Reviewer's report

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

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Reviewer: Charles Swanton

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Summary
This study aimed to identify gene expression indices that were able to predict pathological complete response (pCR) to neoadjuvant anthracycline/taxane-containing chemotherapy regimens in breast cancer. They derive these indices through identifying genes where expression correlates with expression of TOP2A (a target of anthracyclines) and beta-tubulin (a target of taxanes). The indices were used separately and as a combined index. Patients with pCR had higher index scores than patients with residual disease (RD), and index scores were able to predict pCR. The combination index was associated with response in a multivariate analysis.

Comments
Rather than using a top down approach to identify a gene expression signature associated with response, the authors identify genes with expression correlating to expression of two targets of chemotherapy beta-tubulin and TOP2A.

The genes selected for the indices are not described in the main text, and are summarised only in a supplementary table. Do any of the genes identified in this approach have a functional connection to the mechanisms of action of anthracyclines/taxanes? Do any of the genes identified overlap with other gene-expression based predictors of response to these chemotherapies?

The authors show that increased TOP2A expression is associated with response to chemotherapy, and that higher TOP2A expression is observed in patients making pCR compared to those with RD. Is the same true for beta-tubulin expression in the docetaxel treated cohort?

The cohort used to evaluate the association between the b-tubulin index is only 14 patients, profiled in replicate. The authors appear to have treated the replicates as independent samples. What was the concordance between the replicates? If concordance was poor then this suggests that intratumour heterogeneity could confound the utility of this gene expression based approach. Could the authors address this and comment?

It is not clear how a threshold for these indices could be derived that would show clinical utility prospectively, as the differences in index scores between pCR and...
RD groups are small. While the authors acknowledge that a prospective study would be needed to confirm clinical utility, no threshold is proposed that would be used in this setting. Could the authors comment on this?

The specificity of the TOP2A and beta-tubulin indices for anthracycline or taxane response specifically and respectively is unclear.

The manuscript is in general clearly written and is an important contribution. The introduction and discussion are lacking in detail. The authors might want to cite other taxane predictors developed through similar functional-based approaches.