Author’s response to reviews

Title: Do patients and research subjects have a right to receive their genomic raw data? An ethical and legal analysis

Authors:

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Author’s response to reviews:

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Cover letter with responses to the reviewers

Concerning the manuscript:
METH-D-18-00104
Do patients and research subjects have a right to receive their genomic raw data? An ethical and legal analysis Christoph Schickhardt; Henrike Fleischer; Eva C. Winkler, Professor BMC Medical Ethics

We thank the editors of BMC Medical Ethics for sending our manuscript to external reviewers, for the kind responses to our submission, and for the encouragement in rewriting the manuscript in response to the reviewers’ comments.

We particularly thank the reviewers for considering and reviewing our manuscript and for their thoughtful comments and suggestions.

We have intensely revised and modified the paper to take into account the issues raised by the reviewers and to develop and improve the paper following the reviewers’ suggestions.

All changes to the text are indicated by track changes modus. The new literature references and endnotes that we added have been highlighted.
After submitting the revised manuscript we were informed by the BMC editorial office that the formatting structure (the sections) of our manuscript did not exactly meet the formatting required for the Research Articles category. We wrote an email to explain why we had not exactly subdivided our manuscript according to the formatting that BMC usually requires for Research Articles. On the basis of our argumentation, the Handling Editor decided that our manuscript can be taken into consideration for publication as Research Article provided that slight formatting changes are made. We have changed the formatting structure of the manuscript accordingly, using track changes modus.

Please find below a detailed point-by-point response to the reviewers’ comments and suggestions. (In the point-by-point response we refer to the revised version of our paper.)

Point-by-point response to the comments and suggestions

Response to the first reviewer

Aaro Tupasela (Reviewer 1): The manuscript, in hand, discusses a timely and important topic facing genomics research and its interface with the research subjects/patients that it engages with. Before publication, however, there are a few details that I think the authors should attend to to make the argument more precise and clear. I have listed these comments below:

- I found it refreshing and important that the authors took the time to define what they meant by 'genomic raw data.' I think this is an important point to make within the context of the paper. I would, however, like to encourage the authors to perhaps extend this a bit further by referring to 'Raw Data is an Oxymoron' book edited by Lisa Gitelman. After all, how we choose to 'read' the genome is by no means a self explanatory process, but rather requires a number of choices by researchers as to what is considered important to understanding disease and heredity. As such, the genome is just one 'thing' among many which has relevance to people health and how it plays out in life. The authors also at times appear to give the genome a higher status in terms of its relevance to human health as opposed to other factors such as life style, etc...

Response:

This was a very valuable remark for us. We had not thought of the possibility of a “naturalistic” understanding of the term raw data. Based upon the book 'Raw Data is an Oxymoron', edited by Lisa Gitelman, we have added two sentences (at the end of central paragraph on page 3) to address and avoid a potential “naturalistic” understanding of the “ranness” of the data and added a pertaining reference to a chapter of the book by Gitelman.

As to the status and the importance of the genome to human health, we do not think nor mean to say that the genome has more relevance as opposed to other health factors. However, we have not added any revising remark for we are not aware of a paragraph in the paper where we express ideas about the relevance or ranking of the genome as opposed to other health factors, and the comment does not indicate any relevant paragraph in the paper either.

- I would suggest moving the discussion on p.9 relating to the problem of clinical validity and the possibility of mistakes and quality control in research to p.3 where there is a discussion of NGS as a research tool. Although the authors are correct in pointing out that the distinction between research and
treatment can often be unclear, there is a big difference between clinically validated tests and research done without ISO standardisation (for example).

Response:
We have very much appreciated this suggestions and see the need for more detailed specification and differentiation. We have not completely shifted the problem of validity because we consider it still relevant for the discussion of the (limited) utility of genomic raw data; however, we have added a sentence (top of page 4) to the paragraph indicated by the comment in order to point the relevance of the difference clinically validated testing and tools as opposed to research applications of NGS. We have also added a new relevant reference to a paper where this distinction is clarified and emphasized.

- The paper seems to take as its context Europe (at least in the legal discussion). This would be good to make clear at some point or otherwise it would have to provide more discussion of other relevant contexts, such as the US. There is a great deal of literature on the US context, so this choice may make the text too long. If the choice is to focus on Europe, then perhaps examples from elsewhere, such as 23andMe could be left out for the sake of clarity.

Response:
We thank the reviewer for pointing out to us that there is a need to better clarify the scope of the legal discussion of the paper. We also agree with the view concerning the problem of the length/limited space. We have added three sentences (page 4) stating that indeed for reasons of lacking space we cannot examine the US legislation. We have also added a brief remark saying that in some way the EU GDPR has implications reaching beyond the EU. We have not deleted the hint to 23andMe because 23andMed is mentioned in a different (ethical, not legal) context (page14) and because 23andMe or similar services can, in terms of principle, also be used by Europeans costumers.

- The authors explain that the approach that they take draws on the perspective of egalitarian liberalism; although I tend to understand why, it might be useful to explicate why the notable perspectives have been dismissed.

Response:
We thank the reviewer for the attention paid to the normative perspective we draw on. We would be happy to better discuss the reasons why we deem it a egalitarian liberalism a valuable normative approach. However, a discussion of these reasons as opposed to reasons for other normative perspectives would be quite demanding and would be beyond the scope and limited space of the paper. Also, in the realm of social and political ethics, egalitarian liberalism is very popular, almost mainstream. Furthermore, in bioethics, liberalism in general is a quite notable and accepted normative perspective as well. Maybe therefore we deem the need to justify the perspective not as urgent as expressed or implied in the comment. However, to give an exemplary idea of the reasons and peculiarities of the perspective as opposed to at least one other notable approach in bioethics, i.e. principlism, we added endote b (on page 7).

- p.7, l. 11. What is the distinction between data and information. It may be useful to stick to using one term (data) as opposed to others which may introduce confusion.

Response:
This is a very good remark! We completely agree with the reviewer that the distinction between the two
terms should be addressed and possibly clarified. We added endnote d (page 7) attempting to do so. We tend to use the term “information” as referring to something (a datum) which was interpreted and bears a clear meaning or relevance for somebody, whereas a “datum” needs some kind of interpretation to become “meaningful” or “relevant” (for somebody). According to this differentiation we have carried out several changes replacing the word “information” with the word “data”. However, we also found that it is difficult to strictly differentiate between the two terms and to strictly stick to the differentiated meanings throughout the text. Some reasons for these difficulties are that, for instance, the GDPR does not clearly specify /distinguish the two terms, and that many normative concepts such as informational self-determination display the word “information” but also refer to data.

-p.9, top. There seems to be an argument here that if people only had higher levels of knowledge regarding genes and genomes then there would not be this problem. The knowledge-deficit model has been shown to be problematic in many instances and I doubt it would help here either.

Response:
We very much thank the reviewer for this valuable comment which pointed out to us an aspect which required a modified discussion. We carried out several changes (on pages 10 and 11) to address the identified need. We changed the way we mention the argument in order to clarify that essentially it is not our argument but an argument proposed by some authors. Inspired by the comment, we now refer to the argument by the name of “knowledge-deficit argument” (page 10). We also added explications on page 11 to emphasize and better clarify that and why we criticize and dismiss the argument.

-p.11 Although the discussion of costs associated with disseminating genomic data, I think it really distracts from the main discussion and could be edited a great deal to shorten the text. It would be enough to say that information dissemination incurs costs etc instead of getting deep into calculations.

Response:
We understand that the paragraph on costs and burdens associated with the release of raw data is quite detailed and that such technical details might be perceived as distracting be readers with a more conceptual interest. We cut a part of the paragraph (page 13) and added it to endote j so that we hope the paragraph is less distracting now. We would like to refrain from completely deleting the paragraph because the costs aspect plays a key role within the logic and discussions of the paper: first, as discussed in the legal section (page 5 and 6), the right to receive raw data might be restricted if it seriously impairs a research project. Second, as mentioned in the ethical discussion on what the release might mean for researchers, we refer to the costs again as potential objection to the right to genomic raw data and state that the right should be respected as long as costs are reasonable for researchers. Third, in the recommendations for future research projects/grants (page 18) we recommend that “research projects should consider in advance the possibility of participants requiring their raw data when planning grant submissions and projects, and set up a work flow”. For all these arguments, the (expected) amount of costs is critical. As mentioned in the pertaining paragraph on page 13, the amount of costs does also play an important role in the bioethical literature about genomic raw data release. Last but not least, we know from discussions with biomedical professionals that the reference to “unreasonable” amount of costs, lacking feasibility and burdens for professionals is the first and most common objection to efforts to foster and implement patients’ and participants’ rights within the biomedical practice. For all these reasons we generally deem the discussion of the costs relevant and would prefer to retain it in the text/endnote.
- p.12, l.34. There appears to be grammatical issue with the sentences.

