MINISTRY OF EDUCATION AND RESEARCH
"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
DOCTORAL SCHOOL

The Value of Genetic and Imaging Tests in the Diagnostic Protocol of High-Risk Prostate Cancer

SUMMARY OF THE DOCTORAL THESIS

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BUCHAREST
2025

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List of Published Scientific Papers

"Prostate cancer diagnostics: the independent and combined roles of SelectMDx and mpMRI" – article accepted for publication in *Central European Journal of Urology* (Web of Science-indexed journal, impact factor included).

"Applicability of the SelectMDx test in identifying clinically significant Prostate Cancer: insights from an Eastern European cohort" – article currently under review in *Chirurgia* journal.

"Refining the Management of Prostate Imaging Reporting Category 3 Lesions through SelectMDx Urinary Biomarker Evaluation" – article registered in *Maedica – Journal of Clinical Medicine*, issue no. 2/2025.

Introduction

Prostate cancer is the most frequently diagnosed malignancy among men in developed countries, with approximately 1.1 million new cases reported worldwide each year. It is also the second most common non-cutaneous malignancy among men in the United States, with recent estimates indicating 268,490 new cases and 34,500 deaths annually [1].

The diagnosis of prostate cancer is based on multiple diagnostic tools, including elevated prostate-specific antigen (PSA) levels, abnormal digital rectal examination (DRE) findings, and positive family history [2].

A major issue associated with PSA-based screening is the overdiagnosis and overtreatment of low-grade (ISUP 1) cancers, which may never become clinically significant during the patient's lifetime. Approximately 42% of detected cancers are low-grade tumors that do not require active treatment, thereby exposing patients to unnecessary therapies, potential adverse effects, and increased healthcare costs [3,4].

Recent technological advances have enabled the development of molecular analyses and biomarker detection techniques, leading to the identification of several promising novel biomarkers [5].

In conclusion, the main objective in prostate cancer diagnosis is to improve detection accuracy and to distinguish between indolent and aggressive prostate cancers that require treatment. This contributes to better clinical decision-making and to a reduction in morbidity associated with therapy.

The studies described in this thesis aim to enhance prostate cancer diagnosis and may serve as a foundation for future research in this field.

Materials and Methods

Study Design

This retrospective observational study was conducted at Prof. Dr. Th. Burghele Clinical Hospital in Bucharest, an institution affiliated with the Carol Davila University of Medicine and Pharmacy, between January 15, 2022 and December 15, 2023.

The research protocol was approved by the Ethics Committee of Prof. Dr. Th. Burghele Clinical Hospital, Decision no. 143/05.01.2022, in accordance with national legislation and the principles of the revised Declaration of Helsinki. Data collection was carried out using a standardized form specifically designed for this study. This approach allowed the structuring of a database suitable for subsequent statistical analysis according to the research plan. To ensure the quality and integrity of the database, all individual forms were double-checked at different stages of data entry by different members of the research team.

Study Population and Selection Criteria

The cohort analyzed in this study consisted of patients evaluated in the outpatient and inpatient departments of the Prof. Dr. Th. Burghele Urology Clinic in Bucharest between January 2022 and December 2023.

Participant selection was based on a rigorous set of inclusion and exclusion criteria, established prior to study initiation, in line with the European Association of Urology (EAU) guidelines on prostate disease diagnosis and risk stratification.

The study sample size (n = 126 patients) was determined by the consecutive inclusion of all eligible patients meeting the criteria during the study period as part of routine clinical activity.

Inclusion Criteria

Eligible patients were males who simultaneously met all of the following conditions:

- Age between 40 and 80 years, a range considered relevant for prostate cancer screening and early diagnosis;
- Serum PSA ≥ 3 ng/mL, a commonly used threshold in urological practice and in several previously published studies;
- Completion of the SelectMDx molecular test, under standardized collection conditions (first-void urine, immediately after digital rectal examination);
- Undergoing multiparametric MRI (mpMRI), interpreted according to PI-RADS v2.1;

- Performance of transrectal ultrasound-guided prostate biopsy, either systematic or targeted (mpMRI-ultrasound fusion), based on imaging findings.

These criteria were chosen to ensure population homogeneity and to enable valid correlations between molecular, imaging, and histopathological data.

Exclusion Criteria

Patients with one or more of the following conditions were excluded from final analysis:

- Prior prostate surgery, such as Transurethral Resection of the Prostate (TURP), which may alter prostate anatomy and affect both molecular testing and mpMRI accuracy;
- Ongoing treatment with 5α-reductase inhibitors (e.g., Dutasteride, Finasteride) or androgen deprivation therapy, known to impact PSA levels and potentially alter gene expression targeted by the SelectMDx test;
- Absolute contraindications to mpMRI, such as magnetic field–incompatible medical devices (non-compatible pacemakers, implantable defibrillators, mechanical valves, metallic orbital or intracranial fragments of unknown origin);
- Morbid obesity (BMI > 40 kg/m²), which can limit access to mpMRI and degrade image quality through artifacts;
- Incomplete or missing essential data regarding any protocol component: SelectMDx test, mpMRI, biopsy results, or PSA value.

