Author's response to reviews

Title: Use of Next Generation Sequencing Technologies in Research and Beyond: are participants with mental health disorders fully protected?

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Author's response to reviews: see over
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BMC Medical Ethics
Prof. Akira Akabayashi, Editor

Re: Editorial submission “Use of Next Generation Sequencing Technologies in Research and Beyond: are participants with mental health disorders fully protected?” MS: 4554642747182471

Dear Professor Akabayashi,

We considered Reviewers 1’s and 2’s comments and made changes accordingly in the manuscript. These new changes are listed on a point-by-point format in the pages that follow this letter.

Attached please find our revised manuscript.

We hope that our response and amendments we have brought to our previous version meet with your approval and that you find the revised manuscript acceptable for publication.

Thanking you in advance for your consideration, we look forward to hearing from you.

With kind regards,

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Reviewer 1’s comment

A. Major compulsory revisions:

The instructions to the reviewers specify attention to the language of the report. I suggest that this report requires extensive revision with emphasis on the English of the report. One practical suggestion to the authors is to use short sentences. Each sentence should contain a single message. For example, the last sentence of the Introduction can easily be split in three sentences.

Authors’ response

The manuscript language has been thoroughly revised. The last sentence of the Introduction now reads: “This article provides a review of the application of NGS to complex traits and its challenges with BD. We discuss the social and ethical implications of the use of NGS in research from the perspective of protecting participants in genetic research protocols directed to subjects with BD. Our approach covers both research and emergent clinical settings requiring special attention.”

B. Minor essential revisions

Spelling, agreement of verbs and subjects, etc

(1) Section "NGS in Research Applied to Complex Traits", line 13 from top, change "...a genetically predispose condition... to "...a condition with a geneticy predisposition..."

Authors’ response

The sentence has been changed for the following: “Some genetic variants will be absent or underrepresented using this approach, since approximately 15% of patients with a genetically predisposed condition do not have coding sequence mutations.”

(2) Section "Behind Results Diversity of PD"

(a) Change the title

(b) Next to last line: change "...bases..." to "...basis..."

Authors’ response

(a) The title now reads: “Reasons for diversity”
(b) It now reads “basis”

(3) Section ”Disease Phenotype”
(a) Line 4 from top, change "...incline..." to "...inclined..."
(b) Line 6 from top, ommit "(Uhl, 2008)"
(c) Line 11 from top, and in several other sites in the text, change "...ethnical..." to "...ethnic..."

Authors’ response
(a) It now reads “inclined”
(b) (Uhl, 2008) is not in the text
(c) The word “ethnical” has been changed to “ethnic”

(4) Section ”Social and Ethical Implications of NGS Consent"
(a) Make several paragraphs
(b) Line 21 from top, correct ”Concent process requires to consider...” (Does it mean ”The concent process is required to consider...”?)
(c) Line 28 from top, correct ”or misused of results..."

Authors’ response
(a) The section has been divided and paragraphs are now separated
(b) This section was changed and the sentence removed

(5) Section ”Feedback, Return (?) of Results and Incidental Findings”
(a) Line 3 from top, ommit ”it"

Authors’ response
(a) The word “it” was removed

(6) Section ”Informed decision making and autonomy"
(a) Second paragraph, first line, change ”...there is also feasible...” to ”...it is also feasible..."
(b) Second paragraph, line 4 from top, change ”would not only allows the
finding..." to "would allow not only the discovery..."

Authors' response

(a) This sentence has been deleted
(b) This sentence has been deleted

(7) Section "Clinically relevant ethical challenges"
(a) Make additional paragraphs
(b) Line 4 from top, change "helping discerning a great amount..." to "helping to
differentiate a large number..."
(c) Next page (to the page containing the title of the section), line 5 from the
bottom, change "genetic diagnosis" to genetic diagnoses"
(d) Third page, line 6 from top, correct "privative" ("limited")?
(e) Correct the sentence "It becomes also clear...same time research participants
[32]" in lines 25-28 from the top of the same page
(f) Same page, lines 36-41 from top, the sentence needs to be completely changed. This
sentence is one example where creation of several sentences will help the clarity of the text.

Authors’ response

(a) The section has additional separated paragraphs
(b) This sentence has been deleted
(c) The term "genetic diagnosis" or “genetic diagnoses” are no longer in the text
(d) The term “privative” has been removed
(e) The sentence “It becomes also clear...same time research participants” has been deleted
(f) The sentence now reads: “The latter situation resembles the circumstances that
increasingly surround countless medical conditions with an already “known” genetic
background. This circumstance intensifies when – as in many psychiatric disorders –
there is no precise knowledge of the underlying causes of the disease, either genetic
or functional.”

