Reviewer’s report

Title: Pharmacogenetic testing through the direct-to-consumer genetic testing company 23andMe

Version: 0 Date: 16 Jan 2017

Reviewer: Laura Rasmussen-Torvik

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In this paper, Lu et al. describe in detail the pharmacogenetics tests currently available to UK customers of 23 and me. Using information they have obtained through 23andMe's website, through literature review, and review of the CPIC website(s), they detail the consistency of the tests with FDA and CPIC guidance, potential issues with tag SNP choices given LD patterns, and limitations of the tests given untested variants.

Much of the first part of the paper is a collection of information that can be obtained fairly readily though publicly available databases and resources (like the 23andMe website and dbgap). For example, it is unclear to me what table 1 adds significantly over information available on the 23andMe website. This reviewer found the second part of the results detailing the limitations of the tests offered through 23andme (by explaining the limitations of several of their offered tests due to SNP selection (selecting SNPs which may not cover causal loci well in all ethnicities) or omission of certain critical loci) more compelling. The discussion highlights many of the widely discussed issues around both DTC genetic testing and preemptive pharmacogenomic testing, but tailors the text to DTC pharmacogenomics genotyping in the UK.

The paper would benefit from the correction or clarification of several minor inaccuracies or unclear statements.

1) It should be made clear in the abstract that the authors are reviewing 23andme UK tests, given the current state of 23andme offerings in the US, where the company is based.

2) In the intro, the authors state that "23andMe was the most comprehensive pharmacogenomics testing company in 2012 and remains so today" without and explanation or citation.

3) The description of "tests" in the first paragraph of the results is very unclear. Are "tests" the genotyping (which only needs to be done once for CYP2C19, for example, for multiple gene/drug pairs), or do "tests" relate to the drug? The paragraph will read more clearly if "test" is replaced with a more descriptive term.
4) Also in the first paragraph of the discussion, why say 5 "tests" are for cytochrome p450 and the rest are for drug toxicity or ADR? Many of the cytochrome p 450 "tests" are also for ADR?

5) Also in the first paragraph of the discussion it says that CPIC guidelines for dose adjustment are given for all drugs, but not all drugs on the list have CPIC guidelines. Proton Pump Inhibitors, for example, have dutch working group guidelines, but no CPIC guidelines to date.

6) PEG-IFN-alpha and RBV treatment is described as the standard treatment for HCV when polymerase inhibitors have now become first line treatment, in my understanding.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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