Bias Control

To reduce interpretation bias, an independent evaluation procedure was implemented for each step of the diagnostic process.

The radiologist interpreting the mpMRI was blinded to SelectMDx test results, while the pathologist assessing biopsy samples had no access to imaging scores, risk scores, or PSA levels.

This deliberate separation of data ensured a more objective interpretation of each component, minimizing subjective influence and enhancing the internal validity of the study.

Statistical Analysis

To validate the study hypotheses, a full set of descriptive and inferential statistical methods was applied, tailored to the nature of collected variables and study objectives.

Analyses were conducted using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA), and results were interpreted according to current clinical research standards.

Data Processing

After data verification, each variable was labeled, coded, and entered in SPSS-compatible format.

The distribution of continuous variables was tested using the Shapiro–Wilk test, suitable for medium-sized samples, to determine whether data were parametric or non-parametric.

Depending on distribution, variables were presented as mean ± standard deviation (SD) for normal data or as median and interquartile range (IQR) for non-normal data.

Diagnostic Performance

To assess the accuracy of the SelectMDx test in identifying clinically significant prostate cancer (ISUP ≥ 2), the following performance parameters were calculated:

- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)
- Overall Accuracy

Histopathological diagnosis from ultrasound-guided biopsy was used as the reference standard.

Receiver Operating Characteristic (ROC) curves were generated to evaluate discriminatory power, and the Area Under the Curve (AUC) served as a synthetic indicator of diagnostic accuracy.

Logistic Regression Models

To explore relationships among clinical, imaging, and molecular variables and identify independent predictors of clinically significant cancer, binary logistic regression models were developed.

In univariate analysis, each clinical variable (age, PSA, prostate volume, PI-RADS score, SelectMDx result) was tested individually.

In multivariate analysis, only clinically relevant variables with significant correlation ($p < 0.10$ in univariate analysis) were included to prevent overlap or collinearity.

Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI).

Subgroup Analysis

A separate subgroup analysis was conducted for patients with PI-RADS 3, considered clinically equivocal, to assess the added value of SelectMDx for risk stratification.

Sensitivity, specificity, PPV, and NPV were calculated accordingly.

Differences in prostate cancer prevalence across SelectMDx categories were tested using Pearson's Chi-square, and clinical significance was evaluated in terms of missing aggressive disease.

Clinical Utility (Decision Curve Analysis – DCA)

To estimate the clinical benefit of SelectMDx in reducing unnecessary biopsies without compromising detection of significant cancer, Decision Curve Analysis (DCA) was applied.

This method compares the net benefit of diagnostic options at various probability thresholds and complements traditional statistical measures.

Study 1: The Independent and Combined Roles of SelectMDx and mpMRI in the Diagnosis of Prostate Cancer

Introduction

The working hypothesis formulated for this study was that the SelectMDx test, when used as a triage tool among patients with intermediate PSA values, could provide superior diagnostic accuracy compared to its combined use with mpMRI.

The specific objectives were:

To evaluate the diagnostic performance of the SelectMDx test in detecting clinically significant prostate cancer;

To determine the independent predictive value of the PI-RADS score in the presence of a positive SelectMDx result;

To compare the clinical utility of the two methods, used independently and in combination, in avoiding unnecessary biopsies.

Patients and Methods

This study was conducted on the cohort described in the *General Materials and Methods* chapter, including a total of 126 patients evaluated for suspicion of prostate cancer.

All patients met the general inclusion criteria: age between 40 and 80 years, serum PSA levels ≥ 3 ng/mL, SelectMDx testing, mpMRI examination, and prostate biopsy performed between 2022 and 2023.

Results

Demographic and Clinical Characteristics

A total of 126 patients were included in the analysis. The mean age was 63.2 ± 7.24 years, with a median of 64 years (IQR: 58–68.25), ranging between 42 and 80 years.

The mean prostate volume was 54.78 ± 25.91 mL (median: 52 mL; IQR: 35–65.25), and the median serum PSA level was 5.75 ng/mL (IQR: 4.17–8.71).

Most patients (60.3%) had intermediate PSA values (4–10 ng/mL).

A positive family history of prostate cancer was reported in 7.9% of patients, with no significant association with cancer presence ($p = 0.722$**).**

Performance of the SelectMDx Test

The SelectMDx test was positive in 53.2% of patients**. (**Figure 11.2.).

