Reviewer’s report

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

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Reviewer: George Calin

Reviewer's report:

Currently the therapy for hepatocellular carcinoma (HCC) is surgical removal of the diseased part or entire removal of the liver, followed by transplantation of healthy liver tissue. Long term survival of the patients with HCC after transplantation is limited by recurrence of the disease. Because the donor liver organs for HCC patients are limited the identification of a biomarker or biomarkers that can help identify the patients with best chances of recurrence free survival is important as Xie et al. try to demonstrate in their manuscript. Although the idea and approach of the paper is new and original several issues still need to be addressed.

1. The authors reanalyzed the data already shown in one of the gropes publications and added 20 new patients. Please show how the samples were processed for these 20 new patients.

   a) How were the miRNAs isolated? Did the authors started from total RNA?

   b) How was the hybridization of the array performed?

   c) Was the previous batch and the new batch processed in the same way? Otherwise the two batches can't be analyzed together, due to the errors and differences that might have been introduced through different ways of processing the samples and hybridizing the array.

   d) Was the raw data of the array analyzed in the same way? Is the data comparable?

2. Show the results of the microarray. The manuscripts statistical analysis are based on what?

3. Validation through another method of the microarray data is demandable.

4. On page 7 Row 5 in sad of 28 of 50 outside of Milan I think the authors wanted to write 28 of 58 outside of Milan. Check the total number of the patients included in the group that the authors are discussing at this point.
5. On page 7 the first sentence from Feature Selection the authors mention: "The previous results are based on the full microRNA profiles in each sample (847 microRNAs)." Which are these miRNAs that the authors refer to? Please show the data. I imagine that authors are not referring to all 847 miRNAs that are present on the array.

**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.

No

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

Yes

**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

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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