Letter to the Editor

Extracellular vesicles for early detection of hepatocellular carcinoma

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Deaths due to liver cancer continue to increase worldwide. Unfortunately, the majority of patients with hepatocellular carcinoma (HCC), the most common type of liver cancer, are still diagnosed at advanced stages where potentially curative therapies are not recommended (1). There is evidence showing how survival in patients enrolled in HCC surveillance doubles that of those not enrolled in surveillance (2). With less than 25% of eligible patients enrolled in surveillance programs (3), it is imperative to reduce barriers and increase access to early detection programs. One of the reasons for low utilization of HCC surveillance is patients being lost to follow-up after years of the patient actively compliant with surveillance. The causes for this are unclear, but one could speculate that by simplifying surveillance could help mitigate patient attrition on surveillance programs. Specifically, removing the need for an ultrasound and its logistical inconvenience in certain settings might improve surveillance rates. To achieve this, it is imperative to develop accurate biomarkers that can outperform abdominal ultrasound. In pursuit of this goal, we have developed a blood-only biomarker using three small RNA cluster (smRCs) sequences in extracellular vesicles (EVs) isolated from plasma that accurately discriminates between patients with early-stage HCC and controls at risk. There are currently many similar initiatives focused on using liquid biopsy approaches to identify accurate biomarkers for the detection of HCC, which could ultimately remove ultrasound for the surveillance algorithm (4).

The role of EVs as a liquid biopsy tool for HCC surveillance has been barely explored. Most studies have focused on circulating tumor DNA or tumor cells. Our EV-based test had a sensitivity of 86% and specificity of 91% for the detection of early HCC (5). Considering the pooled sensitivity for detection of early stage HCC of the current recommended strategy for HCC surveillance (i.e., biannual abdominal ultrasound with or without serum alpha-fetoprotein) is 65% (6), our study provided additional proof-of-principle of how a blood-only biomarker could transform early detection strategies in HCC. Gondaliya and Patel recently wrote a commentary (7) raising some key questions about our approach. First, they ask if our prostate cancer, multiple EV isolation technology, multiple EV exRNA localization, and multiple biofluid smRC discovery and characterization dataset excluded or biased the discovery of HCC specific smRCs. We wish to point out that we purposely used this comprehensive dataset to establish the essential and ubiquitous properties of smRCs to facilitate not only their detection, but also establish their technical covariance with EV isolation technology and biofluid. We designed this approach to devise sequencing-based filtration and ranking criteria which should be valid beyond early HCC detection. Even though we used these discovery criteria to select smRCs specifically associated with early stage HCC, we also agree with their contention that there still exists a need for a detailed annotation of cellular RNA from liver or HCC cells along with that of exRNA in HCC plasma samples. The authors also expressed concerns about the extent of overlap of our 3 candidate smRCs to contaminant sequence including exogenous and ribosomal RNA sequence, which we mitigated by explicitly

filtering out such sequences using National Center for Biotechnology Information (NCBI) reference databases [*Fig. S4A* in Ref. (8) has extended details on RNA biotypes]. Along those lines, they argue for the need for functional studies to better characterize the specific role of our 3 early-HCC smRC biomarkers. We wholeheartedly agree with the need for functional studies, which are currently being planned. Finally, we also agree on the need for further validation of our and other blood-based biomarkers in the context of phase III biomarker studies. To help in this process, the International Liver Cancer Association has recently endorsed a white paper on best practices for the design, execution, and interpretation of biomarker studies in patients with HCC (8).

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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