Dear Editor,

Thank you for allowing us the opportunity to respond to the peer review comments. Our responses to each comment are below, indicating the nature of corresponding changes made in the revised manuscript. In the manuscript, we have underlined the altered passages of text.

Kind regards,

Theresa Marteau (corresponding author), on behalf of all authors

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.

RESPONSE: This review more than doubles the number of clinical trials that are included in the previous review, increasing their number from 7 to 18. In addition, four of these newly-integrated trials were judged to be at low summary risk of bias, which is notable given that all seven previously included trials were considered to be at high summary risk of bias. The 11 newly-added studies not only increase the power of, and tighten confidence intervals around existing analyses, but enable us, for the first time, to assess effects on additional behavioural outcomes such as alcohol use. Finally, elements of the procedures have been updated and enhanced, including the provision of summary risk of bias assessments for included studies and GRADE assessments of the quality of evidence for

each outcome. In sum, this means that the analysis in this updated review is significantly strengthened and the review is better equipped to provide a definitive assessment of the evidence on this topic than the first review. In addition, the topic is especially timely at this time given the current high levels of interest in personalised medicine, and the high-profile selling of various health-related direct- to-consumer tests in countries including the UK and USA. As such, a revised and updated version is well-placed to inform ongoing practice and policy discussions. The strength of the updated review and its timeliness are reflected in the positive assessments of the peer reviewers, with Reviewers 1 and 3 particularly emphasising the timeliness of the review and the value of incorporating additional trials.

• The conclusions are not all that different from the previous review.

RESPONSE: Whilst the findings remain broadly consistent with the previous review, our conclusions are now able to be significantly more definitive, for reasons outlined in the previous response - in particular because the review now incorporates a great deal more trial data. We have also made further revisions to our conclusions as a result of peer review comments, which are detailed below in the response to Reviewer 1. In our previous review, the principal conclusions had emphasised both the limited evidence (as regards quantity and quality) at that time and the need for more trials to be conducted. Neither of these points are now included in the conclusions, and we are significantly more qualified and conditional when discussing the potential value of additional trials (e.g. Discussion, page 18, paragraph 2).

• One of the refs suggests you could be more definite in saying additional trials aren't needed.

RESPONSE: Please see our response to this comment of Reviewer 1 below.

• The search is now almost a year old. What is the reason for this delay?
• Is an update of the search necessary?

RESPONSE: Updating our original review has been a significant challenge given the complex nature of the review, requiring a large multi-author team and additional consultation with clinical colleagues. In addition, we opted to pursue data from several authors of identified studies where useable data were not reported in published articles – this being preferable to excluding these studies from the analysis. We do not think that an update of the search is necessary, as the review was initially submitted at approximately 9.5 months from when the searches were completed and this revised version will be re-submitted at approximately 11.5 months. We think this would credibly meet expectations of being considered up to date, with in our experience 12 months often considered an approximate yardstick when first assessing systematic reviews for publication.

Cochrane conduct guidance (in the form of the MECIR guidelines) suggests 12 months as an appropriate threshold for the need to re-rerun searches, although this is not directly comparable because it is not mandatory to integrate any new studies found in these re-run searches into that version of a Cochrane review, but simply to report that they have been found.

• 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).

RESPONSE: We have now revised each section within the Results accordingly (pages 12-15) in order to provide the requested information on the genetic tests being used in the studies contributing to each outcome (as well as also being available in Table 1).

• 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.

RESPONSE: We had previously opted not to include this information as it had been included in Table 1 and in the overall description of studies. However, we agree with the reviewers that this information should be included in the Results section and we now do so for the analysis of each outcome (pages 12-15).

We specified that these comparisons would be combined within each meta-analysis in both our peer-reviewed Cochrane protocol and our previous Cochrane review as we regard the different comparisons as sufficiently comparable in their ability to isolate the specific effect of the DNA risk communication intervention, especially given that it is often inevitable that there will be variation in the characteristics of control (e.g. standard care) and intervention arms in any such meta-analysis of intervention effects. In addition, as a result of this comment, we conducted sensitivity analyses that confirm that when only the predominant comparison is used for the analyses i.e. DNA disease risk estimates vs no disease risk estimates, the results are altered negligibly without altering conclusions.

• Please discuss the international context. Are these tests available outside the US?

RESPONSE: Although eight studies were conducted in the USA, the other ten were conducted in the UK, Japan, Finland and Canada (see Table 1 and Results, page 11,

paragraph 2), highlighting that genetic tests are either being used in clinical contexts or are being considered for use, internationally. In terms of direct-to-consumer genetic testing, this is now available in several countries other than the US, with significant expansion into the UK and several other European countries in 2014 and 2015, and press reports suggesting that this expansion will continue, for example, to include Australia (http://www.reuters.com/article/23andme-fda-idUSL2N0P116Z20140620). We have now revised the Introduction, (page 4, paragraph 1) to better reflect this.

