Reviewer’s report

Title: A microRNA biomarker of hepatocellular carcinoma recurrence following liver transplantation accounting for within-patient heterogeneity

Version: 0 Date: 23 Dec 2015

Reviewer: Michiel Dehoon

Reviewer's report:

While this manuscript addresses an important problem and is well-written, I have several comments on the methodology employed and the novelty of these results.

First the comments on methodology. To visualize the data, the t-Distributed stochastic neighbor embedding (t-SNE) technique is used. As this is not a commonly used methodology, I am wondering if a simpler method would suffice. For example, would you reach the same conclusion if you performed just Principal Component Analysis or some other well-established technique?

I don't quite understand why k-means clustering is needed. If the purpose is to distinguish between recurrence and non-recurrence, then why not use a supervised learning method?

In Figure 2, 21 out of 55 samples from recurrent patients in cluster 2 also have at least one sample in cluster 1. How many of the non-recurrent patients in cluster 2 have at least one sample in cluster 1, and is the percentage for recurrent patients significantly higher than for non-recurrent patients?

Regarding the novelty of this manuscript: In the section "Relationship to previously published biomarker approach", you compare your analysis to your previous analysis published in reference 6, where a min/max approach was used. Since the MA-plots of the min/max expression profiles show a similar separation between recurrent and non-recurrent patients as the sample-level analysis, what is the benefit of the approach suggested in the current paper? If there is a benefit, then that should be clearly described in the paper, with appropriate statistics to compare the previous and the current results.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

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