Author’s response to reviews

Title: Clinical Decision-Making and Secondary Findings in Systems Medicine

Authors:
Tobias Fischer (tobias.fischer@uni-greifswald.de;bummelstudent@gmx.de)
Kyle Brothers (kyle.brothers@louisville.edu)
Pia Erdmann (perdmann@uni-greifswald.de)
Martin Langanke (langanke@uni-greifswald.de)

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"Clinical Decision-Making and Secondary Findings in Systems Medicine" (METH-D-15-00089)

Point-by-point response to the comments

@ Reviewer #1

Reviewer #1:
This is a very well written and timely paper on ethical issues surrounding systems medicine or biomedical Big Data. The paper raises several ethical questions about the relationship between statistical research and algorithmic models of health, clinicians and patients. Big Data is influencing medicine from many angles, some of which are covered in this paper, including basic medical research, resource commissioning, risk stratification and clinical decision-making (for instance through clinical decision support systems). This paper rightly questions the validity of the epistemological assumptions of the big data approach, namely that statistical correlations are increasingly treated as actionable knowledge. Correlations have long driven population level
decisions in medicine (e.g. epidemiology, resource commissioning), but the entrance into personalized medicine or decisions made that affect the individual in the clinic seems to be something new, quite apart from the role medical research plays in generating clinical best practice. While the paper addresses an important topic, it would benefit from providing further context and unpacking some of the ethical questions in a number of places. The following points jump out:

p. 4 - The terms Personalized and Individualized Medicine are introduced but not explained. I have a different understanding of Personalized medicine than the others (less to do with omics, more with personal monitoring of health), so it would be helpful to include a brief explanation or history of the terms with some references.

We agree to this comment and have added a short definition and references. The common aspect in different understandings of personalized medicine is surely the connection of the treatment to the individual characteristics of the patient, be it on the level of -omics or other monitored health data alike.

p. 5 (95) - The authors write "This approach, typically referred to as the big data approach, relies on statistical associations rather than mechanistic understandings." Typically according to who?

We agree to this suggestion and have added a reference

p. 7 - Line 134, an 'of' is missing.

yes, it is missing; corrected.

p. 14 - Re: the discussion of the algorithm presenting the patient's body as a black box: this is certainly a risk, but there are ways around this. Decision aids, or algorithms, can be built to show the decision-making logic to the user. Similar issues are being tackled in work on discrimination detection in data analytics algorithms, and how to make classification and personalisation algorithms accountable (perhaps through auditing). It seems odd that systems medicine would actually create technologies that completely leave the clinician and patient in the
dark; surely they would not be accepted at a clinical level and thus never spread (again, there is relevant background research on the diffusion of medical technologies and clinical evidence)?

Existing clinical decision support systems seem to avoid this problem; how are they different from systems medicine?

p. 14 - The authors write "In order for medical care to be successful, clinicians must be able to be accountable for their clinical decisions, and patients must be given grounds for placing trust in the expertise of their providers." This is the crux of the paper; if we don't believe this premise, then there's no reason to take the ethical issues identified in the paper seriously. It should therefore be expanded. Why must clinicians be accountable? Could we not re-define the role of clinicians to remove the diagnostic element, meaning clinicians would become mere collectors of clinical observations and someone to provide support/ advice to patients in making decisions, with diagnoses/treatments recommended by systems medicine? There's relevant work on medicine as a moral practice that covers why accountability, honesty etc. are so important to the success of medicine. Theories of virtue ethics in particular have been applied. I've included some relevant references below.

