Reviewer’s report

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

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Reviewer: Michael P. Mackley

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Title: Return of genetic and genomic research findings: experience of a pediatric biorepository

Experiences, such as those presented in this paper, are important to publish. Other groups aiming to achieve similar goals can look to the experiences of groups such as this one to inform their own decision-making around protocols and consent process. Furthermore, this particular paper is comprehensive in its depiction of return of results from a biorepository, and contributes to the literature a cardiac focus—something that is lacking in crowded by cancers and rare diseases, but becoming increasingly important and actionable. For these reasons, I believe this manuscript will make a valuable contribution to the wider literature and recommend that this paper be accepted for publication with essential minor revisions.

In general, I believe that 4 areas are in need clarification or elaboration by the authors:

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.

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.

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 AMCG59 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.

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.

Minor comments, including elaboration on the above areas at specific points, are outlined by line-number below:

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.

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.
Line 86-87: Too many brackets

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

Line 96: "In this study…" should start a new paragraph.

Line 102-103: Should be genetic and genomic results, as per title

Line 114-117: Break this into two sentences.

Line 121-124: Break this into two sentences.

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.

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?

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

Line 153: incidental ◊ secondary

Line 154: the 59 genes aren't reportable, but pathogenic or likely pathogenic findings in them

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

Line 162: …or SF?

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"

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).

Line 198-200: An estimate 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).

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)."

Line 208-209: The results that come to the RRR committee are dependent on the criteria of the individual research programs?

Lines 214-215: "secondary variant"  "secondary finding", for consistency. See above for comments on secondary findings, broadly.

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.

Line 222: Introduce Table 2 in this section.

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".

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.

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

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.

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

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 counsellor to participant, but "without"
mean from coordinator to physician (with the expectation that disclosure continues from there)? Clarify here and in Figure.

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).

Line 264-264: Clarity is needed around SF, as discussed above.

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

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.

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

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).

Lines 299-302: Important to clarify that these costs are to the research team/program, and not overall.

Line 318: Add a comment around inability to estimate total costs if that is the case.

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.

Line 324-326: The comment on streamlining using technology is a Discussion point, and not one for the conclusion.

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.

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).

Overall, I feel this paper adds to the growing literature on experience dealing with genetic and genomic results in a novel setting. It was a pleasure to review.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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