Reviewer's report

Title: The implications of biomarker evidence for systematic reviews

Version: 1 Date: 8 September 2012

Reviewer: Orestis Panagiotou

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Major Compulsory Revisions:

1. Please specify if you considered other types of markers, e.g. those measured in the blood, urine etc. The search terms focus primarily on genetic-genomic biomarkers, however the title and abstract are broader. I feel that you need to clarify in the text if your approach pertains to all biomarkers (which is what I get as a reader) or only to genomic ones.
   a. If it is the former (all biomarkers), then I am not sure that the search terms used capture all biomarkers sufficiently. For example proteomic biomarkers are likely not to be identified.
   b. If it is the latter (genomic markers), the search is OK but you should focus on that throughout the text and try to avoid generalizability to all biomarkers.
   c. Alternatively, you should clarify that the term biomarker in the text refers specifically to genetic/genomic markers.

I think this quite important to clarify as the search strategy may not be representative.

2. p. 8, “There are many SRs used highly cited biomarkers RCTs and emphasized on studies with highly promising results”: it is not very clear what you mean; maybe you need to rephrase? The SR you mention [Ref 18] did not include RCTs as it implied in the text. Actually, it touched on the issue of bias in biomarker studies by showing the inflation in the effect sizes of many highly cited biomarkers. One could argue that prospective evaluations of biomarkers in RCTs could provide more reliable results about their effects and clinical utility. I think that this could nicely in the discussion about the issue of biomarker RCTs.

3. Another point that might be worth mentioning is the low credibility that nominally significant results of observational biomarker studies confer to the respective association [Ioannidis, Am J Epidem 2008;168:374-83]. This issue as well as the related biases in the primary biomarker studies are better understood by meta-analysis methodologists [Panagiotou & Ioannidis, J Clin Epidemiol 2012; 65(7):740-7], and as a result they are more reluctant to towards systematic reviews/meta-analyses of studies on biomarkers (both RCTs or not).

Minor Essential Revisions:

4. I think that the “Methods” and “Results” sections in the Abstract should be expanded to convey other important information.
5. p. 6, “While only a minority of trials has been included in systematic reviews, this study found that the number of trials involving biomarkers assessed in systematic reviews is even smaller”: please cite where the estimation used for comparison purposes comes from.

Discretionary Revisions:

Some comments/thoughts on my side, not necessarily to be addressed by the authors:

Fig. 1: it is very interesting (or maybe disappointing for the scientific community?) that the number of case reports and non-systematic reviews follows the same pattern with SRs/MAs and RCTs/CCTs. I would expect them to decline as the evidence-based approaches increase by time, but it may be still early to see that. However, it’s nice to see that these publications have a low annual rate.

**Level of interest:** An article of importance 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