Author's response to reviews

Title: Reporting Recommendations for Tumor Marker Prognostic Studies
(REMARK): Explanation and Elaboration

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Version: 2 Date: 12 August 2011

Author's response to reviews: see over
We have taken account of the reviewers’ comments; detailed responses to these are below.

As a result we have made a few changes to the manuscript:

- We have clarified the availability of the checklist as a Word file (p7).
- We added/modified text on pages 13, 14, 15, 16 and 33.
- We removed one figure and replaced one figure (new figure 3 on p44), renumbered these as appropriate, and included statements about permission to reproduce the 4 remaining figures. We made minor adjustments to the references to take account of these changes.
- Changed Table 2 to typed version instead of image from published article (p40)

Douglas G Altman,
12 August 2011
Responses to Reviewers:

Reviewer 1: Dr. Grossman
This reviewer did not suggest any changes.

Reviewer 2: David R Parkinson
Note: my colleague Dr. Alessandra Cesano also reviewed this manuscript and provided comments which are integrated with my own review. The REMARK recommendations concerning the reporting of tumor marker prognostic studies have become the de facto standard for publication of results in this field. The same authors have now produced a well-written and very useful paper which serves as a natural elaboration of the original series of REMARK papers, providing specific recommendations around each of the REMARK list items accompanied by specific “best in class” real world examples. This publication will be extremely useful to clinical researchers, clinical test developers, and journal manuscript reviewers. In addition hopefully it will positively influence both the conduct and reporting of research in molecular diagnostics. Furthermore I would hope that many of these recommendations will be reflected in forthcoming FDA test development guidelines.

Thank you for those comments

I suggest only Discretionary Revisions:

Specific comments:

1. The article is very long and detailed. Much of the detail is useful, and the use of positive examples very effective. By contrast the summaries of the shortcomings of current literature seen in a number of sections almost seem an afterthought, represent a distraction, and might be considered for publication separately if the length of the manuscript is an issue. Alternatively, different ways (e.g. graphics) to represent this data (and their ultimate meaning for the interpretation of the great amount of prognostic biomarker literature out there) should be considered (e.g. a pie chart showing the fraction of “good reports” versus “not so good reports” and for the latter a graphic representation of the different issues distribution/prevalence; such a graph would allow the reader to quickly grasp on one side the magnitude of the problem of poor reporting in literature together with an understanding of where the most frequent shortcomings exist.

   We feel it is better to refer to the poor reporting of specific items within the relevant sections. We did not do this systematically for all items but gave examples for certain important items that illustrate the current level of bad.
   Graphical display of the extent of poor reporting of prognostic studies would make the paper longer, and we do not think this would be an effective way to convey that information.
   We considered including (and indeed drafted) a short summary section “Evidence of poor reporting” that could go between the Introduction and the discussion of the checklist items. Including this text would make the paper 2-300 words longer, and we have not included it in the revision.

2. With respect to the Specimen Characteristics and Assay methods sections a discussion that since it is impossible to control all possible pre-analytic variables, prospectively establishing criteria for sample
acceptance and analysis (i.e. sample specifications) should be considered and described. In addition, although the distinction between biologic controls and assays controls is appropriately mentioned and the biologic controls discussed in detail, the assay controls session (how to control the assay performance specifically) could benefit from an expansion to address the important issue of comparability between studies conducted in different labs and/or different times etc.

We added some brief text to Items 4 and 5 to clarify these points.

3. The specific recommendations presented are very clear, and the provided examples quite useful. However, in a number of cases it would be useful to provide additional background information as to the reasons for a particular recommendation, and practical examples of the implications (in term of final results e.g. misinterpretation) if the recommendation is not followed.

We feel that there are already several places in the paper where we have provided this information. Indeed the whole purpose of the paper is to amplify the checklist items by explaining the underlying rationale of each item. We believe that the implications of failing to supply the requested information are that the one or more of the following apply: the study cannot be properly appraised for methodological rigor, the study cannot be replicated, and the results are unavailable for inclusion in a subsequent systematic review and meta-analysis.

As noted in the opening paragraph of the paper “more transparent and complete reporting of studies would enable others to better judge the usefulness of the data and to interpret the study results in the appropriate context.”

