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Use of the MyProstateScore Test to Rule Out Clinically Significant Cancer: Validation of a Straightforward Clinical Testing Approach

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Abbreviations and Acronyms

DRE = digital rectal examination
GG = grade group
mpMRI = multiparametric magnetic resonance imaging
MPS = MyProstateScore
NPV = negative predictive value
PCA3 = prostate cancer antigen 3
PPV = positive predictive value
PSA = prostate specific antigen
T2:ERG = TMPRSS2:ERG gene fusion

Purpose: The MyProstateScore test was validated for improved detection of clinically significant (grade group ≥2) prostate cancer relative to prostate specific antigen based risk calculators. We sought to validate an optimal MyProstateScore threshold for clinical use in ruling out grade group ≥2 cancer in men referred for biopsy.

Materials and Methods: Biopsy naïve men provided post-digital rectal examination urine prior to biopsy. MyProstateScore was calculated using the validated, locked multivariable model including only serum prostate specific antigen, urinary prostate cancer antigen 3 and urinary TMPRSS2:ERG. The MyProstateScore threshold approximating 95% sensitivity for grade group ≥2 cancer was identified in a training cohort, and performance was measured in 2 external validation cohorts. We assessed the 1) overall biopsy referral population and 2) population meeting guideline based testing criteria (ie, prostate specific antigen 3-10, or <3 with suspicious digital rectal examination).

Results: Validation cohorts were prospectively enrolled from academic (977 patients, median prostate specific antigen 4.5, IQR 3.1–6.0) and community (548, median prostate specific antigen 4.9, IQR 3.7–6.8) settings. In the overall validation population (1,525 patients), 338 men (22%) had grade group ≥2 cancer on biopsy. The MyProstateScore threshold of 10 provided 97% sensitivity and 98%

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References 31 through 36 can be obtained at https://www.jurology.com.

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negative predictive value for grade group ≥2 cancer. MyProstateScore testing would have prevented 387 unnecessary biopsies (33%), while missing only 10 grade group ≥2 cancers (3.0%). In 1,242 patients meeting guideline based criteria, MyProstateScore ≤10 provided 96% sensitivity and 97% negative predictive value, and would have prevented 32% of unnecessary biopsies, missing 3.7% of grade group ≥2 cancers.

Conclusions: In a large, clinically pertinent biopsy referral population, MyProstateScore ≤10 provided exceptional sensitivity and negative predictive value for ruling out grade group ≥2 cancer. This straightforward secondary testing approach would reduce the use of more costly and invasive procedures after screening with prostate specific antigen.

Key Words: biomarkers, tumor; prostatic neoplasms; biopsy; prostate-specific antigen; early detection of cancer

PROSTATE cancer remains the most commonly diagnosed malignancy and a leading cause of cancer death in the developed world.[1] While PSA based screening appears to reduce mortality in men with higher grade cancers,[2,3] PSA is nonspecific for cancer, leading to excess morbidity from negative prostate biopsies and detection of indolent cancers.[4] An optimal testing approach would enable detection of clinically significant cancers (grade group ≥2) while ruling out the need for biopsy in men without cancer or with low grade cancer. Accordingly, clinical guidelines propose adjunct testing with biomarkers or imaging to better define risk of high grade cancer prior to biopsy.[5]

In response to this need, investigators developed a urine based panel, MyProstateScore, which combines urinary prostate cancer antigen 3 and the TMPRSS2:ERG gene fusion with serum PSA (LynxDx, Inc., Ann Arbor, Michigan). MPS was previously validated to improve detection of GG ≥2 cancer relative to PSA and clinical risk calculators combining PSA with digital rectal examination, family history and history of previous biopsy (ie Prostate Cancer Prevention Trial risk calculator).[6] In the current diagnostic paradigm, use of biomarkers such as MPS to rule out GG ≥2 cancer could be a practical means to reduce morbidity resulting from PSA testing,[5,7] without limiting its life-prolonging impact. Although previous data have demonstrated the diagnostic accuracy of MPS, a practical clinical testing approach has not been described.[6]

We therefore sought to identify a MPS threshold (ie cut point) facilitating use as a clinically actionable rule out test for GG ≥2 cancer. We validated use of the threshold in multiple external cohorts and characterized its diagnostic performance prior to initial prostate biopsy in the clinically appropriate testing population.

MATERIALS AND METHODS

Threshold Analysis

We sought to establish and validate a MPS threshold (ie cutoff, cut point) for clinical use to rule out GG ≥2 cancer. Given a lack of consensus approach to threshold identification and use, we used published methods aiming to balance clinical and statistical principles.[8–10] Our approach was based primarily on the clinical need for a test to rule out GG ≥2 cancer with high sensitivity and negative predictive value, ie to minimize false-negatives,[11] such that patients and physicians can confidently defer unnecessary biopsies. Considering GG ≥2 cancer prevalence in published testing populations (ie 17%–31%)[12–16] and the relative harms of false-positive and false-negative results,[17] we proposed a post-test risk of GG ≥2 cancer approximating ≤5% was clinically actionable to defer biopsy in most cases. Thus, we sought a threshold value approximating 95% sensitivity and 95% NPV for GG ≥2 cancer.[18] To best ensure generalizability,[19] we used a demanding approach described by Morrow and Cook,[8] including external validation in 2 appropriate testing cohorts, with attention paid to pertinent subgroups. Our methods were consistent with published guidelines for biomarker evaluation.[20–22] Additional details are provided and reasonable concerns are addressed in the supplementary Appendix (https://www.jurology.com).

Study Population and Protocol

The multivariable MPS model was previously developed in 711 men presenting to academic centers for biopsy, and the locked model was validated in 1,244 men at 7 community clinics.[6] The current training cohort (516) and validation cohort A (977) included biopsy naïve men from the previously described study populations (fig. 1), prospectively enrolled from August 2007 through May 2011.[6] Validation cohort B included 548 biopsy naïve men prospectively enrolled as part of an Early Detection Research Network study of PCA3 and T2:ERG that did not evaluate MPS (December 2009–November 2010).[23] Validation cohort B was an external, locked data set accessible by only 2 study investigators (GL,YZ), and analyses were based on the prespecified plan.

Institutional review board approval was obtained, and all participants provided informed consent (IRB No. HUM00042749). First-catch post-DRE urine was prospectively collected, mixed with stabilization buffer, and frozen to −70C per protocol.[6,23] *PCA3*, *T2:ERG* and *PSA* mRNA were quantified by transcription-mediated amplification, and PCA3 and T2:ERG scores were calculated by normalization to *PSA* mRNA as described (supplementary material, https://www.jurology.com).[6] MPS was calculated based on established, locked-in models including only serum PSA, PCA3 score and

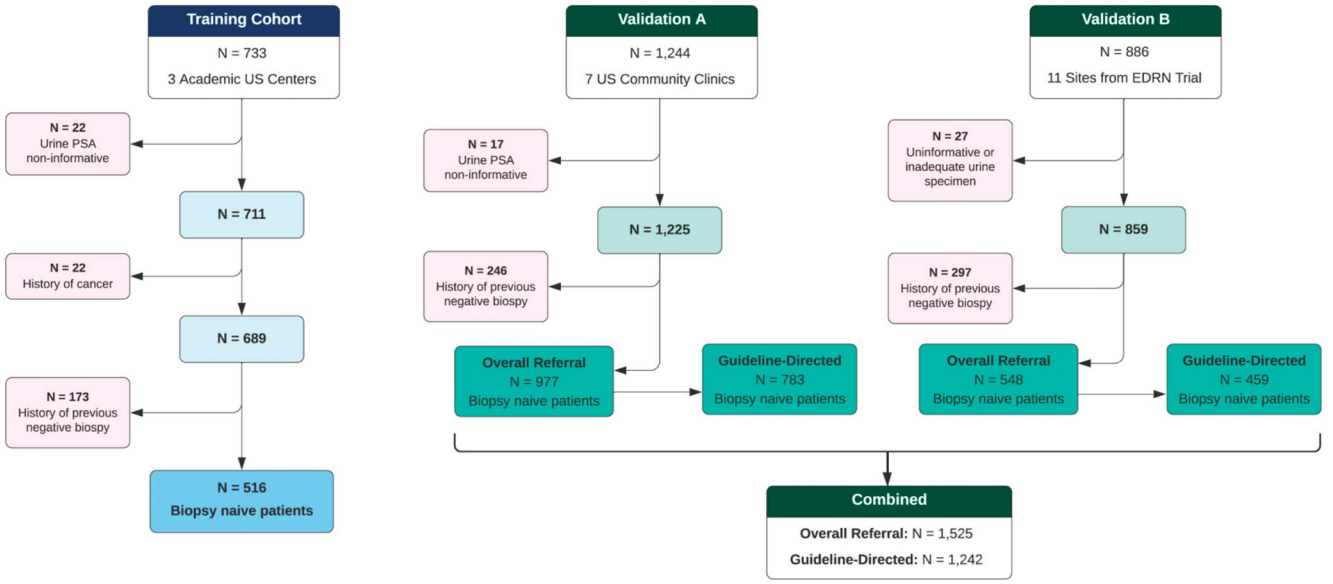

Figure 1. Flow diagram of patients providing urine specimens prior to initial prostate biopsy in training cohort (blue) and validation cohorts (green). MyProstateScore was assessed using validated, locked model including serum PSA, urinary PCA3 score and urinary T2:ERG score. Number of patients meeting National Comprehensive Cancer Network® indications for biopsy (ie PSA 3–10 ng/ml, or PSA <3 ng/ml and suspicious DRE) are listed for validation cohorts (ie guideline directed). *EDRN*, Early Detection Research Network. *US*, United States.

T2:ERG score. MPS values are reported on a continuous scale from 0 (very unlikely to detect GG ≥2 cancer) to 100 (very likely to detect GG ≥2 cancer).

Statistical Analysis

The outcome of interest was GG ≥2 cancer. As determined a priori, MPS threshold values approximating 95% sensitivity were identified in the training cohort. Thresholds were primarily assessed based on sensitivity (as opposed to NPV) given that NPV varies with outcome prevalence across cohorts.[18,24] The threshold providing the optimal balance of sensitivity and negative test rate in the training cohort was applied to validation cohorts, and the sensitivity, specificity, NPV and PPV were calculated.[18,24] We calculated the number (%) of biopsies avoided, the number (%) of unnecessary biopsies (ie negative/GG1) avoided and the number (%) of GG ≥2 cancers missed if the threshold were used to select for biopsy.[17]

Analyses were performed in 1) the overall biopsy referral population and 2) the subpopulation with PSA 3–10 ng/ml, or PSA <3 ng/ml with suspicious DRE, consistent with clinical guidelines (ie guideline directed population).[5] Test performance was assessed in clinically pertinent subgroups, ie suspicious DRE[25] and African American men.[26] Finally, validated numerical methods were used to demonstrate the clinically based threshold model was statistically valid (supplementary Appendix, https://www.jurology.com).[9,10] Analyses were performed using Stata IC v16.1 and R v3.6.1.

RESULTS

Training Cohort and Threshold Identification

The training cohort included 516 biopsy naïve patients of median age 61 years (IQR 56–67), median PSA 4.8 ng/ml (3.6–6.3), and median MPS 21.6 (10.3–39.6). On biopsy, 156 men (30%) had GG ≥2 cancer. The threshold values of 9 and 10 each approximated target sensitivity of 95% (94.9% and 94.3%, respectively; supplementary table 1, https://www.jurology.com). MPS ≤10 captured an additional 3.1% of the population (24.4% vs 21.3% for MPS ≤9) with minimal loss of sensitivity (0.6%) and was selected for validation. Cohort characteristics are listed in table 1.

