Reviewer's report

Title: The role of disease characteristics in the ethical debate on personal genome testing

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Reviewer: Stuart Hogarth

I am very pleased to have had the opportunity to review this paper which I believe is definitely worthy of publication in this journal, since it has originality, a thorough critical approach and high level of policy relevance. However, I believe that the arguments need to be tightened - I recommend publication but only after major compulsory revisions.

The focus of this article needs to be clearer. There is no reason why the analysis presented should be considered to apply

1) only to genome scans, as opposed to companies offering tests for one disease only (as is the case with AMD testing from the company offering MaculaRisk), or
2) only to companies offering tests direct-to-consumer.

To this latter point, it should be noted that the sector is moving fast and the article may have been submitted before FDA regulatory action led a number of US companies to cease to offer their tests DTC. 23andme is now one of a relatively small number of companies offering their tests DTC, with others now offering their tests through physicians. This development in no way renders the paper irrelevant or marginal, it simply suggests that the focus needs to be firmly on susceptibility tests, irrespective of the way in which they are offered. The confusion in focus is clear in the first and second paragraphs of the discussion - in the first para the article refers to “genetic susceptibility testing for multifactorial diseases”, then to “individual direct-to-consumer genetic susceptibility testing” and then the second para refers to “genetic susceptibility testing for multifactorial diseases”. This confusion is common to much of the debate about DTC genetics and susceptibility testing which frequently conflate the two despite the fact that many companies offer susceptibility tests but reject DTC and DTC genetics is not limited to susceptibility testing (eg pharmacogenetics offered by a number).

Disease characteristics – my concern about these is that in focusing on disease characteristics rather than test characteristics the authors have missed the opportunity to provide greater focus on the issue of clinical validity. The poor predictive value of susceptibility testing, the current lack of scientific consensus on some key issues such as additive risk vs. multiplicative risk, the confusion over where all the missing heritability is, the differences in risk predictions from company to company are all highly germane to the issue of ethical evaluation. The authors could argue that since this is a generic concern across all diseases
then its relevance to their argument is limited. However, when discussing severity they spend most of their time talking about clinical validity, which in my view should be treated as a separate issue. To this point the authors need to read and cite the following paper: Burke, W Pinky L and Press N (2001) ‘Categorizing genetic tests to identify their ethical legal and social implications’ American Journal of Medical Genetics 106 233-240. Their claim to originality will to some extent hinge on their ability to show they are going beyond the arguments advanced in this seminal paper.

Also, on the subject of diabetes susceptibility testing in at-risk youths, there is no discussion about the specific clinical validity of applying a susceptibility test to this sub-population, and the type of evidence which would be required. I am also concerned about the “assumption of a moderate predictive ability for the tests themselves”. This is not defined, nor are we told how it relates to what we currently know about the actual predictive value of the three tests.

I am concerned that the issue of false reassurance is not dealt with at greater length when considering the impact of testing for diseases where most of the actionability is around actions which we should all be pursuing – sensible diet, active lifestyle etc. – and where there is concern that identifying a genetic subpopulation may muddy clear simple public health messages targeted at the whole population. This is not a trivial point; it is one of the main justifications for the new European Union regulations governing health claims for foods. Some attention to this argument should be given.

I am unconvinced by the argument that psychiatric disease is more closely bound up with personhood than somatic disease and would want to see more evidence to support this assertion (I recognise that the authors may have been limiting their citations to stay within the designated word limit).

Under Type 2 diabetes the authors make reference to favourable response to the idea of DTC testing for genetic susceptibility but make no reference to expert opinion against this (Khoury, McCarthy etc – I am sure the authors are familiar with the relevant papers). Some balance would be helpful.

On the issue of susceptibility testing for depression, the authors state that to their knowledge no tests are on the market. The field moves quickly so oversights are entirely understandable but they should check the Genetics and Public Policy Center’s most recent table of tests and companies (available from the Center’s homepage) where they will see there are a number of companies offering such testing. They will also see that some companies are offering both susceptibility tests and PGx tests for drug response (eg antidepressants). I would like to see some discussion of this particular combination, which may become more common (another example is Celera’s Kif 6 test for heart disease risk and statin response), as I think it provides an interesting example of the intersections between some of the criteria – eg severity and actionability.

I would like to see some reference to relevant policy literature/guidelines, for instance the OECD guidelines on QA for molecular genetic testing and the Council of Europe Additional Protocol. The reason for citing these, aside from the
fact that they represent a broad transnational consensus on certain issues, is that there are areas of ambiguity around the degree of, or necessity for, medical supervision and genetic counselling, in both documents, an ambiguity which this paper seeks to address by offering an evaluative ethical mechanism for dealing with different types of tests.

I would like to see a separate methodology section before the discussion which provides some detail on the authors’ literature review and their interviews e.g. how many interviews, what format (semi-structured, structured?) What kinds of stakeholders were interviewed? How were stakeholder groups and specific individual interviewees selected? Were interviews transcribed? How were interviews analysed? Again, I recognise that these details may have been omitted in order to keep within the word limit.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**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