Author's response to reviews

Title: Approaches to Informed Consent for Hypothesis-Testing and Hypothesis-Generating Clinical Genomics Research

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Author's response to reviews: see over
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Tim Sands, Ph.D.
Executive Editor, BMC Medical Genomics

Re: Revisions to MS: 8197585546313566 - Approaches to Informed Consent for Hypothesis-Testing and Hypothesis-Generating Clinical Genomics Research

Dear Dr. Sands,

We are grateful to the Reviewer and the Editorial Board for their insightful comments regarding the above-mentioned manuscript. We have addressed each comment below and revised the manuscript accordingly (comments have been appended and are bolded; responses appear below each comment).

Reviewer 1’s Comments Requiring a Response:
Since consent nomenclature is already extensive and confusing (implicit, implied, informed, broad, generic, blanket, bridging, etc.), will this paper clarify or complicate the debate?

We believe that this work will help clinical researchers struggling with these issues by delineating approaches to informed consent that are shaped by the fundamental research questions under investigation (i.e., hypothesis-testing vs. hypothesis-generating research). Our intention is to outline practical elements of the informed consent process in order to clarify the debate and move it to a more concrete realm.

Have the authors considered the professional liability related to their new approach? Since the information is available, what if the researcher does not look at the “problematic part” of the genome? What if there is no specific test available in CLIA-certified laboratories?

The Reviewer’s point about professional liability is interesting and something we have considered extensively while shaping our approaches to informed consent. As we discuss throughout the manuscript, whole genome sequencing has the potential to yield vast numbers of individual genetic variants for each participant. Although professional liability is an important consideration for both clinicians and researchers, specific discussion of this issue was not our intent with this manuscript. As we mention in Issue #5 specifically, and throughout the work generally, clear communication of researcher and participant expectations and obligations works both to enhance understanding and, by extension, can be argued to protect clinical researchers from a liability perspective.

Regarding the return of results, which results will be returned to participants? Will negative results be returned? It is also mentioned that only clinically significant
results will be returned. Will these results be returned even if not actionable?

The Reviewer raises a few specific questions regarding the type of information returned that require clarification. First, in most instances we would not return negative results to research participants. Text has been added under Issue #3, first paragraph, to make that clear. There could be situations in the hypothesis-testing protocol that would warrant the confirmation of a negative result in a CLIA-certified laboratory, but that would not be different from current disease-specific protocols. Secondly, we envision that most results returned would be clinically actionable. To address this we have changed the terminology used in the paper from “clinically significant” to “clinically actionable”. Of note, our approaches to the return of individual genotype results, how we prospectively categorize them for participants, and the choices participants can make are covered in detail in the discussions of Issues #1-4.

Have the authors considered the feasibility of their new approach? Since genetic research often requires large cohorts (ex. populational studies) and longitudinal studies, is it realistic to expect individual re-contact and re-consent, and individual genetic counseling? Has the authors considered the additional cost of re-testing in CLIA-certified laboratories, individual re-contact and re-consent, and individual genetic counseling?

We recognize that the approaches we describe are not relevant to all research studies utilizing MPS, and we emphasize in the last sentence under “General Issues Regarding Return of Results” that the discussion in the paper is relevant only to protocols that plan to return results to participants. Of note, the approaches we describe are actively in use in our protocols and as such, we hope that this provides some concrete guidance for others considering a similar approach from a feasibility perspective. We believe that studies that intend to return results should consider costs associated with CLIA testing and genetic counseling at the outset.

Comments from Editorial Board:
This paper describes an interesting dilemma. It is well written and provides some useful insight into a particular method and thoughtful analysis throughout. I also like the structure of the paper. However, it needs to be supported by more literature/policies/laws, etc. For example, in some sections they seem to be arguing for open consent (a controversial topic) because of the massive amount of information and the unknown of the future research. These arguments have been made in other contexts (biobanking, whole genome research etc). They need to refer to the debate and support their suggested approach.

Intro: More citations on nature of consent/ethics controversies
P 4: The authors make statements about research ethics norms (and I think they are correct). They should reference relevant literature and policies. They touch on the notion of “open ended” (e.g., p 4: “...their genomes in an open-ended fashion, that the goal of the experiment is not predictable at the outset, and that the participant will be presented with downstream situations that are not
currently foreseeable”) consent. This is a hugely controversial and unresolved issue. At a minimum they should reference literature supporting or noting debate.

We thank the Editorial Board for the kind comments. We have added more discussion of existing controversies in the field along with relevant citations to the “General Issues Regarding Return of Results” section (see further comments below), and a few additional references to the “Introduction”. A total of 12 new references have been added to the manuscript.

Page 5, who deems “to be medically actionable”? How can you make an assumption of an “alignment between participants’ goals and the researchers’ aims with respect to primary variants?” There could be therapeutic misconception, the research participants could expect something in return (which isn’t appropriate under some guidelines), the researchers are striving to advance knowledge (incrementally) while participants may assume it is breakthrough research, etc. Please explain and support.

This is a significant issue and both protocols have as one of their goals to investigate participants’ intentions to receive different types of results. In response to the editorial board’s comments, we have revised the language on page 5 and emphasized the ongoing research to assess participants’ intentions. We have also summarized the findings of a recently published paper on this topic under the “Discussion”, page 22.

P. 7, “subjects must be consented initially to the open-ended nature of the project.” Again, this is highly controversial. Some scholars (and some ethics policies) do not think that open ended consent is appropriate. Yes, there are many researchers that have adopted this approach (especially in the context of biobanks), but it is not a resolved dilemma. At a minimum, the authors need to reference some of the (vast) literature on point.

We appreciate the Editorial Board’s point and wholeheartedly agree with the idea that no clear consensus exists with respect to communicating the complexities and nuances of downstream and ongoing use of data generated in next-generation sequencing protocols to participants. Although the comment is directed to the discussion on page 7 (Issue #1: Primary and Secondary Results…) we have added more discussion of this issue to the preceding section of the manuscript (General Issues Regarding Return of Results) because our intent is to describe a number of issues and how we have managed these concerns in a specific way in our protocols in particular. On page 7, we make the argument that participants must be informed of the open-ended nature of our hypothesis-generating study precisely because this protocol was designed to be a continuously evolving exploration of the use of MPS.

Summary: “The informed consent process is both the window through which research participants assess the goals and plans of researchers, and the lens through which the research team focus their goals of advancing biomedical knowledge.” Not
sure this is entirely true. In most jurisdictions, the standard of informed consent is entirely driven by the needs of the participant, not the researchers. While I am sure this is what the authors meant, it comes across in an awkward manner. Can’t unilaterally alter existing consent norms, as implied (again, this may not be the intention).

We thank the Editorial Board for this critique and have altered this sentence significantly. It now reads: “We describe an approach to the informed consent process as a mutual opportunity for researchers and participants to assess one another’s goals in MPS protocols that employ both hypothesis-generating and hypothesis-testing methodologies.”

We sincerely appreciate the comments of the Reviewer and the Editorial Board. Thank you again for consideration of this manuscript, and we look forward to hearing back from you.