Validation of MPS Threshold of 10 in 2 External Cohorts

Among 977 men in validation cohort A, median age was 64 years (IQR 57–69), PSA was 4.5 ng/ml (3.1–6.0) and MPS was 19.0 (8.6–39.0). On biopsy (99% underwent ≥12 core biopsy; supplementary material, https://www.jurology.com), 192 men (20%) had GG ≥2 cancer. MPS ≤10 provided 97.4% sensitivity and 98.2% NPV for GG ≥2 cancer. Clinically, use of MPS would have avoided 28.4% of biopsies and 35.3% of unnecessary (ie negative/GG1) biopsies. Biopsy would have been deferred due to MPS ≤10 in five men with GG ≥2 cancer (2.6% of GG ≥2 cancers). In the guideline directed subpopulation, the MPS threshold of 10 maintained 96.7% sensitivity and 97.7% NPV and would have avoided 27.5% of biopsies, while potentially missing 5 GG ≥2 cancers. The distributions of PSA and MPS values by biopsy outcome are illustrated in figure 2.

In validation cohort B (548), median age was 62 years (IQR 56–67), median PSA was 4.9 ng/ml (3.7–6.8), and median MPS was 23.5 (11.2–40.5). On biopsy (99% underwent ≥12 core biopsy), 146 men

Table 1. *Demographic and clinical characteristics of study cohorts*

	Training Cohort		Validation Cohort A		Validation Cohort B	
No. pts	516		977		548	
Median yrs age (IQR)	61	(56–67)	64	(57–69)	62	(56–67)
No. African American race (%)	52	(10)	73	(7.5)	77	(14)
No. pos family history (%)	119	(23)	181	(19)	126	(23)
No. suspicious DRE (%)	83	(16)	239	(25)	126	(23)
Median ng/ml PSA (IQR)	4.8	(3.6–6.3)	4.5	(3.1–6.0)	4.9	(3.7–6.8)
Median MPS (IQR)	21.6	(10.3–39.6)	19.0	(8.6–38.9)	23.5	(11.2–40.5)
No. biopsy results (%):						
Neg	262	(50.8)	542	(55.5)	286	(52.2)
GG1	98	(19.0)	243	(24.9)	116	(21.2)
GG ≥2	156	(30.2)	192	(19.7)	146	(26.6)

(26.6%) had GG ≥2 cancer. MPS ≤10 again provided very high sensitivity for GG ≥2 cancer in both the overall biopsy referral population (96.6%) and the guideline directed subpopulation (95.6%). The sensitivity, specificity, NPV and PPV of MPS ≤10 in the validation cohorts are listed in table 2.

Performance of MPS Threshold of 10 in Combined Validation Population

In the combined biopsy referral population (1,525), 338 men (22.2%) had GG ≥2 cancer (supplementary table 2, https://www.jurology.com). The MPS threshold of 10 provided 97.0% sensitivity and would have avoided 397 prostate biopsies (26.0%), including 387 unnecessary (negative/GG1) biopsies (32.6%). Considering all 1,525 patients that underwent MPS testing, MPS ≤10 would have missed GG ≥2 cancer in only 0.7% of men (10) and GG ≥3 cancer in only 0.3% (5). Performance measures in the overall biopsy referral population and guideline directed subpopulation are listed in table 3.

Assessment of MPS Threshold of 10 in Pertinent Subpopulations

There were 365 men (24.0%) with a suspicious DRE. GG ≥2 cancer was detected in 108 men (29.6%) with suspicious DRE as compared to 19.8% of men with nonsuspicious DRE. Consistent with the overall cohort, the sensitivity and NPV of MPS ≤10 exceeded 96% in men with suspicious DRE (table 3). Use of MPS ≤10 would have avoided biopsy in 122 men (33.4%) with suspicious DRE, including 45.9% of unnecessary (ie negative/GG1) biopsies, with a negative test result in only 4 men with GG ≥2 cancer (3.7%).

