Author's response to reviews

Title: Personalising health care: feasibility and future implications focusing on a payers' perspective

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Author's response to reviews: see over
Personalising health care: feasibility and future implications for all stakeholder groups principally from a payers’ perspective

Godman, Finlayson, Cheema et al

Addressing reviewer comments

A) Overall

We found the comments from all 3 reviewers very helpful. Below we document our responses

B) Reviewer 1: George P Browman

1) This is a comprehensive narrative review including 230 citations of emerging and future issues to be addressed for the practice, resourcing, and policy implications of personalized medicine. The table at the end of the manuscript is the most relevant message given this reviewer’s understanding of the main purpose of the review, which is to examine from different stakeholder perspectives, most prominent among them, policy makers and payers, the actions that will be required to address issues and barriers in personalized medicine.

This is the most comprehensive description this reviewer has seen of the relevant issues in personalized medicine and there are valuable nuggets of information generously distributed throughout the review that make it interesting reading.

Author response

We thank the reviewer for these comments

2) The most important contribution that this paper could make, would be to clearly and explicitly identify key factors for each stakeholder group to address in terms of the future of personalized medicine (as in the table), but the main messages are completely submerged by the extraordinary detail provided within many of the sections dealing with clinical and biomedical specifics and in most cases far too many examples that confuse rather than clarify the main messages relevant to the policy perspective. For example, the discussion below the subheading ‘biomarkers’ contains 14 examples, and there are 10 more examples under the following two headings - ‘Host genotypes influence responses and toxicities to drug therapies’ and ‘Challenges and concerns for routine use of diagnostic tests’ - there are even more examples comprehensively referenced within the background and ‘general’ sections. Furthermore, there is much too much follow-up information provided for each of these examples that is not relevant to the main thrust of the paper.

Author response

We thank the reviewer for these comments and have re-vamped these sections to include two tables to better inform the readers. In addition, we have now inserted ‘host genotypes’ before ‘biomarkers’ to improve the flow of the paper, as well as inserted Table 4 (previous Table 1) earlier in the manuscript to enhance the focus on key elements of the paper. We hope this is now acceptable.

3) In the specific statement of objectives (a bit unclear and contradictory in this reviewer’s opinion) the authors say, “For the purposes of this paper, personalised medicine involves a degree of pharmacogenomic/ genetic testing” and go on to state ...” We do not include drugs that target for instance a specific protein as opposed to classic cytotoxic chemotherapy, where there are no baseline biomarkers to determine likely responses or genotyping to assess the risk of toxicity or prognosis.” Yet in the following sections there are myriad examples provided of drugs/ biological agents targeted to specific protein receptors.

Author comments

We thank the reviewer for this comment and have now amended this section to remove any misunderstanding. We hope this is now acceptable

4) While the authors claim that “the objective of this paper is to integrate current knowledge about targeted diagnostic and prognostic tests and targeted drug therapies from a payer perspective,” this
relatively important and appropriately narrower perspective is lost in the comprehensiveness of the discussion that includes various biological, clinical and organizational issues.

**Author response**

We thank the reviewer for this and have sought to place more data in tables to increase the flow of the paper from a payer’s perspective. This includes key considerations around medical, legal, economic, organisational and ethical issues as we believe these are important considerations before discussing potential next steps. We hope we have now addressed these concerns.

5) What comes across as clear from this review is that the authors collectively have a vast store of knowledge in this area, have thoughtfully considered the ramifications of personalized medicine from various points of view, have a good sense of the key issues to be addressed — but their objective to integrate their knowledge and insights into a focused coherent message has been lost in unnecessary details that obscure the message for the reader.

**Author response**

Again we thank the reviewer for the comments and hope the new layout including greater use of tables and subdivisions has improved the flow and addressed these concerns.

