genetic testing? I suspect so, but this should be made clear, as the reader my interpret it as phenotypic testing (stress testing, etc).

Response: “Clinical genetic testing” has been used in place of “clinical testing” for clarity on page 9 line 176.

15. Comment (line 162): …or SF?
Response: Included the addition of secondary findings (meeting criteria) to the expansion of our guidelines with the increase in exome and genomes sequenced on page 9, line 183.

16. Comment (line 165): when you say "research testing" do you mean non-clinically validated genetic testing? Just say this. Or say "…confirmed as a true positive in a research laboratory"

Response: We have clarified this by stating that the true positive was confirmed through “a research laboratory using a banked research DNA sample” on page 9 line 188.

17. Comment (line 168): This statement (return to a physician) is inconsistent with Figure 1, which says they were returned to a genetic counselor. As alluded to above, I suspect this comes from differences in the pipeline before and after inclusion of a research genetic counselor. Regardless, it needs to be clarified here in the Process section as well as in figure 1. This will also help clarify where genetic counselors are involved (and clarify the costing point).

Response: As explained above in the response to major comment 2, figure 1 has been modified to reflect the individual actions taken after return to a physician versus a research genetic counselor. The section on “process of return” (pages 9-10) has also been modified to clarify this.

18. Comment (line 198-200): An estimate of the clinical costs would be very valuable and add much to this point. However, if that is not possible, there is still value in the research cost comparison—the research nature of these costs must be highlighted throughout and this may need to be included as a limitation (when considering the cost comparison result, as costs likely move into the healthcare system).

Response: We were not able to produce an estimate of clinical costs at this time and therefore have stated this as a limitation in the limitation section on page 16, lines 338-340.

19. Comment (line 205-208): Make this list with colons and semi-colons for clarity "The types of research tests performed included: targeted genotyping, i.e. multiplex ligation probe assay for 7q11.23 deletion (n=31) and 22q11.2 deletion (n=10); genome-wide SNP array (n=564); targeted sequencing for ELN (n=5) and for TBX5 (n=1); exome sequencing (n=619); and, genome sequencing (n=733)."

Response: Modified as suggested above on page 11, line 229-231.

20. Comment (line 208-209): The results that come to the RRR committee are dependent on the criteria of the individual research programs?

Response: The results that come to the RRR committee are not dependent on the criteria of the individual research programs but are dependent on the guidelines developed by the Biobank RRR committee. In the section on “Reporting of research findings to the biobank” (page 8, line 160-161), we have mentioned that any research findings received by the biobank are re-
interpreted by the biobank bioinformatics team to confirm pathogenicity prior to presenting to the RRR committee.


Response: “Variant” has been changed to “finding” as suggested on page 11, line 239.

22. Comment (line 217): If space is needed, Table 1 could be moved to supplemental material, the reported findings are more important for readers and those who care to see the ones that weren't reported can look them up.

Response: We accepted the reviewer’s suggestion and have moved what was Table 1 to supplements (now Supplement 6).

23. Comment (line 222): Introduce Table 2 in this section.

Response: Modified as suggested on page 12, line 246.

24. Comment (line 224): You say that "Figure 2 outlines the outcome after return", but, depending on how you define return, it does not. "Return" in the figure itself refers to disclosure to participants, in which case it does not outline the outcome after return. If you mean return to be communication to the physician or counselor, then it does outline the outcome, but this isn't the terminology you've used in the figure. As discussed above, the use of the word "return" needs to be clarified throughout, and here should say something along the lines of "Figure 2 outlines the outcome following review by the RRR".

Response: Title of figure 2 has been modified to “Outcome following review by the Return of Results Committee”. This figure 2 has also been modified to include information not only on review and return but also on outcomes after disclosure to participants.

25. Comment (line 224-231): All of these numbers are clearly reported in Figure 2, if space is limited, it may not be necessary to detail them twice.

Response: We have chosen to leave the description of findings in here as space seems to permit.

26. Comment (line 227-228): Why were 4 findings not returned? Was this a decision made by the physician? This would be useful for readers.

Response: The reason for not returning has been added to the manuscript on page 12, line 252-254.

27. Comment (line 232-233): As discussed above, you say that 89% of families opted for clinical confirmatory testing, yet in the abstract (and later in results) you say that "100% had clinical confirmation and 89% opt-in". It is essential that you clarify what you mean
by clinical confirmatory testing, because the difference between clinical confirmatory
testing and testing following opt-in is unclear.