The combined validation population included 150 African American men. Prevalence of GG ≥2 cancer was 27.3% in African American men and 21.6% in nonAfrican American men. Among African

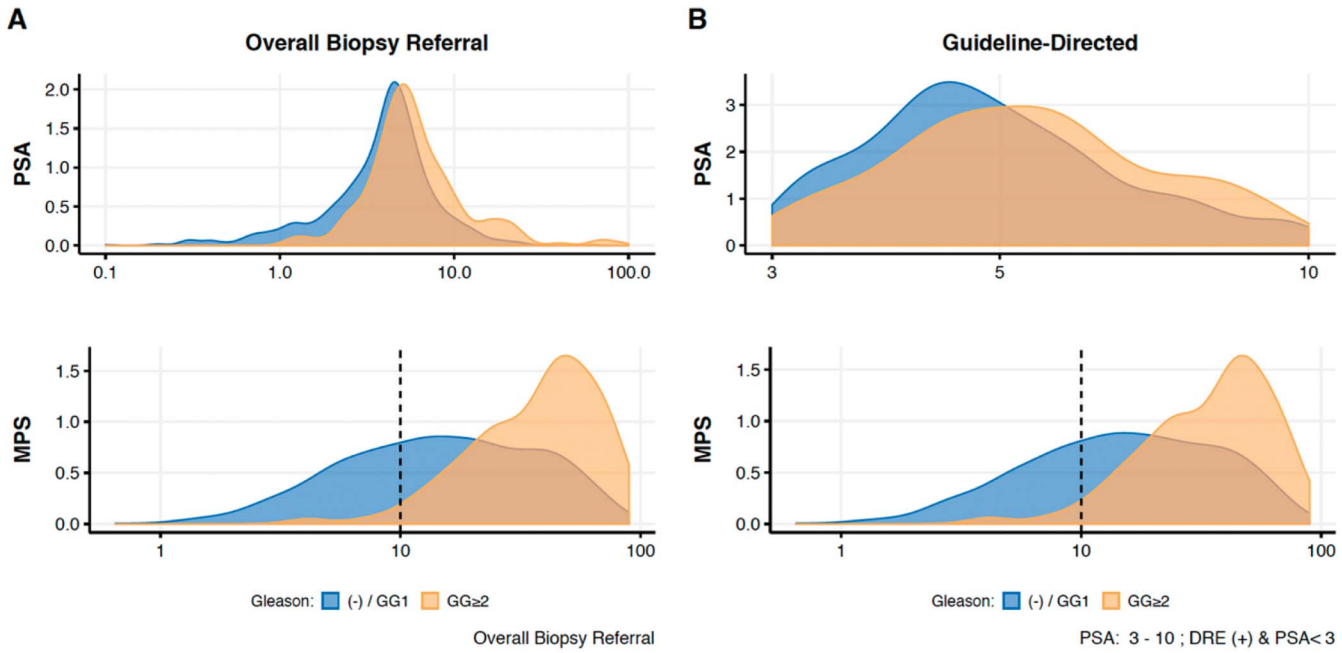

Figure 2. Density plots illustrate serum PSA (upper panel) and MPS (lower panel) in patients with negative (−) or GG1 cancer on biopsy (blue) vs GG ≥2 cancer on biopsy (orange). *A*, data for overall biopsy referral population. *B*, data for guideline directed population (PSA 3 −10 ng/ml, or PSA <3 ng/ml and suspicious DRE). Dashed vertical line represents MPS value of 10.

Table 2. *Clinical performance measures of MPS threshold of 10 in validation cohorts A and B*

	No.	No. GG ≥2 (%)	% Sensitivity	% Specificity	% NPV	% PPV	No. Biopsies Avoided (%)	No. Unnecessary Biopsies Avoided (%)	No. GG ≥2 Diagnoses Missed (%)
Validation Cohort A:									
Overall biopsy referral	977	192 (19.7)	97.4	34.6	98.2	26.7	277 (28.4)	272 (34.6)	5 (2.6)
Guideline directed	783	153 (19.5)	96.7	33.3	97.7	26.1	215 (27.5)	210 (33.3)	5 (3.3)
Validation Cohort B:									
Overall biopsy referral	548	146 (26.6)	96.6	28.6	95.8	32.9	120 (21.9)	115 (28.6)	5 (3.4)
Guideline directed	459	114 (24.8)	95.6	29.0	95.2	30.8	105 (22.9)	100 (29.0)	5 (4.4)

American men, MPS ≤10 provided similarly high sensitivity (97.6%) and NPV (95.5%). Notably, only 22 men (14.7%) had MPS ≤10 and would have been recommended to defer biopsy, with 1 GG ≥2 cancer (2.4%) not detected.

Assessment of Additional MPS Thresholds

The performance measures of additional MPS thresholds are shown in table 4. As expected, test sensitivity decreased and specificity increased with higher thresholds. In the overall validation population, sensitivity ranged from 97.6% (threshold 8) to 90.5% (threshold 15). Similar findings were observed in the guideline directed population.

DISCUSSION

The MyProstateScore test was previously demonstrated to significantly improve detection of GG ≥2 cancer relative to PSA and the Prostate Cancer Prevention Trial risk calculator.[6] In the current analysis, we established and validated a MPS threshold based on the pressing clinical need to rule out GG ≥2 cancer in men referred for prostate biopsy. In a large, clinically appropriate validation population spanning academic and community settings, MPS ≤10 was associated with 97.0% sensitivity and 97.5% NPV for GG ≥2 cancer. Among 1,525 patients, this testing approach would have avoided 387 unnecessary prostate biopsies (33% of negative/GG1 biopsies), while deferring biopsy in only 10 cases of GG ≥2 cancer (3.0% of GG ≥2 cancers; 0.7% of the tested population). From a practical standpoint, risk-stratification using MPS ≤10 would have avoided 26% of all prostate biopsies, while maintaining detection of more than 97% of GG ≥2 cancers. From a patient perspective, a MPS value ≤10 ruled out GG ≥2 cancer with nearly 98% accuracy (ie NPV). These data provide reliable, clinically actionable information to patients and providers and make a strong case for use of MPS to rule out the need for additional testing (eg mpMRI, biopsy) in a substantial proportion of men currently subjected to these interventions.

The limitations of PSA based screening have created a need to reduce the number of unnecessary (ie negative/GG1) biopsies performed, while, ideally, preserving detection of higher grade cancers that stand to benefit from treatment.[2,3] Several blood and urine based biomarkers have been proposed for use in this setting,[12–16] but it remains unclear how to best use these assays, largely due to limitations of available data. The Centers for Medicare and Medicaid Services have referenced a lack of standardized cut points as 1 such limitation,[11] in addition to validation in poorly characterized, inappropriate study populations—in some cases including men with PSA >200 ng/ml. Acknowledging a baseline GG ≥2 cancer risk of 17%–31% in the proposed testing population,[12–16] it is unclear whether clinical tests that miss 7%–13% of GG ≥2 cancers (ie sensitivity 87%–93%)[12–16] provide sufficient risk reduction for physicians to confidently recommend against assessment with biopsy or mpMRI. Using a clear and clinically pragmatic approach, we found that MPS ruled out the need for additional, unnecessary testing in

Table 3. *Clinical performance measures of MPS threshold of 10 in combined validation cohort and pertinent subgroups*

	No.	No. GG ≥2 (%)	% Sensitivity	% Specificity	% NPV	% PPV	No. Biopsies Avoided (%)	No. Unnecessary Biopsies Avoided (%)	No. GG ≥2 Diagnoses Missed (%)
Overall biopsy referral	1,525	338 (22.2)	97.0	32.6	97.5	29.1	397 (26.0)	387 (32.6)	10 (3.0)
Guideline directed	1,242	267 (21.5)	96.3	31.8	96.9	27.9	320 (25.8)	310 (31.8)	10 (3.7)
DRE suspicious	365	108 (29.6)	96.3	45.9	96.7	42.8	122 (33.4)	118 (45.9)	4 (3.7)
DRE nonsuspicious	1,156	229 (19.8)	97.4	28.9	97.8	25.3	274 (23.7)	268 (28.9)	6 (2.6)
African American pts	150	41 (27.3)	97.6	19.3	95.5	31.3	22 (14.7)	21 (19.3)	1 (2.4)
Non African American pts	1,372	297 (21.6)	97.0	34.0	97.6	28.9	374 (27.3)	365 (34.0)	9 (3.0)

DRE data were missing for 4 patients, and race data were missing for 3.

Table 4. *Performance of various MPS threshold (cut off) values in overall biopsy referral population (1,525 patients) and guideline directed population (1,242) of combined validation cohort*

	No. GG ≥2 PCa (%)	% Sensitivity	% Specificity	% NPV	% PPV	No. Biopsies Avoided (%)	No. Unnecessary Biopsies Avoided (%)	No. GG ≥2 Diagnoses Missed (%)
Threshold ≤8:								
Overall biopsy referral	338 (22.2)	97.6	26.2	97.5	27.4	319 (20.9)	311 (26.2)	8 (2.4)
Guideline directed	267 (21.5)	97.0	24.9	96.8	26.1	251 (20.2)	243 (24.9)	8 (3.0)
Threshold ≤9:								
Overall biopsy referral	338 (22.2)	97.6	29.8	97.8	28.4	362 (23.7)	354 (29.8)	8 (2.4)
Guideline directed	267 (21.5)	97.0	28.9	97.2	27.2	290 (23.3)	282 (28.9)	8 (3.0)
Threshold ≤10:								
Overall biopsy referral	338 (22.2)	97.0	32.6	97.5	29.1	397 (26.0)	387 (32.6)	10 (3.0)
Guideline directed	267 (21.5)	96.3	31.8	96.9	27.9	320 (25.8)	310 (31.8)	10 (3.7)
Threshold ≤12:								
Overall biopsy referral	338 (22.2)	93.8	38.6	95.6	30.3	479 (31.4)	458 (38.6)	21 (6.2)
Guideline directed	267 (21.5)	92.1	37.9	94.6	28.9	391 (31.5)	370 (37.9)	21 (7.9)
Threshold ≤15:								
Overall biopsy referral	338 (22.2)	90.5	47.5	94.6	32.9	596 (39.1)	564 (47.5)	32 (9.5)
Guideline directed	267 (21.5)	88.8	46.6	93.8	31.3	484 (39.0)	454 (46.6)	30 (11.2)

approximately 1 in 3 men (32.6%) without GG ≥2 cancer, with false-negative results in only 10 men with GG ≥2 disease (0.7% of the validation population). Thus, MPS appears to provide patients and physicians with clear and reliable data to reduce the potential harms of PSA screening[4]—including unnecessary testing, over diagnosis, overtreatment, and the complications of each—without compromising detection of more aggressive cancers.

