Reviewer’s report

Title: Gene signatures ESC, MYC and ERG-fusion are early markers of a potentially dangerous subtype of prostate cancer

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Reviewer: Qianben Wang

Reviewer’s report:

The authors appear to have more or less addressed the bulk of the reviewers’ comments, and I am quite satisfied with the revised manuscript. I think the authors have had great success extending their primary finding of a dangerous subtype of prostate cancer, showing in the supplemental cohort that 13/29 patients assigned to a poor prognosis subtype with low Gleason score progressed following radical prostatectomy. I find it puzzling that the authors continue to make statements such as, “In most of these cases successful surgery will lead to survival, regardless of whether the tumor is likely to progress…” when they have identified a subtype representing a substantial portion of patients in two independent cohorts for whom surgery was not curative. I believe the authors would be justified in drawing more attention to this valuable result. Ideally, future studies will identify an independent cohort of patients in a “watchful waiting” trial to apply these gene signatures, but for now, given the available datasets, it is clear that important conclusions can be drawn from recurrence/survival data in men following surgery. Finally, the one disappointing response was to my request to evaluate the subtyping strategy on a “by patient” rather than a “by sample” basis. The authors claimed that the study’s focus is on demonstrating within-patient homogeneity from multiple samples with regard to gene panel-based subtyping. This pursuit is largely academic, and I believe that once homogeneity has been established, as the authors have shown, the focus should shift to a patient-centric analysis. That being said, this is not a compulsory matter, but one that I hope the authors will address in future studies and perhaps mention as part of their discussion.

I believe this manuscript is suitable for publication. This was a nice effort that provides valuable technical and practical advances.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests