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ORIGINAL ARTICLE

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A urinary biomarker-based risk score correlates with multiparametric MRI for prostate cancer detection

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Background: Prostate cancer (PCa) diagnostics would greatly benefit from more accurate, non-invasive techniques for the detection of clinically significant disease, leading to a reduction of over-diagnosis and over-treatment. The aim of this study was to determine the association between a novel urinary biomarker-based risk score (SelectMDx), multiparametric MRI (mpMRI) outcomes, and biopsy results for PCa detection.

Methods: This retrospective observational study used data from the validation study of the SelectMDx score, in which urine was collected after digital rectal examination from men undergoing prostate biopsies. A subset of these patients also underwent a mpMRI scan of the prostate. The indications for performing mpMRI were based on persistent clinical suspicion of PCa or local staging after PCa was found upon biopsy. All mpMRI images were centrally reviewed in 2016 by an experienced radiologist blinded for the urine test results and biopsy outcome. The PI-RADS version 2 was used.

Results: In total, 172 patients were included for analysis. Hundred (58%) patients had PCa detected upon prostate biopsy, of which 52 (52%) had high-grade disease correlated with a significantly higher SelectMDx score ($P < 0.01$). The median SelectMDx score was significantly higher in patients with a suspicious significant lesion on mpMRI compared to no suspicion of significant PCa ($P < 0.01$). For the prediction of mpMRI outcome, the area-under-the-curve of SelectMDx was 0.83 compared to 0.66 for PSA and 0.65 for PCA3. There was a positive association between SelectMDx score and the final PI-RADS grade. There was a statistically significant difference in SelectMDx score between PI-RADS 3 and 4 ($P < 0.01$) and between PI-RADS 4 and 5 ($P < 0.01$).

Conclusions: The novel urinary biomarker-based SelectMDx score is a promising tool in PCa detection. This study showed promising results regarding the correlation between the SelectMDx score and mpMRI outcomes, outperforming PCA3. Our results suggest that

Abbreviations: AUC, area under receiver operating curves; DCE, dynamic contrast-enhanced; DRE, digital rectal examination; DWI, diffusion-weighted imaging; FDA, US Food and Drug Administration; GS, Gleason score; mpMRI, multiparametric magnetic resonance imaging; MRSI, magnetic resonance spectroscopy imaging; PCa, prostate cancer; PCA3, Prostate Cancer Antigen 3; PHI, Prostate Health Index; PI-RADS v2, Prostate Imaging Reporting and Data System version 2; PSA, prostate-specific antigen; T2W, T2-weighted; TRUS, transrectal ultrasound.

this risk score could guide clinicians in identifying patients at risk for significant PCa and selecting patients for further radiological diagnostics to reduce unnecessary procedures.

KEYWORDS
multiparametric MRI, prostate cancer, SelectMDx score

1 | INTRODUCTION

Currently, the diagnosis of prostate cancer (PCa) is based on three tools: digital rectal examination (DRE), serum prostate-specific antigen (PSA) levels, and transrectal ultrasound (TRUS)-guided biopsy.[1] Using PSA for (opportunistic) screening has led to a reduction in advanced disease at diagnosis and PCa-related mortality.[2] However, because the lack of specificity of PSA for PCa, it has led to a substantial increase in unnecessary prostate biopsies and detection of low-risk localized disease ("overdiagnosis"), that is, tumors that would not have caused clinical consequences during a man's lifetime. This leads to overtreatment with the potential of unnecessary side effects and high health care costs.[2] Prostate cancer (PCa) diagnostics would greatly benefit from more accurate, non-invasive techniques for the detection of clinically significant disease, leading to a reduction of overdiagnosis and overtreatment.

Magnetic resonance imaging (MRI) is used increasingly for PCa detection and tumor localization and has proven to be a valuable addition to PCa diagnostics.[3] Multiparametric MRI (mpMRI) combines conventional T2-weighted anatomical sequences together with functional techniques, such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE) and/or MR spectroscopy imaging (MRSI). The mpMRI has a high sensitivity and high negative predictive value for clinically significant PCa.[3] The negative predictive value has improved, but still 2.3-20% of patients with a negative mpMRI actually have high-grade PCa (Gleason score ≥7).[4–6]

Recently various biomarkers have been studied to improve detection of PCa, especially to identify patients with clinically significant disease. These new biomarkers include the urinary prostate cancer gene 3 (PCA3) and the prostate health index (PHI). To improve early detection of clinically significant PCa and to reduce additional expenses, novel biomarkers could be used to select patients for mpMRI or these biomarkers could be combined with mpMRI to select for prostate biopsy indication.

To date only a few studies have directly compared the performance of new biomarkers to mpMRI. In a prospective study of Porpiglia et al, the diagnostic accuracy of PCA3, PHI, mpMRI, and combinations of these tests were evaluated in a repeat biopsy setting.[7] The area-under-the-curve (AUC) for prediction of PCa upon repeat biopsy was significantly higher for mpMRI (AUC 0.936) than for the combined PCA3 + PHI model ($P < 0.001$).[7] In another study from the same group, both PHI and mpMRI were found to increase the AUC of predicting clinically significant disease significantly in 100 men eligible for active surveillance ($P < 0.01$), although mpMRI had the highest net benefit in decision curve analysis.[8] Other studies have investigated the combination of biomarkers and mpMRI outcomes for the prediction of clinically significant PCa. Kaufmann et al evaluated the added prognostic value of PCA3 to the mpMRI PI-RADS score in men after prior negative prostate biopsies.[9] They showed that 5 of 15 men with PI-RADS 3 (moderate suspicion of PCa) had PCa in repeat biopsy and all had a PCA3 score greater than 35. The inclusion of PCA3 scores in PI-RADS 3 patients improved predictive accuracy (79.6-91.8%).[9] Leyten et al showed that the PCA3 score was significantly higher in patients with a suspicious lesion on MRI (52 vs 21, $P < 0.001$).[10] Moreover, De Luca et al found a statistically significant association between the PCA3 score and mpMRI PI-RADS grade groups ($P = 0.006$).[11] Therefore, PCA3 could potentially help to differentiate which patients should undergo prostate biopsy with moderate suspicious lesions on mpMRI. However, PCA3 is only registered by the US Food and Drug Administration (FDA) for use after negative biopsies and studies on the value of PCA3, including Gleason score, tumor volume, stage and extraprostatic extension, are contradictory.[12,13]

Biomarkers specifically developed for prediction of high-grade PCa would be more suitable for PCa detection in combination with or selection for mpMRI. A novel biomarker-based risk score (SelectMDx, MDxHealth, Irvine, CA) assessing urinary *HOXC6* and *DLX1* mRNA expression levels combined with traditional clinical risk factors, was recently developed and clinically validated to predict high-grade PCa (Gleason score ≥7) upon prostate biopsy.[14,15] This risk score reached an AUC of 0.86 (95% Confidence Interval [CI] 0.80-0.92) in the validation cohort and could therefore reduce the number of unnecessary biopsies.[15]

The aim of this observational study was to investigate the association between this novel urinary biomarker-based risk score, mpMRI outcomes, and biopsy Gleason score. Moreover, the performance of the SelectMDx score was compared with PCA3.

2 | MATERIALS AND METHODS

2.1 | Study population

All patients in both cohorts described by Van Neste et al[15] who underwent a mpMRI at the Radboud university medical center (Nijmegen, The Netherlands) were evaluated ($n = 174$). Included men had undergone (initial or repeat) prostate biopsies, based on elevated PSA levels (>3 ng/mL), abnormal DRE, or a family history of PCa. The subjects were included between July 2009 and July 2014 and the

mpMRIs were performed between November 2009 and March 2016. Exclusion criteria were 5α-reductase inhibitor therapy, prostate biopsy within 3 months prior to enrolment and invasive treatment for benign prostate hyperplasia (BPH) within six months prior to enrolment. Patient characteristics, biopsy results, mpMRI results, and urine test results were documented. The subjects all gave their informed consent for the mentioned studies[15] and due to the observational nature of this research no formal approval of the Institutional Review Boards was needed.

2.2 | Prostate mpMRI

All mpMRIs were carried out in one specialized centre using a 3 Tesla MR scanner (MAGNETOMTrio or Skyra, Siemens Healthcare, Erlangen, Germany). The T2-weighted (T2W) images were used to assess prostate anatomy. Diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI were used as functional techniques. The mpMRI scans were performed before prostate biopsies ($n = 4$), within 1 year after the urine test ($n = 143$) and more than 1 year after the urine test ($n = 27$). The indications for performing mpMRI were based on persistent clinical suspicion of PCa after negative prostate biopsies or PCa staging after positive biopsies. However, to minimize bias in the mpMRI reports and heterogeneity of the group reassessment took place. In October 2016, all mpMRIs were centrally reviewed by one experienced radiologist blinded for the urine test scores and biopsy outcomes. The PI-RADS version 2 (v2) was used for grading the lesions in all three mpMRI sequences.[16] For each patient a final PI-RADS grade from 1 to 5 was determined by the respective sum score.[16,17] Based on the new reports the mpMRI results were categorized into two groups: suspicion of significant PCa (PI-RADS 4-5) and no suspicion of significant PCa (PI-RADS 1-2-3).

2.3 | Urinary biomarker-based risk score (SelectMDx) and PCA3

First-voided urine was collected after DRE, prior to performing prostate biopsies at the same day. The assays for measuring expression levels of HOXC6, DLX1, KLK3, and PCA3 were described in detail in the publication of Van Neste et al.[15] The SelectMDx score (MDxHealth) is a combination of expression levels from HOXC6 and DLX1 and clinical risk factors (age, DRE, PSA, PSA density, family history, and prior negative prostate biopsies) in a logistic regression model. The chosen cut-off point was −2.8 in the study of Van Neste et al, with a sensitivity of 96% and a negative predictive value of 98% for high-grade PCa (Gleason score ≥7).[15]

2.4 | Prostate biopsy

Transrectal ultrasound (TRUS) guided prostate biopsy (median of 10 cores) was performed per hospitals standard procedure and evaluated by two experienced genitourinary pathologists. Histological grading was assessed according to the Gleason grading system as well as the Gleason Grade Groups.[18,19]

2.5 | Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY). The patient characteristics were analyzed by the independent sample *t*-test and Mann-Whitney *U* test for continuous variables and the Fisher's exact test was used for categorical variables. The diagnostic performance of the SelectMDx score was assessed and evaluated as area-under-the-curve (AUC) of the receiver operating characteristic (ROC). Two-sided *P*-values of <0.05 were considered to indicate statistical significance.

3 | RESULTS

3.1 | Study population

In the total study population, 174 patients underwent mpMRI for PCa detection or staging. Two patients were excluded due to poor image quality. Patient characteristics and biopsy outcomes are summarized in Table 1. The mean age was 63 (±6.3) years, with a median PSA level of 7.4 (interquartile range (IQR) 5.3-11.7). Hundred of 172 (58%) patients were diagnosed with PCa upon prostate biopsy of which 52 (52%) patients had high-grade PCa (Gleason score ≥7).

3.2 | Predictive value of the SelectMDx score for high-grade PCa upon biopsy

The SelectMDx score was significantly higher for patients with positive biopsies compared to negative prostate biopsies (−1.6 [−2.9 to 0.2] vs −2.8 [−3.7 to 2.1], $P < 0.01$). Moreover, the SelectMDx score was significantly higher for high-grade PCa (Gleason score ≥7) versus low-grade PCa (Gleason score ≤6) (−0.7 [−1.7 to 0.6] vs −2.6 [−3.4 to 1.5], $P < 0.01$) (Figure 1A). When looking at the Gleason Grade Groups, the SelectMDx score was significantly higher in Group 2 (3 + 4 = 7) compared to Group 1 (3 + 3 = 6) ($P < 0.01$) (Figure 1B).

3.3 | Association of the SelectMDx score and PCA3 with mpMRI outcome

The association of the SelectMDx score with the mpMRI outcome is shown in Figure 2. The difference in SelectMDx score between a suspicious significant lesion on mpMRI (−1.3 [0.3-0.1]) compared to no significant lesion on mpMRI (−3.1 [−3.8 to 2.2]) was statistically significant ($P < 0.01$). For PCA3 there was also a significant difference between a suspicious significant lesion on mpMRI (174 [85-305]) compared to no significant lesion on mpMRI (87 [37-209]) ($P < 0.01$). The PSA level was also higher in the patients with a suspicion of significant PCa on mpMRI (8.3 vs 6.4, $P < 0.01$). The performance of the SelectMDx score to predict mpMRI outcome was compared with PSA and PCA3 in a ROC analysis (Figure 3). The AUC for the SelectMDx score was 0.83 (95% Confidence Interval [CI]: 0.77-0.89) compared to AUC 0.66 (95%CI: 0.58-0.74) for PSA and AUC 0.65 (95%CI: 0.57-0.74) for PCA3.

TABLE 1 Patient characteristics

	Total cohort (%/IQR)	No PCa (%/IQR)	PCa (%/IQR)	
	n = 172 (100%)	*n* = 72 (42%)	*n* = 100 (58%)	*P*-value
Age, median, yrs	63 (59-68)	62 (58-66)	65 (60-69)	0.96[a]
DRE suspicious	65 (37.8%)	15 (21%)	50 (50%)	<0.01[c]
Prostate volume				
TRUS, median, mL	48 (37-61)	56 (45-75)	42 (33-56)	<0.01[b]
MRI, median, mL	54 (36-69)	66 (49-95)	43 (32-58)	<0.01[b]
PCa in family, %no, yes, unknown	51, 20, 29	50, 19, 31	51, 21, 28	1.0[c,d]
No previous biopsies	145 (84%)	51 (71%)	94 (94%)	<0.01[c]
PSA, median, ng/mL	7.4 (5.3-11.7)	6.7 (5.0-11.4)	8.0 (5.7-12.1)	0.06[b]
SelectMDx score, median	−2.3 (−3.3 to −0.9)	−2.8 (−3.7 to −2.1)	−1.6 (−2.9 to −0.2)	<0.01[b]
PCA3, median	119 (64-267)	85 (38-207)	167 (82-294)	0.02[b]
PCa upon biopsy, *n*	100 (58%)			
Gleason group 1 (GS ≤ 6)	48 (48%)			
Gleason group 2 (GS3 + 4 = 7)	24 (24%)			
Gleason group 3 (GS4 + 3 = 7)	10 (10%)			
Gleason group 4 (GS8)	9 (9%)			
Gleason group 5 (GS9-10)	9 (9%)			
mpMRI				
PI-RADS 1	6 (3%)	6 (8%)	-	
PI-RADS 2	63 (37%)	47 (65%)	16 (16%)	
PI-RADS 3	10 (6%)	6 (8%)	4 (4%)	
PI-RADS 4	26 (15%)	6 (8%)	20 (20%)	
PI-RADS 5	67 (39%)	7 (10%)	60 (60%)	

DRE, digital rectal examination; GS, Gleason score; IQR, interquartile range; PCa, prostate cancer; TRUS, transrectal ultrasound.
[a]*t* test.
[b]Mann Whitney *U* test.
[c]Chi-Square test/Fisher's Exact test.
[d]The *P*-value when only taking into account those patients for which the information was available.

3.4 | Association of the SelectMDx score and PCA3 with mpMRI PI-RADS grade

In total 6 (3%) patients had a PI-RADS 1 lesion, 63 (37%) patients PI-RADS 2, 10 (6%) patients PI-RADS 3, 26 (15%) patients PI-RADS 4, and 67 (39%) patients PI-RADS 5. The distribution of Gleason scores by PI-RADS grade is shown in Figure 4. The association between SelectMDx score and the final PI-RADS grade 3-4-5 is shown in Figure 5A. There was a statistically significant difference in SelectMDx score between PI-RADS 3 and PI-RADS 4 ($P < 0.01$) and between PI-RADS 4 and 5 ($P < 0.01$). There was no statistical difference in PCA3 ratio between PI-RADS 3 and 4 and between PI-RADS 4 and 5 (see Figure 5B).

4 | DISCUSSION

To improve the identification of patients with significant PCa new imaging techniques and molecular markers have been studied. The high sensitivity and negative predictive value of mpMRI for identifying aggressive disease caused an increasing use of this imaging modality in PCa-diagnosis.[3] The novel urinary biomarker-based risk score, SelectMDx, has shown a high sensitivity and negative predictive value for high-grade PCa.[15] The present study aimed to investigate the association between the SelectMDx score and mpMRI outcomes in patients who underwent prostate biopsies. The mpMRI outcomes were dichotomized with PI-RADS 1-2-3 considered as no suspicion of significant cancer and PI-RADS 4-5 considered as suspicious for significant PCa. The SelectMDx score was significantly higher in the patients with PI-RADS 4-5 on the mpMRI ($P < 0.01$). Moreover, SelectMDx outperformed PSA and PCA3 in the ROC curve analysis with an AUC of 0.83 versus 0.66 and 0.65.

For using mpMRI in PCa-diagnosis, the number of patients with a false-negative mpMRI outcome is point of concern.[20] In this study, 79 patients had no suspicion of significant PCa on mpMRI. However, 20 (25%) men of this group had positive prostate biopsies: 19 (95%) patients had Gleason score ≤6 and 1 (5%) patient Gleason score 7 (Figure 4). This patient, indicated as PI-RADS 3, would have been missed using mpMRI detection only. For this specific case, the SelectMDx score (−1.5) was higher than the chosen cut-off point with a

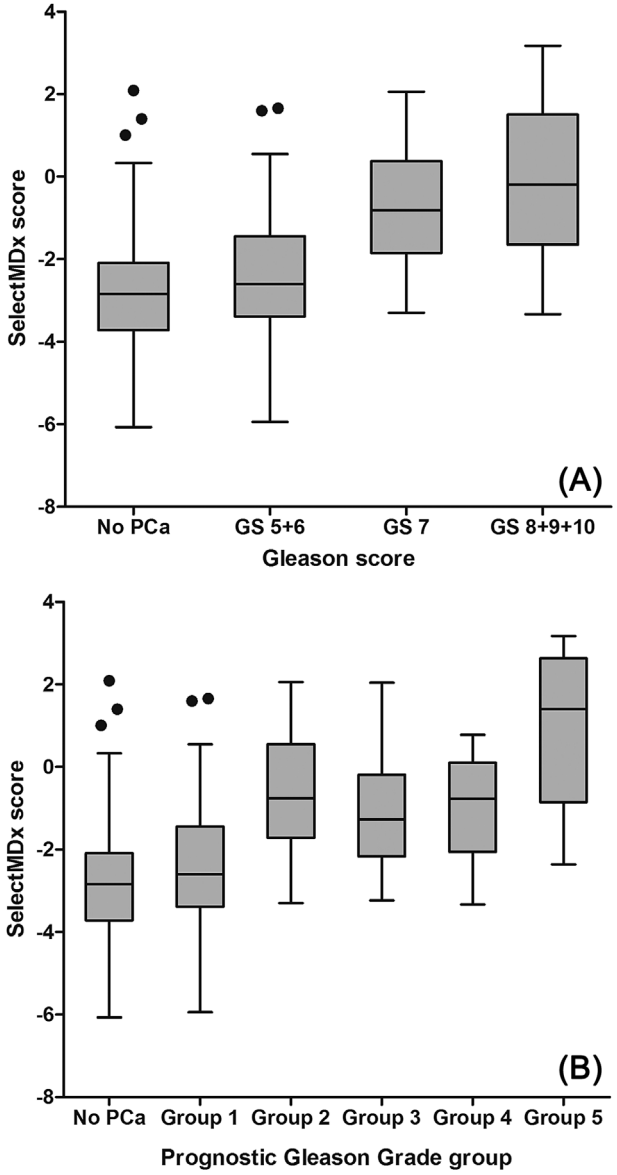


FIGURE 1 SelectMDx score distribution by biopsy Gleason score (A) and prognostic Gleason Grade group (B)

sensitivity of 96% and a negative predictive value of 98%.[15] Therefore, this example illustrates the possible additional value of the SelectMDx score in the PI-RADS 3 subgroup. On the other hand, 93 patients had a suspicious significant lesion on mpMRI of which 13 (14%) had no PCa upon first biopsy (Figure 4). In the follow-up, eight of these patients underwent a repeat-biopsy. Five patients were diagnosed with PCa (three patients Gleason score 6 and two patients Gleason score 7) and three patients had negative biopsy result. The SelectMDx scores of the two patients with Gleason score 7 were −2.8 and 0.04. Therefore, the SelectMDx scores would have resulted in further diagnostics.

Studies have shown that PCA3 was predictive for prostate cancer on (repeat) biopsy, however, no consistent correlation with Gleason score was found. There were contradictory results regarding the correlation between PCA3 and mpMRI outcome or PI-RADS grade.

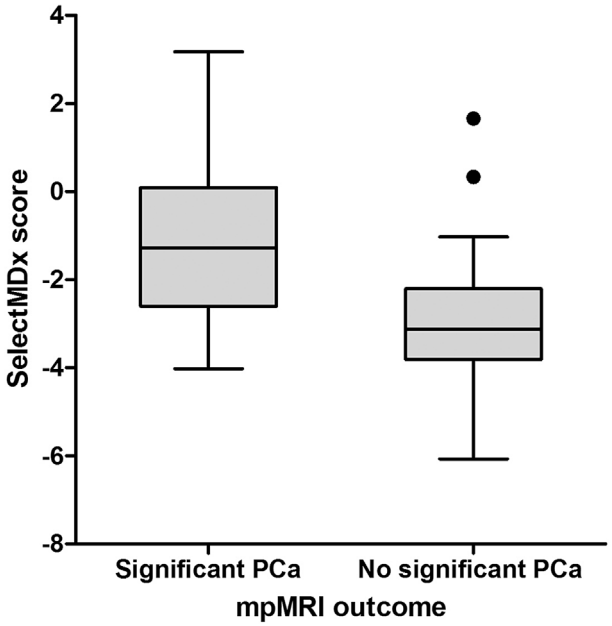


FIGURE 2 The association of the SelectMDx score with mpMRI outcome

Leyten et al showed a correlation between PCA3 and dichotomized mpMRI outcomes.[10] De Luca et al showed a significant association between PCA3 and PI-RADS 3.[11] On the contrary, there was no correlation between PCA3 and PI-RADS grade in the study of Kaufmann et al.[9] The SelectMDx score was specifically developed to predict Gleason score ≥7 and in the present study a correlation was found with the mpMRI outcome and the PI-RADS grades 3-4-5. The use of SelectMDx in patients with a PI-RADS 3 lesion on mpMRI could potentially help in decision-making regarding the need for (targeted) biopsy.

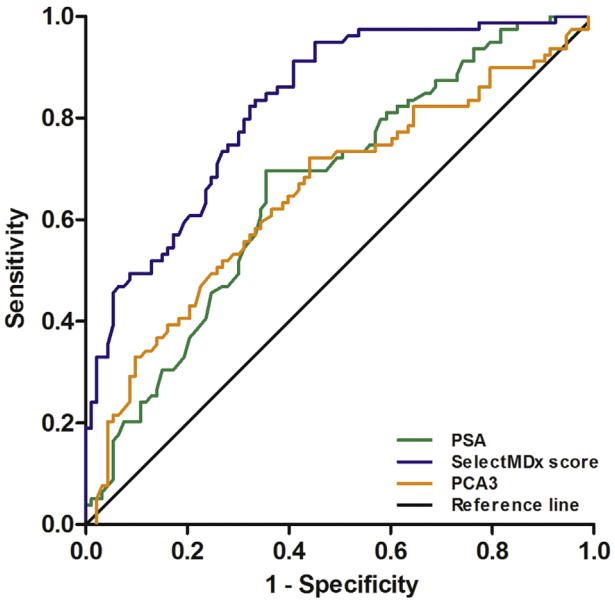


FIGURE 3 ROC curves for PSA, SelectMDx score, and PCA3 by mpMRI outcome

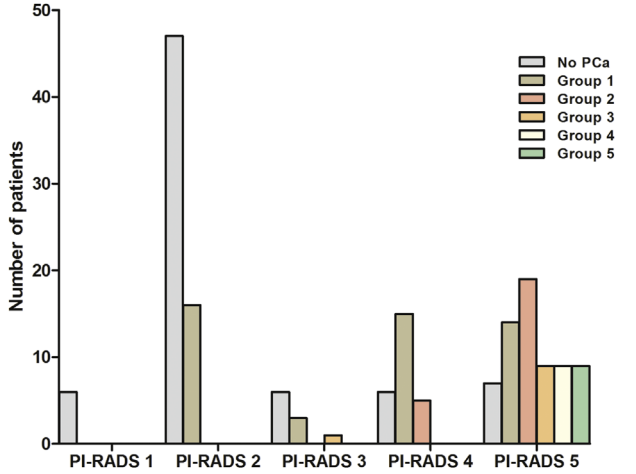
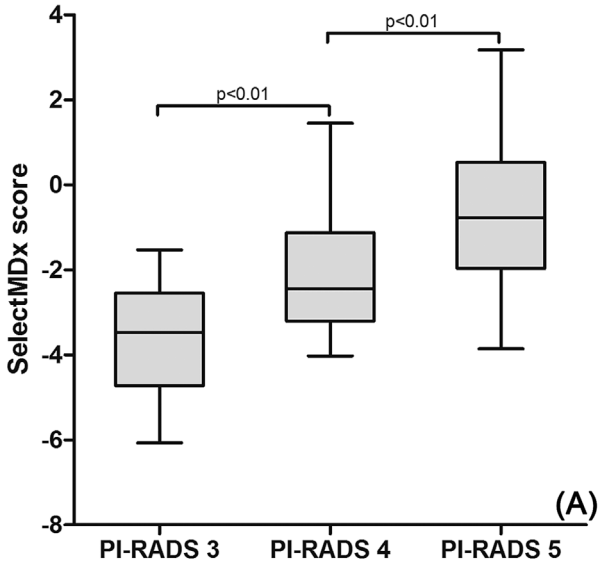


