Reviewer's report

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

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Reviewer: David R Parkinson

Reviewer's report:

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.

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.

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.

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.

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.

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.

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.