Author's response to reviews

Title: Can learning health systems help organisations deliver personalised care?

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Author’s response to reviews:

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Paulina Szyszka
Associate Editor
BMC Medicine

Dear Paulina,

Re: Can learning health systems help organisations deliver personalised care? (BMED-D-17-00313)

Thank you for your letter dated 6th June 2017 and the welcome opportunity to revise our paper. We have carefully considered the very constructive expert peer-review and editorial feedback received and have in the light of this made a number of revisions to our paper. For your convenience, we reproduce the feedback received in full before detailing our revisions:

REVIEWER #3:

The authors address a foundational problem common to both precision medicine and learning health systems conceptual frameworks: integration of all relevant information about both patient and disease to produce effective interventions that improve health. While the manuscript does not break much new ground in its enumeration of issues or proposal of solutions, its strength is in
laying out the many factors that must contribute to a functional system. Unsurprisingly, the authors are quite well-informed, and the principles they address are well-delineated.

Comment

I did find their conceptual framework a bit jarring, primarily in the boundaries they set for precision medicine and learning health systems. In the former case, they cite the definition of precision medicine from the US NIH Working Group (p 7, ms line 127 et seq), which identifies the core of precision medicine as being able to account for the variety of factors needed to optimize treatment of *this patient's* illness. However, much of their detailed description for precision medicine reads more generally as describing molecular medicine; the precision is limited to finer understanding of the disease process. This detailed understanding of disease etiology and modifiers is without question a prerequisite for precision medicine, but the manuscript seems to set these up as defining the scope of precision medicine more than the current (early) state of the field. Similarly, the description of learning health systems, while appropriately including a focus on clinical implementation, anchors the LHS scope very closely in health care delivery, which again seems limiting in comparison to models such as the IOM's. While these definitions may reflect current foci of activity in each field, and do serve the authors' purpose of setting up a dichotomy between PM and LHS, I can imagine researchers in either area who read this paper feeling that key elements of "their" framework have been shifted elsewhere. Implementation science is placed between these two poles, and while it has certainly been a topic of greater discussion in the LHS than the PM arena, it has been acknowledged in both. Ultimately, however, this is a question of labels more than substance, so I would not consider it more than a minor, if potentially grating, limitation. The important substance is the clear articulation that an effective PM strategy must consider integration into clinical care, and an effective LHS strategy must account for all sources of evidence.

Response

We thank the reviewer for the frank, constructive feedback. We have in the light of this expanded on our conceptual framework and in so doing have sought to blur the boundaries between precision medicine and learning health systems (pg. 5 and 6, lines 114-119; pg. 7, lines 132-137).

Comment

The authors' proposed solutions include a detailed list of requirements for digital infrastructure capable of supporting the type of full-spectrum knowledge integration that both the PM and LHS conceptual models advocate(p13, ms line 257 et seq). While the level of detail possible in an opinion paper such as this is limited, I wonder whether the authors might consider devoting a bit more text to two areas. First, as they note from their initial sentence, the extension of biomedical research into numerous -omics has led to major shifts in the way we approach pathology and therapeutics. In particular, we are realizing more and more the extent to which health outcomes result from combined influences of multiple factors; cases where only a single factor is critical may be in the minority. Incorporating this understanding into clinical care requires not only the ability to interrogate a wider variety of determinants, as noted on p6, ms line 246 et seq, but also
the ability to interrogate the interactions among a large number of individually minor influences. This latter aspect likely presents a greater challenge to effective implementation than simply adding new risk factors, pharmacogenetic traits, or the like. The authors may be thinking along these lines when they mention an increased role for machine learning techniques, but it might be helpful to lay out the impact of combinatorics in a little more detail. Second, the authors advert in several places -- including the end of their list of requirements -- to the importance of governance (or what the Human Genome Project termed "ethical, legal, and social implications") of large-scale data integration. These factors -- in particular, concerns regarding privacy of individuals, return of results, and incidental identification of future risks -- are already critical and often limiting elements in population studies and clinical decision support, and the paper might benefit from outlining key themes at present, in a manner similar to the way the authors lay out the core parts of molecular medicine and implementation science.

Response

We have, as suggested, now expanded the discussion to consider the complex array of influences on health outcomes (pg. 16, lines 337-344) and the issues of data privacy and security (pg. 13, lines 280-291).

Comments

Less important than these conceptual suggestions, but of potential value to the authors, are several minor observations in proofreading:

p3, ms line 69: typographic error: "needs" should be "need"

p5, ms line 102: typographic error: "applying" should be "apply"

p5, ms line 106: typographic error: "feedback" should be "feed back"

p9, ms line 183: typographic error: "are" should be "is"

p11, ms line 203: missing "and" or "and are" between clauses

p14, ms line 261: redundant "and"

p14 ms line 270: typographic error: "potentials" should be "potential"

p14, ms line 276: use of the term "un-dimensional" is atypical, though I think I understand the intent

p14, ms line 278: missing closing parenthesis

p15, ms line 297: typographic error: "include" should be "includes"

p15, ms line 301 et seq: the enumeration shifts from participial to substantive phrasing
This opinion piece was a nice summary of the ways that precision medicine and learning health systems could be brought together by data science and implementation research. I have only a few recommendations for how to improve the piece.

Comment

1. The authors should include how they see clinical trials fitting into the picture. They advocate for changing medical practice based on clinical research but don't address how randomized clinical trials or pragmatic clinical trials fit into the picture. See PMIDs: 24830497, 28340241.

Response

We have now expanded the discussion on how learning health system infrastructures are being exploited to support the undertaking of clinical trials and have also included supporting references to illustrate this point (pg. 5 and 6, lines 114-119).

Comment

2. The authors define learning health systems but give no examples of how they have been implemented or used to improve patient care/outcomes. I would like to see more discussion of this in the manuscript, and how LHS's can decrease adverse events.

Response

We have now provided two examples to illustrate the implementation of learning health system to improve patient outcomes and decrease adverse events (pg. 7 and 8, lines 139-166).

Comment

3. The authors state that asthma biomarkers are being used for research purposes but not clinically. An expansion of why this hasn't been done and how a LHS would facilitate it would be helpful.
Response

We have now expanded this discussion to highlight the fact that many biomarkers are yet to be validated against relevant clinical endpoints, which is a necessary preliminary step before these are implemented in everyday clinical care (pg. 10, lines 216-217)

Comment

4. Linking small amounts of genomic data to clinical EHRs has been done in pharmacogenetics and elsewhere. Many of the ethical, policy, economic, and technical challenges have been addressed by these groups but the technical challenges will grow as the amount of data to be included grows. PMIDs: 24645908, 25612602, 25292429

Response

We thank the reviewer for this important point. We have now provided additional discussion around the issues of data privacy, safety, and the technical considerations that will need to be addressed as the volume and complexity of the data increases (pg. 13, lines 280-291).

Comment

5. Figure 2 contains some abbreviations that need to be defined in the figure legend (AHR, BM).

Response

These abbreviations have now been defined.

Overall I think this is an important topic that will be interesting to many readers.

Response

Thank you

We express our sincere thanks to the reviewers who pointed out areas of our manuscript that needed corrections and improvement. We also thank you for granting us the opportunity to resubmit a revised copy of our paper.

We hope that you will find the revised manuscript suitable for publication in BMC Medicine and we look forward to your decision in due course.

With kind regards,

Bright Nwaru, Charles Friedman, John Halamka and Aziz Sheikh