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Letters to the Editor

Response to "The need for validation of MI GPSai in patients with CUP: Comment on: "Machine learning analysis using 77,044 genomic and transcriptomic profiles to accurately predict tumor type" by J Abraham et al."

Carcinoma of Unknown Primary (CUP) represents a challenging clinical scenario with poor outcomes and an urgent need for better approaches to optimize clinical management [1]. Despite published guidelines for establishing a CUP diagnosis [2], cases labeled as CUP by ordering oncologists and sent to Caris Life Sciences for molecular profiling represent a very heterogeneous set of malignancies and clinical circumstances. We have taken advantage of the data generated by our Whole Exome and Whole Transcriptome sequencing clinical testing platform to assign tissue of origin lineage to specimens received and labeled as CUP. Further, we identified predictive biomarkers necessary for therapy selection.

In his summary of our work, Dr. Greco makes a number of erroneous statements. He states that assay performance was decreased in poorly differentiated cases. We did not examine the relationship between the degree of differentiation and miGPSai performance. Notably, "poorly differentiated" is a subjective descriptive term utilized by pathologists in cases that diverge sharply from normal cell phenotypes towards a more primitive cell state. This subjective feature was not assessed in our study. However, given that we included over 70,000 cases in our training, test, and validation cohorts, our tool was developed and validated against a broad range of cancer cell differentiation. Dr. Greco also states that performance was decreased in metastatic cases. Our validation data of 92.2% call rate and 92.5% sensitivity in metastatic tumors is not significantly different than the 94% call rate and 94.1% sensitivity seen in primary tumors.

Dr. Greco repeatedly refers to the accuracy and validation of the CancerTypeID based on studies he has authored while neglecting to mention the results of the recent prospective randomized controlled trial which failed to demonstrate that therapy selection on the basis of CancerTypeID improved patient outcomes in CUP cases [3]. CancerTypeID may be 'validated' to produce a diagnosis similar to an expert pathologist, but if this diagnosis does not lead to better patient outcomes, a new approach is needed. Molecular profiling with biomarker directed therapy shows promise for clinical benefit in CUP cases [4], and is the approach for a currently accruing prospective clinical trial [5]. Identification of the lineage of a CUP case additionally allows the appropriate testing and interpretation of context-dependent biomarkers such as PD-L1.

Dr. Greco suggests that one method of validation is "Molecular classifiers should also be blindly compared to IHC (the accepted historical diagnostic standard) in known cancers and others with challenging metastatic cases with poorly differentiated or undifferentiated tumors", which is exactly what was done. We did a prospective validation of 13,661 patients which included challenging metastatic cases with poorly differentiated or undifferentiated tumors. Dr. Greco proposes the 52 patient study done by Biotheranostics as a proper comparator, however this is a poorly powered study to assess diagnostic performance across 30 different cancer types.

The final issue with Dr. Greco's letter is that he failed to disclose his financial conflict of interest. He is the medical advisor for the CancerTypeID assay he so often references, and is financially compensated by Biotheranostics.

https://www.biotheranostics.com/anthony-greco-md-appointed-medical-advisor-for-cancertype-id

See COI in https://pubmed.ncbi.nlm.nih.gov/20427384/ for example.

Unfortunately, the only conclusion we can come to is that Dr. Greco is attempting to undermine our work because of competitive reasons, as the assay he is defending is inferior to what we have developed.

CRediT authorship contribution statement

Jim Abraham: Writing – review & editing. **Chadi Nabhan:** Writing – review & editing. **Matthew Oberley:** Writing – original draft, Writing – review & editing. **Wolfgang Michael Korn:** Writing – review & editing. **David Spetzler:** Writing – original draft, Writing – review & editing.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JA, CN, MO, WMK, and DS are employees of Caris Life Sciences.

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