In Reply

We are grateful to Tan et al. for clarifying important differences between the gene signatures validated and compared in our article. We agree with them and are pleased that Tan et al. support our call for molecular stratification of renal cell carcinoma (RCC) to be considered in investigation of RCC therapeutics.

Clinically robust assays depend on development of highly sensitive and specific gene signatures, and several issues exist regarding the use of distinct tissue sources. Gene expression analysis of formalin-fixed paraffin-embedded (FFPE) tissue may be less reliable due to the partial RNA degradation, which may increase with time in storage. In fact, the expression measurements of thousands of genes may vary in FFPE samples compared with paired fresh frozen (FF) samples [1]. Therefore, we agree that the thresholds optimized for FFPE (or FF) samples may lose performance when applied to FF (or FFPE) samples.

Another key element in gene signature design is the number of genes in the gene signature. A gene signature of at least 15 and at most 200 genes is the recommended size for use with Gene Set Enrichment Analysis (GSEA) [2]. More genes may provide redundancy when signatures are applied to noisy/high variance data, but after a certain number of genes, little is gained. However, the number of genes that provide robustness to stochastic loss of gene signal, or renal tissue heterogeneity, such that a gene signature could be applied across range of technologies, has yet to be determined.

Our study of 54 patients has a low sample size and is not a definitive comparison. We were pleased that despite the relative small sample size, we were able to reproduce the model and to find significant relationships with the 34-gene model predictor (ClearCode34) [3]. A definitive and larger sample size is necessary to ensure a representative distribution and it should be mandatory in order to generalize the results or transfer to the clinic. Collaborations like the International Metastatic Renal Cell Carcinoma Database Consortium may help further validate these signatures [4]. Currently, there must be thousands upon thousands of FFPE kidney cancer samples worldwide, which, if associated with comprehensive clinical information, will prove to be one of the most valuable scientific resources for this tumor. We should make an effort to share genomic signatures and codes, which will make future research speedier and more effective.

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Disclosures

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