(C) Discretionary Revisions

I have two suggestions to assist the reviewers of a revision:
(a) Double the space between lines

(b) Number the pages of the manuscript

Authors’ response

Pages are numbered and text is double-spaced
Reviewer 2’s comment #1: Major compulsory revision

- As said above, I think this manuscript could be greatly improved when the authors would focus on what they promise to be the subject of this review: NGS for mental disorders. What are the specific challenges of NGS for this group of participants/patients? In the current version the authors give a too general discussion of the ELSI aspects of NGS technology (which has already been done elsewhere). An explanation of the specific challenges for this group would be the real added value of this manuscript. For example, participants with bipolar disorders are usually considered vulnerable. There has been debate on who should be considered ‘vulnerable’ in research and for what reason, but the potential diminished capacity to consent and the context of being for example institutionalized are generally considered as inferring a need for special protection in medical research. Psychiatric patients are considered to be “cognitively vulnerable” – there is plenty of literature demonstrating that “mental incapacity to make decisions on treatment is common in people admitted to psychiatric wards”, This is a theme the authors could further explore. I enclosed one of our papers (van der Baan et al, in press) that discusses consent in psychiatric biobanks – the topic and references may be useful.

Authors’ response:

Several new paragraphs were added along the manuscript to explain the specific challenges presented by the use of NGS technologies in research and in clinical practice for mental health and in particular for BD research participants and patients. We are also commenting on and presenting new references specific to the subjects of vulnerability and autonomy related to mental health and BD.

An abbreviated list of the new material containing the corresponding sections and paragraphs follows. We thank Dr. Bredenoord for providing her manuscript (van der Baan et al, 2012) and suggesting using the associated references. Please, note there are also new bibliographic references related to BD and cognition impairment.

Introduction:

3rd paragraph: “Given the important social and economic burden of BD throughout the world, finding factors...”

Social and ethical implications of NGS:
Consent

2nd paragraph: “In terms of capacity to comprehend the subject that prompts... In which case patients experiencing a highly diminished capacity to consent [26] could be asked to understand and decide on the implications of current genetic research technology.”

3rd paragraph: “Distinct protective measures should be put in place for any consent process involving NGS technologies and BD... to safeguard individual autonomy and maintain the integrity of research projects.”

Risk to participants

2nd paragraph (end): “Receiving results indicating a predisposition for a psychiatric disorder could initiate the expression of first symptoms [28], or could well affect self-image, increase anxiety or induce depression[28, 30].”

Feedback, return of results and incidental findings

2nd paragraph (middle): “Age of onset, available therapies and preventive treatments for a given health... three factors are not clearly defined at time of sharing results [28].”

4th paragraph: “In Misra et al, BD patients were questioned... population if not accompanied with adequate education and counselling.”

9th paragraph (middle): the following was added “Previous reports indicate that individuals with mental disorders and their immediate relatives are more prone...”

Informed decision making and autonomy

1st paragraph (end): “While P. Bielbi explained that the consent process must not...”

2nd paragraph (end): “As previously discussed [39], competence to consent to participate in research implies...”

Clinically relevant ethical challenges

3rd paragraph: “There are expected benefits associated with the use of...”

4th paragraph: “Initial symptoms of BD may appear as early as mid-adolescence...”

6th paragraph: “Two major ethical concerns arise from the use...”

Minor essential revisions

1st:
- In each paragraph, the authors discuss a relevant issue but the different paragraphs are lacking some focus—it’s a bit of a blur of information. For example, the Consent paragraph provides the reader with a large amount of information not only related to consent (for example on data sharing and confidentiality). Why do you not discuss those issues in a separate paragraph? In addition, it remains unclear what exactly is the main ethical challenge of Consent in NGS for BD. What makes consent issues in BD research different from other NGS studies? A short summary finalizing each paragraph may be helpful here.

Authors’ response:

The Consent section is now divided into three segments: Consent, Risks to participants and Protecting participants. We believe that the separation of these subjects as suggested by the reviewer gives more focus on each topic.

The following was added to the Consent section:

1st paragraph (end): “… and lower income – the latter a potential consequence for individuals living with mental health disorders [20] –…”

2nd paragraph: “In terms of the capacity to comprehend the issue… could be asked to understand and decide on the implications of current genetic research technology.”

3rd paragraph: “Distinct protective measures should be put in place for any consent… and participants’ decision-making capacity.”

4th paragraph: “As discussed by… of research projects.”

2nd:

- Throughout the manuscript it is sometimes not clear whether the authors give an overview of the debate or whether they express their own opinion.

Authors’ response:

To help discriminate the source of information and opinions we added the following expressions through the paper: “as reviewed by”, “As discussed by” (Consent section); “We agree with other commentators” (Protecting participants); “For instance, using these parameters, Bunnik et al”, “In Misra et al,” (Feedback section); “we believe the process of”, “we infer that” (Clinical relevant ethical challenges section).
3rd:
- Regarding the methods: could the authors give a motivation / explain how they came to selection of those 6 issues and why they chose to focus on NGS for BD in particular?

