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Platinum Priority – Editorial

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Multiparametric Magnetic Resonance Imaging with Targeted-only Biopsy—A New Standard for Guidelines on Prostate Cancer Detection?

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In this issue of *European Urology*, Kasivisvanathan et al [1] report on their timely meta-analysis of two randomized trials comparing prebiopsy magnetic resonance imaging (MRI) with targeted biopsy (TBx) only (ie, no systematic biopsies) versus standard transrectal ultrasound biopsy (TRUS-Bx) in biopsy naïve-men at risk of prostate cancer. The key findings are that the MRI plus TBx was superior to TRUS-Bx in detecting clinically significant cancer by approximately 8% (36.3% vs 27.6%) and reduced diagnosis of low-grade prostate cancer by 12%. Using this protocol, approximately one-third of patients could avoid a biopsy on the basis of negative MRI findings. This is high-level evidence, and the authors suggest that future studies may not have equipoise for randomizing patients to TRUS-Bx in the future. So where do we move the field from here?

First, let us recap a few decades of progress in this field so that we can point to a clear future direction. As a graduate of a US urology residency that started and finished in the 1990s, I have seen several incremental changes in the diagnosis and treatment of prostate cancer. My residency mentors had trained in the era before prostate-specific antigen (PSA) measurement and had minimal experience with radical prostatectomies in their training and early careers. By contrast, they were more experienced in diagnosing locally advanced or metastatic disease, which often presents with significant symptoms such as pain, bleeding, and bone fractures. The introduction of PSA testing led to a significant increase in the detection and treatment of clinically localized disease—a term that then referred to anything confirmed as cancer. The serum PSA test coupled with TRUS and 18-gauge needle devices were synergistic in improving the efficiency of diagnosis and led to a significant increase in detection and earlier stage shifts. Staging imaging studies included computed tomography and a bone scan for most all newly diagnosed cases; however, MRI was characterized as too expensive and a less accurate modality.

Despite the significant changes in prostate cancer diagnosis and treatment that followed the introduction of PSA testing and TRUS-Bx, we now recognize the serious chaos that resulted from a combination of overdetection of low-grade prostate cancer, sepsis related to TRUS-Bx, incorrect diagnosis, and the slow natural history of prostate cancer that led to well over a decade of assumed patient benefit while clinical trials were in progress. MRI was then reinvented with the multiparametric approach (mpMRI) that improved diagnostic metrics, such that progress towards more accurate detection and a possible reduction in unnecessary biopsies seemed to be feasible.

The three most common indications for mpMRI in early disease are: (1) elevated PSA or an abnormal digital rectal examination in the biopsy-naïve setting; (2) persistent risk of prostate cancer in cases with a prior negative biopsy; and (3) ongoing monitoring for active surveillance. It has taken a number of studies with high-level evidence to make progress in rolling out the equipment, imaging protocols, and diagnostic imaging interpretation skills necessary, in addition to insurance provider acceptance. According to an analysis of commercial and Medicare data by Soerensen et al [2], prebiopsy use of MRI increased from 0.5% in 2007 to 35% in 2022. We are clearly making progress, but we need better

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utilization of MRI and a discussion regarding possible holdups. There are a few key drivers, including: (1) access to high-quality MRI; (2) the availability of secondary biomarkers that can improve selection for biopsy; and (3) recommendations in major guidelines on what to do.

The three key guidelines published by the National Comprehensive Cancer Network (NCCN) [3], the American Urological Association (AUA) [4], and the European Association of Urology (EAU) [5] differ in their wording regarding the use of prebiopsy MRI. Focusing on the sections applicable to suspicion of prostate cancer in the biopsy-naïve setting, the NCCN guideline recommends that mpMRI should be used "if available" and includes an either/or bullet point list of mpMRI and secondary biomarkers. The AUA guideline states that mpMRI "may" be used. The EUA includes mpMRI in a diagram of diagnostic options and recommends two separate considerations: (1) use mpMRI, risk calculators, and/or urinary tests to determine risk stratification for a biopsy; and (2) perform prebiopsy MRI if not performed already at the risk stratification step. The text further discusses the key benefits of prebiopsy MRI without making a clear recommendation to avoid TRUS-Bx without MRI.

Secondary biomarkers clearly have a potential role, and I refer readers to the recent validation of the My Prostate Score 2.0 test [6], which demonstrates how the test and other competitive biomarkers can also reduce unnecessary biopsies, especially in settings in which mpMRI is not available or is contraindicated. However, I agree with the authors of this meta-analysis of two randomized studies that MRI with TBx in the biopsy-naïve population should "form the basis of international guidelines." Given the higher level of evidence and the more direct connection of the test to diagnosis, risk classification, and treatment planning, I believe that the guidance should be more definitive regarding the use of prebiopsy MRI, keeping secondary biomarkers as an option for more complex situations. Such guidance may be an initial challenge for providers who do not have access to high-quality MRI, but I would hope that it will encourage health systems to invest resources in this direction.

Finally, there is one more nugget deep in the discussion section of the paper—what about MRI-invisible disease? A possible critique of the studies is that we do not really know what happens to patients with a negative MRI-TBx who did not undergo TRUS-Bx, or patients with negative MRI findings who do not undergo biopsy. Will they just show up a year later with persistent risk and have a repeat workup, possibly showing a missed cancer? The authors discuss and cite emerging data suggesting that MRI-invisible disease is less clinically significant than MRI-visible grade group $\geq$2 disease. If evidence continues to support this finding, then the diagnostic choices will be clearer regarding the ability to omit systematic biopsies, what to do for MRI-negative biopsy cases, and future biopsy indications for patients with a previous negative biopsy or on active surveillance.

Conflicts of interest: The author has nothing to disclose.

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