In the emerging field of MRI in prostate cancer (PCa) diagnosis, it has become clear that targeted biopsy with MRI guidance has additional value over systematic transrectal ultrasound-guided biopsies (TRUS-Bx) alone. The targeted biopsy approach driven by a positive MRI increases the diagnostic yield of high-grade [Gleason score (GS) \( \geq 3+4 \)] or clinically significant (cs) PCa, while concomitantly reducing the number of biopsy cores and the detection of low-grade PCa (GS 3+3) (1-3). Consequently, the question arises what the diagnostic accuracy of MRI (with or without targeted biopsies) in current clinical practice would be? Ahmed and his co-authors have recently published a prospective multicenter-paired validation study, titled the PROstate Mri Imaging Study (PROMIS) (4) that begins to fill this void in the literature. This study, which has a very sound methodology, evaluates the MRI (index test 1) in combination with transrectal ultrasound guided biopsies (TRUS-Bx) (index test 2) in reference with template mapping prostate biopsies (TMP-Bx) in biopsy-naïve men. They started from the hypothesis that targeted biopsies would have similar diagnostic accuracy as compared to TMP-Bx. We need to be aware of that MRI targeted biopsies were not included in this study design.

The authors’ main conclusion is that TRUS-Bx performs poorly as a diagnostic test for clinically significant prostate cancer. Prostate MRI, used as a triage test before first prostate biopsy, could identify a quarter of men who might safely avoid an unnecessary biopsy, can also reduce over-diagnosis of clinically insignificant prostate cancer, and might improve the detection of clinically significant cancer. And yes, we believe that the PROMIS study works in daily clinical practice as advertised if we do not expect to find all significant disease, if we accept that results depend on the current definitions of clinical significance, and if we assure the quality of the diagnostic process (including MRI scanner, MRI protocol, biopsy procedures, MRI scans, interpretation and reporting), and have robust training for radiologists and urologists.

### Diagnostic test accuracy for MRI and TRUS-guided biopsies

Looking in more detail to these recently published results, we focused on the most commonly used definition for csPCa; any Gleason score 7 (3+4) or higher, detected on template mapping prostate biopsy findings.

For TRUS-Bx the sensitivity and specificity were 0.48 and 0.99, respectively (Figure 1). This demonstrates that the missed csPCa following the TRUS-Bx pathway is 52% (n=159) of all csPCa (n=308). This might be unacceptable. In contrast, for MRI the sensitivity and specificity were 0.88 and 0.45, missing 12% (n=38) of all csPCa. This might be acceptable.

This is however only half the story of the diagnostic test accuracy, as predictive values are at least as relevant for clinicians. They are mainly concerned with pre-test and post-test probabilities (predictive values) of a diagnostic test, rather than its sensitivity or specificity.

For MRI the positive and negative predictive values were 0.65 and 0.76, demonstrating the relatively high
false positives (35%) and false negatives of MRI: still 1 out of 4 csPCa (24%) is being missed with prostate MRI. In contrast, the negative predictive value of TRUS-Bx was 0.63, showing that even 1 out of 3 men with csPCa is being missed with TRUS-Bx. Hence, we may conclude that MRI performs better in detecting csPCa than TRUS-Bx. However, prostate MRI as a stand-alone cannot yet be considered as the perfect test. When missing 1 in 4, these data shows that csPCa is not equal to visible lesions on MRI. We need to accept the imperfection, and we need to be aware that we miss csPCa if we use MRI as a triage test in biopsy-naïve patients, as suggested by the authors.

We have however lived for decades with the false negative results of systematic TRUS-Bx and we may start accepting this for prostate MRI. Still, it is important to realize that the PROMIS conclusions are based on the assumption that targeted biopsies would achieve similar diagnostic accuracy as TMP-Bx. What is currently lacking is however the assessment of correlation between lesion location on MRI and TMP-Bx, to be able to justify the assumption made.

### Avoiding biopsies with the MRI pathway

According to the PROMIS data, a negative MRI (i.e., no suspicious lesions are visible) may potentially avoid unnecessary TRUS biopsies in 28% (Figure 1); 21% would be justified based on the true negative results (TN), however 7% would not be justified based on false negative (FN) results. From the published results, it is not possible to assess whether these csPCa’s detected by TMP-Bx would have been detected by additional systematic TRUS-Bx.

In addition, the use of multivariate risk stratification in a clinical scenario of opportunistic screening with TRUS biopsies in biopsy-naive men could potentially avoid 20% to 33% unnecessary biopsies without missing hardly any csPCa (5,6). Although these results are not referenced to TMP-Bx and therefore not comparable with the potential biopsy reduction of 28% in the PROMIS, still a substantial benefit may be hypothesized from (complimentary) multivariate risk stratification. At least, it would be very interesting to further explore this combination.

On the basis of the low specificity of the MRI diagnostic test (45%), we should still accept the fact of considerable overdiagnosis, as most of the men with positive MRI will receive an invasive targeted biopsy. Within the context of further reducing overdiagnosis and biopsy procedures, Alberts et al. showed that half of the prostate MRI’s could have been avoided by upfront multivariate risk stratification, using the Rotterdam Prostate Cancer Risk Calculator (RPCRC) (7).

### Generalizability of PROMIS results

The prevalence of csPCa in the PROMIS study was 53% based on the reference TMP-Bx, with transperineal biopsies at 5 mm intervals. Predictive values are strongly dependent of the prevalence of csPCa in the studied cohort study. To be able to extrapolate the diagnostic test results from the PROMIS to one’s clinical practice, an estimate of the...
prevalence in your clinical population should be available. This dependency is nicely shown in a recent publication on the negative predictive value of prostate MRI, graphically presenting these values against the prevalence of many reports on MRI and targeted biopsies (8).

Nonetheless, the likelihood of having TMP-Bx results available in biopsy-naive men will be extremely rare. Therefore, to generalize the PROMIS study results to one’s clinical setting, we may use the detection rate of 26% csPCa by TRUS-Bx within this study, instead. This csPCa rate is probably comparable to rates of other clinical biopsy-naive patient cohorts in Western countries with opportunistic screening, varying from 11% (9), 16% (10), 20% (6), 27% (11) to even 39% (12). Therefore, we believe that the PROMIS results are generalizable to other Western biopsy-naive patient cohorts, however, we observe a large variability in prevalence, resulting in insuperable differences in MRI predictive values.

The authors should be applauded with this laudable effort. The PROMIS study is based on quality control checks and quality assurance for MR images by independent imaging clinical research organization, blinding of MRI results to biopsy procedures, repeated centralized training for radiologists, and on-site training of TMP-Bx for urologists.

We advocate a policy that each prostate cancer center evaluates their own MRI and biopsy test results, to determine their positive and negative predictive values, and improve in constant dialogue between radiologist, pathologist and urologist.

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Footnote

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