Reviewer's report

Title: Personalising health care: feasibility and future implications for all stakeholder groups

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Reviewer: Martin Kennedy

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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.

- 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.

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.

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.

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.

- 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.

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.

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

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

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…”

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.”

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

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.


14. p9: last paragraph, the sentence “These will help predict within24 hours…” should be moderated by replacement of the word “will” with “may”, as this is fairly preliminary work.

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]."

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.

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.

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

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?’.”

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.”

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.”

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

- Major Compulsory Revisions

None

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

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.