6) There also is one set of essential issues missing from the discussion under what has been coined “melsi” issues (medical, ethical, legal and social) with ethical and social considerations less represented in the discussion. Related to this, the role of societal values in informing policy decisions around funding priorities is missing and would seem to be a relevant area to cover, especially since these societal values are expressed differently in healthcare policies of the US, Canada and different parts of Europe and Latin America. This reviewer is not suggesting that this very comprehensive piece be further extended by including a discussion on ethics, values and societal issues, only that in the context of informing payers and policy makers, this would seem the more important areas to consider and perhaps should supersede a lot of the other biologically and medically oriented discussion with the over abundance of redundant examples — compelling as each example may be.

This reviewer suggests that the issues raised by the authors be re-framed, that the objectives be clearer and more narrowly focused, that the dominant perspective(s)/ audience for whom the paper is intended be clarified and that perhaps Table 1 be used as the starting point for deciding how to frame the text. The authors might also consider using tables rather than text to illustrate examples of biomarkers and their application, and summarizing the main messages that the examples are supposed to illustrate.

**Author comments**

We thank the reviewer for these comments and have now included a new Table (Table 3) discussing key MELSI issues from a payer’s perspective as we believe (like the reviewer) that these are important considerations. We agree with the reviewer about Table 4 (old Table 1) and have introduced this earlier to improve the flow of the paper. In addition, we agree that more tables should be used and have now inserted new Tables 1 and 2 in addition to a new Table 3. We hope this is now OK.

7) There definitely are a few language issues that will need editing. **Quality of written English:** Needs some language corrections before being published

**Author comments**

We thank the reviewer for this, and have further edited the paper. We hope this is now acceptable.

C) **Reviewer 2: Vural Ozdemir**

a) This is a timely manuscript that offers a payer’s perspective on personalized medicine as a field. Hence its publication should be informative for the readership. The submission brings together multiple stakeholder groups which is another strength of the paper.

**Author comments**

We thank the reviewer very much for these comments — very much appreciated!
b) I have only minor comments for revisions that are optional/discretionary by the authors:
1. The title could be amended to be more clear that the payers’ perspective is being offered.

We thank the reviewer for this comment and have now amended the title accordingly. We hope this is acceptable

2. The methodology states that only peer reviewed articles were analysed whereas methodology at the end mentions papers that were not peer reviewed were also included. Please clarify.

We thank the reviewer for these comments and have now changed the article to a ‘Review Article’ negating a methodology section.

3. The authors might want to refer to the works of Dr. Muin J Khoury and colleagues at the US CDC who developed a 3-tier classification system for candidate genetic/genomics applications. This has high relevance in terms of which tests are to be reimbursed as that classification system synthesizes the latest evidence including actionability. Please consider citing: Khoury MJ, Coates RJ, Evans JP. Evidence-based classification of recommendations on use of genomic tests in clinical practice: dealing with insufficient evidence. Genet Med. 2010; 12(11):680-3.

We thank the reviewer very much for these comments and have inserted references to the EGAPP project throughout the manuscript. We hope this is now OK.


We thank the reviewer for pointing out this omission, and have now inserted comments regarding the development of personalised medicine in Sri Lanka and other Asia-Pacific countries.

5. An expanded horizon scanning section at the end of the paper would be informative for the new emerging subspecialties of personalized medicine with the introduction of new technologies such as metagenomics and the highly relevant new field of “pharmacomicrobiomics” pioneered by Dr. Ramy Aziz et al. Please consider discussing these new fields of personalized medicine that will continue to inform and challenge the payment decisions in the years to come: Rizkallah MR, Gamal-Eldin S, Saad R, Aziz RK. The PharmacoMicrobiomics Portal: A Database for Drug-Microbiome Interactions Current Pharmacogenomics and Personalized Medicine 2012; 10(3): 195-203.

We thank the reviewer for this comment and have now made brief mention to the evolving field of pharmacomicrobiomics. However, we did not devote much space to this subject in view of the data we wanted to capture and communicate generally on personalised medicine. We hope this is acceptable.

c) Overall, this is a meritorious paper that deserves publication with consideration of the above minor points to make the manuscript more topical.

