

# Development of a gene signature for stratifying cisplatin treatment of NSCLC patients

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## Introduction

Cancer is not a single disease, reflecting that no single treatment can be broadly effective to diverse patient population. The future of cancer treatment lies in the personalized approach. Patient derived xenografts (PDXs, HuPrime®) mimic patient tumors from which they are derived, and are believed to respond to therapy predictive of how patient would. They could be used as surrogate test subjects. We have recently established a large cohort of NSCLC-PDX(>200)<sup>[1]</sup>, many of which were extensively genomic-profiled, including gene expression, mutation, fusion and copy #, etc. In order to develop a molecular signature (HuSignature™) predictive of response to cisplatin among NSCLC patients, we subjected a cohort of randomly selected NSCLC-PDX to a mouse clinical trial (MCT) with efficacy readout  $\Delta T/\Delta C$  (relative tumor volume change between the treatment group and the control group). The trial results demonstrated that each model responded to the treatment differently as anticipated. A molecular signature based on gene expression of a few selected genes, or HuSignature™, is then developed based on efficacy data from the tested cohort (training set), and further validated by using published human clinical observations (validation set). This signature could potentially be useful to guide clinical use of cisplatin for the treatment of patients of NSCLC.

## Result

A total of 74 candidate signature genes were selected from 18553 genes with valid expression values after applying P-value and expression fold change thresholds. Using a set of specific pathway analysis tools, we identified 9 of the 74 candidate genes are related to NSCLC. Various biological interactions exist among them (Figure 1). Some of the 9 genes are known prognosis/efficacy/diagnosis biomarkers, which are also targets of many drugs in various clinical phases.

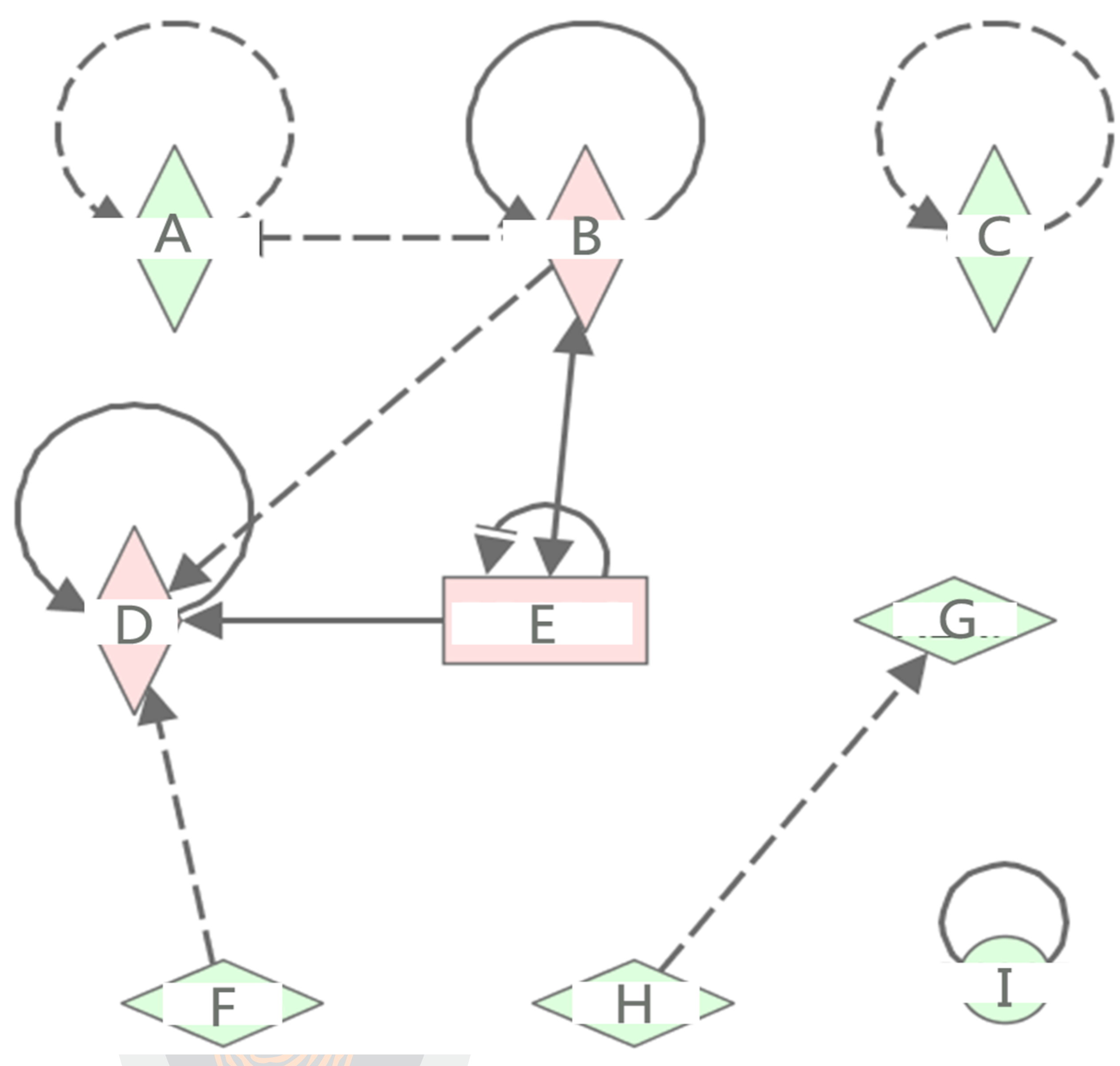


Figure 1. Signature genes. The expression of red genes is positively correlated with  $\Delta T/\Delta C$ , and the expression of green genes is negatively correlated with  $\Delta T/\Delta C$ .