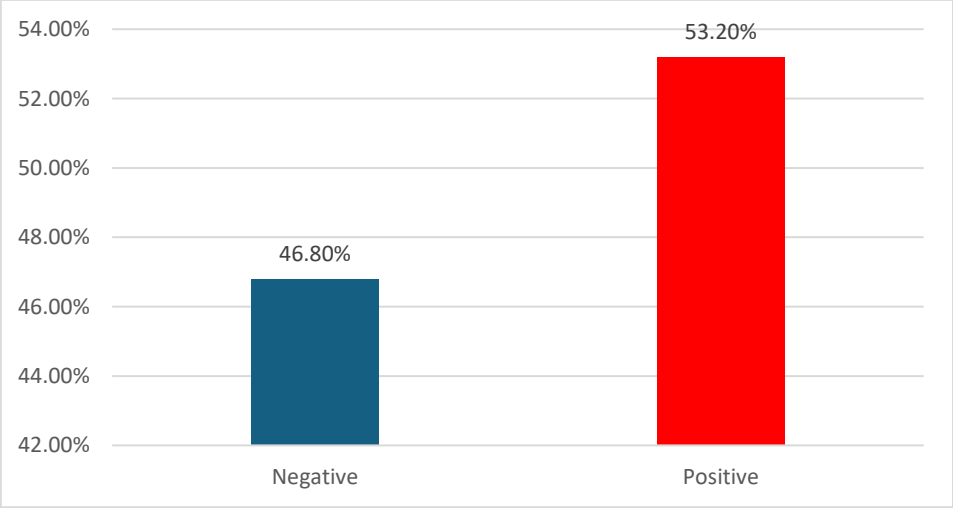

Figure 11.2. Distribution of patients according to the SelectMDx test result

Among these, 89.2% had clinically significant prostate cancer (Grade Group ≥ 2), compared with only 10.8**%** in the negative group, a statistically significant difference ($p < 0.001$).

Diagnostic performance parameters:

- Sensitivity: 89,19%
- Specificity 61,8%
- PPV: 49,25%
- NPV: 93,22%
- Accuracy: 69,84%

Table 11.5. Distribution of patients according to prostate cancer presence and SelectMDx test result

Cancer/ Result	**Absent**		**Present**		**p***
	Nr.	**%**	**Nr.**	**%**	
Negative	55	61.8%	4	10.8%	**<0.001**
Positive	34	38.2%	33	89.2%	

***Fisher's Exact Test**

In the subgroup of patients with PSA values between 4-10 ng/mL (n = 97):

- Sensitivity: 90.62%
- Specificity: 70.42%
- PPV: 58%
- NPV: 94.34%
- Accuracy: 76.7%