Author comments
We thank the reviewer very much for these comments!

d) Quality of written English: Acceptable

Author comments
We thank the reviewer very much for these comments!
D) Reviewer 3 : Martin Kennedy
a) General comments.
This is an interesting and ambitious article which seeks to clarify a very complex and multifactorial problem, that of limited translation of pharmacogenomic knowledge into clinical care. In particular, the manuscript approaches this topic from a payer’s perspective, a viewpoint which has not so far been well represented in the literature. I have only minor points to raise, as outlined below.

I think this manuscript is more suited to the category of review article, than correspondence.

Author comments
We thank the reviewer for this comment and have now indicated a Review Article and removed the methodology section.

b) Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. The paper makes some useful points, although it does not provide a particularly in-depth treatment of all relevant areas. For example, despite having a section entitled “Challenges and concerns for routine use of diagnostic tests” there is no coverage of TPMT gene testing, one of the most established pharmacogenetics tests. What is the current payment situation for this test? Also, under the heading “Future research activities including collaboration between FDA and EMA” it may have been useful to include some commentary on pharmacoeconomic studies.

Author comments
We thank the reviewer for this and have now added in TPMT testing into the manuscript/ tables. We have also included comments regarding economic considerations into the new Table 3. We hope this is acceptable.

2. The manuscript would benefit from tighter proof reading, particularly with regard to the structure of some sentences and multiple typographical errors. Many typographical errors also occur in the reference section.

Author comments
We thank the reviewer for this, and have been through the revised manuscript to address these errors. We hope this is now OK.

3. p10: paragraph 3. This paragraph begins by mentioning both clopidogrel and warfarin, then moves on to discuss CYP2C19 testing. However, CYP2C19 is only relevant to clopidogrel, as CYP2C9 is one of the two key metabolic genes for warfarin. This distinction is unclear in the earlier parts of this paragraph and should be clarified.

Author comments
We thank the reviewer for this, and have now added in more details about warfarin. We hope this is now OK.

4. p14: last paragraph. “This is seen with the disappointing predictive yield of the GWAS studies to date, only a few geno- or phenotyping tests currently being used routinely in clinical practice and only a limited number of targeted treatments currently available.” It is true that GWAS have not yielded many predictive tests, although that was never their primary function, and as a means of dissecting the genetic basis of complex disease they have been extraordinarily successful.

So first, I find it inappropriate to use the word “disappointing” in this context, as GWAS are the most successful strategy for dissecting complex phenotypes that the world has ever seen! And second, the authors have overlooked the fact that GWAS have actually been extremely useful for identifying major genetic effects underpinning many adverse drug reactions, a point they do not consider at all in their paper, and which might usefully be raised. Useful references in this regard are: Zhou, K. and Pearson, E.R. (2013) Insights from genome-wide association studies of drug response. Annu Rev Pharmacol Toxicol, 53, 299-310; and Daly, A.K. (2012) Using genome-wide association studies to identify genes important in serious adverse drug reactions. Annu Rev Pharmacol Toxicol, 52, 21-35.
Author comments
We thank the reviewer for this comment and have now altered the section accordingly and included both references. Hopefully, this is now acceptable.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
5. Acronym NNT (number of patients needed to treat) used in abstract without clarification.

Author comments
We have now highlighted this in bold to illustrate where we have defined NNTs. We hope this is acceptable.

6. Under “Background: General” in para 2 and 3, the phrase “…this new knowledge..” is used without qualification, and it is unclear precisely to what “new knowledge” refers.

Author comments
Thank you – we have now clarified the situation.

7. Last line p4: Sentence beginning “As a consequence, potentially alter drug development….” needs some rewording as grammatically incorrect.

Author comments
Thank you – now changed and we hope this is now OK.

8. p5: this sentence needs work: “Ideally, this will be translated into adjusted in treatment approaches to reduce these and, consequently, conserve resources”.