FIGURE 4 The distribution of prognostic Gleason Grade group by PI-RADS grade



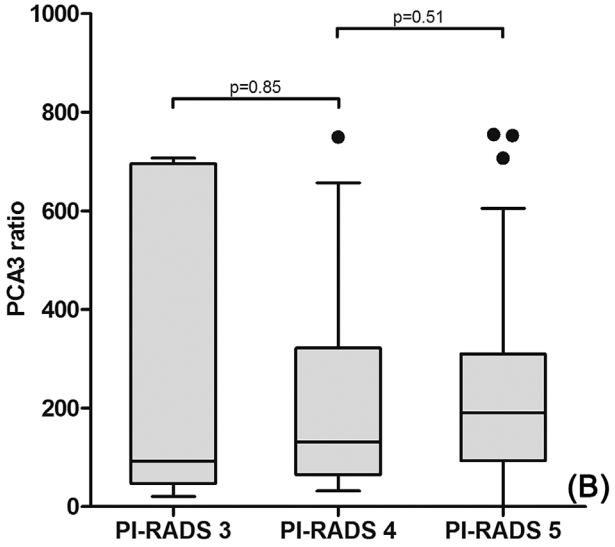


FIGURE 5 The association between SelectMDx score (A) and PCA3 (B) with PI-RADS 3, 4, and 5 on mpMRI

Besides improving detection of significant PCa, improving reliable selection of patients with low-risk PCa for active surveillance is another clinical need. In a recently published long-term active surveillance cohort, Klotz et al[21] showed that after 8.1 years of follow-up from first biopsy, 2.8% of active surveillance patients had metastatic disease and a mortality rate of 1.5%. The accuracy of selecting patients for active surveillance and the prediction of disease progression need to be improved. The prognostic role of SelectMDx and/or mpMRI considering this dilemma needs further studies.

The retrospective analysis of this study is a limitation. The patients in this study were preselected due to the fact that they had undergone a SelectMDx urine test and prostate biopsies in previous study protocols.[15] The indications for performing mpMRI were based on clinical grounds, which created a selection bias in this observational cohort. However, to minimize the heterogeneity, strength of this study is the fact that all mpMRI images were centrally reviewed by one experienced radiologist and the new PI-RADS v2 was used. A prospective study with a urine test and mpMRI for all patients is needed to overcome the selection bias. Furthermore, the accuracy of TRUS-guided random prostate biopsies is known to be limited, for future studies targeted biopsies need to be included.

The present study was not designed to prove superiority of the SelectMDx score or the mpMRI for PCa detection, however, to generate hypotheses for future clinical studies. To identify, compare and combine predictors of high-grade PCa, multivariate logistic regression models need to be used. Because of the selected study population and the non-standardized indications for performing mpMRI, we were not able to perform these statistic analyses. However, the results of this study indicate that the SelectMDx score can contribute to the stratification of patients for advanced imaging (mpMRI). Moreover, this relatively simple urine test could be of additional value when a PI-RADS 3 lesion is found and, likely, in selecting patients for mpMRI after negative prostate biopsy. The potential synergy of the SelectMDx score and mpMRI needs to be confirmed in a prospective study with a homogenous study population with univariate and multivariate regression analyses and decision curve analysis. At the same time, the SelectMDx score needs to be compared head-to-head with other biomarker tests, that is, the Prostate Health Index. The cost-effectiveness of new biomarker tests, the use of mpMRI and targeted biopsies are subject of discussion and need to be studied to improve PCa diagnostics.

5 | CONCLUSIONS

In conclusion, the novel urinary biomarker-based SelectMDx score is a promising tool in PCa detection. This study showed promising results regarding the correlation between the SelectMDx score with mpMRI outcomes and PI-RADS grading. Our results suggest that this risk score could guide clinicians in identifying patients at risk for significant PCa

and selecting patients for further diagnostics to reduce unnecessary diagnostics and overtreatment.

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DISCLOSURE

JAS, PFAM, and WvC report consultancy with honoraria for MDxHealth. The other authors declare no conflict of interest.

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REFERENCES

1. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol*. 2014;65:124–137.
2. Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and overtreatment of prostate cancer. *Eur Urol*. 2014;65:1046–1055.
3. Futterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. *Eur Urol*. 2015;68:1045–1053.
4. Watson MJ, George AK, Maruf M, et al. Risk stratification of prostate cancer: integrating multiparametric MRI, nomograms and biomarkers. *Future Oncol*. 2016;12:2417–2430.
5. Filson CP, Natarajan S, Margolis DJ, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. *Cancer*. 2016;122:884–892.
6. Wysock JS, Mendhiratta N, Zattoni F, et al. Predictive value of negative 3T multiparametric magnetic resonance imaging of the prostate on 12-core biopsy results. *BJU Int*. 2016;118:515–520.
7. Porpiglia F, Russo F, Manfredi M, et al. The roles of multiparametric magnetic resonance imaging, PCA3 and prostate health index-which is the best predictor of prostate cancer after a negative biopsy? *J Urol*. 2014;192:60–66.
8. Porpiglia F, Cantiello F, De Luca S, et al. In-parallel comparative evaluation between multiparametric magnetic resonance imaging, prostate cancer antigen 3 and the prostate health index in predicting pathologically confirmed significant prostate cancer in men eligible for active surveillance. *BJU Int*. 2016;118:527–534.
9. Kaufmann S, Bedke J, Gatidis S, et al. Prostate cancer gene 3 (PCA3) is of additional predictive value in patients with PI-RADS grade III (intermediate) lesions in the MR-guided re-biopsy setting for prostate cancer. *World J Urol*. 2016;34:509–515.
10. Leyten GH, Wierenga EA, Sedelaar JP, et al. Value of PCA3 to predict biopsy outcome and its potential role in selecting patients for multiparametric MRI. *Int J Mol Sci*. 2013;14:11347–11355.
11. De Luca S, Passera R, Cattaneo G, et al. High prostate cancer gene 3 (PCA3) scores are associated with elevated Prostate Imaging Reporting and Data System (PI-RADS) grade and biopsy Gleason score, at magnetic resonance imaging/ultrasonography fusion software-based targeted prostate biopsy after a previous negative standard biopsy. *BJU Int*. 2016;118:723–730.
12. Ploussard G, Haese A, Van Poppel H, et al. The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies? *BJU Int*. 2010;106:1143–1147.
13. Schalken JA, Hessels D, Verhaegh G. New targets for therapy in prostate cancer: differential display code 3 (DD3(PCA3)), a highly prostate cancer-specific gene. *Urology*. 2003;62:34–43.
14. Leyten GH, Hessels D, Smit FP, et al. Identification of a candidate gene panel for the early diagnosis of prostate cancer. *Clin Cancer Res*. 2015;21:3061–3070.
15. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of high-grade prostate cancer using a urinary molecular biomarker-based risk score. *Eur Urol*. 2016;70:740–748.
16. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging—reporting and data system: 2015, version 2. *Eur Urol*. 2016;69:16–40.
17. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol*. 2012;22:746–757.
18. Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL, Committee IG. The 2005 international society of urological pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma. *Am J Surg Pathol*. 2005;29:1228–1242.
19. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int*. 2013;111:753–760.
20. Grenabo Bergdahl A, Wilderang U, Aus G, et al. Role of magnetic resonance imaging in prostate cancer screening: a pilot study within the goteborg randomised screening trial. *Eur Urol*. 2016;70:566–573.
21. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33:272–277.

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