Response:
We corrected the sentence (top page 14).

-p.13, around line 35. there seems to be an assumption in this argument that there is such a thing as a high quality testing tool. The challenge in my opinion is not about the quality of the testing tools, but the interpretations and clinical validity of the data more than anything else and not the quality of the tools. Perhaps this could be clarified to point that the problem is interpretation and validity more than anything else.

Response:
We considered the comment helpful suggestion to get this point right and accordingly changed the text (top page 15).

-p.14. I realise that I am splitting hairs here, but I do not think that all patients should have access to their medical records. Patients with psychiatric conditions, for example, are one such case, but I suppose that these individuals would be considered as having limited capability of making decisions about themselves in any case.

Response:
We think the point is not negligible at all; it had already been addressed within the legal section (page 5) as follows:
"Article 23 (1 i) GDPR allows restrictions to be placed on this right under EU law or the laws of the Member State to which the data controller or processor is subject, as long as ‘the restriction respects the essence of the fundamental rights and freedoms and is a necessary and proportionate measure in a democratic society to safeguard the protection of the data subject or the rights and freedoms of others’. This is most likely intended to refer to cases where there is a therapeutic necessity to do so."
We have now added a hint (page 15) within the paragraph indicated by the comment in order to mention the point and to refer to the passage of the legal section.

-p.15, l23-24. What do the authors mean by 'consideration'. Such a word is rather loose and can mean many things. It either needs to be omitted or requires an explanation of what types of 'considerations' justify not sharing genomic data.

Response:
We agree with the comment concerning the vagueness of the term “consideration” and are grateful for this suggestion. We have removed the term and changed the sentence (page 17) in order to give a clearer meaning of what we mean to say: that the relatives’ concerns do not justify restrictions on the right to genomic raw data, but bear sufficient ethical weight to require at least some efforts, namely to raise awareness through the information process.

Recommendations: perhaps my biggest problem with the paper has to do with the recommendations in that they seem to solve the problems with the classical informed consent approach. Although I am in general agreement with the right to receive such data the idea that one simply provides information, sign a brief 'receipt' and you are on your way is somewhat problematic, since it comes down to what information you are providing. There is a great deal of literature out there on how people do not read,
understand etc informed consent forms or procedures. As such, I cannot understand why it is introduced here as a solution, except as a legal exercise to limit liability. But why should this be the case if people are part of an egalitarian/liberal society where they are autonomous as has been argued. I think the whole paper comes undone at this point by assuming that the consent is what makes it all ok. Perhaps I come from a different theoretical perspective, but I do not think that IC is a solution or answer to this problem. Perhaps a better and more fruitful approach would be to question the relevance of genomic data in the first place. There are a number of good examples, such as from the US, where medical societies have listed conditions which should be reported back (being validated and actionable), leaving the rest of conditions to researchers to validate first. This approach also seems to have the most relevance and applicability at the national level in healthcare services. This way one does not end up with a spectrum of different approaches adopted by different institutions within one country or region, which would significantly contribute to inequality.

Response:

As to the role of the information offer we recommend, we would like to specify some aspects and reasons why we advocate such an offer. On the one hand, strictly speaking, the normative function of the information offer we recommend is distinct from the normative function of informed consent. Whereas informed consent is required to justify the intervention into a person’s right, the information offer we advocate shall help the data subject to make a possibly well informed use of her right to receive raw data. On the other hand, we see the comment’s point: the information offer encompasses written information and personal discussion as informed consent procedures do. As indicated by the comment, this raises concerns with respect to persons’ understanding of information communicated through written presentation and personal discussion. However, data subjects actively requesting the release of their raw data from a biomedical institution might have a higher degree of motivation to get through information and understand things than normal patients have in usual informed consent situations. The information offer is mainly conceived with a view on addressing the risk of data subjects lacking adequate understanding and potential concerns of relatives. We advocate it as an (additional) duty of releasing professionals/ institutions on ethical grounds. Indeed we argue that the information offer should accompany the release of genomic raw data which is warranted as a legal right by the GDPR. We cannot think of a better alternative compatible with the data subject’s right to access genomic raw data. We have added the endote g (page 12) to explicite these aspects. Also, any other possible alternative to the release of raw data, such as, for instance, return of individual results to patients and participants on the basis of their previous decision to have potential results returned back, appears to raise similar concerns with respect to the need to inform patients and to get their informed consent or “opt-in”-decision.