Author comments
Thank you – now changed and we hope this is now OK.

9. p5: the word “will”, used twice in this sentence, should be replaced by “may” as this is a hoped for but not yet proven outcome: “This will result in healthcare systems maximising the health gain of their patients with available resources, and will lead to the stratification of treatments…”

Author comments
Thank you – now changed.

10. p6: This sentence not grammatically correct: “As a result, provide guidance to all key stakeholder groups on potential ways forward to enhance future utilisation and funding of new personalised approaches.”

Author comments
Thank you – now changed and we hope this is now OK.

11. p7: last paragraph “metabolisers lack an analgesic effect with codeine” insert “effect”.

Author comments
Thank you – now changed.

12. p9: the introductory sentence under “Host genotypes influence…” should be expanded to give a little more context; at present it relies on the section heading alone for context.

Author comments
We thank the reviewer and we hope we have now clarified this before inserting the new table to enhance the flow of this section.

**Author comments**
Thank you – now changed.

14. p9: last paragraph, the sentence “These will help predict within 24 hours...” should be moderated by replacement of the word “will” with “may”, as this is fairly preliminary work.

**Author comments**
We have now removed this sentence to give broader discussions on host genotypes and biomarkers.

15. p10: The meaning of this sentence (particularly around “interests”) is unclear: “This was because the pooling of the interests of all Medicare patients reduced its value in practice [3].”

**Author comments**
Thank you for pointing this out. We have now removed the reference because of the ambiguity it caused.

16. p10: This sentence describes presumably unpublished material: “In fact when the test was used in stage II patients there was a 17% reduction in the use of post operative chemotherapy [Parneet Cheema Personal Communication].” Given the importance of this statement, more detail needs to be supplied. If a peer reviewed publication supporting this statement cannot be located, then the institutional affiliation of Dr Cheema needs to be supplied, and more information about the source of that figure obtained.

**Author comments**
We thank the reviewer for this and have now amended this section. We hope this is now OK.

17. p12: paragraph 2, “genome-wide association studies” used earlier in paper. The acronym should have been defined then, and used here in place of the full description.

**Author comments**
Thank you – we have now addressed this.

18. p12: this sentence needs reworking: “As a result, more rapidly assimilate valued developments into routine clinical practice”.

**Author comments**
We have sought to clarify comments such as these in the revised manuscript. We hope this is OK now.

19. p14: this sentence needs reworking: “Subsequently, address issues such as ‘Which putative genetic risk do I want to mitigate against and at what cost?’.”

**Author comments**
We have now removed this sentence in view of the ambiguity caused. In addition, covered to some extent in Table 3.

20. p14: Only one of the sentences in this paragraph is grammatically correct: There are considerable benefits with new technologies that can improve the diagnosis, prognosis and treatment of patients. This achieved through reducing the number of patients needed to treat and increasing the number of patients needed to harm. In addition, reducing the cost and consequences of ADRs [14,16,30,31,62,63]. As a result, improve the health of patients within finite resources.”

**Author comments**
Thank you – we have now re-phrased this sentence.
21. p14: In this sentence, the impact is not on gene mutations; rather, this should be phrased in a way that indicates the gene mutations impact on the biological systems or penetration: “However the complexity of biological systems and the diversity of genetic penetration patterns, as well as their impact on gene mutations, may not always express themselves into important phenotypic changes in disease patterns to identify potential biomarkers and new targeted treatments.”

**Author comments**
Thank you for this – we have now re-phrased the sentence.

22. P27, Table 1: delete duplicated words: “This should include an assessment of the of the likely..”

**Author comments**
We have been through Table 1 (now Table 4) and rephrased some of the sentences. We hope this is OK.

c) Major Compulsory Revisions – None

**Author comments**
We thank the reviewer for this.

d) **Quality of written English:** Needs some language corrections before being published

**Author comments**
We thank the reviewer for this and have edited the manuscript.