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European Association of Urology



## Letter to the Editor

**Reply to Erik Rud, Peter Lauritzen, and Eduard Baco's Letter to the Editor re: Henrik Grönberg, Martin Eklund, Wolfgang Pickler, et al. Prostate Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric Magnetic Resonance Imaging. Eur Urol 2018;74:722–8**

We are glad to avail of this opportunity to address the questions posed by Rud et al regarding our recent paper on the combination of the Stockholm3 blood test and magnetic resonance imaging (MRI) for prostate cancer diagnosis [1].

This pragmatic study included men scheduled for a biopsy or diagnostic MRI at any of the three participating sites, with the aim of generating a representative sample of a clinical biopsy population. For this reason, the population also included men with a previous negative biopsy. Differences in the patient population at the different sites therefore simply reflect variations in local clinical practice. A priori, the study was powered for the main endpoint on the entire study population.

Results broken down by site differ, but to a limited degree (as demonstrated in our Supplementary tables [1]). For example, analysis of imputed data showed that the relative sensitivity for detection of International Society of Urological Pathology grade  $\geq 2$  disease dropped from 0.98 (95% confidence interval [CI] 0.88–1.07) to 0.95 (95% CI 0.87–1.05) while the proportion spared biopsy procedures increased from 42% to 55%. It is noteworthy that the results from the Stockholm site, where the previous experience from targeted biopsies was lower, showed somewhat lower cancer detection rates and a concomitant higher proportion of biopsies spared. This illustrates the low-risk nature of the study population in Stockholm, the learning-curve associated with targeted biopsies, and the important balance between detection of high-grade cancer and diagnostic procedures avoided. We suggest that site-specific data are interpreted with caution, but find that although the exact patient selection processes might differ among the study sites, there are no obvious biases in the

estimated effect sizes. Furthermore, Rud et al state that patient selection is not addressed in our paper. On the contrary, it is clearly described in the Study design subsection (Section 2.1, including details on handling of missing data) and the outcomes for these selection criteria are reported in Table 1 [1].

Systematic biopsies for all the men in the cohort was the prespecified reference standard for the study, since this is the biopsy procedure that was used in screening trials demonstrating a mortality benefit from prostate cancer screening [2] and is still a widespread clinical standard. Rud et al argue that performing both systematic and targeted biopsies in all men would increase the detection of high-grade cancer. However, this strategy does not represent a clinical reference standard, nor does it represent the true prevalence of prostate cancer. Furthermore, our Figure 2 [1] shows that using this strategy would not decrease overdiagnosis and would not avoid any biopsy procedures, which is why we find it less attractive for clinical use.

To further investigate the use of the Stockholm3 model together with MRI-targeted biopsies, we are now performing the STHLM3MRI Main Study using a screening-by-invitation setting in a randomized trial involving 25 000 men (clinicaltrials.gov NCT03377881).

We conclude that many men with a low risk of prostate cancer are referred for prostate cancer workup and that blood-based risk prediction using the Stockholm3 test and MRI-targeted biopsies can markedly decrease the number of biopsies performed and the diagnosis of low-grade cancer when compared to performing systematic biopsies on all men. These conclusions are both concrete and supported by the data presented in our paper.

**Conflicts of interest:** Henrik Grönberg has five patents pending that are related to prostate cancer diagnostics, has patent applications licensed to Thermo Fisher Scientific, and might receive royalties from sales related to these patents. Martin Eklund is named on four of these five patent applications. Karolinska Institutet collaborates with Thermo Fisher Scientific in developing the technology for the Stockholm3 test.

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