• Interesting study, but the 3 behaviours are known to be very resistant to change: diet, smoking, exercise.

RESPONSE: Whilst we do not disagree that these behaviours are typically difficult to change, there is a wide range of evidence for the effectiveness of interventions in changing health-related behaviour including smoking cessation programmes (West, May, West, Croghan, & McEwen, 2013), weight loss programmes (Jebb et al., 2011) and face-to-face interventions to increase physical activity (Richards et al, 2013). Crucially, it has been proposed that genetic testing could be one such effective intervention, as we highlight in the paper's Introduction. These tests continue to be used internationally in clinical and direct-to-consumer settings supported in part by claims that they are likely to be especially potent in motivating behaviour change.

• 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.

RESPONSE: Behaviour and the ability to control behaviour is influenced by a myriad of processes some of which have a genetic basis others of which do not. Importantly, none of the genetic influences have a deterministic role or even a dominant role in the manifestation of the behaviours that are the focus of this review. Genetic variants on chromosome 15q25 locus (of which rs1051730 is one) are associated with both health outcomes (risk of lung cancer) and behaviour (smoking cessation). It appears that both these effects are largely explained by heaviness of smoking (Munafo et al 2012; Taylor & Munafo 2014), a phenotype that is a negative predictor of smoking cessation. There is, however, an absence of evidence comparing quit rates in those with equivalent levels of heaviness of smoking but with different genotypes, to know whether an identified genetic basis to heaviness of smoking further predicts quitting.

• Ref 37 is the protocol of a RCT, there are no data in there.

RESPONSE: These data which are from a completed but as yet unpublished study were made available to us following a request to the authors. This has now been stated in Table 1 in the entry for this study.

• 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.

RESPONSE: Thank you. We agree - the confidence interval crosses zero and represents small effect sizes - and this has been removed as requested both in the Abstract, and elsewhere where a similar formulation had been used (Abstract, page 3, paragraph 1; Results, page 14, paragraph 1; Discussion, page 16, paragraph 2).

• 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.

RESPONSE: We have now clarified this procedure in revising the manuscript, adding the text below to the 'Data extraction and synthesis' section in Methods (page 8, paragraph 3):

"This involved, following the methods outlined in the Cochrane Handbook (sections 7.7.7. and 9.4.6)[26], first computing standard errors for these studies by entering the data separately as dichotomous and continuous outcome type data, as appropriate, and converting the confidence intervals for the resulting log odds ratios and standardised mean differences into standard errors. Log odds ratios were then converted to standardised mean differences by multiplying each by the required constant."

** 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.

RESPONSE: We have now done this (Results, page 13, paragraph 1).

2) 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"

RESPONSE: Thank you for pointing this out. We have now reworded this passage in a similar form to that suggested and it now reads as follows (page 15, paragraph 3):

"The inability of 14 of 18 studies to meet criteria for low summary risk of bias reflected…"

3) 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”

RESPONSE: On reflection, we broadly agree with the Reviewer. In sum, our analysis is highly suggestive of the limited potential impact of these types of interventions, in spite of the lack of high-quality research evidence within each and every possible behavioural domain, and we agree that additional trials will need to be well justified. We have therefore removed the text cited by the Reviewer (which was originally within paragraph 3, page 20) and we are significantly more qualified and conditional when discussing the potential value of additional trials (page 18, paragraph 2).

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.

RESPONSE: We have made reference to the wider evidence base for the limited behavioural impact of risk communication (For example, Interpretation of study results, page 18, paragraph 2).

- 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".

RESPONSE: Thank you for this helpful point. As the reviewer points out, we did include this study (Nielsen) because participants with a genotype linked to an increased risk of sodium-sensitive hypertension were given a targeted recommendation for sodium intake on this basis. In response to the comment, we have now added to the Discussion (page 20, paragraph 2), pointing out that:

"The communication of genetic information may differ in respect to how much it is framed as a 'risk' to health, or used to inform recommendations for wellness (even if these are derived from associations with increased risk). For example, nutrigenomic information may not be presented or characterised as risk information, but may be used to inform behavioural recommendations which can be highly specific and targeted. This is demonstrated by one of the included studies[43], which used nutrigenomic testing to provide specific intake recommendations for foods. However, as yet, there are too few trials to assess whether this type of genetic testing differs in impact from more traditional genetic testing providing information about the likelihood of a health harm."

- 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.).

RESPONSE: This is an interesting point but we think, as the reviewer points out, that any such analysis is beyond the scope of the paper.

- 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.

RESPONSE: We have attempted throughout to place the review in the context of the claims made by proponents of personalised medicine and we have amended the Discussion (page 19, paragraph 3) to be more explicit in drawing this link. However, as the Reviewer points out, we think that a more expansive and critical discussion would be more appropriately placed in an editorial, were the review to be accepted.

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.

RESPONSE: Thank you to the reviewer for their comments.