Author’s response to reviews

Title: Structural Racism in Precision Medicine: Leaving no one behind

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Authors’ response to reviews:
Dear Associate Editor, Dr. Simona Giordano, dear reviewers,

We thank the editor and reviewers for the effort and time put in the revision of the manuscript and for the opportunity to re-submit an improved version of our manuscript including your constructive comments. We have carefully considered all comments made by the editor and reviewers, Dr Simon Woods and Dr Pradeep M. Muragundi point-by-point, and we have made changes accordingly to the manuscript.

Changes to the manuscript are indicated by the line numbers in the revised manuscript.

Best regards,
Lester Geneviève

Reviewer 1’s comments:

1. I think you should give a slightly more detailed (and clearer) account of what PM is (in your
account you might also evaluate the claim that there are reasons to think the PM 'ideally' is a more equitable strategy for treating people. Perhaps a few more references at p 3 (the reference you do use #2 is mainly about trust which isn't the point at hand).

RESPONSE:
We thank the reviewer for this important suggestion, which has undeniably helped in improving our manuscript. A more detailed and clearer account of PM is now given in the background section, lines 59 – 83, including an evaluation of the claim on why PM is ideally a more equitable strategy for treating people. More references were also added to this section, which include:

2. I am not sure that your use of 'Animal Farm' helps your argument (though I can see why you have used it). It isn't obvious to me that the introduction of PM will necessarily go in that direction.

RESPONSE:
As rightly pointed out by the reviewer, we also think that PM will not necessarily go in the direction where only a few privileged ethnoracial groups will reap all benefits from advances made in healthcare. However, we make this analogy to highlight that what the worst-case scenario for PM initiatives would look like. At the same time, we believe that our hyperbolic analogy contributes to raise awareness concerning the potential insidious impacts of structural racism on health equity for all ethnoracial groups in the era of PM. In any case, we summarized the first section referring to Animal Farm (lines 52 to 58) and thereby put less emphasis on this worst-case scenario.

3. At page 4 your example using the two examples e.g. failing of black mothers and kidney transplantation should be expanded to bring out the specific link to PM. I agree with the issue regarding black mothers (recent reports in UK have shown similar patterns) however you really need to make a stronger and more explicit link to PM Similarly with the kidney example - surely cause of kidney failure is not the issue here/ I don't think you are doing justice to the complexity of ethnicity as a factor in kidney transplantation.

RESPONSE:
We thank the reviewer for these very pertinent comments. Regarding the unfortunate experiences of black mothers with their healthcare system, we explained in greater depth (with additional references) how structural influences contributed to such disparities in outcomes (lines 109-118). Additionally, the link to PM was reinforced by contrasting how structural realities that contribute to health inequalities of minority populations are generally neglected by PM initiatives, an important point supported by two eminent scholars in the field, Ronald Bayer and Sandro Galea (lines 118-121).

The reviewer is right regarding the kidney transplantation example. We explained in more details the complexity of ethnicity by highlighting that socio-economic, cultural, environmental and other
biological factors could explain such disparities in health outcomes between different ethnoracial groups (lines 126-130).

4. The argument at p 7-8 doesn't really explain or substantiate the claim that PM approaches will be based on biased data (again you are moving too quickly from examples of racial bias in clinical practice to the presumption that PM will also be so tainted) - I don't think you give enough evidence or develop the plausibility of your claim.

RESPONSE:
The claim on how biased data can corrupt PM initiatives by provoking discriminatory outcomes was reported more broadly by Ferryman and Pitman in their report titled “Fairness in Precision Medicine”, where several experts in the field of PM from eminent bioethicists, biomedical researchers, patient advocates and technologists debated these issues. We cited this source (lines 237-242) and highlighted additional limitations of data sources used in PM (e.g. limited data available due to external factors and apprehensions that minority groups might have). For instance, minority groups participating to PM initiatives expressed concerns that by providing their data, results of these initiatives might wrongly be used to create more racial discrimination by third parties (e.g. employers and health insurers) (lines 248-255).

5. The argument you develop at 9-11 is a very important one but again it could be more robustly defended with evidence. (I would also like some explanation of your comment at line 281 'except for the United Kingdom and Ireland' - because I couldn't follow it.

RESPONSE:
We totally agree with the reviewer. Regarding biased clinical guidelines, we gave a concrete example on risk assessment scores (e.g. the Framingham risk score) and elaborated on how such score overestimates the risk of coronary heart disease in some minority groups and other populations (European and Asian), which are different to the US population on which it was originally developed. We also made it clearer that until such scores are calibrated, we run the risk of not capturing essential data on minority groups (lines 271-279).