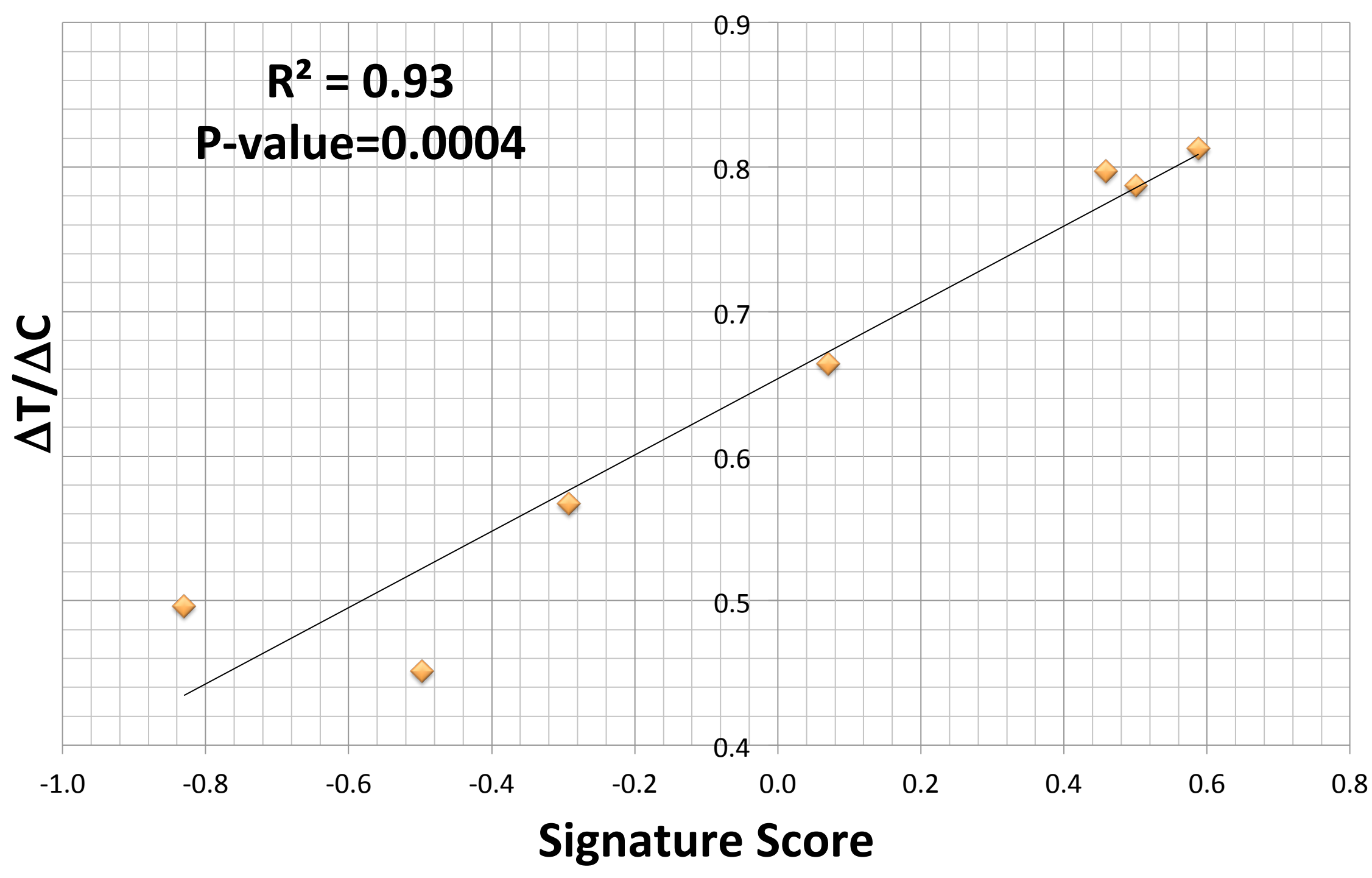


Figure 2. A signature score based on the expression of the 9 biomarker genes is predictive of cisplatin treatment effect in NSCLC PDX models, which has good predictive power in the discovery panel consisted of 9 PDX models.