As to the very suggestion that the return of results based upon a list, as mentioned in the comment, is a good alternative to release of raw data, we have added a paragraph (page 12) to discuss (and eventually dismiss) this idea from our perspective. As to the idea and desideratum of an international harmonization of handling of genomic raw data, we believe that offering return of results based upon a defined a list cannot really replace the release of raw data, one reason being that, as we understand it, the GDPR warrants the legal right to access raw data (in the EU member states). Although we have a different view on the subject, we very much thank the reviewer for the inspiring suggestion and thereby enabling us to discuss the idea in the text.

General comment: The paper takes its starting point that institutions are responsible for how genomic information is made available. The paper would become much stronger if it pointed out that a number of countries, such as Denmark and Finland are in the process of drafting legislation concerning genome
information (Denmark), or already have laws in place (Finland), which cover the management of genomic information (see for example Tupasela and Liede, 2017 on the Finnish case)

Response:
Generally, due to lack of space and to the mainly ethical (and not legal) nature of the paper, we do not aim to offer an analysis of the law applicable to the question of release of raw data in single EU member states. We think that this would be beyond the scope of the article (and also beyond the reasonable expectations towards the competencies of the paper’s authors). Analyzing the applicable law in single EU member states would need to meet the challenge of interpreting the national law in light of its relation (applicability, specificity, subsidiarity etc.) to the new GDPR. We have added endnote a) (page 4) to explain this and the (different/limited) approach/scope of our paper. However, in endnote a) we also briefly refer to the Finish biobanking legislation and the paper cited in the comment that we have added as a new reference to the paper.

Response to the second reviewer

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
N/A - no experiments or analyses

Statistics - Is the use of statistics in the manuscript appropriate?
N/A - there are no statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The overall impression of this study is very positive. It is in fact a normative analysis using ethical principles to better understand and clarify what patients and research ppts should have in the way of getting access to raw data.
REQUESTED REVISIONS:
One issue that would strengthen the ms is if the authors used citations for some of their larger statements. For example, what is raw data? who says so? why and what are the variations around something so critical as raw data to the publication?

Response:
We thank the reviewer for this suggestion. We have added several citations for some of our larger statements throughout the text, beginning with the paragraph on raw data as indicated in the comment. More precisely, we have added one citation on page 3 (raw data); two citations on page 8 (the privacy-as-context approach by Nissenbaum); one citation on page 10 (CLIA-certified laboratories and private testing services); one citation on page 12 (difference between release of raw data and return of genetic findings); one citation on page 13 (costs as reason/justification to reject participants’ right to receive raw data).

ADDITIONAL REQUESTS/SUGGESTIONS:

overall the ms seems stronger in the what is right category compared to the what to do about it category? it would help if authors drew more conclusions about what differently should be done to get to what is right.

Response:
The article’s main focus is to give an ethical-normative account of patients’ and participants’ right to receive their raw data upon request. In this sense, the article has a rather theoretical approach. However, we completely agree with the comment that after theoretically defining what is right, it is important to define how to translate and implement abstract analyses into the practice. To this end, we elaborated the recommendations. As to the suggestion to emphasize what differently should be done, we would like to specify that the goal of the paper and the recommendation is not to revise a given practice or to get things right that are currently carried out in a problematic way, since we assume that there is no current given/established practice of handling requests for genomic data release. We mainly address a very recent/new phenomenon and want to contribute to shape the upcoming practice of release of genomic raw data right from the beginning. However, given the right to request raw data and given the likelihood that requests will increase in number, we advocate that researchers and funders should think of potential requests when planning, conceiving, applying for and funding future research projects. These recommendations are indeed meant to urge for immediate change/revision of the current practice planning and funding future research projects.