4. It would be useful to have a more detailed discussion about the particular issues of retrospective analysis of samples acquired from prospectively conducted clinical trials. These are an important and efficient tissue source for molecular diagnostics development but require particular considerations. For example, the importance of locking the analytical results database before un-blinding the clinical data and other documented procedural steps to maintain data integrity might be emphasized.

Thank you for this suggestion. We have added a few sentences and a new reference to item 10h.

5. The use of the call out “boxes” to summarize important recommendations is very effective. In the same spirit, a major concluding table linking the complete REMARK checklist with the specific recommendations (and possibly the implications of not following these recommendations) would be a very useful future tool for manuscript reviewers generally.

A Word version of the checklist is available on the EQUATOR website (www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines/remark), as noted on p9. That checklist has a column for authors to insert where in their manuscript they provided the information requested by each item in the checklist.

Reviewer 3: David L Rimm

This paper is not a traditional paper, but rather a reference for collection of the key elements of the REMARK guidelines. The paper does not change any aspect of REMARK, but is more or less the “biomarkers for dummy’s” version. That is it provides a more detailed and granular approach for how to write a comprehensive and rigorous biomarker paper. This work is very detailed and spans many pages,
but is full of potentially valuable tables. Although perhaps a bit too formulaic, many tables will be valuable for scientists and clinicians at all levels. The work could be especially valuable for junior colleagues and training courses for translational scientists.

Overall, the work is comprehensive and represents a great guide for use as a reference. There will clearly be points that are included in some biomarker studies that are not addressed here and there will be some good biomarker papers that do not necessarily address every point raised in this paper. The work touches on every critical area, thus it is hard to suggestion further expansion. If any area is slightly weaker, it would be the section on assay methods. However, overall the paper is excellent and is likely to be an excellent tool for educators in translational science programs.

We thank Dr Rimm for his positive comments. He made few specific suggestions. The point he raised that was not already raised by Dr Parkinson is that the relative importance of different checklist items will vary from study to study; that is undoubtedly true. However, as we have noted in the last paragraph of the Introduction, the REMARK recommendations represent minimal recommendations for reporting studies (in common with other reporting guidelines such as CONSORT). Thus it is desirable that authors address every item even if only to indicate in some places that the relevant data are not available. Further, it is always appropriate to report all important aspects of what was done in a study even if it is more than the minimum called for in the checklist.

Comments from PLoS Medicine editors

1) Can authors include the checklist file and flowchart (preferably as editable Word documents) to make available as supporting information files with this paper - so readers can download, fill out and use in reporting their biomarker studies

   There is indeed a Word file of the checklist that can be downloaded. As noted in the paper, this is available at http://www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines/remark
   We are also submitting it as a web appendix.
   We do not have a template for a flow diagram – these studies do not have standard structure.

2) The paper is very long and I understand the "meat" of the reporting guidance probably cannot be realistically cut. But recommend some of the introduction could be condensed, eg the "we have attempted to minimise distractions" paragraph and "the paper is structured as the original checklist" paragraph, "one suggestion in the remark checklist was to include a diagram showing the flow" paragraph. *Introduction statement that this guideline applies to other studies than cancer -- not clear this applies given the frame of reference and development of the guideline. This may also potentially lead to problems of overlap between the guideline and other (current or future planned) guidelines. Recommend keeping the guideline focussed and oriented around the original theme.

   The authors feel that shortening a couple of paragraphs would make minimal difference and prefer to leave the highlighted sentences in the text.
   There is almost nothing in the REMARK checklist that is specific to marker studies in cancer and indeed, as we note near the end, some authors have found REMARK very helpful when assessing marker studies in other medical areas. Thus we don’t wish to delete this important idea, especially as the paper is being published in general medical journals.
3) Multiple figures and tables are copied from what I assume are not OA journals. This raises copyright problems. Recommend authors replace such items with items available in open access journals which allow free reuse. If this isn't possible, the items will need to be removed and replaced with a reference (e.g., "see figure X in reference [y]"). Unfortunately, redrawing material that is copied from a non OA source does not obviate copyright problems, if the redrawn item looks substantially similar to the original.

We obtained permission to reproduce 3 figures and have dropped two figures, one of which we have replaced by a new figure from an open access article. All the tables have been retyped from the originals, so we understand that there is no copyright issue. In particular, we have replaced the published version of Table 2 that was in the previously submitted manuscript by a Word table.