Reviewer's report

Title: DNA methylation profiling reveals novel diagnostic biomarkers in renal cell carcinoma

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Reviewer: Susanne Fuessel

Reviewer's report:

Lasseigne et al. performed genome-wide DNA methylation analyses in paired tumor and non-malignant renal tissues from 96 patients with different types of renal cell carcinoma (RCC). They identified differentially methylated CpGs as potential diagnostic markers, which may help to discriminate between tumor and normal tissue. For the validation of their results they used publicly available data from 732 RCC patients from The Cancer Genome Atlas (TCGA). The authors performed comprehensive biostatistics and clustering analysis, looked for discriminating models and for potentially affected genes and corresponding pathways. They report these models and markers for all analyzed RCC subtypes and for the subgroup of clear cell RCC.

In general, the manuscript is well written and describes an elaborate and comprehensive work in a suitable manner. Nevertheless, some revision is necessary.

Major Compulsory Revisions:

1. Information and references given in the introduction for treatment of RCC seem not to be suitable and have to be updated.

2. Explanation of gene set enrichment analysis is relatively broadly speaking. Possibly, more details could be provided, e.g. for prominent genes affected, also in relation to other studies.

3. The authors should discuss in more detail, whether the CpGs contributing to the PAM classifier panels were already described in the literature and whether information is available on the epigenetic regulation of the potentially associated genes.

4. The usefulness of the identified alterations in CpG methylation for diagnosis of RCC has to be emphasized more clearly and concretely. The mentioned "differential genomic markers" such as SEPT9 and PCA3 are not appropriate for this question in RCC. The authors rather should discuss diagnostic approaches for the application of RCC-specific methylation markers identified in this and in previous studies.

Minor Essential Revisions

5. Did the authors also perform survival analyses, since they mention survival data of some patients?

6. Did they present their own results or TGCA data in Fig. 4C? There is a
discrepancy.

7. The legend to Suppl. Fig. 2 should be more informative. Which genes are shown there?

8. Abbreviations in the text body, the figures and tables have to be explained.

9. Quality of the figures should be improved. Finally, some linguistic deficiencies should be revised.

Quality of written English: Needs some language corrections before being published.

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.