To explicate the different scope of our recommendations (shape the future vs revise the current practice) we have added a sentence on page 17.

We thank the reviewer for helping us to be aware of these differences and for allowing us to explicate them in the text.

On behalf of the authors, I very much thank the reviewers for considering our manuscript and for their highly valuable comments and suggestions. If you have any questions, please do not hesitate to contact me.
Cover letter with responses to the reviewers

Concerning the manuscript:
METH-D-18-00104
Do patients and research subjects have a right to receive their genomic raw data? An ethical and legal analysis Christoph Schickhardt; Henrike Fleischer; Eva C. Winkler, Professor BMC Medical Ethics

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We particularly thank the reviewers for considering and reviewing our manuscript and for their thoughtful comments and suggestions.

We have intensely revised and modified the paper to take into account the issues raised by the reviewers and to develop and improve the paper following the reviewers’ suggestions.

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Please find below a detailed point-by-point response to the reviewers’ comments and suggestions. (In the point-by-point response we refer to the revised version of our paper.)

Point-by-point response to the comments and suggestions

Response to the first reviewer

Aaro Tupasela (Reviewer 1): Th manuscript t hand discusses a timely and important topic facing genomics research and its interface with the research subjects/patients that it engages with. Before publication, however, there are a few details that I think the authors should attend to to make the argument more precise and clear. I have listed these comments below:
- I found it refreshing and important that the authors took the time to define what they meant by 'genomic raw data.' I think this is an important point to make within the context of the paper. I would, however, like to encourage the authors to perhaps extend this a bit further by referring to 'Raw Data is an Oxymoron' book edited by Lisa Gitelman. After all, how one choose to 'read' the genome is by no means a self explanatory process, but rather requires a number of choices by researchers as to what is considered important to understanding disease and heredity. As such, the genome is just one 'thing' among many which has relevance to people health and how it plays out in life. The authors also at times appear to give the genome a higher status in terms of its relevance to human health as opposed to other factors such as life style, etc...

Response:
This was a very valuable remark for us. We had not thought of the possibility of a “naturalistic” understanding of the term raw data. Based upon the book 'Raw Data is an Oxymoron', edited by Lisa Gitelman, we have added two sentences (at the end of central paragraph on page 3) to address and avoid a potential “naturalistic” understanding of the “rawness” of the data and added a pertaining reference to a chapter of the book by Gitelman.

As to the status and the importance of the genome to human health, we do not think nor mean to say that the genome has more relevance as opposed to other health factors. However, we have not added any revising remark for we are not aware of a paragraph in the paper where we express ideas about the relevance or ranking of the genome as opposed to other health factors, and the comment does not indicate any relevant paragraph in the paper either.

- I would suggest moving the discussion on p.9 relating to the problem of clinical validity and the possibility of mistakes and quality control in research to p.3 where there is a discussion of NGS as a research tool. Although the authors are correct in pointing out that the distinction between research and treatment can often be unclear, there is a big difference between clinically validated tests and research done without ISO standardisation (for example).

Response:
We have very much appreciated this suggestion and see the need for more detailed specification and differentiation. We have not completely shifted the problem of validity because we consider it still relevant for the discussion of the (limited) utility of genomic raw data; however, we have added a sentence (top of page 4) to the paragraph indicated by the comment in order to point the relevance of the difference clinically validated testing and tools as opposed to research applications of NGS. We have also added a new relevant reference to a paper where this distinction is clarified and emphasized.

- The paper seems to take as its context Europe (at least in the legal discussion). This would be good to make clear at some point or otherwise it would have to provide more discussion of other relevant contexts, such as the US. There is a great deal of literature on the US context, so this choice may make the text too long. If the choice is to focus on Europe, then perhaps examples from elsewhere, such as 23andMe could be left out for the sake of clarity.

Response:
We thank the reviewer for pointing out to us that there is a need to better clarify the scope of the legal discussion of the paper. We also agree with the view concerning the problem of the length/limited space. We have added three sentences (page 4) stating that indeed for reasons of lacking space we cannot examine the US legislation. We have also added a brief remark saying that in some way the EU GDPR has implications reaching beyond the EU. We have not deleted the hint to 23andMe because
23andMed is mentioned in a different (ethical, not legal) context (page14) and because 23andMe or similar services can, in terms of principle, also be used by Europeans costumers.

