Pharmacogenomic Strategies May Not Provide a Rational Approach to the Treatment of Cisplatin-Resistant Patients with Advanced Lung Cancer

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A major goal of personalized medicine is to predict, before administering a treatment, whether the patient will respond to it. Recently, Hsu et al.[1] published an article in JCO using genomic signatures to make such predictions in the context of lung cancer, focusing on cisplatin and pemetrexed. Starting with expression profiles of cell lines with known sensitivity to the target agents, they select the most and least sensitive lines to contrast. The genes showing the most significant differences form the elements of a genomic signature for that drug, with weights based on a singular value decomposition (SVD). Given this weighted signature, both the cell line and patient sample profiles are then scored, with higher scores indicating a greater probability of response to the drug.

This approach closely tracks that of Potti et al.[2], where profiles and sensitivity information for the NCI60 cell lines were used to assemble signatures for 7 drugs. Hsu et al.[1] use additional cell line data from Györffy et al.[3] to assemble the signature for cisplatin, and NCI60 data for pemetrexed. Unfortunately, as noted in Coombes et al.[4], we encountered problems with the Potti et al.[2] report. Most of these problems are also present in the paper of Hsu et al.[1] Specifically,

1. We cannot reproduce their selection of cell lines. The sets of "sensitive" and "resistant" GI50 concentrations for pemetrexed overlap.

2. The lists of genes reported are wrong, due to an off-by-one indexing error.

3. Using their software, we can perfectly reproduce the published heatmaps for both cisplatin and pemetrexed. However, after correcting for the off-by-one error, we can only match the

gene list exactly for pemetrexed.

4. For cisplatin, their software returns only 41 of the 45 reported probesets. The remaining 4 are "203719_at", "210158_at", "228131_at", and "231971_at" which correspond to ERCC1 (U133A), ERCC4 (U133A), ERCC1 (U133B), and FANCM (U133B) respectively. These probesets cannot be identified from the training data. Indeed, *the last two probesets are not physically present on the U133A arrays used in the training set.* ERCC1 and ERCC4 are the only genes named in the paper. Their paper also notes enrichment of the cisplatin signature for DNA repair genes. Their reported list contains 5 probesets with this function, 4 of which are those mentioned above.

5. In the case of pemetrexed, the sensitive/resistant labeling has been reversed. Using the model with this labeling suggests administering the drug only to the patients it would not benefit.

Points 1-4 are qualitatively identical to points 1-4 of Coombes et al.[4]. Point 5 here is roughly analogous to point 6 in Coombes et al.[4], where label reversal appeared to affect the results for adriamycin.

We have not checked the results of using the models for prediction, as we do not know precisely which samples were used. For example, GSE3149 for ovarian cancer, contains quantifications for 153 arrays, but the paper reports using 59.

We would be delighted to use cell line data to predict patient response. Unfortunately, we are not yet persuaded that this can be done as described.

Details of our analysis are given in a supplementary report (lung01.pdf). This report, together with the data, code, and documentation are available from `http://bioinformatics.mdanderson.org/Supplements/ReproRsch-Lung`. Running the main script reproduces the results reported here.

References

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