Clinical Utility of 4Kscore®, ExosomeDx™ and Magnetic Resonance Imaging for the Early Detection of High Grade Prostate Cancer

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Abbreviations and Acronyms

DRE = digital rectal examination

GG = Gleason grade group

MRI = magnetic resonance imaging

mpMRI = multiparametric magnetic resonance imaging

PCa = prostate cancer

PI-RADS™ = Prostate Imaging—Reporting and Data System

PSA = prostate specific antigen

PSAD = prostate specific antigen density

TRUS = transrectal ultrasonography

UCSF = University of California, San Francisco

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Purpose: We aimed to evaluate 4Kscore® and ExosomeDx™ with multiparametric magnetic resonance imaging in the detection of high grade prostate cancer and number of biopsies avoided.

Material and Methods: Patients had 1 liquid biomarker test with or without multiparametric magnetic resonance imaging. High grade prostate cancer was defined as Gleason grade group 2 or greater. The overall number of avoided biopsies (with Gleason grade 1 or less), and number of missed Gleason grade 2 or greater cancer among the biopsied patients, were determined.

Results: Of the 783 patients in the overall cohort 419 (53.5%) underwent biopsy. 4Kscore and ExosomeDx scores higher than the manufacturers' cut point were associated with PI-RADS™ scores 3 to 5 and Gleason grade 2 or greater prostate cancer. Limiting biopsy to the men with liquid biomarker scores above the manufacturers' cut point would have resulted avoiding 29.5% to 39.9% unnecessary biopsies overall, while missing 4.0% to 4.8% Gleason grade 2 or greater prostate cancer in the biopsy group. Screening algorithms with up-front liquid biomarker testing followed by multiparametric magnetic resonance imaging if the biomarker is above the manufacturers' cut point, then followed by biopsy if the multiparametric magnetic resonance imaging is positive or if 4Kscore 20 or greater or ExosomeDx 19 or greater would have missed 4.8% to 5.6% of Gleason grade 2 or greater prostate cancer in the biopsy group while avoiding 39.4% to 43.0% biopsies and 29.5% to 39.9% multiparametric magnetic resonance imaging overall. Similar algorithms with up-front multiparametric magnetic resonance imaging followed by liquid biomarker testing for negative multiparametric magnetic resonance imaging would have missed 2.4% of Gleason grade 2 or greater prostate cancer in the biopsy group but only avoided 17.2% 19.3% biopsies overall.

Conclusions: Screening algorithms with up-front liquid biomarker testing followed by multiparametric magnetic resonance imaging and biopsy at certain biomarker thresholds could reduce unnecessary biopsies, multiparametric magnetic resonance imaging and overdetection of Gleason grade 1 prostate cancer.

Key Words: prostatic neoplasms; early detection of cancer; biomarkers; magnetic resonance imaging; biopsy

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THE current prostate specific antigen directed screening paradigm has poor specificity, leading to unnecessary biopsies and overdiagnosis of low risk prostate cancer in many healthy men with only a small overall improvement in PCa specific survival[1] and is associated with potential treatment related toxicity, expense and anxiety for the patient.[2,3] During the last decade there have been significant efforts to develop novel biomarkers to improve the specificity of prostate specific antigen.[4] The 4Kscore® is derived from a composite score of serum markers total PSA, free PSA, intact PSA and human kallikrein 2 applied to a model accounting for age, history of previous prostate biopsy and digital rectal examination.[5] ExosomeDx™ measures *PCA3* and *ERG* RNA expression in exosomes, small RNA containing vesicles that prostate cells shed into the urinary tract, without the need for DRE.[6] Both liquid biomarkers have been shown to have high discrimination for clinically significant PCa.[7–11]

Multiparametric magnetic resonance imaging of the prostate with targeted biopsy improves the detection of clinically significant PCa while decreasing the detection of lower risk disease[12–14] and has also been proposed as an imaging based screening tool before prostate biopsy.[15] Clinical guidelines suggest combining mpMRI with liquid biomarkers when further risk stratification is desired to decide if a prostate biopsy can be omitted,[16] but the optimal sequence and timing of these biomarkers in order to maximize the detection of clinically significant PCa while limiting the detection of indolent disease remains to be determined.

In this study we evaluate 2 commercially available liquid biomarkers with or without mpMRI to determine the number of avoided biopsies and missed clinically significant PCa. While combining mpMRI with liquid biomarkers could significantly improve detection of clinically significant PCa, we hypothesize that mpMRI can be avoided in a select group of patients with positive biomarker results without missing clinically significant PCa.

MATERIALS AND METHODS

Patient Cohort

The cohort was drawn retrospectively from men referred to the University of California, San Francisco with elevated PSA or abnormal DRE from 2016 to 2019. The inclusion criteria included at least one liquid biomarker test (serum based 4Kscore Test [OPKO, Elmwood Park, NJ, USA] or urinary based ExosomeDx [Exosome Diagnostics, Inc., Waltham, MA, USA]) performed before prostate biopsy, PSA <20 ng/mL and no previous diagnosis of PCa. The study was approved by the UCSF institutional review board (IRB No. 17-23776).