- The authors explain that the approach that they take draws on the perspective of egalitarian liberalism; although I tend to understand why, it might be useful to explicate why the notable perspectives have been dismissed.

Response:
We thank the reviewer for the attention paid to the normative perspective we draw on. We would be happy to better discuss the reasons why we deem it a egalitarian liberalism a valuable normative approach. However, a discussion of these reasons as opposed to reasons for other normative perspectives would be quite demanding and would be beyond the scope and limited space of the paper. Also, in the realm of social and political ethics, egalitarian liberalism is very popular, almost mainstream. Furthermore, in bioethics, liberalism in general is a quite notable and accepted normative perspective as well. Maybe therefore we deem the need to justify the perspective not as urgent as expressed or implied in the comment. However, to give an exemplary idea of the reasons and peculiarities of the perspective as opposed to at least one other notable approach in bioethics, i.e. principlism, we added endote b (on page 7).

- p.7, l. 11. What is the distinction between data and information. It may be useful to stick to using one term (data) as opposed to others which may introduce confusion.

Response:
This is a very good remark! We completely agree with the reviewer that the distinction between the two terms should be addressed and possibly clarified. We added endnote d (page 7) attempting to do so. We tend to use the term “information” as referring to something (a datum) which was interpreted and bears a clear meaning or relevance for somebody, whereas a “datum” needs some kind of interpretation to become “meaningful” or “relevant” (for somebody). According to this differentiation we have carried out several changes replacing the word “information” with the word “data”. However, we also found that it is difficult to strictly differentiate between the two terms and to strictly stick to the differentiated meanings throughout the text. Some reasons for these difficulties are that, for instance, the GDPR does not clearly specify /distinguish the two terms, and that many normative concepts such as informational self-determination display the word “information” but also refer to data.

-p.9, top. There seems to be an argument here that if people only had higher levels of knowledge regarding genes and genomes then there would not be this problem. The knowledge-deficit model has been shown to be problematic in many instances and I doubt it would help here either.

Response:
We very much thank the reviewer for this valuable comment which pointed out to us an aspect which required a modified discussion. We carried out several changes (on pages 9 and 11) to address the identified need. We changed the way we mention the argument in order to clarify that essentially it is not our argument but an argument proposed by some authors. Inspired by the comment, we now refer to the argument by the name of “knowledge-deficit argument” (page 9).We also added explications on page 11 to emphasize and better clarify that and why we criticize and dismiss the argument.
Although the discussion of costs associated with disseminating genomic data, I think it really distracts from the main discussion and could be edited a great deal to shorten the text. It would be enough to say that information dissemination incurs costs etc instead of getting deep into calculations.

Response:
We understand that the paragraph on costs and burdens associated with the release of raw data is quite detailed and that such technical details might be perceived as distracting by readers with a more conceptual interest. We cut a part of the paragraph (page 13) and added it to endnote j so that we hope the paragraph is less distracting now. We would like to refrain from completely deleting the paragraph because the costs aspect plays a key role within the logic and discussions of the paper: first, as discussed in the legal section (page 5 and 6), the right to receive raw data might be restricted if it seriously impairs a research project. Second, as mentioned in the ethical discussion on what the release might mean for researchers, we refer to the costs again as potential objection to the right to genomic raw data and state that the right should be respected as long as costs are reasonable for researchers. Third, in the recommendations for future research projects/grants (page 17) we recommend that “research projects should consider in advance the possibility of participants requiring their raw data when planning grant submissions and projects, and set up a work flow”. For all these arguments, the (expected) amount of costs is critical. As mentioned in the pertaining paragraph on page 13, the amount of costs does also play an important role in the bioethical literature about genomic raw data release. Last but not least, we know from discussions with biomedical professionals that the reference to “unreasonable” amount of costs, lacking feasibility and burdens for professionals is the first and most common objection to efforts to foster and implement patients’ and participants’ rights within the biomedical practice. For all these reasons we generally deem the discussion of the costs relevant and would prefer to retain it in the text/endnote.

- p.12, l.34. There appears to be grammatical issue with the sentences.