Response: Opt-in for clinical genetic testing happens prior to clinical confirmation. The sequence
by which these occur has been modified throughout the manuscript for clarity. The proportion of
families who opted for clinical genetic testing and counseling is now 86% after updating pending
results.

28. Comment (line 235): For consistency put the percentage in brackets, ie. "Of the 9 results
received by participants, 8 families (89%)…"

Response: Modified as suggested on page 12, line 257.

29. Comment (line 253-254): As discussed above, please clarify what you mean by with and
without a genetic counselor. Does "with" mean from coordinator to genetic counselor to
participant, but "without" mean from coordinator to physician (with the expectation that
disclosure continues from there)? Clarify here and in Figure.

Response: We have clarified that with a genetic counselor refers to a research genetic counselor
(line 254) who would be involved in disclosing the findings directly to the participant contrary to
when findings are returned to the primary care physician for disclosure to their patient.

30. Comment (line 258): You can't necessarily draw this conclusion from the fact that opt-in
was high. Certainly participants see the importance of following these things through,
but, from the numbers alone, that doesn't mean they were well-received (although they
may have been).

Response: We have used the term “high uptake” in place of “well received” on page 13, line 284.

31. Comment (line 264-264): Clarity is needed around SF, as discussed above.

Response: Clarity surrounding secondary findings has been modified in our criteria for return on
page 9, line 174.

32. Comment (line 267): As discussed above, clarity is needed around "clinical confirmation"
as this seems inconsistent with the 8/9 figure reported.

Response: This sentence has been modified to read “The majority of participants in whom results
were disclosed chose to be referred to clinical genetics to pursue clinical confirmation of
findings…” on page 14, line 293-294.

33. Comment (line 269): If not 100%, is it still true that there was no difference between the
groups. Regardless, the numbers are small, so it's likely not significantly different.

Response: As several of the outcomes from returned findings that were “in progress” at the time
of the original submission are now known, these have been updated in this resubmission.
Consequently, there is now a difference in acceptance rate for clinical genetics referral between the communicators (100% for physician’s vs 71% for genetic counselor). This has been added to the results (page 12, lines 257-258) and discussion (page 14, lines 296-297) section.

34. Comment (line 271-273): This is methods and should be earlier, and expanded to clarify the clinical confirmatory testing piece, as discussed above.

Response: This sentence has been removed from the discussion and is explained in the methods on page 10.

35. Comment (line 281): Great point—there is some literature around discomfort in genetics among non-genetic professionals that could be worthwhile citing here (eg. Christensen 2016).

Response: This suggested paper has been cited in reference #33 on page 14, line 303.

36. Comment (lines 299-302): Important to clarify that these costs are to the research team/program, and not overall.

Response: We have clarified that the genetic counselor was employed by the research team to clarify that these are costs to the research program on page 14, line 303.

37. Comment (line 318): Add a comment around inability to estimate total costs if that is the case.

Response: This has been added to the limitations section on page 16, line 338-340.

38. Comment (line 321): "...genomics and biobanking supported projects where return of actionable results is expected should include the option of return of results and future re-contact in the informed consent form..." Did you find this in your paper? This seems unrelated to the results presented—the paper relies justification RRR and re-contact, and doesn't make a case for it on its own. Perhaps this could be added earlier in the paper, if it were a part of the discussions and experiences of the repository, but here is a conclusion unlinked to the paper's results. I would remove from the conclusion and focus on the experiences of the group.

Response: The statement mentioned above by the reviewer was removed from the conclusion on page 16.

39. Comment (line 324-326): The comment on streamlining using technology is a Discussion point, and not one for the conclusion.

Response: This statement has been moved from the conclusion and incorporated into the discussion on page 15, lines 313-314.
40. Comment (Figure 1): This figure needs to be clarified. It should either demonstrate both forms of the pipeline (with and without a genetic counselor) or only one, and be clear about that. "Pathogenic" --&gt; "Pathogenic or likely pathogenic"? If it is the case that the difference between the two forms of the pipeline is in the final wide box (physician or research genetic counselor) that is not clear elsewhere in the paper, particularly where a genetic counsellor is involved upstream in both cases.

Response: Figure 1 has been modified to demonstrate both pathways when returning to the physician versus research genetic counselor. “Likely pathogenic” has been added to the figure.

41. Comment (Figure 2): You could add a box below the reportable results to indicate how many of the disclosed findings were clinically confirmed. Perhaps move 5 Returned and 4 Returned to the bottom and then connect them to a wider box outlined what happened downstream (to further clarify your results).

Response: Figure 2 has been modified as suggested.