Biomarker Selection, mpMRI and Prostate Biopsy Protocol

Biomarker selection, biopsy decision and timing of the biopsy were at the discretion of the treating provider, patient preference and based on insurance coverage. No biomarker or mpMRI finding mandated that a biopsy be performed or omitted. Clinical staging was determined with transrectal ultrasonography and/or mpMRI. PSA density was assessed using TRUS or mpMRI if no TRUS information was available.[17] All mpMRIs were performed using a 3T MRI and interpreted by radiologists with expertise in prostate mpMRI, using the Prostate Imaging–Reporting and Data System (PI-RADS™) version 2 scoring system. Prostate biopsies were done within 12 months of biomarker testing. All systematic prostate biopsies were performed using a standard template with 10 or greater cores. Targeted biopsies were performed for PI-RADS 3 to 5 lesions using the UroNav fusion system (Invivo, Gainesville, Florida). Lesions visible on TRUS were also biopsied. Patients who did not undergo biopsy were followed at provider discretion. If a prostate biopsy was subsequently performed more than 12 months after biomarker testing, pathology results were recorded but not included in the analysis. Followup PSA results 12 months after initial biomarker testing were recorded for analysis. High grade PCa is defined as Gleason grade group 2 or greater.

Statistical Analysis

The manufacturers' cut points were used to define a positive vs negative biomarker test. 4Kscores 7.5% or greater and ExosomeDx Prostate IntelliScore 15.6 or greater were considered positive. The mpMRI results were considered positive if reported as PI-RADS 3 to 5.

Patient groups were compared with chi-square tests for categorical variables and ANOVA or Wilcoxon rank sum tests for continuous variables. Demographic and clinical characteristics were compared between the biopsied and nonbiopsied groups by PI-RADS scores and by biopsy results (benign vs GG1 vs GG2 or greater). A Cochran-Armitage test for trend was used to compare biomarkers by PI-RADS scores. In the group of patients with dual biomarker testing done at any point during the study timeframe, Spearman correlation coefficient was calculated to determine the relationship between the biomarkers. The frequency of avoided biopsies was determined as the number of negative tests divided by the total cohort. The frequency of missed high grade PCa was determined as the number of false negative tests divided by all high grade diagnoses and was therefore derived from the group of patients that were biopsied in spite of having a negative test. When a biomarker was combined with mpMRI the negative tests were those with negative biomarker *and* negative mpMRI and the positive tests those with positive biomarker *or* positive mpMRI. Statistical significance was set at $p < 0.05$. Statistical analysis was done with STATA® 16 (StataCorp, College Station, Texas).

RESULTS

Clinical Characteristics of the Cohort

A total of 783 patients met the inclusion criteria, with 617 patients having 4Kscore testing, 228 ExosomeDx

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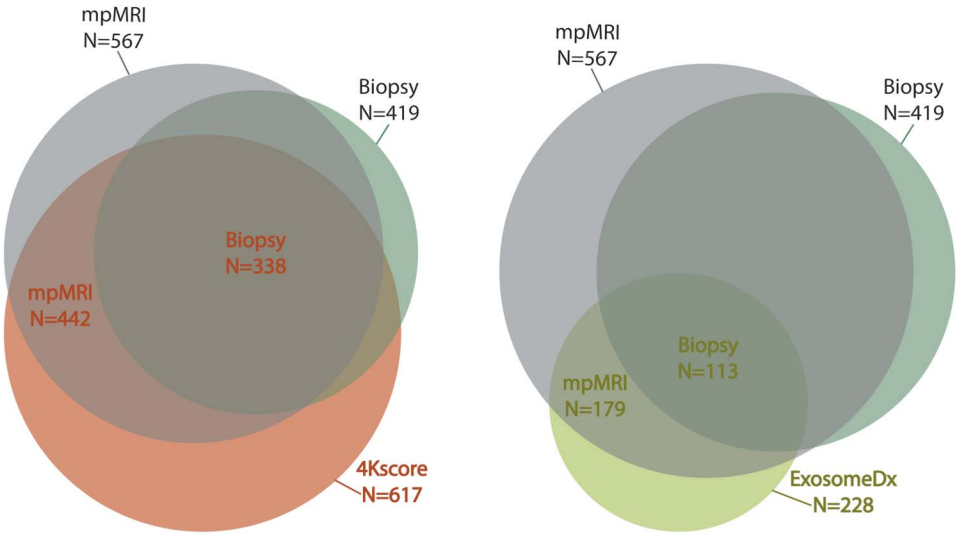

Figure 1. Venn diagram representation of overall patient cohort

testing and 567 patients mpMRI (fig. 1). In the overall cohort median age was 66.0 years (IQR 60.8–70.6), median PSA was 6.3 ng/ml (IQR 4.8–8.6) and 68 (8.7%) patients had an abnormal DRE. In all, 435 (70.5%) patients had a positive 4Kscore and 137 (60.1%) positive ExosomeDx. Of these, 292 (67.1%) and 89 (65.0%) underwent biopsy, respectively. Patient characteristics in the biopsied and nonbiopsied groups are summarized in table 1.