Response:
We corrected the sentence (top page 14).

-p.13, around line 35. there seems to be an assumption in this argument that there is such a thing as a high quality testing tool. The challenge in my opinion is not about the quality of the testing tools, but the interpretations and clinical validity of the data more than anything else and not the quality of the tools. Perhaps this could be clarified to point that the problem is interpretation and validity more than anything else.

Response:
We considered the comment helpful suggestion to get this point right and accordingly changed the text (top page 15).

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Response:
We think the point is not negligible at all; it had already been addressed within the legal section (page 5) as follows:
Article 23 (1 i) GDPR allows restrictions to be placed on this right under EU law or the laws of the Member State to which the data controller or processor is subject, as long as “the restriction respects the essence of the fundamental rights and freedoms and is a necessary and proportionate measure in a democratic society to safeguard the protection of the data subject or the rights and freedoms of others”. This is most likely intended to refer to cases where there is a therapeutic necessity to do so.

We have now added a hint (page 15) within the paragraph indicated by the comment in order to mention the point and to refer to the passage of the legal section.

-p.15, l23-24. What do the authors mean by 'consideration'. Such a word is rather loose and can mean many things. It either needs to be omitted or requires an explanation of what types of 'considerations' justify not sharing genomic data.

Response:
We agree with the comment concerning the vagueness of the term “consideration” and are grateful for this suggestion. We have removed the term and changed the sentence (page 16) in order to give a clearer meaning of what we mean to say: that the relatives’ concerns do not justify restrictions on the right to genomic raw data, but bear sufficient ethical weight to require at least some efforts, namely to raise awareness through the information process.

Recommendations: perhaps my biggest problem with the paper has to do with the recommendations in that they seem to solve the problems with the classical informed consent approach. Although I am in general agreement with the right to receive such data the idea that one simply provides information, sign a brief 'receipt' and you are on your way is somewhat problematic, since it comes down to what information you are providing. There is a great deal of literature out there on how people do not read, understand etc informed consent forms or procedures. As such, I cannot understand why it is introduced here as a solution, except as a legal exercise to limit liability. But why should this be the case if people are part of an egalitarian/liberal society where they are autonomous as has been argued. I think the whole paper comes undone at this point by assuming that the consent is what makes it all ok. Perhaps I come from a different theoretical perspective, but I do not think that IC is a solution or answer to this problem. Perhaps a better and more fruitful approach would be to question the relevance of genomic data in the first place. There are a number of good examples, such as from the US, where medical societies have listed conditions which should be reported back (being validated and actionable), leaving the rest of conditions to researchers to validate first. This approach also seems to have the most relevance and applicability at the national level in healthcare services. This way one does not end up with a spectrum of different approaches adopted by different institutions within one country or region, which would significantly contribute to inequality.

Response:
As to the role of the information offer we recommend, we would like to specify some aspects and reasons why we advocate such an offer. On the one hand, strictly speaking, the normative function of the information offer we recommend is distinct from the normative function of informed consent. Whereas informed consent is required to justify the intervention into a person’s right, the information offer we advocate shall help the data subject to make a possibly well informed use of her right to receive raw data. On the other hand, we see the comment’s point: the information offer encompasses written information and personal discussion as informed consent procedures do. As indicated by the comment, this raises concerns with respect to persons’ understanding of information communicated through written presentation and personal discussion. However, data subjects actively requesting the
release of their raw data from a biomedical institution might have a higher degree of motivation to get through information and understand things than normal patients have in usual informed consent situations. The information offer is mainly conceived with a view on addressing the risk of data subjects lacking adequate understanding and potential concerns of relatives. We advocate it as an (additional) duty of releasing professionals/ institutions on ethical grounds. Indeed we argue that the information offer should accompany the release of genomic raw data which is warranted as a legal right by the GDPR. We cannot think of a better alternative compatible with the data subject’s right to access genomic raw data. We have added the endote g (page 12) to explicate these aspects. Also, any other possible alternative to the release of raw data, such as, for instance, return of individual results to patients and participants on the basis of their previous decision to have potential results returned back, appears to raise similar concerns with respect to the need to inform patients and to get their informed consent or “opt-in”-decision.