Authors’ response:
Responding on our motivation to this manuscript’s subject, the following paragraph was added to the introduction:
3rd paragraph: “Given the important social and economic burden of BD throughout the world…”
To explain how we selected the subjects and papers, the new Methods section now starts: “In order to determine the social and ethical issues currently reviewed…”. We removed information about other subjects encountered in the literature and focused on NGS and mental health, in particular BD. The paragraph now concludes “A total of 217 studies were relevant for our project and constituted the sample upon which we performed a detailed analysis of the ethical issues raised by NGS when it is applied to mental disorders, and in particular to BD.”

4th:
- The genetic background information is useful but quite extensive – perhaps too extensive for an ethics journal?

Authors’ response:
The following paragraph was removed from the section “Behind results diversity of BD”: “Natural cellular activity is kept by networks of proteins that interact ...between genotype and phenotype are many times missed, and so are clinically useful results derived from genetic studies[14].”
In addition, the following was removed from the Feedback section “It was proposed that the decision of which results are returned be based on the expected type of outcome of a given technique, for instance “genome-wide association studies (GWAS) findings...”
We agree that the explanation on the importance of genetic and biological diverse background of BD should remain clear. Discussing the relationship between type of genomic study and nature of mutations linked to return of results to BD patients may
deserve further discussion in a different context.

5th:
- Please check the entire text for typos and incorrect sentences.

Authors’ response:
The text was revised to ensure proper language.

6th:
Under Consent
- “Clear understanding….stigmatization”: what do the authors mean with ‘reducing pre-conception’?
- What is the TCPS 2nd Edition? Please explain the abbreviation.

Authors’ response:
- By reducing pre-conception we mean misunderstanding. The sentence now reads “reducing misunderstandings and potential feelings of stigmatization.”
- TCPS refers to the Tri-Council Policy Statement, a set of regulations used to conduct research in human subjects in institutions where research is funded by Canadian government agencies. The current version is its second edition. The text now reads “Tri-Council Policy Statement (TCPS)”.

7th:
Feedback, Return of results and Incidental Findings
- The authors mention that return of results could distort the aim of the research by generating therapeutic misconception, but I think an ethically more salient aspect of the therapeutic misconception is that people become research participant for the wrong reason and that they do not take autonomous, informed decisions. Could the authors comment on that?
- In most countries REB is not a well-known abbreviation.
- In this paragraph the authors do not clarify what’s new or specific for feedback in the context of BP disorders.

Authors’ response:
– Therapeutic misconception and lack of autonomous decisions:
The following new paragraphs were added to the section “Feedback, return of results and incidental findings” in response to the reviewers comment:
4th paragraph “In Misra et al, BD patients were questioned...”
And
9th paragraph “Previous reports indicate that individuals with mental disorders...”
- REB is now explained as “Research Ethics Boards (REBs)”
- New insights on feedback of results for participants with mental health disorders:
The following new paragraphs were added to the section “Feedback, return of results and incidental findings” in order to increase specificity in the context of BD:
- 2nd paragraph (middle) “Age of onset, available therapies and preventive treatments for a given health
- 4th paragraph: “In Misra et al, BD patients were questioned...”
- 9th paragraph: “Previous reports indicate that individuals with mental disorders...”

8th:
Clinically relevant ethical challenges
- Also in this paragraph, the authors give a too general discussion of NGS. Again, I would suggest they focus on NGS for BP disorders.
- The authors mix several types of genetic testing, e.g. prenatal, postnatal, adult. These different timings however evoke different ethical questions. I think the authors should concentrate on one of these, and that will most likely be NGS for adults.

Authors’ response:
– In order to focus on NGS for BP disorders the following was added:
– 3rd paragraph: “There are expected benefits associated with the use of NGS technologies in clinical settings for BD, by allowing, for instance, early intervention... costs for drugs is becoming increasingly doubtful.”
– 4th paragraph: “Initial symptoms of BD may appear... The influence of NGS for BD in the clinical field is reinforcing a growing need for genetic counselling.”
- 5th paragraph: “Two major ethical concerns arise from the use of NGS for BD in adolescents, as... influence their descendants”

- Following the reviewer’s comment, we removed all discussion on prenatal and postnatal genetic testing and restricted the ethical challenges in NGS applied to BD (paragraphs 4 and 5 as described above). At the end of the 4th paragraph we explain that “Based on age of onset and the need to determine early signs of BD, we infer that NGS will impact child, adolescent and adult clinical settings, the latter probably because of the quest for more personalized therapies and the desire to know the genetic susceptibility of their offspring. The influence of NGS for BD in the clinical field is reinforcing a growing need for genetic counselling.”