Author’s response to reviews

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

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Editor Comments:

RESPONSE: Additional changes made –

Corrected 23andme to 23andMe in various places [no need to make this obvious in the re-submitted paper]

Reviewer reports:

Reviewer 1: 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.

RESPONSE: Reviewer 1 is correct that the information in Table 1 comes mostly from the 23andMe website, but we feel that combining this information in a single resource makes the remainder of the paper easier to interpret, and this table therefore is a central component of our paper. Also, since these tests are not available in the US, the details may be difficult to find for some readers.

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.

RESPONSE: This is a good point, and we have added two references to ‘UK tests’ in the abstract, and more in the main text of the paper.

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.

RESPONSE: We apologise for the omission of the reference (Chua & Kennedy, which was cited in the Discussion). The reference has been added, and the following sentence edited slightly to reflect the evidence shown

“23andMe was the most comprehensive DTC pharmacogenetic testing company, and it remains active, although its portfolio of pharmacogenetic tests has reduced substantially since scrutiny by the FDA in 2013. “

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.

RESPONSE: The term ‘test’ in this paragraph and elsewhere has been replaced by ‘report’, which better captures the combination of gene/drug/outcome. We retain the term ‘test’ in subsequent places, where it more accurately refers to a genotype test.
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?

RESPONSE: This has now been clarified as “The remaining seven reports are for non-cytochrome P450 drug toxicity and adverse events, such as …”

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.

RESPONSE: We thank the reviewer for picking up this discrepancy, and have edited this sentence to

“Not all pharmacogenetic tests with FDA recommendations or CPIC guidelines are reported by 23andMe.”

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.

RESPONSE: This has been revised to a more general statement “In peginterferon alpha (PEG-IFN-alpha) and ribavirin (RBV) combined therapy for the chronic infection of hepatitis C virus (HCV), 25-40% of patients fail to respond.”

Reviewer 2: This is generally an appropriate report. A few suggestions are listed below.

1. Introduction. Paragraph 4. It would be helpful to stress more that all the decisions about what to include in the tests offered by 23 and me are made by the company. It is 23 and me that decides whether a test is "potentially eligible" not a regulator.

RESPONSE: This has been clarified as follows:

23andMe’s criteria [3] for including a genetic test its portfolio are that the drug response tests are eligible if there are either existing clinical practice guidelines provided by CPIC and other clinical organisations, or if information from regulatory agencies or in drug labels "acknowledges the impact of the genetic marker on drug response". 23andMe regards pharmacogenetic tests as potentially eligible if “there is meaningful interpretation of a positive
result”, and at least three scientific research papers identify consistent clinical effects of the marker tested.[3]

2. Oesophageal cancer. Please state that the risk being considered here is for squamous cell carcinoma not adenocarcinoma. In addition, the risk has been demonstrated only in East Asians to date probably because the ALDH SNP being analysed is only common in this ethnic group.

RESPONSE: The sentence introducing this test has been changed to: “The report for acetaldehyde toxicity, leading to increased risk of oesophageal squamous cell carcinoma in people of East Asian ancestry, …”  and each instance of oesophageal cancer has been changed to oesophageal squamous cell carcinoma. (Interestingly, 23andMe do not make this distinction clear on their documentation.)

3. Phenytoin. The FDA table lists both CYP2C9 and HLA-B*15:02. The text on p.7 needs to make clear that the table lists both CYP2C9 and HLA-B since currently it seems to be suggesting that the FDA do not mention CYP2C9 at all.

RESPONSE: We have clarified this by adding the word ‘additional’, so the relevant sentence now reads:

“For phenytoin, 23andMe reports on drug sensitivity from CYP2C9*2 and *3 variants, but the U.S. FDA additionally lists pharmacogenetic information on HLA-B*15:02, …”

4. p.8 Poor metabolisers. Individuals with the alleles listed may be poor metabolisers-carriage of the alleles is not sufficient to make an individual a poor metaboliser so change "are poor metabolisers" to "may be poor metabolisers".

RESPONSE: Change made.

5. p.9 rs4149056 has a minor allele frequency of 0.19 in Europeans so the 1% mentioned on the last line of this page is not correct. 3% approx. of Europeans are predicted to be homozygous for this variant. The frequency in East Asians is only slightly lower than in Europeans. It is therefore not correct to state that this variant is very rare and it is actually an important risk factor for simvastatin-induced myotoxicity. Please include some relevant references on this point.
RESPONSE: We apologise for this error – our original values reported frequency of the high risk genotype conferring simvastatin-induced myotoxicity from homozygosity of rs4149056. This has now been corrected to allele frequencies as follows:

“For Simvastatin-induced myopathy, the frequency of the minor allele of rs4149056 is highest in European and Asian ancestries, with very low frequencies in African populations.[26]”

6. p.14. Discussion. In the era of genome sequencing, the risk of tests being mentioned here being "out of date" seems low. The main problem with the tests being offered currently appears to be that they are too geared towards white Europeans. I would also disagree that because the FDA does not list a test that it is uninformative-the rs4149056 point mentioned under 5 above is a good example of a test that is of some value but not listed by FDA.

RESPONSE: We have re-ordered the points in Discussion, p14, so that white-European point is reported first. We have also rephrased the ‘out of date’ point to read:

“2. Better mechanisms should be in place to ensure that tests reflect the latest science. Pharmacogenetic research can move quickly, and producing out-of-date or incomplete reports raises ethical questions.”

Point 3 has been rewritten as:

3. More consideration of what tests should be reported. Many 23andMe customers will not be knowledgeable about the relative importance of the different tests, and reporting tests that are not supported by the FDA or other guidelines could cause unnecessary concern or anxiety for customers.

Reviewer 3: This is a clinically useful paper - many physicians often ask about which 23andMe results are useful. However, this paper strikes me more as a review than original research - there is no set hypothesis tested or original findings.

Recs:

- There is no statistical testing done when discussing the differences in allele frequencies for different ancestries. Many publicly available data sources such as the Exac Browser provide allele counts which could be used to statistically show which variants have ancestry-based differences.
RESPONSE: We have focussed here on examples where large differences exist, based on substantial datasets. We elected not to test differences statistically, since the pharmacogenetic test is still valid regardless of the frequency difference, but it is of less relevance.

- Any differences between what 23andMe reports in the UK vs elsewhere?

RESPONSE: This is a good point, and exploring the website shows that these pharmacogenetic test reports are not available to 23andMe’s US customers.

We have added the following sentence on p13:

“These pharmacogenetic results are available to 23andMe customers in the UK, Canada and some EU countries, but are not currently provided to US customers.”

It is difficult for

- Might be useful to pull in the actual CPIC information on drugs covered, particularly ones that have different treatment regimens as a result of genetic data. (Another column on Table 1)

RESPONSE: We have added a column to Table 1 listing the guidelines available:

“Guidelines from [https://www.pharmgkb.org/view/dosing-guidelines.do](https://www.pharmgkb.org/view/dosing-guidelines.do) published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) or the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG)”

- Could you comment on how this data might be incorporated in a clinical encounter? Would the physician place the 23andMe results in a chart, or would they require validation/retesting?

RESPONSE: This is a good point, particularly since 23andMe does not provide specific medical advice, only reports the genotype and risks of adverse events or response. We have expanded this section (Discussion, p13) to read:

“23andMe’s public website and reports for registered customers make clear that they do not provide a medical service and the report is not a diagnostic test. Reports give risks (%) of an adverse event, and general comments such as ‘may benefit from a different dose’, and instructs customers to “consult with a healthcare provider about … appropriate next steps”, and not to “make any changes to any current treatment without first consulting a healthcare provider”.”