As to the very suggestion that the of return of results based upon a list, as mentioned in the comment, is a good alternative to release of raw data, we have added a paragraph (page 12) to discuss (and eventually dismiss) this idea from our perspective. As to the idea and desideratum of an international harmonization of handling of genomic raw data, we believe that offering return of results based upon a defined a list cannot really replace the release of raw data, one reason being that, as we understand it, the GDPR warrants the legal right to access raw data.

Although we have a different view on the subject, we very much thank the reviewer for the inspiring suggestion and thereby enabling us to discuss the idea in the text.

General comment: The paper takes its starting point that institutions are responsible for how genomic information is made available. The paper would become much stronger if it pointed out that a number of countries, such as Denmark and Finland are in the process of drafting legislation concerning genome information (Denmark), or already have laws in place (Finland), which cover the management of genomic information (see for example Tupasela and Liede, 2017 on the Finnish case).

Response:
Generally, due to lack of space and to the mainly ethical (and not legal) nature of the paper, we do not aim to offer an analysis of the law applicable to the question of release of raw data in single EU member states. We think that this would be beyond the scope of the article (and also beyond the reasonable expectations towards the competencies of the paper’s authors). Analyzing the applicable law in single EU member states would need to meet the challenge of interpreting the national law in light of its relation (applicability, specificity, subsidiarity etc.) to the new GDPR. We have added endote a) (page 4) to explain this and the (different/limited) approach/scope of our paper. However, in endnote a) we also briefly refer to the Finish biobanking legislation and the paper cited in the comment that we have added as a new reference to the paper.

Response to the second reviewer

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective
DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
N/A - no experiments or analyses

Statistics - Is the use of statistics in the manuscript appropriate?
N/A - there are no statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The overall impression of this study is very positive. It is in fact a normative analysis using ethical principles to better understand and clarify what patients and research ppts should have in the way of getting access to raw data.

REQUESTED REVISIONS:
One issue that would strengthen the ms is if the authors used citations for some of their larger statements. For example, what is raw data? who says so? why and what are the variations around something so critical as raw data to the publication?

Response:
We thank the reviewer for this suggestion. We have added several citations for some of our larger statements throughout the text, beginning with the paragraph on raw data as indicated in the comment. More precisely, we have added one citation on page 3 (raw data); two citations on page 8 (the privacy-as-context approach by Nissenbaum); one citation on page 10 (CLIA-certified laboratories and private testing services); one citation on page 12 (difference between release of raw data and return of genetic findings); one citation on page 13 (costs as reason/justification to reject participants’ right to receive raw data).

ADDITIONAL REQUESTS/SUGGESTIONS:
overall the ms seems stronger in the what is right category compared to the what to do about it category? it would help if authors drew more conclusions about what differently should be done to get to what is right.

Response:
The article’s main focus is to give an ethical-normative account of patients’ and participants’ right to receive their raw data upon request. In this sense, the article has a rather theoretical approach. However, we completely agree with the comment that after theoretically defining what is right, it is important to define how to translate and implement abstract analyses into the practice. To this end, we
elaborated the recommendations. As to the suggestion to emphasize what differently should be done, we would like to specify that the goal of the paper and the recommendation is not to revise a given practice or to get things right that are currently carried out in a problematic way, since we assume that there is no current given/established practice of handling requests for genomic data release. We mainly address a very recent/new phenomenon and want to contribute to shape the upcoming practice of release of genomic raw data right from the beginning. However, given the right to request raw data and given the likelihood that requests will increase in number, we advocate that researchers and funders should think of potential requests when planning, conceiving, applying for and funding future research projects. These recommendations are indeed meant to urge for immediate change/revision of the current practice planning and funding future research projects.

To explicate the different scope of our recommendations (shape the future vs revise the current practice) we have added a sentence on page 17.

We thank the reviewer for helping us to be aware of these differences and for allowing us to explicate them in the text.

On behalf of the authors, I very much thank the reviewers for considering our manuscript and for their highly valuable comments and suggestions. If you have any questions, please do not hesitate to contact me.

Yours sincerely

Eva Winkler

Prof. Dr. med. Dr. phil. Eva Winkler
Attending physician and head of the research program "Ethics and patient oriented care" at the National Center of Tumor Diseases (NCT), Heidelberg, Germany.