Reviewer's report

Title: A target based approach identifies genomic predictors of breast cancer patient response to chemotherapy

Version: 1 Date: 2 March 2012

Reviewer: Ander Urruticoechea

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Hallett and co-workers revisit in this manuscript the controversial area of target based prediction of response to standard primary chemotherapy in breast cancer. They propose a provocative approach to this issue combining extensive gene expression profiling and individual target aprioristic hypothesis.

The results support authors’ conclusions partly and they acknowledge some of the limitations of the study.

While provocative in nature this study faces major limitations in order to qualify the findings as clinically relevant or sounded.

The most important limitation of the study refers to its concept. As previously demonstrated, after years of gene profile platforms publication, it is now clear that almost any multi-gene profile strategy overperform the predictive or prognostic value of individual markers. To this extent it has been published that most multigene platforms, while presenting a negligible overlap on individual genes among them, capture a similar underlying phenomenon, namely, proliferation. Hence, the TOP2A and B-tubulin signatures, presented here, may well predict response to therapy due to its involvement of proliferation related genes more than due to its co-regulation with the theoretical targets of the drugs. This issue is particularly relevant to discuss given the largely controversial literature of the predictive value of the individual targets, in particular of TOP2A. This way, with the data provided, authors cannot conclude that the predictive value of the signatures is based on the relationship with TOP2A and B-tubulin.

In order to do so, authors should present a comparison with other signatures, built following the same methodology, but based in other relevant gens as estrogen receptor, or proliferation related genes. This comparison, and not the comparison to individual genes like the one reported, could base the “target related” nature of the predictive value of the proposed signatures.

Other issues that the authors should address to improve the quality of the manuscript are:

- Why results with individual transcripts of TOP2A are reported while the same with B-tubulin are not.
- Why the TOP2A signature is not tested in the docetaxel-only population (GSE22513) where, if the conclusions of the authors are true, it should not show a relevant predictive value.
Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests