Reviewer’s report

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

Version: 0 Date: 01 May 2017

Reviewer: L. Charles Bailey

Reviewer’s report:

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.

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.

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.

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

p15, ms line 304: "context that" appears to mismatch with verbs "define and set"

p16, ms line 312: typographic error: "edit" should be "edited"
Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal