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Refining the Management of Prostate Imaging Reporting Category 3 Lesions through SelectMDx Urinary Biomarker Evaluation

Petrino-Cristian CALINOIU[a, b], Daniel BADESCU[a, b], Ovidiu-Catalin NECHITA[a, b], Cristian-Valentin TOMA[a, b], Diana NECULAI[a], Stefan RASCU[a, b], Razvan-Cosmin PETCA[a, b], Justin AURELIAN[a, b], Cristian-Sorin SIMA[a, b], Viorel JINGA[a, b, c]

[a]Department of Urology, "Prof. Dr. Th. Burghele" Clinical Hospital, Bucharest, Romania

[b]Department of Urology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[c]Medical Sciences Section, Academy of Romanian Scientists, Bucharest, Romania

ABSTRACT

Objectives: *This study aimed to evaluate the clinical utility of the SelectMDx urinary biomarker test in men with PI-RADS 3 lesions identified through multiparametric magnetic resonance imaging (mpMRI), a subgroup in which prostate cancer diagnosis remains uncertain. The primary objective was to assess whether SelectMDx can improve risk stratification for clinically significant prostate cancer and thereby reduce unnecessary prostate biopsies.*

Materials and methods: *A prospective cohort of 40 patients with serum prostate-specific antigen (PSA) levels ≥3 ng/mL and PI-RADS ≥ 3 lesions on mpMRI was analyzed. All participants underwent mpMRI, followed by targeted magnetic resonance imaging/transrectal ultrasound (MRI/TRUS) fusion-guided biopsy and standard TRUS-guided biopsy. Prior to biopsy, urine samples were collected post-digital rectal examination for SelectMDx analysis. The test evaluates messenger ribonucleic acid (mRNA) expression of distal-less homeobox 1 (DLX1) and homeobox C6 protein (HOXC6), integrating molecular data with clinical parameters to generate individualized risk scores. Diagnostic performance was assessed through sensitivity, specificity, predictive values and logistic regression analyses.*

Results: *Among patients with PI-RADS 3 lesions (n=40), a significant correlation between SelectMDx results and biopsy-confirmed clinically significant prostate cancer was observed. Clinically significant cancer was detected in 57.1% of patients with a positive SelectMDx result, compared to 18.2% in those with a negative result (p=0.031). The test demonstrated a sensitivity of 57.14%, a specificity of 81.82%, a positive predictive value of 40% and a negative predictive value of 90%, with an overall diagnostic accuracy of 77.5%. While age emerged as the only independent predictor in multivariate analysis, SelectMDx showed a strong potential to exclude malignancy and support more selective biopsy strategies.*

Address for correspondence:
Ovidiu-Cătălin Nechita
Email: ovidiu-catalin.nechita@drd.umfcd.ro

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Conclusions: *SelectMDx appears to be a valuable adjunctive tool in the diagnostic evaluation of patients with equivocal mpMRI findings, particularly PI-RADS 3 lesions. Its high negative predictive value supports its use in reducing unnecessary biopsies without compromising the detection of clinically significant prostate cancer. The integration of molecular biomarkers with imaging and clinical parameters may offer a more refined approach to personalized risk stratification in prostate cancer diagnostics.*

Keywords: prostate cancer, PI-RADS 3, SelectMDx, urinary biomarkers, multiparametric MRI, risk stratification.

INTRODUCTION

Prostate cancer (PCa) is a major global health issue. It represents the second most commonly diagnosed cancer among men and one of the leading causes of cancer-related mortality (1). Early detection is crucial for successful treatment and prostate-specific antigen (PSA)-based screening has been widely utilized for this purpose. However, PSA-based screening has notable limitations. It may lead to unnecessary prostate biopsies, potentially resulting in complications. Additionally, PSA screening can contribute to overdiagnosis, which can subsequently cause overtreatment, exposing patients to side effects without improving survival outcomes (2).

To address these issues, multiparametric magnetic resonance imaging (mpMRI) has been introduced into clinical practice. The procedure provides detailed images of the prostate, assisting in identifying suspicious areas that may require biopsy and improving the detection of clinically significant prostate cancer (csPCa). Nevertheless, mpMRI is not without limitations (3). Lesions classified as PIRADS 3 remain ambiguous, as their imaging characteristics do not reliably distinguish between benign and malignant pathology. This ambiguity complicates clinical decision-making regarding appropriate subsequent management (4).

