Author's response to reviews

Title: Genotype-Driven Recruitment: A strategy whose time has come?

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Author's response to reviews:

Re: Submission of our revised version of the manuscript “Genotype-Driven Recruitment: A strategy whose time has come?”

Please find attached a new version of our manuscript “Genotype-Driven Recruitment: A strategy whose time has come?” that we have revised considerably in response to the comments from the reviewers. We would like to thank the reviewers for their thoughtful comments and believe that the revision paper is strengthened by addressing their concerns. Below please find below our point-by-point response to the reviewer comments.

Comments from referee 1

Minor essential revisions

1. I am very familiar with several of the articles cited, either because I am a co-author on the article or a colleague on the research study. I think this paper would be strengthened with a bit more careful review of references cited. For example, the first sentence of the section, "Potential future uses of GDR" includes two citations. I think the authors could safely add references 16, 17, 18, and possibly 2. Given the small amount of empirical work that has been done on this subject, I would recommend that the authors make sure that for each point they make (including those in Table 1) they cite all of the appropriate references.

We conducted an expanded literature search using both Pubmed and Google Scholar to make sure that we had captured all appropriate references. Articles which specifically discussed or mentioned the ethical aspects of GDR were selected from the search results. The entire paper was reviewed (including Table 1) to check that the appropriate works, including those that the reviewer points out, are properly referenced.

2. The last sentence of the Summary is incorrect and out of place given the focus of the paper. Many of the studies cited in the bibliography are empirical studies of recruiting individuals into GDR studies. Also, at least two of them (16 and 17)
report on the differences in recruiting both healthy and non-healthy volunteers.

The sentence was removed from the text and the Summary replaced by a “Conclusion and future considerations” section.

Discretionary revisions

1. In the middle of the section "Potential future uses of GDR," the authors write "stored as data in non-clinical biobank collections." It's unclear what they mean by a "non-clinical" collection; more specifically, it's unclear to me exactly what a "clinical" collection might be—one created from “leftover” clinical samples? Can this be described slightly differently?

The term “non-clinical collection” was removed from this section and the text was further developed to explain the types of studies we were referring to and why we think that the use of GDR may expand to new areas.

2. I was a bit taken aback by the fact that the Results section is only 1 paragraph. Can the authors beef up this section a bit? I appreciate that much of the results are portrayed in Table 1, but it still seems thin.

The results section has been developed in more depth to describe 1) ethical issues in GDR identified from the literature and 2) the already published recommendations made in the literature to address these issues. In addition, a third sub-section was added to the Results section to describe the results from our conceptual analysis and the reasons why we think that the recommendations may or may not suffice under a broader utilization of GDR. Some of these points had previously been reported under the Discussion section, which is now shortened.

3. The last paragraph of the Discussion (beginning "These issues cannot..." is vague and weak.

This sentence was moved under the “Conclusion and Future Considerations” section and further qualified in the next sentences which describe strategies that should be developed further.

Comments from referee 2

Major compulsory revisions

1) The background section would benefit from an explanation distinguishing GDR and phenotype driven recruitment. Not all of the readers will know about this difference.

For simplification, we removed the term “phenotype” from our paper and chose to provide in the introduction concrete examples of the difference between GDR and studies that recruit based on other types of information, e.g. the presence of a given disease.

2) The Potential future uses of GDR section can benefit from further discussion on how genetic information from individuals through DTC genetic testing or from
medical diagnosis will be obtained by researchers who will then contact individuals. The entire premise of the arguments put forward by the authors hinges upon this scenario being a reality. Yet there is limited discussion on whether this actually could or would be done. For example, is it common practice for DTC genetic testing companies to share private customer information with other researchers or pool it in common databases? Similarly, if whole populations would be screened, “both healthy and sick individuals,” why would this information be so freely available to researchers? If someone receives a genetic test for medical reasons, how would this information be available or shared with researchers? I think this discussion needs to talk about the feasibility that genotypic information will be available to researchers. Is this being currently done? What are the privacy measures in place? Without a thorough discussion, I am not likely to believe that the scenario the authors propose will be a reality and if so, the arguments they put after do not rest on solid footing.

This section was further developed to explain the importance of Precision Medicine as described by the National Academies of Science. This approach will develop a molecular taxonomy of disease whereby the ability to select on genotypes will figure prominently. We describe different sources through which genetic data could become available to researchers who want to conduct GDR studies. First, we describe in more detail the development of national projects which plan to sequence whole populations with the objective to provide better health care and create research resources. These projects plan to generate large genetic datasets that may be made accessible to researchers through data access applications. We provide additional references to articles in the scientific press and presentations from the projects which describe data sharing plans. Second, we explain in more details why genetic datasets produced by DTC genetic testing companies could be shared with third parties or sold to research groups. There are already calls for research collaboration between 23andMe where they describe possibilities for studies that rely on GDR. We also refer to relevant articles in the scientific press and reports from academic institutions which explain that DTC genetic testing companies may give greater priority to selling DTC customer data to commercial entities to increase their return on investment. As a note, our paper does not cover an all-inclusive coverage of the potential routes by which GDR may grow, individuals themselves can make their genotypes available; as witnessed by the initiatives in the Genetic Alliance and rare disease community where patients themselves want their genotypes included in research aimed at elucidating how specific variants can be targeted to understand disease etiology and treatment.

3) This research begins by systematically identifying the available literature on GDR by performing keyword searches on PubMed prior to performing a conceptual analysis of the ethical issues and the recommendations written in the articles they collected. Although I have recommended four additional aspects to include in their search methods below, I do not think the authors need to be so specific in their search methods for a conceptual paper as it is currently written. The paper is about analyzing recommendations on GDR and arguing that they do not adequately cover cases when GDR research may be performed in cases
where individuals are recruited as non-research subjects. The purpose of the paper is not to conduct a systematic review of the arguments (e.g., see the methods proposed for such activities in papers by Daniel Strech Neema Sofaer in the J Med Ethics 2012 and Bioethics 2012). My suggestion is to either address the four points below, or write the search methodology more generally saying that a literature search on the topic was performed.

We chose to follow the suggestion from the reviewer and decided not to describe the search method for our literature review in too much detail. We conducted an expanded literature search using both Pubmed and Google Scholar to make sure that we had captured all appropriate references and included in our reference list a few articles that had not been referenced in the first version of our paper (e.g. paper by Jill Oliver and Amy McGuire, Genome Medicine, 2011).

4) The first argument made in the Discussion section (pages 6-7) needs further substantiation. I am not convinced that because there is no informed consent previously obtained will amplify ethical concerns of “unnecessary distress and anxiety among individuals.” From my understanding, there is very little empirical evidence suggesting that consumer knowledge of the results of genetic testing causes distress and anxiety. Empirical research on this should be referenced. If this is the case, then why would the authors believe that this low level of distress and anxiety would be “amplified” in their proposed scenario? Although this point is somewhat mentioned in the second argument at the end of page 7-beginning page 8, I would like to see the authors further flesh out this argument by discussing what evidence is out there, and perhaps despite the lack of evidence of distress and anxiety caused by an individual’s knowledge of their genetic information, why the authors believe this concern will be amplified if informed consent was never obtained.

The three main arguments in the Discussion section have been significantly re-worked and moved to the Results section (sub-section: Do the recommendations suffice under a broader use of GDR?) as they are used to explain why we think that current recommendations would not suffice in a context of broader use of GDR. In this new sub-section, we provide three main arguments as follows: the recommendations may not suffice in a context of broader use of GDR because: 1) The individuals invited to enroll an original GDR study may not be prepared to receive such an invitation; 2) The individuals invited to enroll in an original GDR study may not be prepared to receive own genetic research results; and 3) The establishment of independent governance bodies to coordinate all GDR research projects may be too challenging.

In our revised version of the paper, what was previously our first argument is now split between argument 1 and argument 2. We explain under argument 1 that GDR recruitment of individuals who do not have previous experience from research or a relationship with the researchers may potentially be problematic because these individuals have not been prepared to receive such an invitation. The same applies to the disclosure of research results to the individuals enrolled. We explain that although recent empirical studies show that such disclosure normally does not trigger any particular distress or anxiety, the results from these
studies may not be transferrable to the context of original GDR studies. The individuals who have participated in the referenced empirical studies already had a relationship with researchers or were aware of the presence of a genetic variant in their family while this may not be the case for individuals recruited in original GDR studies through e.g. their health care system or directly by a private company. There is per today’s date no empirical evidence on the effects of receiving genetic results without having been prepared to it.

5) The third argument made in the Discussion section (page 8) does not add any really new insight beyond the point that greater integration and coordination is needed if an independent body is to manage data access requests. The same model can be used, but it now has to possibly consider data and information about individuals collected from population wide genomic screening, DTC information, and other sources. Stating that a greater degree of integration and coordination is needed is minimal and does not really deepen our understanding of the problem presented. Can the authors comment on how this could be handled, would it be feasible for an independent body to handle such additional information, what policy mechanism might be needed e.g., legislation requiring DTC and other private companies or medical organizations to provide information to the independent body.

We developed the third argument further to explain that the establishment of independent governance bodies to coordinate all GDR research projects may be too challenging and this for two main reasons. First, it may be difficult for these independent bodies to have a legal authority over both publicly-funded research projects and private companies because they evolve in different legal landscapes. We refer to articles in the scientific press and reports from academic institutions which support our argument. Second, it may be difficult for these independent bodies to have a scientific authority over a variety of publicly-funded research projects and private companies as it would require an extreme level of coordination. We provide concrete examples to illustrate how difficult such coordination may be.

Minor essential revisions

6) The Results written on page 5 only partially correspond to Table 1. Not all the results summarized in Table 1 are written in the text, only a few highlights seem to be included. Perhaps the last sentence explaining that an overview of ethical concerns in Table 1 should be the first sentence in the paragraph along with a sentence explaining that the authors are only highlighting some of the concerns in the text.

As explained earlier, the results section was significantly developed to capture main findings and include the results from our conceptual analysis. Reference to Table 1 was moved to the first paragraph of the Results section.

7) On page 9, the word “an” should be placed before “individual” in issue number 3.
This is done.