At the same time, adoption of diagnostic mpMRI has shifted the landscape of prostate cancer detection.[27] While mpMRI with fusion biopsy has facilitated targeting of MRI-visible lesions, an increasing body of evidence has revealed that a relatively high prevalence of clinically significant cancers are not detectable by mpMRI.[28–30] At one extreme, relative to surgical pathology, mpMRI missed 1 or more foci of GG ≥2 cancer in 34% of intermediate and high risk patients—an alarmingly high rate, even considering the reference standard.[28] Thus, the relatively lower NPV of mpMRI could limit its reliability as a rule out test.[28–30,31] Moreover, there are several practical reasons that mpMRI might not be an ideal first line assessment after PSA testing, including its high cost, resource burden, and limited availability, as well as dependence on radiological interpretation with high inter-reader variability.[32,33] Notably, mpMRI is not reimbursed for a substantial proportion of biopsy naïve patients at our institution. Based on the current analysis, MPS testing provides an objective, clinically practical, and highly accurate approach to ruling out GG ≥2 cancer in this population, effectively reducing the number of men required to undergo more costly or invasive assessments. Furthermore, these data indicate that MPS ≤10 remains highly sensitive in African American men (96.7%) and could provide the greatest benefit (ie reduction in unnecessary biopsies) in men with a suspicious DRE (45.9%). Thus, MPS testing appears to be useful in populations traditionally considered less likely to benefit from biomarker testing.[11]

It is important to consider the overall data describing MPS testing. Previous studies have demonstrated improved overall predictive accuracy (ie area under the receiver operating characteristic curve) with stepwise addition of PCA3, T2:ERG, and the combined MPS model to PSA and the Prostate Cancer Prevention Trial risk calculator.[6] Furthermore, decision curve analysis revealed that use of MPS provided net clinical benefit relative to clinical models and reduced the number of biopsies performed,[6] consistent with a recently published clinical study.[34] Still, the optimal testing approach in any clinical setting depends on several factors, including relative harm of false-negative and false-positive tests.[8] The particular limitations of PSA and the landscape of cancer diagnosis are such that broad measures of performance (ie AUC) are less consequential, and "rule in" tests (ie characterized by high specificity and PPV) are currently less attainable than a highly reliable rule out test, which can practically reduce the population-wide burden secondary to PSA testing, while preserving detection of higher grade cancers. We therefore validated a practical approach to MPS testing that provides patients and clinicians with clinically actionable information to rule out the need for additional testing. Acknowledging the limitations of cross-study comparisons, MPS appears to compare favorably to other testing options, providing optimal sensitivity and negative predictive value to rule out GG ≥2 cancer in the clinical testing population.[12–16,31]

The current study has limitations. For one, systematic biopsy as a reference standard appears to miss 15%–20% of cancers, including a proportion of

GG ≥2 cancers. Furthermore, not all cases of GG ≥2 cancer will prove to be clinically significant. These limitations merit the need for additional validation with longer term outcomes. Second, the current analysis did not include men with a history of negative biopsy. Notably, however, given the favorable risk profile conferred by previous negative biopsies,[35,36] a rule out testing approach would be expected to perform as well or better in the repeat biopsy setting.[18] Third, the current study was performed outside the context of mpMRI, which is increasingly used in the diagnostic setting. That said, these data demonstrate that MPS has very high NPV as a standalone test after PSA screening, suggesting a potential role for MPS prior to mpMRI as an objective and widely available test to reduce the need for mpMRI or biopsy altogether. Additional data are needed to explore the combined use of MPS with mpMRI, to confirm our initial findings in clinically important subgroups (eg African American men), and to further assess the clinical utility of the proposed testing approach. Finally, predictive values (ie NPV) are dependent on disease prevalence, which varies by study population. For this reason, we focused our discussion on sensitivity, and we provided the sensitivity, specificity, NPV and PPV in all cases to provide a full picture of our findings. As conclusions on the relative performance of tests cannot be drawn from cross-study comparisons, we have conveyed only that MPS appears to compare favorably to other available data.

CONCLUSIONS

In a large, clinically appropriate testing population, a MPS threshold of 10 was highly sensitive for GG ≥2 cancer. Use of MPS ≤10 would have avoided 26% of biopsies, including 33% of unnecessary (negative/GG1) biopsies, while potentially missing only 3% of GG ≥2 cancers. This practical testing approach was derived in light of the current diagnostic pathway and was externally clinically validated across community and academic settings—increasing the likelihood that our findings are highly generalizable. As such, MPS appears to be a practical, highly reliable option to rule out the need for more costly or invasive testing in men referred for diagnostic prostate biopsy.

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