We slightly disagree here. This part of our paper concerns questions of epistemology not clinical practice, as we say in the following lines “Based on this analysis, then, we argue that the top-down dimension of systems biology must be viewed as a basic science – as an approach for generating hypotheses. Whatever potential this approach may hold, it must be mediated by more responsible approaches to medical care, and must therefore not be applied prematurely to clinical care.” The parts of our paper dealing with challenges for clinicians through the translation of this basic research to bedside are chapter 3 and chapter 4. For more comments on the issue of “the role of clinicians” please see our final remark to Reviewer #1

But we are quite thankful for the references the reviewer provided. While the discussion of virtue ethics is not part of our paper (see our remarks to the last comment of reviewer #1) we take the hint towards his own research as a welcome (and so far missing) link to imbed our paper deeper in the discussion on big data ethics. We have therefore added the reference: Mittelstadt, Brent Daniel, and Luciano Floridi. 2015. 'The Ethics of Big Data: Current and Foreseeable Issues in Biomedical Contexts'. Science and Engineering Ethics, May, 1-39. doi:10.1007/s11948-015-9652-2.

p.15 - Lines 319-20. Similar to the previous comment. If systems medicine merely provides recommendations, why can't the clinician bring in the missing human elements to the clinical
decision-making process? It's not clear why we should assume that the entire clinical encounter would become automated by systems medicine.

As we stated in line 407+, we consider that the “perception of greater predictive power inevitably increases the likelihood that such scores will be used as justifications apart from other important considerations, like provider judgments.” We don’t consider systems medicine to fundamentally change or automate the whole system of clinical care but to strengthen the already strong influence of (so called) objective markers and weakens subjective ones – be it on the side of the clinicians or the patient. We agree with Reviewer #1 that it is too early to tell if these changes are actually welcomed by clinicians for providing a more solid base for clinical decisions or a threat to their role as providers of a certain medical and moral practice. C.f. our response to his final comment.

p.15 - Line 328 - If it's just a case of scale, can we just extrapolate from the ethics of risk stratification to ethics of systems medicine?

As further explained in chap. 3.1 and 3.2, the big-data-approach is said to perfect the algorithm of predictions, thereby adding the missing sensitivity and specificity which (until now) restricted their importance as decision-aid-algorithms. Our aim was to identify this as a raising issue which should be addressed while rethinking the impact of big data on clinical decision making.

p.16 - Lines 331-2 - This is a very important point that is not stated enough. What is the source of this obligation?

Our response to this comment is included in our response to his final comment.

p.20 - Lines 438-439 - Again, see the above comment about virtue ethics and re-defining the role of the doctor.

Our response to this comment is included in our response to his final comment.

Beyond these specific issues, I was slightly disappointed some of the interested ethical questions identified throughout the paper weren’t unpacked a bit further. Perhaps you can choose one or
two to expand on, for instance questions on the acceptability of re-defining the role of clinicians to work with systems medicine (prior work on the ethics of automation and labor are relevant).

We completely agree with Reviewer #1. The precise impact of systems medicine on physicians is as interesting as it is widely missing in our paper. We barely touched the areas of medical professionalism, virtue ethics and ethical obligations. As we stated, systems medicine is for most parts still basic research making the ethical implications remain hypothetical. Reviewer #1 is completely right in his critique, that we know nothing about the final acceptability of systems medicine as we can only predict its impact. For this reason, we decided to focus this very paper on the rising issues that are most likely to be expected. Questions concerning the re-defining role of clinicians as mere data-collectors or loudspeaker of computer generated scores are actually our next task, but rather not on a theoretical base but based on empiric research. We are doing interviews with clinicians and researchers of systems medicine right know.

@ Reviewer #2

“The only real weakness of the paper was that the diagrams were not included, and to this end it was not possible to assess their quality, accuracy, or relevance. Judging by the quality of the paper, my guess is that they are likely to be suitable, however they need to be seen in the peer review process before the paper can be published. Apart from this, I am happy to recommend publication. I found the article relevant, interesting, well-written, perspicuous, and timely, given current concerns regarding the ethical implications of using 'big data' in clinical decision-making.”

The non-inclusion of the diagrams to the text-file was part of the guideline of the BMC Medical Ethics. We have attached and uploaded the diagrams using the online submission tool. They are in the “file inventory” of my authors account (Tobias Fischer) and are automatically added to the pdf-file when clicking the “action link” “view submission”. I suppose it’s a technical issue rather than a revive we can do.

@ Editor

We corrected some typos and updated some affiliations because of address changes and re-name-issues of my departments in Greifswald