Reviewer's report

Title: Identification of Fluorescence in Situ Hybridization Assay Markers for Prediction of Disease Progression in Prostate Cancer Patients on Active Surveillance

Version: 0 Date: 22 Jul 2017

Reviewer: Chris Warlick

Reviewer's report:

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The authors present a study using FISH markers to identify men on active surveillance with an increased likelihood of progression. This is an interesting study that addresses a significant problem in management of prostate cancer. The study may be strengthened by addressing the following.

1) The authors use change in number of cores positive for cancer as well as changes in the volume of cancer seen per core as evidence of disease progression. However, it is understood that men who show changes in disease characteristics within the first 1-2 years on active surveillance, likely represent men who had the more aggressive disease all along, but was missed simply due to sampling error. Therefore it is unclear whether the men who showed "progression" truly developed genomic changes, or whether some of them represent men with more aggressive disease who were missed due to sampling. Of the men who progressed on active surveillance, what was the average time to progression? Also, for men who showed more cancer per core as evidence of progression, was there a threshold increase required to be defined as "progression", or was any increase at all defined as progression. Small changes would be unlikely to be clinically relevant. Further PSA changes may be from a variety of different reasons and may not represent disease progression, but perhaps more patient or physician anxiety, if they occur in the absence of any other sign of progression. Thus there are some inherent limitations in the definitions used. These should be clarified and discussed.

2) Do the authors know the fraction of men in the biopsy cohort with fewer than 12 cores sampled in their biopsy? Men with fewer cores than this are likely undersampled and may have been harboring more aggressive disease. If a large fraction of the cohort were
in this category, this may impact results. At a minimum, this should be considered a limitation in the discussion.

3) Please clarify whether the Gleason grades were centrally read using current criteria as the criteria for Gleason scoring changed after most of the specimens in this study were obtained. This may have skewed results as well. The authors report that their ability to discriminate between indolent vs aggressive disease was best for intermediate risk patients. Again, this may be reflective of changes to grading between when the samples were obtained and current grading criteria. This should be discussed if the samples were not centrally re-graded using current criteria. At a minimum, if not centrally reviewed, this needs to be discussed as a limitation.

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.

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.

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