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Re: Tobias Nordström, Andrew Vickers, Melissa Assel, Hans Lilja, Henrik Grönberg, Martin Eklund. Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. Eur Urol 2015;68:139–46

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In July 2015, we published results from the STHLM2 study in *European Urology* [1]. We compared the four-kallikrein panel (known commercially as the 4Kscore) and the Prostate Health Index (PHI) for predicting high-grade and overall prostate cancer on biopsy.

Although it was apparent that the discrimination of the kallikrein panel for high-grade disease (0.718) was lower than reported previously (for instance, discrimination was 0.820 in the ProtecT study [2]), we originally considered this to be part of the typical variation seen between different research results.

Zappala et al [3] recently reported a formal meta-analysis of studies on the kallikrein panel. Our 2015 study was an outlier and, critically, when excluded from the meta-analysis, heterogeneity between studies was no longer statistically significant. As a result, we

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Hans Lilja holds patents for free PSA, hK2, and intact PSA assays, and is named, along with Andrew J. Vickers, on a patent for a statistical method to detect prostate cancer. The marker assay patents and the patent application for the statistical model has been licensed and commercialized as the 4KscoreTM by OPKO Diagnostics. Drs. Vickers and Lilja receive royalties from sales of this test. Additionally, Dr. Lilja owns stock and Dr. Vickers owns stock options in OPKO.

undertook a careful re-evaluation of the data to try to explain the statistically significant differences between the STHLM2 findings and the rest of the literature.

The first possible explanation for the observed differences was that in a typical prostate marker study, a blood sample is taken shortly before biopsy and analytes from that sample are compared to the biopsy outcome. However, it turns out that in STHLM2, approximately one in eight men had blood draws more than 6 mo before biopsy, and some up to 2 yr before. We also found that the values for total and free prostate-specific antigen entered into the 4Kscore statistical algorithm were not those measured by Dr. Lilja's laboratory responsible for the four kallikrein markers (Wallenberg Research Laboratories at Skåne University Hospital). Instead, the values used were those measured at Karolinska University Hospital, which was responsible for measurement of the PHI markers. The Karolinska and Skåne laboratories use different assays (Roche vs Perkin-Elmer). This possibly influences our findings as the coefficients used in the statistical algorithm are based on a specific assay.

We submit that the use of bloods taken many months before biopsy, and in particular the use of inconsistent assays, might explain the apparently poorer properties of the kallikrein panel in the STHLM2 study.

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