Reviewer's report

Title: Simultaneous copy number gains of NUPR1 and ERBB2 predicting poor prognosis in early-stage breast cancer

Version: 2 Date: 15 June 2012

Reviewer: Kylie Louise Gorringe

Reviewer's report:

Thanks to the authors for their efforts in addressing the comments raised in review.

Minor:

1. Please could there be more detail of the IHC scoring in the methods – what level of staining (e.g. Allred scale or 0-3) was considered to be positive for ER, PR and especially HER2?

2. Please could you add the description of “cancer genes” to the legend for Table 2.

Major:

1. Was the FDR correction in Supp table 2 performed on a genome-wide scale? The values don’t seem to be very different from the original p-value, as I would have thought if correction was being made across hundreds of copy number segments.

2. The definition of Luminal A and Luminal B is the same in the methods (ER+/PR+/HER2-). How were these distinguished (e.g. Ki67)? If ER/PR/HER2 is only available, these groups should be combined into a single Luminal group. As this point was originally discretionary in the first review, the authors could remove the subtype information from the paper if preferred.

3. The numbers of HER2 cases do not add up. In Table 1 HER2 IHC positive cases are given as n=24 for the discovery set, but only 4 are listed in the HER Subtype group below. In addition, only 1 out of these 4 cases have HER2/ERBB2 copy number gain, which suggests that the HER2 staining is not very accurate. Similarly, 29% of cases are stated to have high-level amplification of ERBB2 but 50% have positive staining. What is the correlation between HER2 staining and HER2 amplification? The copy number should be the gold standard for HER2 amplification.

If the HER2 staining is determined to be unreliable, one suggestion could be to put the ERBB2 amplified samples (by array or QPCR CN) as a “HER2+” group (as in Thompson et al), and split the rest into Luminal and TNBC groups based on the ER/PR staining.

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