The Issue of Tissue in Molecular Stratification

We are pleased that de Velasco et al. [1] have compared the performance of a 34-gene model predictor (ClearCode34) developed by several authors [2] with our 8-gene predictor [3] in an independent RNA-sequencing dataset derived from frozen metastatic renal cell carcinoma (mRCC) samples [4]. We are also glad that that the authors have successfully reproduced our analyses as reported in reference [3]. We wish to add a key point that would be helpful for readers to consider alongside the published article.

Establishing external validity is a crucial step in documenting value of any score or assay. We believe that validation for clinical application would ideally be in a prospective real-world setting, using an independent cohort of formalin-fixed paraffin-embedded (FFPE) tissue materials. In our view, it would have been relevant for readers to consider additional background that our 8-gene predictor was developed and optimized specifically on FFPE RCC tissue, and that the 34-gene model predictor reported by the authors was developed on frozen-tissue microarray data, with additional validation in FFPE RCC tissue [2]. Thus, we hope de Velasco et al. would agree that outcomes in testing from a 54-sample frozen-tissue RNA-sequencing dataset requiring additional data preprocessing, although an interesting adjunct for consideration, may not be a definitive comparison of these two scores, especially for a real-world clinical setting. Underlining this consideration of tissue type is the observation that our 8-gene quantitative PCR predictor, when applied on FFPE tumor tissue, effectively stratified survival outcomes in 48 mRCC patients receiving tyrosine-kinase inhibitor therapy [3], retaining significant correlation after adjustment for Memorial Sloan-Kettering Cancer Center classification, in contrast with the results obtained by the authors.

We are in agreement with de Velasco et al. that it is time for molecular stratification of RCC to be considered in investigation of RCC therapeutics. For example, we have recently reported that improved molecular stratification for frozen tissue correlates with immunotherapy (high-dose interleukin-2) outcomes in mRCC [5]. Extending this work to investigating outcomes of immune checkpoint inhibitors in FFPE tissue would be of interest. We would be very pleased to work together with de Velasco et al., as well as any interested researchers worldwide, to establish molecular subtyping for their RCC FFPE samples in the collective goal to improve outcomes of RCC patients worldwide.

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Disclosures

Min-Han Tan: 8-gene signature model (IP), Lucence Diagnostics Pte Ltd (E); **Yukti Choudhury**: 8-gene signature model (IP), Lucence Diagnostics Pte Ltd (E); **Puay Hoon Tan**: 8-gene signature model (IP). The other authors indicated no financial relationships.

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