Reviewer's report

Title: DNA Methylation Gene-Based Models Indicating Independent Poor Outcome in Prostate Cancer

Version: 3 Date: 11 April 2014

Reviewer: Joseph Koopmeiners

Reviewer's report:

I'd like to thank the authors for their revised manuscript but there are still several major statistical issues that call into question the scientific conclusions of this manuscript.

Major Compulsory Revisions

1. While I appreciate the author's adding Harrell's c-index and Gonen & Heller's c-index to Table 3 and agree that both are appropriate measures of the classification accuracy of the proposed models, I am still concerned that the text of the manuscript focuses exclusively on the likelihood ratio statistic. The likelihood ratio statistic is in no way a measure of the predictive accuracy of a predictive model and drawing conclusion regarding the predictive accuracy of your model based on this statistic is inappropriate. Furthermore, the p-value referenced in the second to last paragraph does not evaluate the incremental value of adding gene methylation to a risk prediction model and does not support the conclusion that incorporating gene methylation improved the risk prediction of current clinical variables.

2. As I pointed out in my original review, summaries of the classification accuracy estimated using the same data that were used to build the model will be optimistic and a cross validation procedure should be used to reduce the bias in these estimates. This is true for any summary of the classification or predictive accuracy of the model such as Harrell's c-index, Gonen & Heller's c-index or the Kaplan-Meier curves presented in Figure 3. For illustration, consider Harrell's c-index for models C and D: 0.831 for model C and 0.835 for model D. These two values are nearly identical and it is entirely possible that the apparent improvement is due entirely to adding additional predictors and overfitting the data. A cross-validation procedure would allow for a fair comparison of the two models.

3. In my previous review, I noted that death from other causes is a competing risk but this comment was ignored. I concede that summaries of classification accuracy, such as Harrell's c-index, have not been developed to account for competing risk but extension to the Cox model that account for competing risk are available and should be used in this case.

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests