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Response to: Letter to the Editor, EURUROL-D-14-00573

W. Kimryn Rathmell, Samira A. Eerooks, Joel S. Parker, and Matthew E. Nielsen

Dear Dr. Catto,

Thank you for the opportunity to respond to this critique of our integrated molecular risk prediction tool. There are several salient points of discussion that were raised that are important for consideration as we move to validate more molecular tests guiding our clinical decisions.

The major issue is the difference from prior performance of the established clinical risk predictors. As a dataset, our group of patients shares similar, but not identical demographic features to prior cohorts. A more difference is that all of the patients included in these cohorts not only underwent surgery, but also had tumors large enough, and solid enough, to contribute tissue for these analyses, and tissue availability will always introduce a source of bias in tissue biomarker studies. In this case, it inherently excludes a group of either small or cystic tumors that would be expected to contribute substantially to the clinical risk calculation. In addition, as a more contemporary set of patients, changes in modes of detection or disease management may affect outcomes, even without new conventions of peri-operative treatments. Other unknown differences in patient population, or in assignment of risk components such as tumor necrosis, which was discussed in the manuscript may also contribute to differences. The statistical comparisons were performed using a standard C-index (interchangeably referred to as co-occurrence or concordance index), and was estimated using the popular `corrcoeffs` function in the R package `rmisc` authored by Frank Harrell.

We share our colleagues caution that novel biomarkers require validation in multiple study sets prior to moving towards clinical adoption. The ClearCode34 biomarker requires more extensive investigation before it becomes a standard clinical test. Ultimately prospective testing in a large group of patients will be necessary, and this report is only the first demonstration that moving the ClearCode34 biomarker into FFPE specimens is feasible. This is likely only among the first of several emerging biomarkers to be integrated with existing clinical-based risk prediction algorithms, and this study further demonstrates the importance of considering molecular findings in the context of standard or widely used clinical features in bringing risk predictors to the clinic.

Thank you for this opportunity to clarify our findings, and we welcome further discussions.

Sincerely,

W. Kimryn Rathmell, Samira A. Eerooks, Joel S. Parker, and Matthew E. Nielsen