response index (MDRI) of 0.68 *vs* 0.10, respectively; for mismatch, 25.2% were assigned as S and 75.8% were assigned as R, with mean MDRI of 0.71 *vs* 0.11, respectively. Other major prognostic factors also had similar distributions (S *vs* R) between match and mismatch. These results indicate that if the assay is only prognostic, the association with patient outcome should be consistent between match and mismatch analyses. In other words, the difference reported was unlikely explained by the confounding effects of prognostic factors. To further control the potential confounding factors, we also included a multivariate analysis in our study which further demonstrated the differences in patient outcome between the match and mismatch analyses (Tian *et al*, 2014).

We agree with Korn and Freidlin (2015) that evaluating the predictive value of chemoresponse assays is challenging. As with any observational study, it is impossible to entirely exclude bias, and a definitive answer relies on randomised clinical trials. However, randomised trials to evaluate predictive markers are highly challenging in rare tumour types such as recurrent ovarian cancer, particularly when a large number of treatment options are available. The length of time for patient accrual alone is likely to obfuscate clinical utility. Thus, observational studies and other non-randomised prospective studies must continue to have an important role in evaluating chemoresponse assays in this cancer type. We feel that in the appropriate circumstance, our proposed match/mismatch analysis can provide helpful information regarding an assay's potential prognostic and/or predictive value.

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## CONFLICT OF INTEREST

DJS received compensation for consulting work from Helomics Corporation. MJG, SLB and CT are paid employees of Helomics Corporation.

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# Response to Comment on: 'Evaluation of chemoresponse assays as predictive biomarkers'

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**Sir,**

We thank Tian *et al* (2015) for their comments on our paper (Korn *et al*, 2015). They appear to agree with us that their analytic methods proposed in Tian *et al* (2014) do not work unless the following two assumptions hold: (1) the treatments have approximately equal efficacy in the overall population; and (2) the treatments the patients received were essentially assigned randomly (and not associated with factors that have prognostic importance). We note that these two assumptions are very strong, and, following Tian *et al* (2015), we review their plausibility in the context of recurrent ovarian cancer considered by Rutherford *et al* (2013). For assumption (1), one might question whether single-agent cisplatin or carboplatin works as well as the other treatments (e.g., combinations with platinum) on the population studied by Rutherford *et al* (2013), which contains ~45% of patients who were resistant to their initial platinum chemotherapy. If single-agent platinum drugs do not work as well, then assumption (1) is violated.

Assumption (2) allows one to treat observational data as if it were from a randomised clinical trial. It is impossible to prove that this assumption is satisfied, as there may always be important unmeasured prognostic characteristics of the patients that clinicians are implicitly using to help decide which treatments have to be given to which patients. However, it is possible to show that the assumption is questionable by finding a known important prognostic variable that is associated with the treatment the patients received. In the present case, consider the recognised important prognostic variable defined by whether patients are platinum sensitive or platinum resistant to their initial platinum chemotherapy (Jayson *et al*, 2014). It is known that patients with platinum-sensitive recurrent disease are more likely to be treated with combination of drugs including a platinum agent, whereas patients with platinum-resistant recurrent disease are more likely treated with a single (non-platinum) drug (Jayson *et al*, 2014). Indeed, this appears to be the case with data analysed by Rutherford *et al* (2013), where 27% of the platinum-sensitive patients received (non-platinum) single drugs whereas 50% of the platinum-resistant patients did (Table 1). This suggests a violation of assumption (2) that patients had their treatment chosen randomly.

It can be difficult to assess in any given clinical situation whether the required assumptions for the analytic methods of Tian *et al* (2014) are reasonable. In particular, the required assumptions seem questionable in this recurrent ovarian cancer setting.

**Table 1. Distribution of patients cross classified by treatment received and platinum status (data are abstracted from Supplementary Table S1 of Rutherford *et al* (2013))**

| | Platinum sensitive | Platinum resistant |
|---|---|---|
| Non-platinum single drugs[a] | 35 (27%) | 56 (50%) |
| Platinum-containing combinations[b] | 95 (73%) | 57 (50%) |
| Total | 130 (100%) | 113 (100%) |

[a]PLD, topotecan, gemcitabine, paclitaxel.
[b]Carboplatin/paxlitaxel, carboplatin/gemcitabine, carboplatin/docetaxel, cisplatin/gemcitabine, cisplatin/paxlitaxel, carboplatin/topotecan.

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