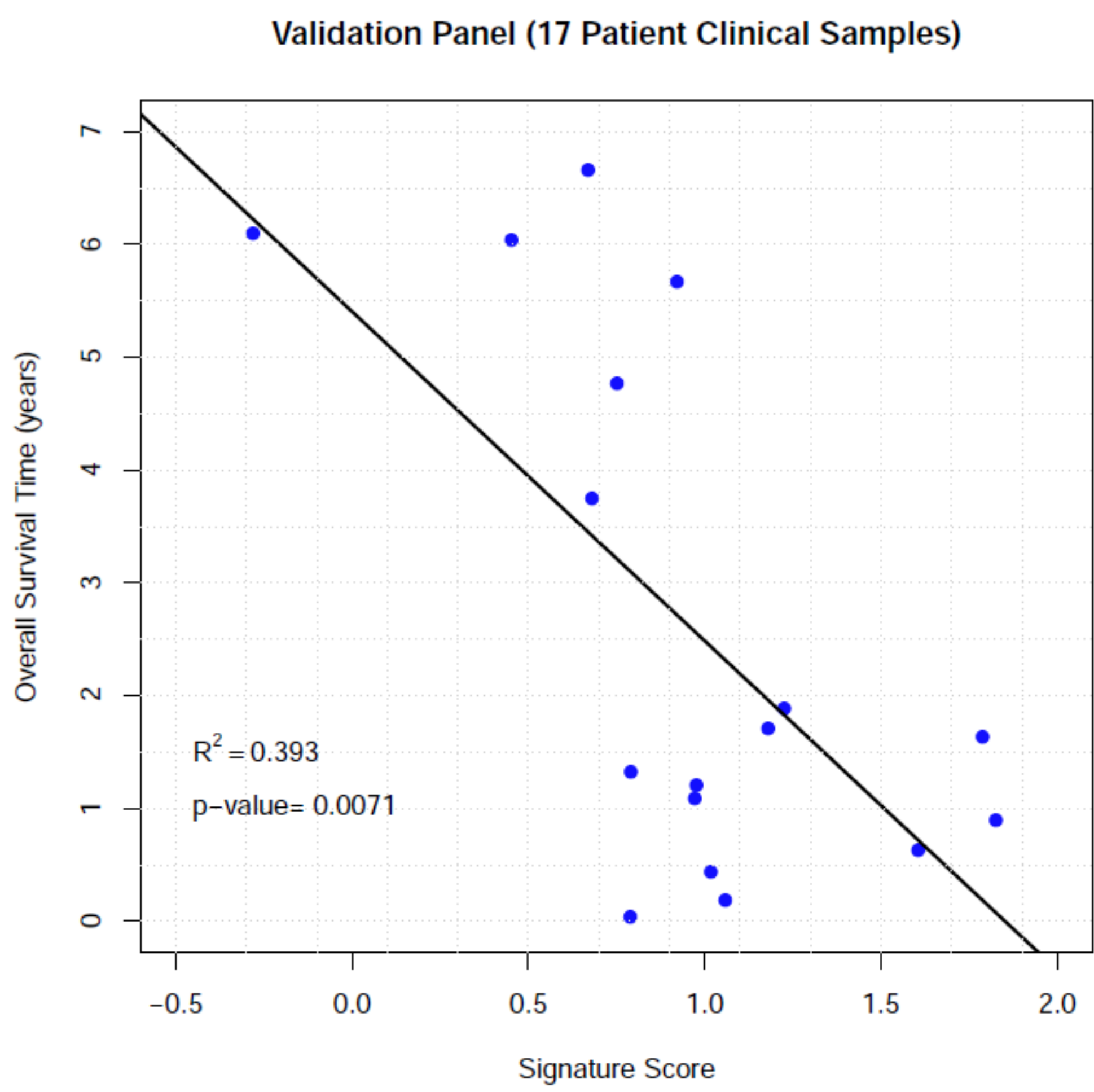


Figure 3. HuSignature™ derived from PDX models is predictive in patient samples. We evaluated the HuSignature™ in an independent validation panel consisted of 17 patient samples, which are from a clinical trial and are adjuvant cisplatin/vinorelbine (ACT) treated early-stage non-small-cell lung cancer (NSCLC) <sup>[2]</sup>. We used 17 samples with known overall survival time (years). Gene expression in these samples was measured by different microarray chip (Affymetrix U133A) from ours (Affymetrix U219). The HuSignature™ shows good predictive capability (Figure 3). A signatures like this or of a more refined version can be potentially useful for patient stratification of cisplatin treatment.

### Conclusions

- 1. A signature (HuSignature) predictive of the response to cisplatin treatment of NSCLC has been developed using PDX trial (HuTrial)
- 2. The signature seems validated with independent human clinical data
- 3. The signature may have significance in stratifying clinical treatment of human patients

### References

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2. Zhu CQ, Ding K, Strumpf D, Weir BA, Meyerson M, Pennell N, et al. Prognostic and predictive gene signature for adjuvant chemotherapy in resected non-small-cell lung cancer. *J Clin Oncol*. 2010;28:4417-24.



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