EDITORIAL

# Awaiting the perfect diagnostic test: optimal prostate cancer care begins without a diagnosis



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Given the limitations of PSA as a marker for prostate cancer, there is a critical need for diagnostic tools that can reduce the use of unnecessary biopsies while preserving early detection of potentially-lethal cancers. In patients presenting with elevated PSA, the current diagnostic approach suggests that clinicians offer multi-parametric magnetic resonance imaging (mpMRI) and consider serum- or urine-based biomarkers to better define the risk of high-grade cancer prior to biopsy [1]. Still, the optimal use and interpretation of current diagnostic tools are not clearly defined, in large part due to the limitations of available clinical data [2].

In the current report, Hendriks et al. performed both urine-based SelectMDx-testing and mpMRI prior to biopsy in 599 biopsy-naïve men with PSA ≥ 3 ng/ml [3]. All men underwent systematic biopsy, and patients with suspicious mpMRI also underwent MR-guided biopsy. The authors then assessed projected clinical outcomes under each of four potential testing strategies: (1) SelectMDx-testing-only, with biopsy performed if the SelectMDx test was positive; (2) mpMRI-only, with biopsy performed if mpMRI was positive (PI-RADS ≥ 3); (3) SelectMDx-testing followed by mpMRI if the SelectMDx test was positive, and biopsy performed if mpMRI was positive (conditional-strategy; biopsy performed only if *both* tests were positive), and (4) SelectMDx-testing and mpMRI in all patients, with biopsy performed if either test was positive (joint-strategy). Projected outcomes included the number of biopsies avoided, detection of high-grade (Grade Group [GG] ≥ 2) cancer, and detection of low-grade (GG1) cancer. SelectMDx was considered negative for scores less than −2.8, a cutoff associated with a 13% risk of detecting GG ≥ 2 cancer on biopsy after a negative test [4].

Using each strategy, the proportion of men who would have undergone SelectMDx testing and mpMRI are listed with the subsequent clinical outcomes in the Table 1 As could be expected, the sensitivity for detecting GG ≥ 2 cancer was associated with the proportion of patients who underwent biopsy under each strategy. For example, the joint strategy – under which patients proceeded to biopsy if *either* SelectMDx or mpMRI were positive – led to the highest rate of biopsy (72%) and the highest rate of detecting GG ≥ 2 cancer (98%). The conditional strategy – under which biopsy was performed only if *both* SelectMDx and mpMRI were positive—led to the lowest rate of biopsy (40%) and the lowest rate of GG ≥ 2 cancer detection (87%), while notably also providing the greatest reduction in overdiagnosis of GG1 cancers (58% reduction). On decision curve analysis, the mpMRI-only strategy—under which 51% of men underwent biopsy and 95% of GG ≥ 2 cancers were detected—demonstrated the highest net benefit. The conditional strategy (i.e. biopsy performed only if both tests were positive) provided the second-highest net benefit across the majority of risk thresholds.

The use of mpMRI has been shown to improve diagnostic yield of prostate biopsy and has emerged as a key component of diagnostic testing [5]. Clinically, the greatest concern with population-wide adoption of mpMRI is its highly variable accuracy across institutions and among individual radiologists [6, 7]. For example, Sonn et al. found the negative predictive value (NPV) of mpMRI for GG ≥ 2 cancer ranged from 40 to 87% across radiologists at a single academic center [6]. In a recent meta-analysis, Sathianathen et al observed a pooled NPV approximating 90%, although published values ranged as low as 62% by study [7]. Moreover, these data were obtained largely from experienced academic centers, as the authors acknowledged there are insufficient published data for planned analyses of nonacademic centers. Notably, the positive predictive value (PPV) of mpMRI appears to be similarly variable. In a meta-analysis of 26 experienced imaging centers [8], PI-RADS 4 lesions had an estimated overall PPV of 39%, with an interquartile range (IQR) of PPVs extending from 25 to 55%. Similarly, the interquartile range of PPVs for PI-RADS 5 lesions extended from 61 to 82% across centers. As previous authors have emphasized [7], in light of inter- and intra-institutional variability of mpMRI reading and interpretation, determining the potential utility of mpMRI in a given practice setting requires knowledge of local mpMRI data.

Considering these data and practical limitations of mpMRI (e.g., access to high-quality imaging; adherence to technical standards; time, labor, and cost associated with testing) [9], objectively-measured biomarkers obtainable in routine practice could be more practical for initial reflex testing after PSA. In the current study, it is notable that mpMRI provided 95% sensitivity for GG ≥ 2 disease—a value likely exceeding what would be expected from population-wide use of mpMRI [6, 7, 10]. Still, the conditional strategy of initial biomarker testing, followed by mpMRI for positive biomarker tests only, resulted in the greatest reduction in biopsy (60% of patients avoided biopsy), the greatest reduction in overdiagnosis of GG1 cancers (58%), and maintained reasonably high detection of GG ≥ 2 cancers (87%). As the authors report, this approach provided the second-highest net benefit across the majority of pertinent risk thresholds. Thus, a conditional, biomarker-first testing approach – likely to be most feasible for population-level application—may also prove most clinically-beneficial under "real-world" (i.e. de-centralized) interpretation of MRI or using an alternative biomarker (or alternative cutoff of the current biomarker) with different performance metrics [11].

Ultimately, the authors are to be commended for this well-performed, prospective assessment of two clinically-available diagnostic tools. While additional studies, including head-to-head comparisons and cost-effectiveness analyses, will continue to inform the optimal diagnostic approach, these prospective data provide benchmarks of relative risks and benefits under combined testing approaches. As clinicians, a working knowledge of such

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**Table 1.** Tests performed and projected clinical outcomes under four diagnostic testing strategies.

| | Determined by testing strategy | | Clinical impact of test results | | |
|---|---|---|---|---|---|
| Testing strategy | SelectMDx performed (%) | mpMRI performed (%) | Biopsies avoided (%) | GG ≥ 2 PCa detected (i.e., sensitivity) | Reduction in overdiagnosis of GG1 PCa |
| (1) SelectMDx-only | 100% | 0% | 38% | 90% | 35% |
| (2) mpMRI-only | 0% | 100% | 49% | 95% | 44% |
| (3) Conditional (biopsy if both tests positive) | 100% | 62% | 60% | 87% | 58% |
| (4) Joint (biopsy if either test positive) | 100% | 100% | 28% | 98% | 21% |

data allows us to best identify which available tools can inform decision-making with the level of certainty sought by each of our patients. As the late, great Donald S. Coffey often responded when asked how much risk of prostate cancer death (in exchange for reduced morbidity) was too much risk: "That's not a medical question, that's a personal question." Until the perfect diagnostic test emerges, guiding our patients through personalized, shared decision-making will remain a most essential component of prostate cancer care.

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## AUTHOR CONTRIBUTIONS

JJT drafted this comment in reference to a recently published study (Hendricks et al, reference [3] in comment)

## COMPETING INTERESTS

JJT is a co-founder of LynxDx, Inc.

## ADDITIONAL INFORMATION

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