Reviewer's report

Title: Amplification of HER2 is a Marker for Global Genomic Instability

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Reviewer: David G Hicks

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I have read with interest the article entitled "Amplification of HER2 is a marker for global genomic instability" By Ellsworth et. al. In this study the authors demonstrate that the frequency of AI is significantly higher in HER2 amplified tumors compared to HER2 negative ones. Specific alterations seen in chromosomes 11,16 and 18 appear to show an association to the HER2 status. This paper is well written and the goals and the data are clearly presented. I have the following comments to make on what has been presented.

1. On page 4 in the first paragraph, the authors state that the incidence of HER2 overexpression is 25-30% of human breast cancers. This number really depends on the population of patients being evaluated and the 25-30% range is more relevant to the patient population with metastatic disease that were treated in the early pivitol clinical trials. In contemporary consecutive series of breast cancer, the incidence is more in the 10-15% range.

2. In the second paragraph on page 4 the authors make reference to genes that modify the clinical response to trastuzumab, including p27, PTEN IGF1R and TOP2a. I am unaware of any studies that have looked at the response to trastuzumab in terms of TOP2a and there is no reference to this listed in the cited references. the authors should site a reference if one exists or modify this sentence.

3. On page 5, the authors state that amplification of HER2 was defined as a ratio of greater than 2. I am sure that the authors are aware of the new ASCO/CAP guidelines published last year in the JCO and Arch of Pathol that have re-defined amplification as a ratio of greater than 2.2. this new definition creates a new HER2 fish category of equivocal patients who have ratios between 1.8-2.2. Although they are likely to have very few patients in the equivocal category, it would be important for the authors to analyze their results into three categories, neg, equivocal and amplified. the purpose of creating the equivocal category was due to the fact that little was known about this group and more research is needed to better understand the clinical significance and potential benefit of treatment for these patients.

4. On page 7 in the second paragraph of the results section, the authors state that 5 samples received neo-adjuvant chemotherapy before sample collection and that none of these patients where HER2 +. Was the HER2 status assess on the pretreatment sample or on the post treatment sample? Does the analysis remain the same if these cases are eliminated from the HER2 - group? Are these
cases really necessary given that they already have 153 HER2 negative patients?

5. On page 9 near the top of the page the authors are referring to trastuzumab resistance and the need to improve our understanding of the biology of aggressive disease and patient response to treatment. I think the authors need to make it clear here that the data presented can not at this point be extrapolated to say anything about predicting which patients will respond and which ones will not. the data is however hypothesis generating and this hypothesis is supported by the results obtained in the NSABP B31 study which showed that co-amplification of C-MYC and HER2 predicted for a better response to herceptin (presented by Paik et al at SABCS). did the authors look for and/or see any change in the C-MYC locus?

**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.

**Declaration of competing interests:**

'I declare that I have no competing interests'