Reviewer's report

Title: Intratumoral genetic heterogeneity in metastatic melanoma is accompanied by variation in malignant behaviors

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Reviewer: Helen Rizos

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This is a well-written paper detailing genetic heterogeneity in FFPE melanoma tissue samples, and derived single cell clones. The conclusions are not new however, as it is well established that melanoma is highly heterogeneous. The fact that short-term cell cultures are also heterogeneous, but retain characteristics and oncogenic drivers of the parental tumour is very interesting, and it is a shame that this was not expanded further.

Discretionary Revisions:
For instance, does heterogeneity diminish in the melanoma cell cultures over time, ie did the investigators compare cultures at various time points. Similarly, it would have added significantly to this work if the evolution of melanoma could have been analysed, ie if multiple independent metastases from an individual had been analysed and compared. More details are also needed regarding the passage number of these cell clones.

Minor essential revisions:
I also felt that some of the data did not add significantly to the conclusions, and needed to be reworked and perhaps included as supplementary data. In particular, the mutations screening essentially concludes that most mutations were not genuine and artefacts of either low coverage sequencing or fixation. All of these results do not need inclusion in the main text.

The copy number data would also have been more informative if shown as line plots showing copy number rather than histograms with number of copy number aberrations (ie as shown in Figure 2A). The investigators could also have selected smaller genomic regions to highlight copy number variations between samples.

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.