Reviewer's report

Title: CDO1 Promoter Methylation is a Biomarker for Outcome Prediction of Anthracycline Treated, Estrogen Receptor-Positive, Lymph Node-Positive Breast Cancer Patients

Version: 2 Date: 24 March 2010

Reviewer: Kristina Warton

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Discretionary Revisions
These are adequately addressed by the authors.

Minor Essential Revisions
These are adequately addressed by the authors.

Major compulsory revisions.
1) Clarify the clinical significance of the aim and study outcome.
This was adequately addressed by the authors.

2) Clarify whether the p-value obtained for CDO1 in the validation set was corrected for multiple comparisons.
   Author Reply 8: The p-values provided in the article have not been corrected for multiple testing. An over optimistic assessment of markers due to multiple testing issues was avoided by the design of the study: Due to the usage of an independent patient population as a testing set, such a correction is not necessary. This correction would have been required if all marker candidates were analyzed in one patient population with no subsets such as validation and training sets.
   This issue still needs to be addressed. To clarify my query: prior to screening the 6 potential biomarkers (CDO1, APC, ZBTB16, NCR1, POU4F3, CXCL12) it was not known which of them would have predictive value. Hence the validation set was used to select (rather than validate) CDO1 from amongst the 6 potential biomarkers selected in the training set. I suspect that this requires a correction for multiple comparisons to be introduced, however, this issue is best reviewed by a biostatistician.

3) Provide additional supplementary information.
   Author Reply 9: Since most of the analyzed genes did not show any methylation,
we think
that such supplementary data is only of limited value. The methylation raw data would only
be meaningful for CDO1 because this is the only gene which showed statistically
significant
information in the training as well as in the validation set. However, the
information gained as
compared to the information contained in Table 3 seems to be rather minimal.

Rather than supplying methylation data for all of the analysed genes, most of
which did not shown any methylation, the authors could provided data for the 37
genes which did show some differential methylation between the samples. This
information would be of interest for groups studying the methylation of these
genes in a particular cancer.

**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the
statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.