Biomarker and PI-RADS Score Association

Overall 224 (39.5%) patients had PI-RADS 1 to 2 lesions, 123 (21.7%) PI-RADS 3, 135 (23.8%) PI-RADS 4 and 85 (15.0%) PI-RADS 5 lesions. A discordance between 4Kscores and PI-RADS scores was observed in 173 (39.1%) patients. The discordance rate was 41.3% (74 patients) for ExosomeDx. Higher 4Kscores and ExosomeDx scores were associated with higher PI-RADS scores ($p < 0.001$ and $p = 0.001$ respectively, fig. 2, *A* and *B*). TRUS stage T2a or greater and PSAD 0.15 or greater were also associated with higher PI-RADS scores ($p < 0.001$ for both, supplementary table 1, https://www.jurology.com).

Biomarker and Gleason Grade Group Association

Among the 419 biopsied patients 263 (62.8%) were diagnosed with any prostate cancer (GG1 or greater) and 159 (37.9%) with higher grade prostate cancer (GG2 or greater). Higher liquid biomarker scores were associated with higher grade PCa on biopsy ($p < 0.001$ for both 4Kscore and ExosomeDx, fig. 2, *C* and *D*). Abnormal DRE, PSAD 0.15 or greater, TRUS stage T2a or greater and PI-RADS 3 to 5 scores were also associated with higher GG on prostate biopsy ($p = 0.002$ for DRE, $p < 0.001$ for the rest, supplementary table 2, https://www.jurology.com).

Correlation Between Biomarkers

A total of 62 patients had 4Kscore plus ExosomeDx testing. Interestingly, 4Kscore and ExosomeDx were concordant in only 37 (59.7%) patients. In addition, only a moderate correlation was noted between 4Kscore and ExosomeDx ($r = 0.345$, $p = 0.006$; supplementary fig. 1, https://www.jurology.com).

Biopsies Avoided and Missed High Grade PCa Using Manufacturers' Cut Points

We determined the number of avoided unnecessary biopsies (all nonbiopsied patients and those with GG1 or less on biopsy). We also determined the number of missed high grade PCa in the biopsied group. Limiting biopsy to the men with positive liquid biomarker scores, using manufacturers' cut points, would have resulted in avoiding 182 (29.5%) and 91 (39.9%) biopsies overall, while missing high grade disease in 5 (4.0%) and 2 (4.8%) patients among those biopsied, for 4Kscore and ExosomeDx respectively. Conversely, PSAD 0.15 or greater alone would have avoided 438 (63.7%) biopsies overall and missed high grade disease in 55 (36.4%) among those biopsied. Combining any liquid biomarker with mpMRI (PI-RADS 3 to 5) would have resulted in missing high grade disease in only 2 patients among those biopsied and adding PSAD 0.15 or greater would have resulted in missing no high grade PCa. However, both combinations would have resulted in avoiding fewer unnecessary biopsies than the biomarkers alone (table 2).

Maximizing the Clinical Benefit of Biomarkers with Screening Algorithms

We then compared several screening strategies to find an algorithm that would balance unnecessary biopsies and missed high grade disease while also avoiding

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Table 1. *Patient demographics and clinical characteristics*

	Men Who Did Not Undergo Biopsy	Men Who Underwent Biopsy	p Value
No. (%)	364 (46.5)	419 (53.5)	
Median age (IQR)	65.7 (60.9–70.2)	66.2 (60.6–70.7)	0.81
No. race/ethnicity (%):			
Native American	1 (0.27)	0 (0)	0.45
Asian/Asian Pacific Islander	41 (11.3)	46 (11.0)	
Black/African American	13 (3.6)	25 (6.0)	
White	266 (73.1)	296 (70.7)	
Other/unknown	43 (11.8)	52 (12.4)	
No. Hispanic/Latino (%):			
No	318 (87.3)	370 (88.3)	0.63
Yes	20 (5.5)	17 (4.0)	
Unknown	26 (7.1)	32 (7.6)	
No. family history of PCa (%):			
No	314 (86.2)	349 (83.3)	0.51
Yes	39 (10.7)	55 (13.1)	
Unknown	11 (3.0)	15 (3.6)	
No. DRE finding (%):			
No nodule	267 (73.4)	356 (85.0)	<0.001
Nodule	15 (4.1)	53 (12.6)	
Unknown	82 (22.5)	10 (2.4)	
No. previous negative biopsy (%):			
No	235 (64.6)	335 (80.0)	<0.001
Yes	129 (35.4)	84 (20.0)	
No. clinical T-stage* (%):			
Less than 2a	208 (57.1)	188 (44.9)	<0.001
2a or greater	64 (17.6)	229 (54.8)	
Unknown	92 (25.3)	2 (0.5)	
No. PSAD (%):			
Less than 0.15	220 (60.4)	218 (52.0)	<0.001
0.15 or greater	51 (14.0)	199 (47.5)	
Unknown	93 (25.5)	2 (0.5)	
No. 4Kscore of 617 pts (%):			
Less than 7.5	136 (48.7)	46 (13.6)	<0.001
7.5 or greater	143 (51.3)	292 (86.4)	
No. ExosomeDx of 228 pts (%):			
Less than 15.6	67 (58.3)	24 (21.2)	<0.001
15.6 or greater	48 (41.7)	89 (78.8)	
No. PI-RADS™ of 567 pts (%):			
PI-RADS 1–2	131 (69.3)	93 (24.6)	<0.001
PI-RADS 3–5	58 (30.7)	285 (75.4)	
Median PSA in ng/ml (IQR)	5.93 (4.50–8.21)	6.57 (5.00–9.10)	<0.001
Median PSAD (IQR)	0.09 (0.07–0.13)	0.14 (0.10–0.20)	<0.0001
Median 4Kscore (IQR)	8.00 (4.00–16.0)	21.0 (11.0–39.0)	<0.0001
Median ExosomeDx (IQR)	14.5 (10.1–23.2)	31.2 (17.4–41.9)	<0.0001

* Clinical staging determined by TRUS by default or mpMRI if no TRUS information was available.

unnecessary mpMRIs (fig. 3, Supplementary fig. 2, *A* and *B*, https://www.jurology.com). We found that after up-front 4Kscore testing, limiting mpMRI to the patients with 4Kscore 7.5 or greater while limiting biopsy to the patients with 4Kscore 20 or greater or to those with 7.5 or less than 4Kscore less than 20 and PI-RADS 3 to 5 on mpMRI (Algorithm 2, fig. 3) would avoid 29.5% mpMRIs. A similar screening algorithm with up-front ExosomeDx testing was defined (Algorithm 4, fig. 3) resulting in 39.9% mpMRIs avoided. Both Algorithms 2 and 4 avoided more unnecessary biopsies than 4Kscore or ExosomeDx alone and only missed 4.8-5.6% high grade PCa. Algorithms with up-front mpMRI followed by liquid biomarker were also defined. In Algorithms 6 and 8 (fig. 3), biopsy would be performed after a negative mpMRI only if 4Kscore≥20 or ExosomeDx≥19 respectively and would have only missed 2.4% of GG≥2 PCa in the biopsy group but only avoided 17.2-19.3% biopsies overall (Supplementary fig. 2, *A* and *B*, https://www.jurology.com, figure 4).

Followup of the Nonbiopsied Group

Of the 364 men that were not biopsied, due to presumed low risk for higher grade cancer, 235 (64.6%) had a followup PSA recorded and 4 (1.1%) subsequently had a prostate biopsy. Median time to followup PSA was 31.3 months (IQR 23.8–42.8); 124 (52.8%) of those patients had a lower PSA than the initial PSA. Among the patients with a followup PSA higher than the initial PSA, the median rate of change was +15.5% (IQR 6.9–29.3). Two out of 4 patients were ultimately found to have PCa on biopsy (1 GG2 and 1 GG3). Supplementary table 3 (https://www.jurology.com) summarizes the clinical data of these 2 patients.

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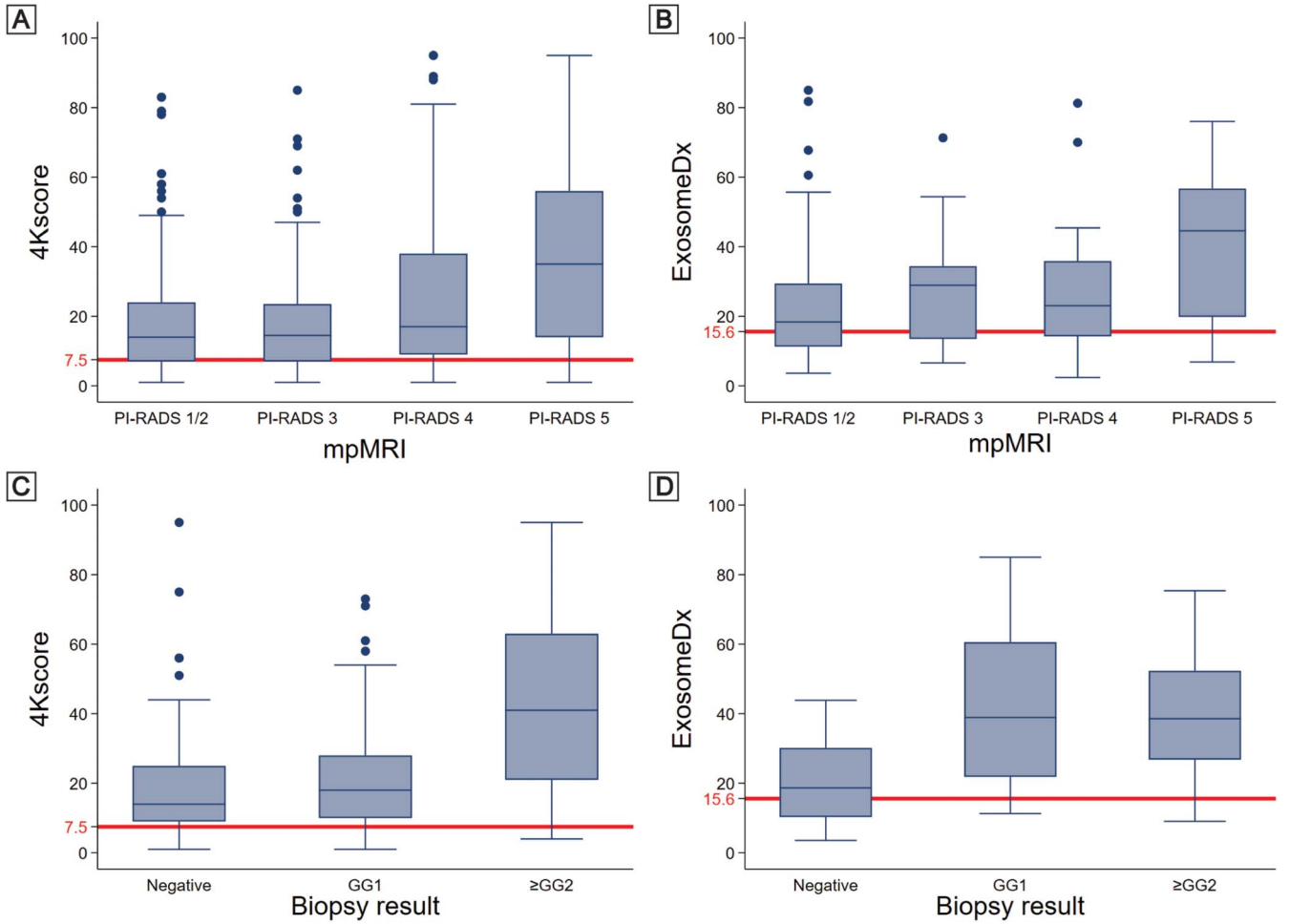

Figure 2. Higher biomarker scores were associated with higher PI-RADS™ scores and higher grade PCa on biopsy, with (*A*) 4Kscore (442), (*B*) ExosomeDx (179), (*C*) 4Kscore (338), (*D*) ExosomeDx (113). Red lines represent manufacturers' cut points. *HG*, high grade.

DISCUSSION

In a retrospective study of 783 patients evaluated with liquid biomarkers we found that using the 4Kscore or ExosomeDx alone resulted in avoiding 29.5% to 39.9% unnecessary biopsies overall while missing 4.0% to 4.8% GG2 or greater disease among

Table 2. *Number of avoided biopsies, mpMRIs avoided and missed high-grade cancers using each screening strategy*

Screening Strategy	No./Total No. Biopsies Avoided (%)	No./Total No. mpMRI* Avoided (%)	No./Total No. Missed GG2 or Greater Cancers (%)
4Kscore 7.5 or greater alone	182/617 (29.5)	617/617 (100)	5/125 (4.0)
4Kscore 7.5 or greater +mpMRI	45/442 (10.2)	0/442 (0)	1/110 (0.9)
4Kscore 7.5 or greater +mpMRI +PSAD 0.15 or greater	37/442 (8.4)	0/442 (0)	0/110 (0)
ExosomeDx 15.6 or greater alone	91/228 (39.9)	228/228 (100)	2/42 (4.8)
ExosomeDx 15.6 or greater +mpMRI	37/179 (20.7)	0/179 (0)	1/38 (2.6)
ExosomeDx15.6 or greater +mpMRI +PSAD 0.15 or greater	24/178 (13.5)	0/178 (0)	0/38 (0)
mpMRI alone	224/567 (39.5)	0/567 (0)	18/140 (12.9)
PSAD 0.15 or greater alone	438/688 (63.7)	688/688 (100)	55/159 (35.6)
PSAD 0.15 or greater +mpMRI	167/566 (29.5)	0/566 (0)	6/140 (4.3)
Algorithm 1	247/617 (40.0)	182/617 (29.5)	14/125 (11.2)
Algorithm 2	243/617 (39.4)	182/617 (29.5)	7/125 (5.6)
Algorithm 3	118/228 (51.8)	91/228 (39.9)	11/42 (26)
Algorithm 4	98/228 (43.0)	91/228 (39.9)	2/42 (4.8)
Algorithm 5	45/617 (7.3)	0/617 (0)	1/125 (0.8)
Algorithm 6	106/617 (17.2)	0/617 (0)	3/125 (2.4)
Algorithm 7	37/228 (16.2)	0/228 (0)	1/42 (2.4)
Algorithm 8	44/228 (19.3)	0/228 (0)	1/42 (2.4)

* PI-RADS 3–5

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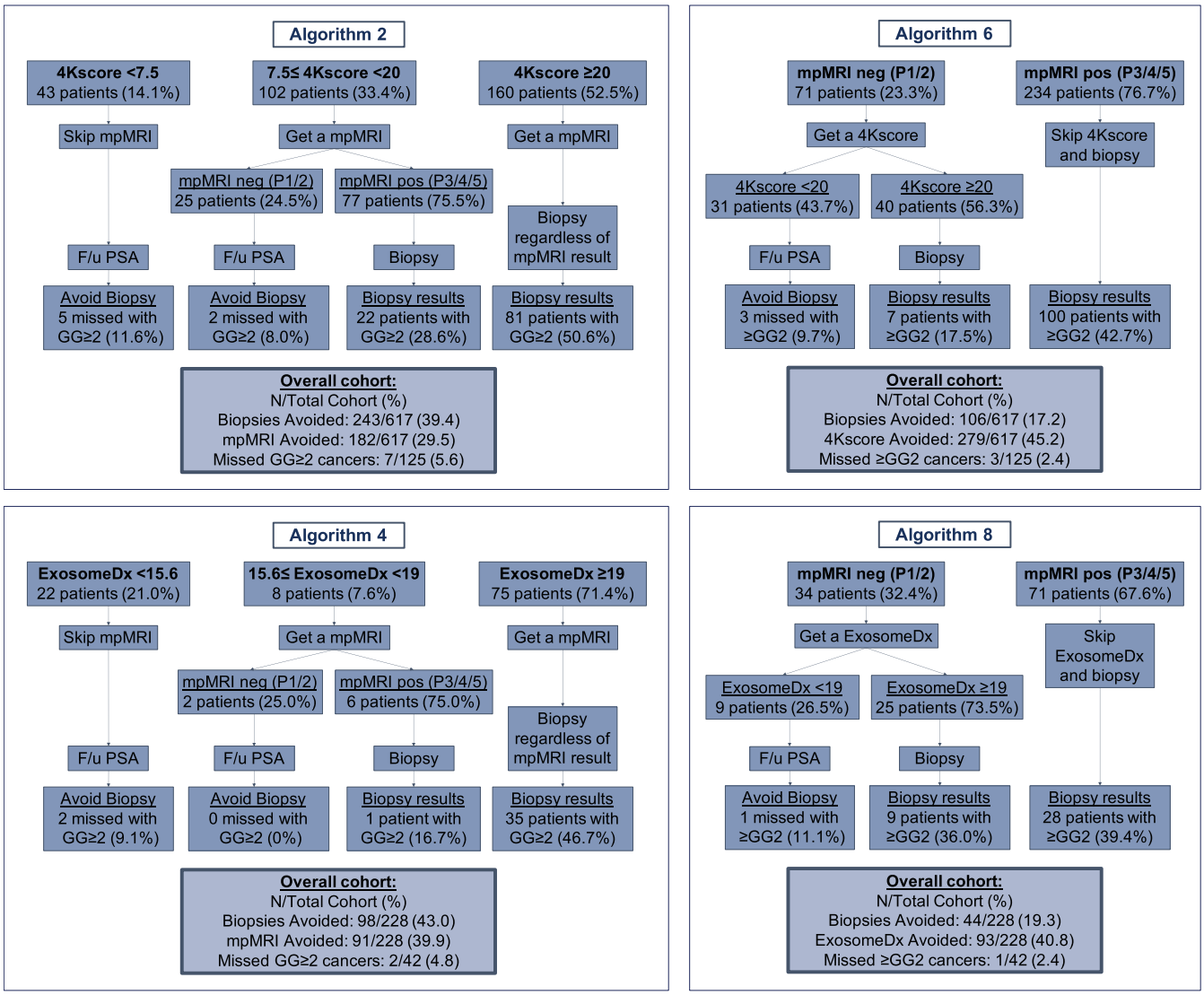

Figure 3. Screening algorithms with up-front liquid biomarker or up-front mpMRI (2, 4, 6 and 8). Numbers reported in this figure are taken from cohort of patients who were biopsied and had mpMRI. Summary box at end of each algorithm reflects application to overall cohort. Numbers reported in table 2 also reflect outcomes of each algorithm when applied to overall cohort. Algorithms 1, 3, 5 and 7 are depicted in supplementary fig. 2, *A* and *B* (https://www.jurology.com.) *P1/2*, PI-RADS™ 1/2; *P3/4/5*, PI-RADS™ 3/4/5; *F/u*, followup.

the biopsied patients despite having a negative biomarker test. Combining any biomarker with mpMRI resulted in missing 0.9% to 2.6% GG2 or greater disease while avoiding only 10.2% to 20.7% unnecessary biopsies. We also evaluated screening algorithms with up-front 4Kscore or ExosomeDx testing that could lead to avoiding more biopsies and mpMRIs while limiting the number of missed high grade PCa and compared them to algorithms with up-front mpMRI.

The 2 commercially available liquid biomarkers assessed here aim to improve the detection of high grade PCa while avoiding prostate biopsies in men with low grade disease. Similar to previous findings we found that using the manufacturers' cut points, positive biomarker tests were associated with GG2 or greater disease. 4Kscore or ExosomeDx alone resulted in missing less than 5% high grade PCa while avoiding 30% to 40% unnecessary biopsies.

Interestingly, 4Kscore and ExosomeDx did not correlate well with each other. Although few patients in the cohort had dual testing, correlation between 4Kscore and ExosomeDx has not been previously evaluated. These findings may indicate that the RNA transcripts and proteins included in each assay reflect on different aspects of cancer biology. We would also note that test-retest reliability is not well-established for any of these assays, and the degree of randomness in these comparison analyses cannot be readily discerned.

We also found that a positive mpMRI (PI-RADS 3 to 5) was associated with higher grade disease,

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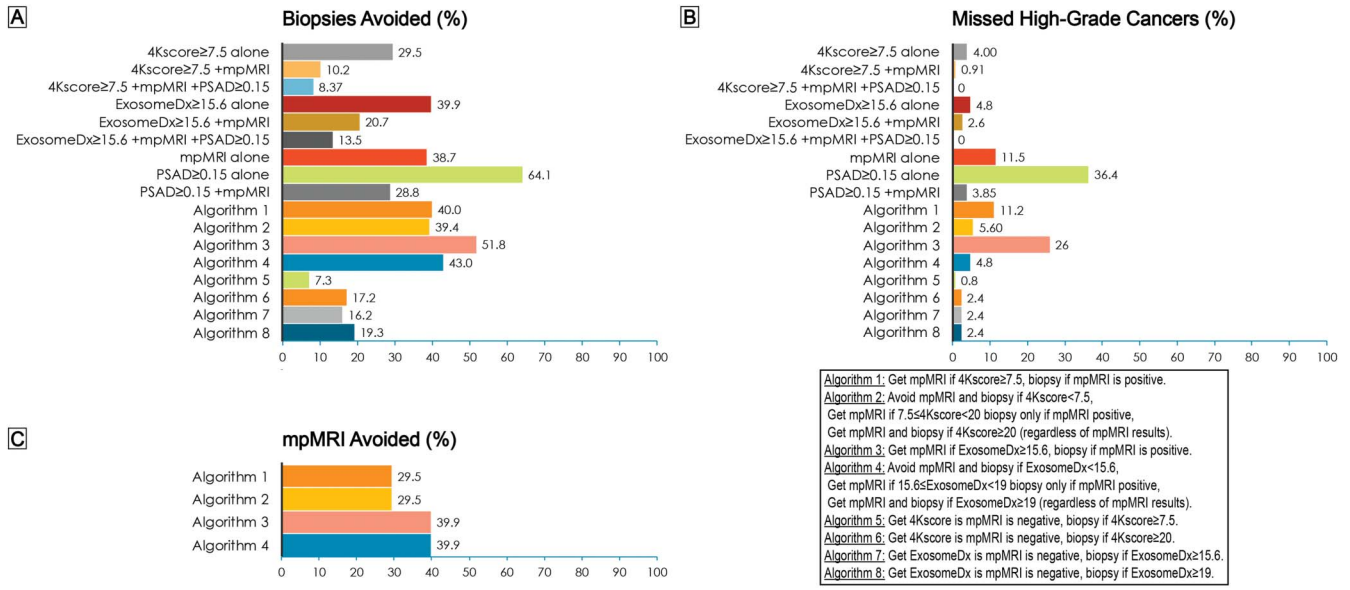

Figure 4. Percent avoided biopsies (*A*), missed high grade cancers (*B*) and mpMRIs avoided (*C*) using each screening strategy. Positive mpMRI defined as PI-RADS™ 3–5.

however mpMRI alone missed 12.9% of higher grade PCa among men undergoing biopsy despite a negative mpMRI. Although mpMRI is an appealing tool for PCa diagnosis, the National Comprehensive Cancer Network guidelines caution providers to combine mpMRI results with other clinical parameters such as PSAD or other liquid biomarkers to mitigate mpMRIs' inherent false negative rates.[16] In our study higher 4Kscores and ExosomeDx scores were associated with higher PI-RADS. In addition, combining any liquid biomarker with mpMRI resulted in missing less than 3% of high grade PCa among those biopsied, and adding PSAD 0.15 or greater as an additional criterion to proceed with biopsy brought the number of missed high grade PCa to 0 for all biomarkers. As a tradeoff, the number of avoided biopsies decreased from greater than 30% using the biomarkers alone to less than 14% when combining biomarker with mpMRI and PSAD 0.15 or greater. Previous studies have assessed combining mpMRI with biomarkers.[18] In a study combining 4Kscore with mpMRI it was found that both screening tools combined improved the prediction for high grade disease missing only 2% of high grade cancers.[19]

We defined 2 screening algorithms with up-front 4Kscore and ExosomeDx testing (Algorithms 2 and 4) that may avoid mpMRI and unnecessary biopsies without missing many GG2 or greater cancers. In Algorithm 2, among the 7 (5.6%) missed high grade cancers 6/7 had 4Kscores 5 or greater. Decreasing the lower limit for mpMRI to a 4Kscore 5 or greater would have resulted in 4 (3.2%) missed high grade cases while avoiding 28.8% biopsies. Punnen et al tested an algorithm using mpMRI when 4Kscore 7.5 or greater followed by biopsy if the mpMRI is positive, but it missed 33% of high grade PCa (vs 11.2% in our cohort, Algorithm 1).[19] In a cohort of 266 patients Falagario et al proposed a similar screening algorithm to Algorithm 2 but with a more stringent cut point of 4Kscore 18 or greater for mandatory biopsy (instead of 4Kscore 20 or greater as proposed in Algorithm 2) leading to 2.7% missed high grade disease and 34.2% avoided biopsies.[20] Mannaerts et al defined an algorithm that used the Rotterdam Prostate Cancer Risk Calculator followed by mpMRI if the risk calculator advised to perform biopsy and then actually biopsy if the mpMRI was positive, resulting in 6% missed high grade PCa and 37% avoided biopsies.[21] We also defined algorithms with up-front mpMRI to determine the utility of the liquid biomarker after a negative mpMRI. Algorithms 6 and 8 would have missed only 2.4% of high grade cancers but only avoided 17.2% to 19.3% biopsies. Prospective validation studies are needed to determine the optimal screening strategy however this cohort suggests that dual risk stratification with liquid biomarkers followed by conditional mpMRI, or the reverse, may be the most efficient and effective way to screen men with elevated PSA.

There are limitations to our study that need to be acknowledged. First, the study is retrospective, the majority had 4Kscore testing and 46.5% of the cohort did not undergo a prostate biopsy. But most of those men had a low risk of clinically significant disease, and lower PSA or expected PSA velocity at median time to followup of 31.3 months. Yet our

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reported GG2 or greater cancers missed may be underestimates to some extent since at least some men in the nonbiopsied group might have had undiagnosed high grade disease. Second, the decisions to perform or omit a biopsy were not necessarily consistent across the 2 liquid biomarkers. Therefore, these results should not be used for comparisons between the markers. Finally, most of the cohort only had 1 liquid biomarker test performed, so the interbiomarker comparisons are based on limited subsets. However, our cohort is one of the largest to date and is reflective of real-world clinical practice incorporating several clinical parameters such as PSA, 2 different liquid biomarkers and mpMRI, and we present the first screening algorithms with ExosomeDx and mpMRI. These screening algorithms will need to be validated in other cohorts or in prospective randomized trials.

CONCLUSIONS

Screening algorithms with up-front 4Kscore or ExosomeDx testing followed by mpMRI and biopsy at certain 4Kscore or ExosomeDx thresholds could improve risk stratification to decide if a prostate biopsy is needed or not. Such biomarker-directed screening is of value for clinicians and patients to avoid unnecessary biopsies and reduce over detection of low grade cancers, minimize the use of mpMRI and should be validated in a larger prospective trial.

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EDITORIAL COMMENTS

It is currently unclear whether men with a worrisome PSA should next be evaluated by a liquid biomarker or MRI. This study sheds light on this question, modeling data for a large convenience cohort of men treated by prevailing clinical practice who had a biomarker that influenced the decision on biopsy. Several informative patterns are apparent. First, use of either biomarker as the trigger for biopsy resulted in avoiding 30% to 40% of unnecessary biopsies (ie ones likely to find no or GG1 cancer) while missing a remarkably low (less than 5%) number of those with greater than GG2 disease. Second, adding MRI with or without PSAD (for which MRI is needed to calculate accurately) after a biomarker further reduced the rate of missed GG2 disease to less than 2.6%, albeit at the expense of many more unnecessary biopsies (only 10% to 20% avoided). Using MRI first followed by a biomarker for those with no PI-RADS™ greater than 3 lesions similarly resulted in very few missed GG2 cancers (2.4%) while avoiding only 20% of unneeded biopsies. Finally, the 2 biomarkers, both of which are validated to predict the presence of greater than GG2 disease, performed similarly in avoiding unnecessary biopsy and missed greater than GG2 disease despite being discordant in 40% of patients, an observation that remains unexplained.

Although the data are limited by the lack of a uniform approach to each patient, they establish a baseline estimate of the performance of these approaches that could be used to estimate sample size and power calculation for a randomized trial comparing a biomarker first followed by MRI vs MRI followed by a biomarker, with defined criteria for biopsy in each arm. In the meantime, given uneven insurance coverage for MRI in the U.S. and patient preference for a blood or urine test vs MRI (at least in my practice), these data support the use of a biomarker before MRI because they seemingly avoid more unneeded biopsies without sacrificing sensitivity for finding GG2 cancers.

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This study evaluates the performance of 4Kscore and ExosomeDx with or without multiparametric magnetic resonance imaging in the detection of high grade prostate cancer and number of avoided prostate biopsies. The European Association of Urology prostate cancer guidelines recommend imaging and/or an additional serum or urine based biomarker test to avoid unnecessary biopsies.[1] The optimal sequence of biomarkers and imaging remains to be determined.

A total of 783 patients have been included in the present study, of whom 419 underwent prostate biopsy. The authors found that screening algorithms with up-front 4K score or ExosomeDx could have avoided up to 40% unnecessary biopsies and reduce overdetection of low grade prostate cancer, while it would have missed up to 5.6% of high grade PCa. Algorithms with mpMRI first followed by one of the 2 biomarkers in case of negative mpMRI would have missed very few high grade PCa (2.4%) but only avoided up to 19% biopsies. The authors report that up to 30% to 40% of mpMRI could have been avoided by an algorithm with up-front 4K score or Exosome Dx, respectively. Interbiomarker comparisons were limited in this study as most of the included patients only had 1 biomarker test performed.

The presented results should be validated in larger prospective trials including comparisons among different biomarkers.

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