Additional references included:

We also highlighted the difference between decisions biased through implicit bias of healthcare providers and those biased through machine learning mechanisms (section: Structural Racism in Healthcare and Research, lines 291-294).

Additional reference:
In the UK and Ireland, they have more race-conscious policies whereas, for continental European countries, such as in France, colour-blind policies are maintained. We modified the paragraph to make it clearer and more easily understandable. Please see it copy-pasted below (lines 326-338):

Some critics might argue that continental European research, in the field of AI, is less impacted by structural racism due to the continental adoption of race scepticism, i.e. there is only one human race (with the exception of the United Kingdom and Ireland, which were affected differently by Nazi-Germany and hence adopted a different racial approach from other European countries) [54]. Indeed, following the racially-motivated atrocities of Nazi-Germany and the fear that scientists might normatively or covertly negate race scepticism, there was a general consensus at the European level that there is only one human race [54]. This deconstructivist approach by racial skepticists [54] could potentially reduce the chances that race will be used as a discriminatory feature by European AI technologies. Nonetheless, it would be dangerous to presume that colour-blind policies are sufficient to eliminate the risk of racial discrimination by AI technologies in healthcare and research, as historical biases or other variables (such as country of origin) in the training datasets of AI can also shape algorithmic decisions.

6. The discussion/comparison of CF and SCD is important but again I find your speculation about the future of PM being one that will merely reinforce existing discrepancies thinly argued for.

I think your proposed 'strategies for solutions are interesting and important.

RESPONSE:

We thank the reviewer for this pertinent comment. We provided more evidence to the potential racial discrimination on drug development regarding CF and SCD in the era of PM, by looking at personalized medicines approved by the FDA during the last five years. We studied the reports of the Personalized Medicine Coalition for the years 2014 to 2018 and found the same trend regarding personalized drugs approved for the two diseases. Two new drugs were approved for CF (Orkambi in 2015 and Symdeko in 2018) but none for SCD. We also highlighted, with evidence, that for PM to achieve its equity goals, it needs to ensure that minority groups see the clear benefits that their communities will get in return for their participation.

Modifications were made to the section Third Node: Influence of structural racism, lines 361-365, lines 387-391 and lines 395-398.

Reviewer 2’s comments:

General comment:
The manuscript "identifies" three nodes where structural racism can impact. I feel that these nodes pre-exist in the design (definition) of precision medicine and authors rightly argue with evidence how structural racism interfere at these nodes.

RESPONSE:
We thank the reviewer for highlighting this point and agree with his comment. Changes were made accordingly to the manuscript and abstract, where we changed “identify” to “analyse” when referring to the nodes.

1. I want to point out that the whole argument is around "biased data". At First Node authors argue
on production of biased data due to subjective interpretation. Second Node they discuss on how collection and integration of this biased data (at first node) leads to faulty interpretation. Third Node they argue that risk of racial discrimination is due to discriminatory efforts of feeding biased data into healthcare framework. Hence my argument is that the biased data recognised by authors at first node has a cascading effect at second and third node if not taken care of. Rather than looking into these nodes independently we can have a process flow (data production, integration and feeding into framework) approach for precision medicine.

RESPONSE:
We agree with the reviewer and thank him for highlighting these points. In the previous version, we also wanted to show this cycle of how biased data collected and fed into PM initiatives will only lead to more discrimination (Original Figure 1).

In the revised version, we made sure that the process flow was highlighted (section Background, lines 174-177 and Section First Node, lines 259-260). We also highlighted the cascading effects of biased health datasets on the health of minority groups (Section Connecting the dots, lines 408-410)

2. All the actions suggested by the authors are very well identified and justified. Considering the above argument by me it is prudent to include action points (solutions) in same process flow approach.
3. These action points can be indicated in the figure 1 also.

RESPONSE to Comments 2 and 3:
We thank the reviewer for his positive comments and agree with his suggestions. We split the solutions to ensure that each node was considered individually in the process flow (collection, integration of biased health data and deliverables being fed back into learning healthcare framework) (Section Potential Actions Node 1, lines 450-459; Section Potential Actions Node 2; line 460; Section Potential Actions Node 3, lines 521-523).

Regarding the point of including directly the solutions after the description of the problems arising from each node, we believe it would limit the clear interpretation of these sections for the readers. Hence, we preferred to elaborate on the problems arising from each node and then propose solutions for each step of the process flow. However, we agree with the reviewer on Figure 1, where we included the solutions at each node. Figure 1 was also modified to show the cascading effects of feeding biased health data from minority groups into PM initiatives.