Urine-based tests represent a promising, non-invasive approach to improving diagnostic accuracy. These assays examine urine samples obtained during a digital rectal examination (DRE), which contain prostate-derived cells and molecular markers. One example is the SelectMDx test, which evaluates urinary levels of two specific genes, distal-less homeobox 1 (DLX1) and homeobox C6 protein (HOXC6). This test has shown potential in distinguishing high-risk prostate cancer from low-risk forms, potentially reducing the number of unnecessary biopsies (5).

Combining mpMRI with urinary tests such as SelectMDx could enhance diagnostic accuracy, particularly for patients with ambiguous PIRADS 3 lesions. By utilizing both imaging data and molecular information, clinicians could more accurately evaluate the risk of csPCa and make better informed decisions about the necessity of a biopsy.

This study aims to evaluate the utility of the SelectMDx test in patients with PIRADS 3 lesions identified by mpMRI. The objective is to determine if this test can identify individuals at increased risk of csPCa, thus reducing unnecessary biopsies and minimizing risks associated with overtreatment. ❑

MATERIALS AND METHODS

Patients were prospectively enrolled based on clearly defined criteria: serum PSA ≥3 ng/mL and the presence of suspicious prostate lesions identified via mpMRI, specifically lesions classified with PI-RADS score ≥3. Individuals previously treated for prostate cancer or those lacking complete clinical datasets were excluded from analysis.

Multiparametric MRI scans were conducted using a 3 Tesla Siemens Magnetom Vida scanner (Siemens Healthineers, Erlangen, Germany). Imaging strictly followed the Prostate Imaging Reporting and Data System version 2.1 guidelines, encompassing T2-weighted imaging, diffusion-weighted imaging (DWI) sequences using b-values of 0, 500 and 1000 s/mm^2, and dynamic contrast-enhanced (DCE) sequences (6). An experienced radiologist evaluated all scans, as-

signing PI-RADS scores. Lesions categorized as PI-RADS ≥3 were classified as suspicious for prostate cancer and recommended for targeted biopsy.

Patients with suspicious mpMRI findings underwent targeted magnetic resonance imaging/transrectal ultrasound (MRI/TRUS) fusion-guided biopsies in addition to systematic transrectal ultrasound-guided biopsy. Procedures were performed using a bk3000 ultrasound system equipped with the bkFusion software and a transrectal biplanar probe, following standard clinical guidelines.

Before undergoing biopsy, each patient provided post-DRE urine samples. Genetic analyses were carried out with the SelectMDx biomarker-based risk score assay (MDx Health, Irvine, CA, USA). This assay measured the mRNA expression levels of DLX1 and HOXC6 genes in post-DRE urine samples (7). Molecular data were combined with clinical characteristics such as serum PSA levels, DRE findings, patient age and family history to offer unique prostate cancer risk scores.

The diagnostic performance of SelectMDx in the PI-RADS 3 subgroup was statistically evaluated. Measures including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were calculated by using biopsy-confirmed histopathological results. The Pearson's chi-square test was used to analyze differences in cancer prevalence based on SelectMDx results. Logistic regression analyses, both univariate and multivariate, were used to investigate correlations between SelectMDx results, patient age, PSA levels, prostate volume, family history and detection of Grade Group ≥2 prostate cancer. Statistical significance was considered as p-values < 0.05. ❑

RESULTS

Among patients with a PI-RADS score of 3 (n=40), a statistically significant association was observed between SelectMDx results and the presence of clinically significant prostate cancer (PCa). As shown in Figure 1, 57.1% of patients with a positive SelectMDx test result were diagnosed with PCa, in contrast to only 18.2% among those with a negative result ($p = 0.031$). Conversely, the absence of cancer was confirmed in 81.8% of patients with negative test results,

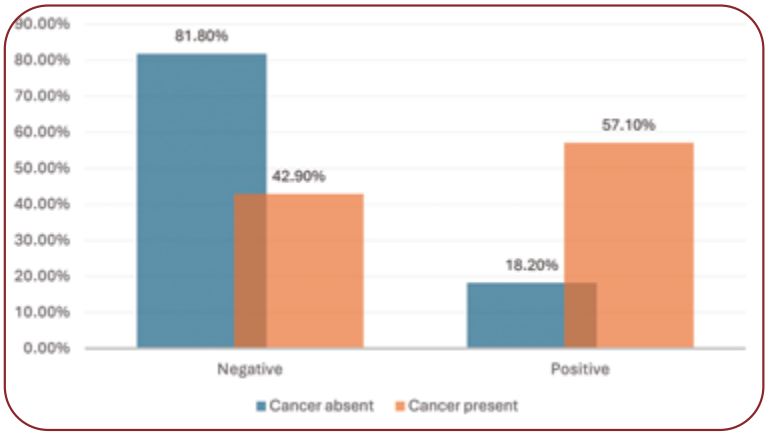

FIGURE 1. Patients' distribution according to the presence of prostate cancer and the result of the SelectMDx test

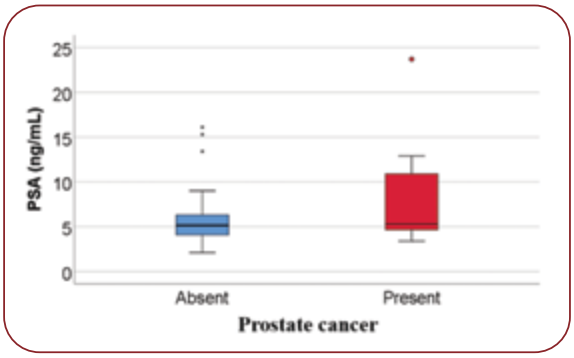

FIGURE 2. Comparison of PSA values in relation to the presence of prostate cancer in patients with a PI-RADS score of 3

underscoring the potential role of SelectMDx primarily in excluding malignancy and minimizing unnecessary biopsies.

Diagnostic performance indicators of the SelectMDx test in this cohort revealed a sensitivity of 57.14%, specificity of 81.82%, PPV of 40%, NPV of 90% and an overall accuracy of 77.5%. However, the area under the ROC curve (AUC 0.695, 95% CI 0.460–0.930, $p = 0.109$) did not reach statistical significance, suggesting a limited predictive discrimination in this subgroup, potentially due to the small sample size.

PSA levels did not significantly differ between patients with and without cancer (Figure 2). Median PSA values were 5.3 ng/mL in the PCa group *versus* 5.14 ng/mL in the cancer-free group ($p = 0.326$), despite non-normal distributions confirmed by the Shapiro-Wilk test.

Similarly, prostate volume showed no significant difference based on cancer status, with median values of 52 mL in patients with prostate cancer and 53 mL in those without ($p = 0.626$).

Conversely, patient age proved to be a significant distinguishing factor, with a median age of 67 years (IQR 67–69) in cancer patients – significantly higher than the median age of 61 years (IQR 57–66.5) observed in those without cancer (p = 0.012).

Family history of prostate cancer was not significantly associated with cancer presence in this cohort (p = 0.134), despite a numerically higher frequency among cancer-positive individuals.

Univariable logistic regression analyses (Table 1) identified age [odds ratio (OR) 1.249, 95% CI 1.026–1.520, p = 0.027)] and SelectMDx positivity (OR 6.000, 95% CI 1.054–34.143, p = 0.043) as significant predictors of prostate cancer, but in the multivariable model, only age retained independent predictive value (OR 1.225, 95% CI 1.001–1.498, p = 0.049), while the association with SelectMDx was no longer statistically significant (p = 0.145).

When analyzing only patients with negative SelectMDx results, 90% (27/30) were confirmed cancer-free, and none of the 30 patients had a positive family history (Figure 3). Although three patients (10%) did have PCa, all cases were clinically significant (Grade Group ≥ 2). PSA values in this subgroup again did not significantly differ between those with and without cancer (p = 0.283).

Analysis of prostate volume and patient age in relation to SelectMDx results revealed no significant differences (p = 0.724 and p = 0.081, respectively; Table 2) and PSA density also lacked a statistically significant association with cancer presence in SelectMDx-negative patients (p = 0.554), thus limiting its usefulness in biopsy decision-making within this subgroup. ❑

TABLE 1. Univariate and multivariate binomial logistic regression models used to predict the presence of prostate cancer in patients with a PI-RADS score of 3

Parameter	Univariate		Multivariate	
	OR (95% C.I.)	p	OR (95% C.I.)	p
PSA	1.148 (0.971-1.358)	0.106	-	-
Prostate volume	0.982 (0.943-1.024)	0.398	-	-
Age	1.249 (1.026-1.520)	**0.027**	1.225 (1.001-1.498)	**0.049**
Family history	6.200 (0.704-54.612)	0.100	-	-
SelectMDx +	6.000 (1.054-34.143)	**0.043**	4.099 (0.614-27.376)	0.145

OR=odds ratio; CI=confidence interval

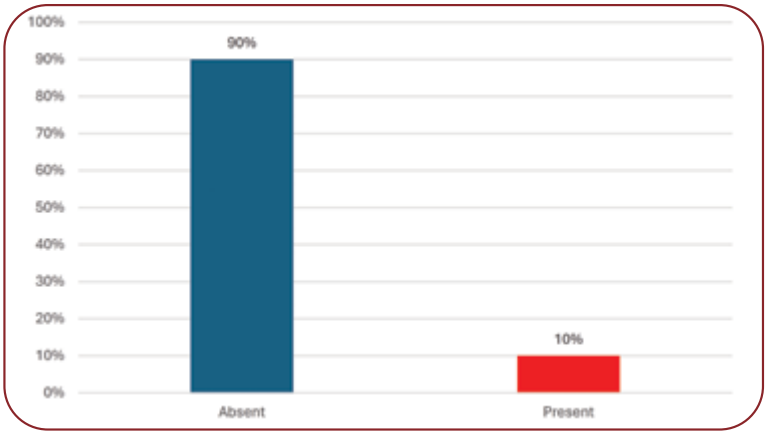

FIGURE 3. Distribution of patients with a negative SelectMDx result and a PI-RADS score of 3 in relation to the presence of prostate cancer

DISCUSSION

The process of diagnosing prostate cancer has considerably improved in recent years, with increased focus on combining imaging and molecular testing to enhance detection accuracy while avoiding unnecessary biopsies (8). Our findings contribute to this expanding framework by supporting the selective use of the SelectMDx urine biomarker in individuals with equivocal mpMRI findings, particularly those classified as PI-RADS 3.

While mpMRI is highly recommended in biopsy-naïve men with a presumed diagnosis of

TABLE 2. Comparative analysis of clinical indicators in PI-RADS 3 patients

Analyzed parameter	Subgroup	Mean ± SD	Median (IQR)	Mean rank	p	Statistical test
Prostate volume	Negative Select MDx(p=0.028)	59.73 ± 25.86	52.5 (42.5–75)	20.88	0.724	Mann-Whitney U test, Shapiro-Wilk Test
	Positive Select MDx (p=0.200)	54.1 ± 19.46	52.5 (39–61.5)	19.35		
Age	Negative Select MDx (p=0.570)	61.83 ± 6.19	62 (57–67)	—	0.081	Student T-test, Shapiro-Wilk, Levene's test
	Positive Select MDx (p=0.482)	65.8 ± 5.63	67 (59.5–69.5)	—		
PSA density	Cancer absent (p<0.001)	0.114 ± 0.086	0.09 (0.061–0.123)	15.15	0.554	Mann-Whitney U test, Shapiro-Wilk Test
	Cancer present (p=0.108)	0.280 ± 0.343	0.102 (0.082–0.389)	18.67		

prostate cancer (PCa) (9), its diagnostic benefit in PI-RADS 3 lesions remains uncertain. Reported cancer detection rates within this subgroup vary considerably, with clinically significant PCa being identified in only 10–30% of cases (10). Our findings are consistent with this ambiguity and suggest that SelectMDx may provide additional value in optimizing biopsy decision-making. These results align with those of Rubio-Briones *et al* (11), who demonstrated that the incorporation of a urinary molecular test could prevent over one-third of unnecessary biopsies, without significantly delaying csPCa diagnosis. In our cohort, SelectMDx exhibited a high negative predictive value among patients with PI-RADS 3 lesions, supporting its role as a triage tool for mitigating overdiagnosis and overtreatment.

Similar findings were presented by Van Neste *et al* (12), who demonstrated that the two-gene SelectMDx panel (HOXC6 and DLX1) served as a robust predictor for both prostate cancer (PCa) and clinically significant PCa (csPCa). Although our ROC curve did not reach statistical significance – likely due to the limited sample size – our sensitivity and specificity estimates are in line with previous multicenter studies, which have reported AUC values ranging between 0.75 and 0.85 (13).

Another notable aspect of our findings is the lack of statistical significance in SelectMDx in the multivariable logistic regression model, when age was the only independent predictor. This also highlights the importance of integrating biomarker data with clinical information. Age has long been a known risk factor for PCa, and its predictive value has been supported in many studies (14). Our results reinforce the idea that molecular scores should complement rather than replace fundamental clinical characteristics in risk stratification model settings.

Consistent with the prevailing evidence from the literature regarding the diagnostic value of PSA, prostate volume and PSA density, in particular in men with intermediate PSA levels or indefinite MRI results (15), our study also did not find a clinically significant correlation between these factors and the presence of cancer, further questioning their value in decision-making regarding biopsy.

Although encouraging results, a few limitations should be noted. The small number of PI-RADS 3 patients limits statistical power for subgroup analysis as well as generalizability. In addition, while SelectMDx showed promising diagnostic performance, we did not test its cost-effectiveness – a key consideration for its potential use in the clinic. Earlier studies have estimated SelectMDx might be cost-saving by avoiding unnecessary biopsy procedures and related complications (16), but real-world economic modeling across different healthcare systems is limited.

Given these findings, SelectMDx appears to be a useful tool for refining risk assessment, particularly in patients with ambiguous imaging results, though larger multicenter studies are needed to confirm its clinical value and determine how best to integrate it into practice. ❑

CONCLUSIONS

This research contributes further evidence suggesting SelectMDx can be a useful addition in the diagnostic evaluation of patients with ambiguous mpMRI results, most notably those with PI-RADS 3 lesions. By adding molecular information to imaging, the test has the capability of decreasing the rate of avoidable prostate biopsies, thus reducing the exposure of patients to risks from procedures themselves without compromising the detection of clinically significant prostate cancer. However, the predictive performance of SelectMDx seems highly dependent upon individual-level clinical factors, notably age, highlighting the significance of risk models integrated across domains rather than isolated markers. ❑

Conflicts of interest: none declared.

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References

1. **Wang L, Lu B, He M, et al.** Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. *Front Public Health* 2022;10:811044. https://doi.org/10.3389/fpubh.2022.811044.
2. **Fenton JJ, Weyrich MS, Durbin S, et al.** Prostate-Specific Antigen-Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2018;319:1914-1931.
3. **Sosnowski R Zagrodzka M, Borkowski T.** The limitations of multiparametric magnetic resonance imaging also must be borne in mind. *Cent Europ J Urol* 2016;69:22-23. https://doi.org/10.5173/ceju.2016.e113.
4. **Schoots IG.** MRI in early prostate cancer detection: how to manage indeterminate or equivocal PI-RADS 3 lesions? *Transl Androl Urol* 2018;7:70-82. https://doi.org/10.21037/tau.2017.12.31.
5. **Hendriks R.** Clinical use of the SelectMDx urinary-biomarker test with or without mpMRI in prostate cancer diagnosis: a prospective, multicenter study in biopsy-naïve men. *Prostate Cancer Prostatic Dis* 2021;24:1110-1119. https://doi.org/10.1038/s41391-021-00367-8.
6. **Turkbey B, Rosenkrantz AB, Haider MA, et al.** Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur Urol* 2019;76:340-351. https://doi.org/10.1016/j.eururo.2019.02.033.
7. **Shore N, Hafron J, Langford T, et al.** Urinary Molecular Biomarker Test Impacts Prostate Biopsy Decision Making in Clinical Practice. *Urol Pract* 2019;6:256-261. https://doi.org/10.1016/j.urpr.2018.09.002.
8. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;101:374-383. https://doi.org/10.1093/jnci/djp001.
9. **Mottet N, van den Bergh RCN, Briers E, et al.** EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2021;79:243-262. https://doi.org/10.1016/j.eururo.2020.09.042.
10. **Maggi M, Panebianco V, Mosca A, et al.** Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus* 2020;6:463-478. https://doi.org/10.1016/j.euf.2019.06.014.
11. **Rubio-Briones J, Borque-Fernando A, Esteban LM, et al.** Validation of a 2-gene mRNA urine test for the detection of ≥GG2 prostate cancer in an opportunistic screening population. *The Prostate* 2020;80:500-507. https://doi.org/10.1002/pros.23964.
12. **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. https://doi.org/10.1016/j.eururo.2016.04.012.
13. **Haese A, Trooskens G, Steyaert S, et al.** Multicenter Optimization and Validation of a 2-Gene mRNA Urine Test for Detection of Clinically Significant Prostate Cancer before Initial Prostate Biopsy. *J Urol* 2019;202:256-263. https://doi.org/10.1097/JU.0000000000000293.
14. **Dijkstra S, Govers TM, Hendriks RJ, et al.** Cost-effectiveness of a new urinary biomarker-based risk score compared to standard of care in prostate cancer diagnostics – a decision analytical model. *BJU Int* 2017;120:659-665. https://doi.org/10.1111/bju.13861.
15. **Ferro M, Lucarelli G, de Cobelli O, et al.** The emerging landscape of tumor marker panels for the identification of aggressive prostate cancer: the perspective through bibliometric analysis of an Italian translational working group in uro-oncology. *Minerva Urol Nephrol* 2021;73:442-451. https://doi.org/10.23736/S2724-6051.21.04098-4.
16. **Govers TM, Hessels D, Vlaeminck-Guillem V, et al.** Cost-effectiveness of SelectMDx for prostate cancer in four European countries: a comparative modeling study. *Prostate Cancer Prostatic Dis* 2019;22:101-109. https://doi.org/10.1038/s41391-018-0076-3.