Subject: BMJ - Decision on Manuscript ID BMJ.2015.030916

Body: 21-Jan-2016

Dear Dr. Hollands

Manuscript ID BMJ.2015.030916 entitled "The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Georg Roeggla
groggla@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=3a34b5c6e40a4bb19802dac44b6a812c

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Manuscript meeting 21.01.2016

Jose Merino (chair), Rafael Perera (stats), Alison Tonks, Kristina Fister, Elizabeth Loder, Georg Roggla, Wim Weber, Tiago Villanueva, Rubin Minhas, Jessamy Bagenal, 2 guests

Decision: Ask for revision

The committee was interested in the topic of your research. The following concerns were mentioned:

• Please discuss what this revised and updated version of a Cochrane review from 2010 adds to the previous paper.
• The conclusions are not all that different from the previous review.
• One of the refs suggests you could be more definite in saying additional trials aren't needed.
• The search is now almost a year old. What is the reason for this delay?
• Is an update of the search necessary?
• We'd appreciate a clearer description in each results section of the diseases being tested for-not just the outcomes. For example, under "smoking cessation" you write "Pooled analysis (n=2663) showed no statistically significant effect of DNA risk communication on this outcome" but don't say what genetic tests were used (presumably tests for predisposition to cancer of the lung or oesophagus).
• In the methods you also mention comparing DNA tests v other risk assessments, DNA tests plus other risks assessments v other risk assessments alone, and DNA tests v no other risk assessments. We didn't notice a demarcation of these three lots of comparisons in the results section. It's not always clear which comparison is being made.
• Please discuss the international context. Are these tests available outside the US?
• Interesting study, but the 3 behaviours are known to be very resistant to change: diet, smoking, exercise.
• There is also a slight paradox in the approach, as we know that there are many genes linked to (or controlling?) behaviours, e.g. the SNP rs1051730 is directly to nicotine dependence (SNPedia), so one wonders how communicating this would affect behaviour; perhaps it is not even susceptible to change.
• Ref 37 is the protocol of a RCT, there are no data in there.
• We thought this looks well carried out and well reported. In the Abstract, please delete the 'marginal' non-significance? Basically, based on this evidence communicating results from genetic testing has no impact on behaviour.
• In terms of methods, we question the combination of continuous and dichotomous data using the GIV method. You need to have done a transformation beforehand and then used GIV (not GIV directly). This needs clarifying.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to the additional comments by the committee.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
The authors conducted a systematic review of clinical trials that tested the hypothesis that genetic risk information can be used to motivate behavior change. This is an excellent and timely review of a topic in which there needs to be greater recognition. There has been persistent enthusiasm for the role of genetic risk testing to change patient behaviors without enough acknowledgement that risk information (of any type) is rarely sufficient to motivate patients to change difficult behaviors such as unhealthy eating, insufficient exercise, or smoking. This review does an excellent job of gathering all existing trials and demonstrating the limited to lack of impact of genetic risk testing for these challenging behavior changes.

A thorough review and explicit screening process yielded 18 clinical trials. The authors did an excellent job of framing the research issue in the introduction, the methods appear robust, and the data presentation is clear. The worthwhile review updates a prior Cochrane review from 2010 that more than doubles the number of trials.

My primary conern, discussed in more detail below, is the authors' narrow principle message that further research is needed.

Minor points:
1) P12: clarify what sub-group was analyzed in the Alzheimer study.

3) P14: Clarify what "This" refers to (as written, it sounds like it refers to the studies with low summary risk, which is not the authors intent).

"Only four of the 18 studies were considered to have a low summary risk of bias, having met all of the specified criteria 32 36-38. This reflected both a lack of clarity in reporting…" Could say "Studies not meeting low summary risk of bias lacked clarity in reporting…etc"

4) P18: "While the results of the current review are strongly suggestive of, at most, small effects on health behaviours, there is currently insufficient high-quality research evidence to be able to be confident of this for each individual behaviour included in the review. This would require additional, better designed and conducted trials."

Additional large trials are probably not necessary given the weight of the evidence, and thus the discussion can be more nuanced. There are significant costs associated with conducting larger and larger research studies to chase after what is certainly a small (if any) effect, and the cost of genetic testing solely for risk assessment to guide behavior change is also an unnecessary cost burden to patients and care systems. Patients who smoke know they need to quit; overweight patients with diabetes know they need to change their lifestyles. Research and care delivery investments should be going towards identifying more effective ways of motivating behavior change, not chasing down more genetic testing options. Based on this assessment, I strongly disagree with the conclusion: "the principal implication for research is that data from better quality randomised controlled trials are needed"

Additional Questions:
Please enter your name: Richard Grant MD MPH

Job Title: Associate Professor and Research Scientist

Institution: Division of Research, Kaiser Permanente Northern California

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
This is an interesting and much needed review. It is a timely topic and the authors have tackled the issues extremely well. This review has several strengths, including the fact that it looks at both intention to change and possible fatalistic behaviour. I believe I know the literature in this area well and, to the best of my knowledge, the authors have captured all the important work to date.

The methods are solid (though methods is not my area of expertise).

I highly recommend publication. No major revisions required.

The following comments are only suggestions:

- More on how genetic risk information compares to other risk information.
- Some have suggested that there is too much emphasis on "risk information". For example, nutrigenomic information about how individual metabolisms react can be framed as something different that "disease risk" (see http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0112665 - the authors include this study but, I assume, characterize as "risk"). It has been suggested by some that information about how food is metabolized may result in more behaviour change than "risk" information. While I am very sceptical about these claims (indeed, I think they are likely wrong), it would be useful for the authors to address or mention. This seem particularly important given the rise of wellness / lifestyle DTC companies that rely on this kind of approach. Indeed, the frame is more "this is best for you" and not "you are at risk".
- While this may be beyond the scope of this paper, it would be interesting to explore the conflicts of interest of some of the authors of the relevant behaviour studies (involvement with DTC companies, etc.).
- It might be nice if the authors tied their conclusions a bit more closely to the push for personalized approaches to health improvement/public health. There have been many high-profile claims about the value of genetic risk information. This work has important implications for this area. However, the editors (and authors) may feel this kind of editorial comment is not appropriate in a review of this nature.

Additional Questions:
Please enter your name: Timothy Caulfield

Job Title: Professor

Institution: University of Alberta

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I am part of the Genome Canada funded initiative PACEOMICS, a research project on the health policy implications of personalized medicine (http://paceomics.org). I attended a 23andMe funded workshop in San Fransisco in November of 2015.

Reviewer: 3

Recommendation:

Comments:
This update of a previous Cochrane review with meta-analysis of controlled trials on the impact of communicating genetic risks of disease in risk-reducing health behaviour is timely, given that several additional controlled trial have been published following the publication of the original meta-analysis in 2010.

The authors have implemented a very rigorous study methodology, the manuscript is very well written, and the introduction and discussion link the review/meta-analysis to previous, related reviews. Overall this is a high-quality review and I believe the topic is relevant to readers of the British Medical Journal. I recommend publication without further changes.

Bettina Meiser

Additional Questions:
Please enter your name: A/Professor Bettina Meiser

Job Title: Head of Psychosocial Research Group

Institution: Prince of Wales Clinical School, University of New South Wales Australia

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

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Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

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When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

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a. Title: this should include the study design eg "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
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iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

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g. Footnotes and statements

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Date Sent: 21-Jan-2016