Author’s response to reviews

Title: BCL-2 expression aids in the immunohistochemical prediction of the Oncotype DX breast cancer recurrence score

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We thank Dr. Geffen for his review. Below are our responses to editor and reviewer suggestions.

Editor Comments

Please confirm whether informed consent, written or verbal, was obtained from all participants and clearly state this in your Methods and Ethics approval and consent to participate sections. If verbal, please state the reason and whether the ethics committee approved this procedure. If the need for consent was waived by an IRB or is deemed unnecessary according to national regulations, please clearly state this, including the name of the IRB or a reference to the relevant legislation.

We have edited the Methods section to include IRB exempt status (line 87) belonging to Category 4 regulation. It is eligible for exempt status due to the fact that the analysis was retrospective (which we have now added to line 75) and was obtained in a deidentified fashion by an honest broker (line 86).

Reviewer reports

David Barry Geffen, MD (Reviewer 2): This paper is a very well written report of the use of techniques of straining for BCL2 and a mathematical transformation in addition to image analysis staining for ER PR and HER2 to predict Oncotype DX results. The ability to predict Oncotype results from locally obtained clinical -pathologic information would be of great benefits where the expense of Oncotype is too great a burden to enable doing the test.

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I am not a statistician so I suggest statistical review of the transformation techniques.

I am not a pathologist so I cannot comment on the techniques of IHC and image analysis other than to say that as a breast oncologist the techniques and results in this study seem very reasonable.

I suggest adding to the paper a note that with a total of 158 patients spread over 7 years the numbers in each category are relatively small and this study should be regarded as hypothesis generating to be verified in a larger group patients. From the data presented it would seem that RS can be predicted in 60% or so of cases, potentially saving resources significantly.

We have added a note in the Discussion section stating that the results would be aided with a larger sample size (line 302).

I would replace reference 49 or add to the references another study by Gage et al recently published - Combined pathologic-genomic algorithm for early stage breast cancer improves cost-effective use of the 21 gene recurrence score assay. Annals of Oncology 29:1280, 2018. They report on the use of their algorithm in 1268 patients with 5 year clinical followup using just ER and PR staining, and were able to show that they could predict as well as the RS for low and high risk patients and could avoid doing the RS in about 44% of patients.

We agree and have added reference to this paper (line 46, new reference 22).