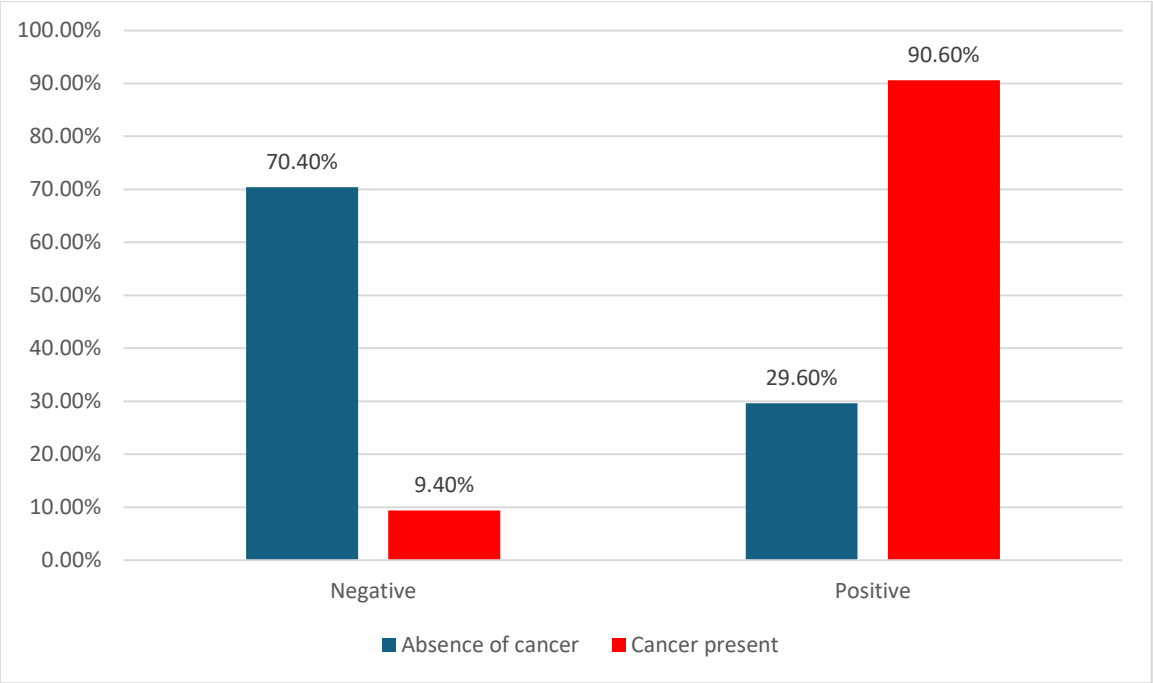

Figure 11.3. Distribution of patients with low or borderline PSA values (<10 ng/mL) according to prostate cancer presence and SelectMDx test result

PI-RADS Score and Association with Prostate Cancer

The mean PI-RADS score was 3.48 ± 1.27, with a median of 3 (IQR: 3–5).

Lesions classified as PI-RADS ≥ 4 were associated with a higher prevalence of significant cancer (78.4%) compared with PI-RADS < 4 (21.6%, $p < 0.001$).

In univariate analysis, PI-RADS ≥ 4 increased the odds of aggressive prostate cancer 7.13-fold (OR: 7.129; CI: 2.905–17.494; $p < 0.001$).

However, after adjustment for SelectMDx and age, the association lost statistical significance (adjusted OR: 1.493; $p = 0.555$).

Combined Performance of SelectMDx and PI-RADS

We analyzed the combined performance of PI-RADS ≤ 2 and a negative SelectMDx result to identify low-risk patients.

This combination was present in 27 patients (21.4%), of whom only one was diagnosed with clinically significant cancer, resulting in a negative predictive value (NPV) of 96.3%, though specificity was modest (29.2%).

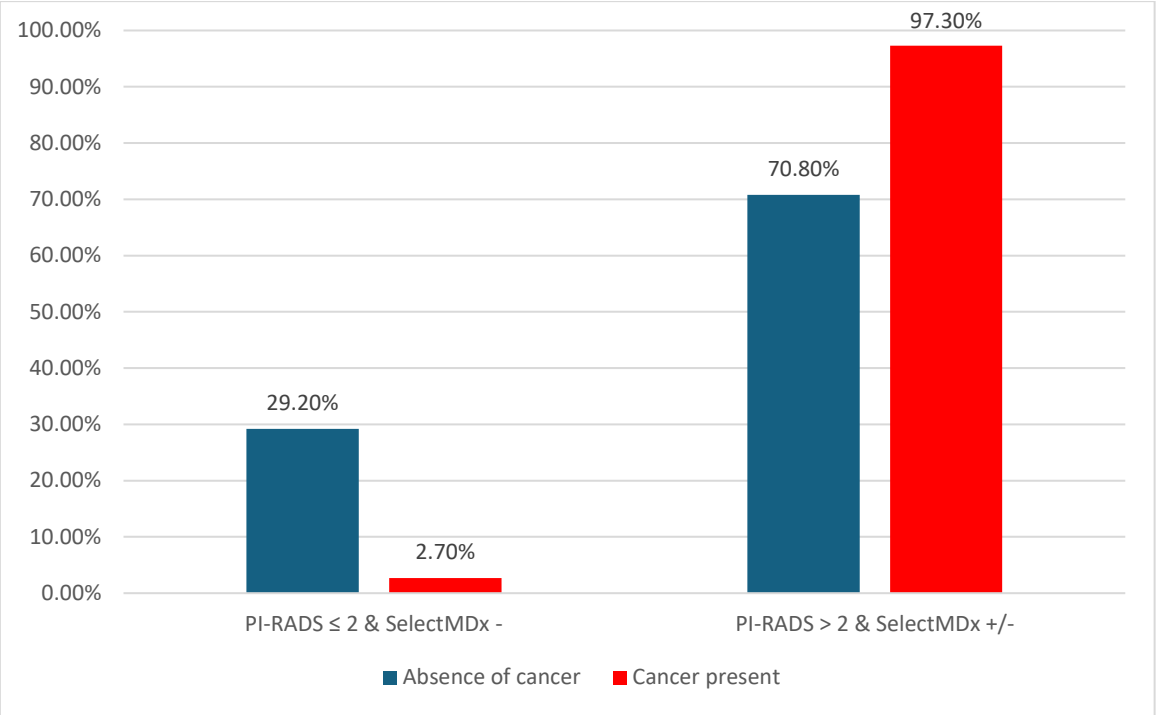

Figure 11.5. Distribution of patients according to prostate cancer presence and combined criteria of PI-RADS ≤ 2 and negative SelectMDx result

ROC and DCA Analysis – Comparative assessment between combinations

The ROC curves generated for each individual test and for the combinations of tests demonstrated that the SelectMDx test, when used alone, achieved the highest diagnostic performance, with an AUC value of 0.755 (95% confidence interval: 0.667–0.843), indicating a superior ability to discriminate between patients with and without clinically significant prostate cancer. This performance was not only statistically superior but also clinically relevant, as an AUC above 0.7 is generally considered acceptable for evaluating the diagnostic accuracy of non-invasive tests.

Therefore, the results suggest that, within cohorts characterized by intermediate PSA values, the SelectMDx test remains the most robust tool for risk stratification when used independently (Figure 11.6).

The ROC curves generated for each test and for each combination of tests demonstrated that the SelectMDx test, when used individually, exhibited the highest diagnostic performance, with an AUC value of 0.755 (95% confidence interval: 0.667–0.843), indicating a superior discriminative ability between patients with and without clinically significant prostate cancer. This performance was superior not only from a

statistical standpoint but also from a clinical applicability perspective, as an AUC greater than 0.7 is generally considered acceptable in the evaluation of non-invasive diagnostic tests.

Therefore, the results suggest that, within cohorts presenting intermediate PSA values, the SelectMDx test remains the most robust tool for risk stratification when used as a standalone method (Figure 11.6).

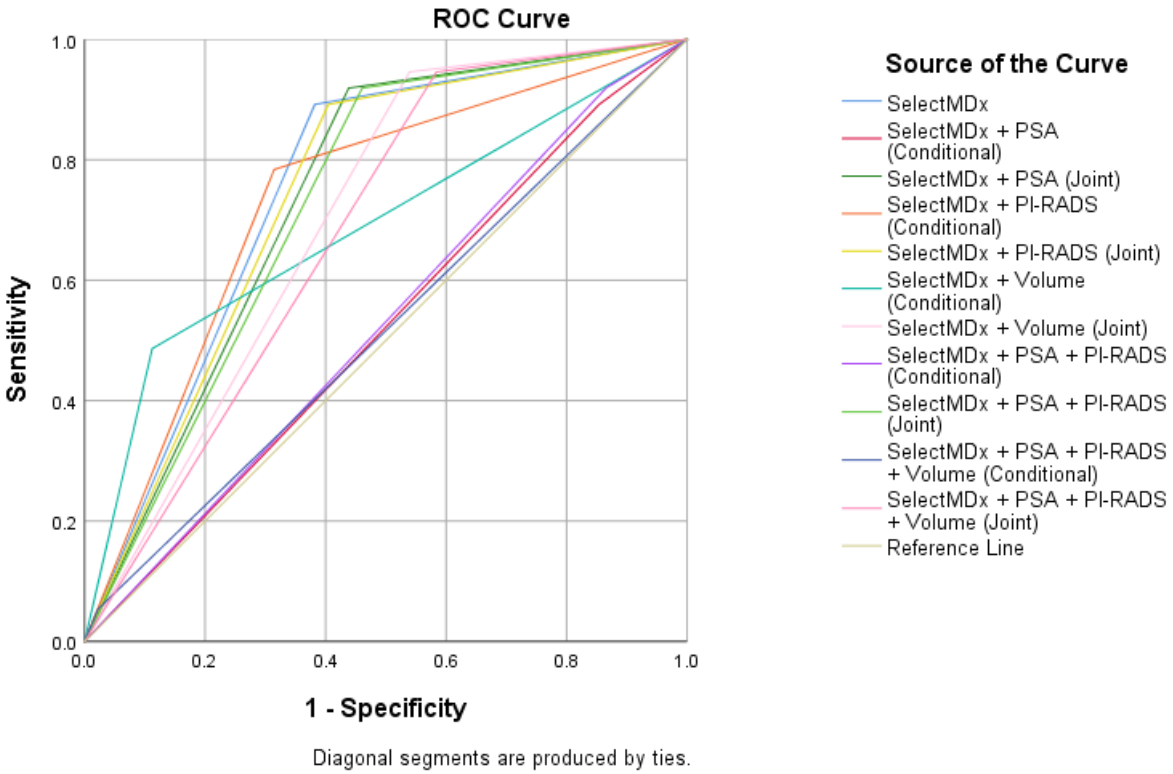

Figure 11.6. ROC curve for prostate cancer prediction using the proposed combinations of diagnostic tools

In the Decision Curve Analysis (DCA), used to quantify the net clinical benefit of various diagnostic strategies, the SelectMDx test consistently emerged as the approach offering the greatest advantage in reducing the number of unnecessary biopsies. Compared with other diagnostic methods or combinations of tools (such as PSA, PI-RADS, prostate volume, or their combinations), SelectMDx generated the largest area under the net benefit curve across the entire range of analyzed clinical probabilities (Figures 11.7–11.10).

More specifically, the DCA curves demonstrated that strategies such as biopsying all patients (“biopsy all”) or using combined diagnostic approaches (either in conditional or joint form) yielded a lower net clinical benefit. By contrast, SelectMDx, when used as a

standalone tool, provided a superior ability to discriminate between patients truly at risk for clinically significant prostate cancer and those at low risk, thereby minimizing unnecessary interventions and reducing the risks associated with invasive procedures.

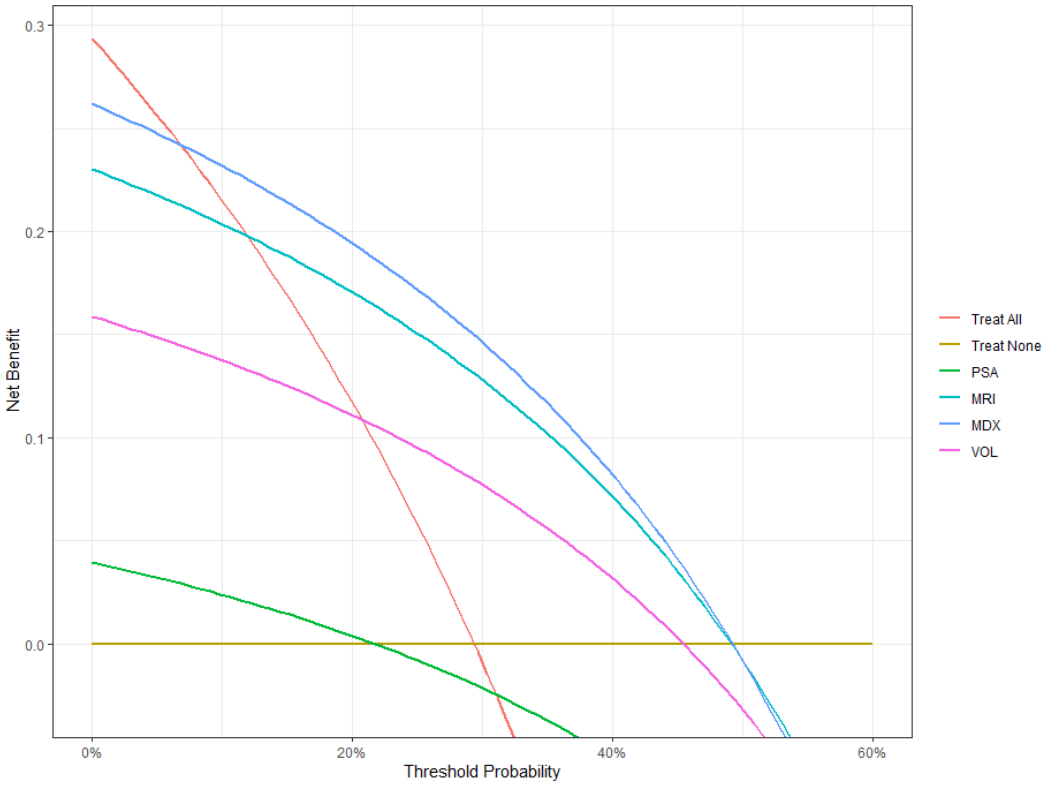

Figure 11.7. Decision Curve Analysis (DCA) using each diagnostic test for prostate cancer diagnosis

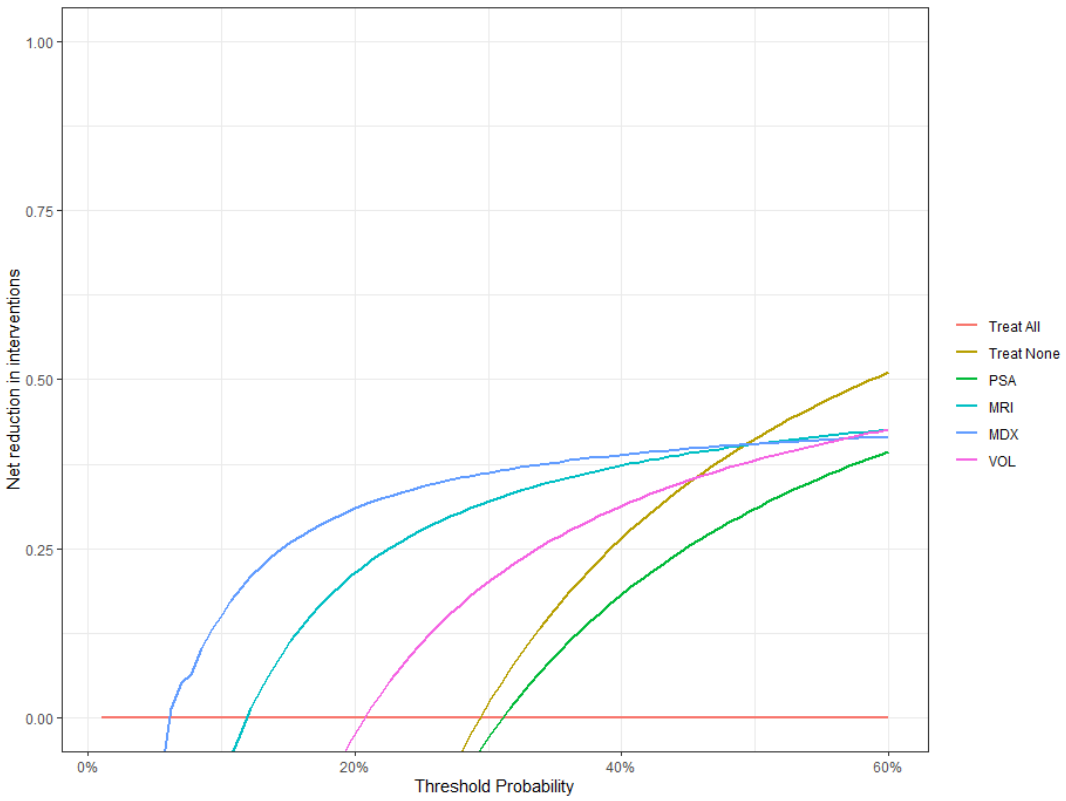

Figure 11.8. DCA using each diagnostic test for prostate cancer diagnosis (illustrating the biopsy avoidance rate)

This superiority is clearly reflected in the biopsy avoidance rate, where SelectMDx outperformed all other analyzed scenarios. The DCA analyses therefore support the role of SelectMDx as a valuable standalone tool in clinical decision-making, particularly in the current context in which the personalization of medical care and the reduction of overdiagnosis represent major priorities in urologic oncology..

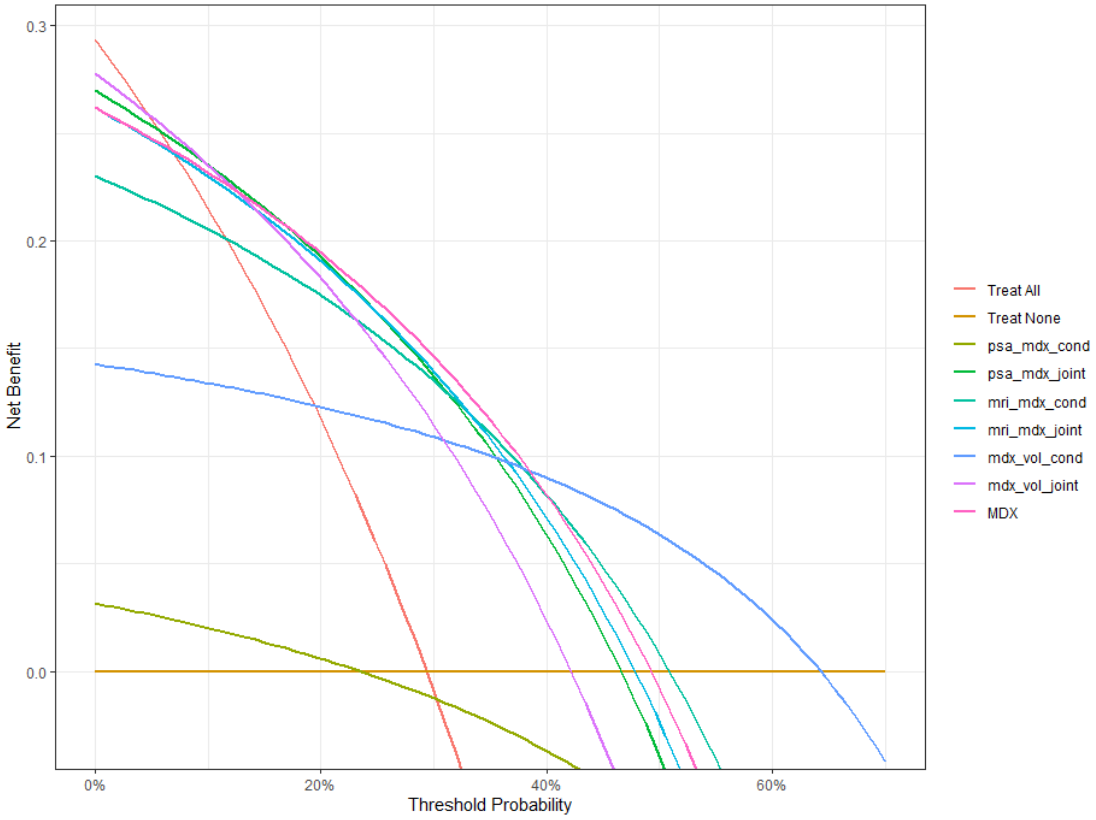

Figure 11.9. DCA using each diagnostic test in combination with the SelectMDx test for prostate cancer diagnosis

These findings carry additional clinical significance, particularly in a context where decisions regarding the indication for prostate biopsy are often based on uncertain factors or nonspecific risk scores. In practical terms, using SelectMDx as an initial filtering tool enables efficient triage of patients who can be safely monitored through active surveillance, without the need for immediate invasive procedures. Thus, the benefit is not merely statistical — it translates into a reduction in biopsy-related complications, decreased patient anxiety, and optimized use of medical resources, all of which are essential elements of a

modern and sustainable healthcare system.

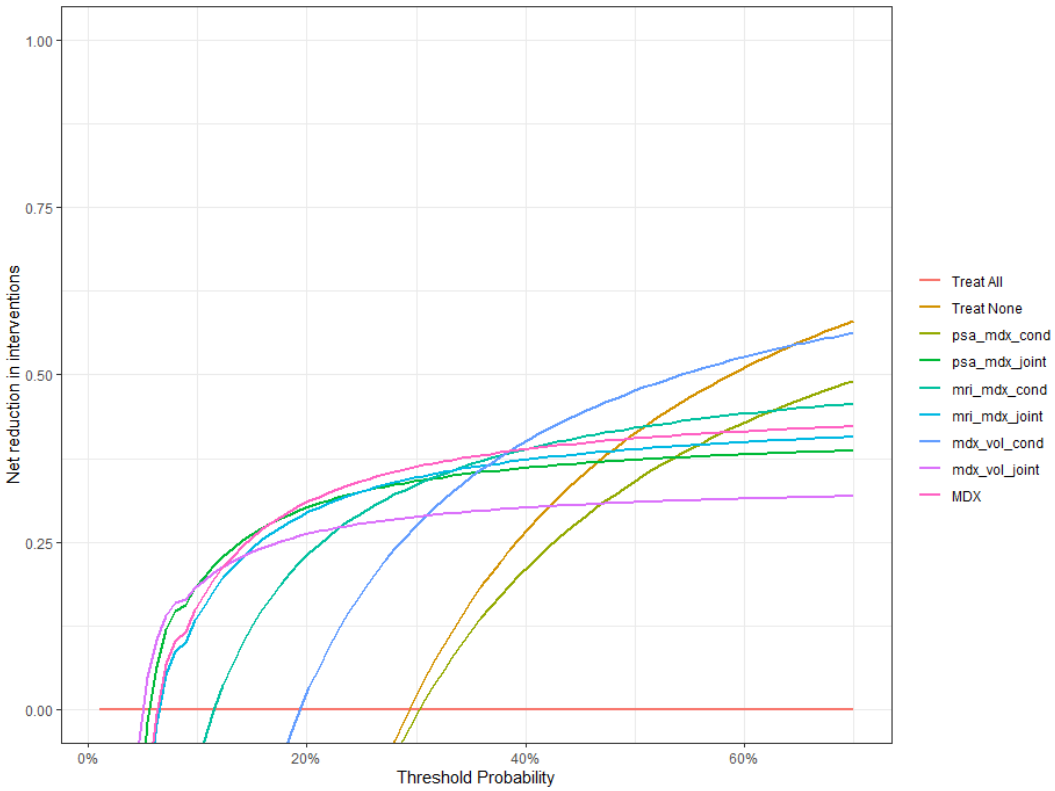

Figure 11.10. DCA using each diagnostic test combined with SelectMDx for prostate cancer diagnosis (illustrating the biopsy avoidance rate)

Discussion

The PI-RADS score, used in the interpretation of mpMRI, represents a valuable tool for risk stratification prior to performing a prostate biopsy. In our study, a PI-RADS score ≥ 4 was associated with a 7.13-fold higher risk of diagnosing clinically significant prostate cancer**.**

In our study, SelectMDx demonstrated a sensitivity of 90.62% and a negative predictive value of 94.34%, supporting its applicability as an exclusion test. These results are consistent with those reported by Hendriks and colleagues in a prospective multicenter study published in Prostate Cancer and Prostatic Diseases, in which SelectMDx showed similar performance in biopsy-naïve patients.

The fact that the SelectMDx test should be integrated into a modern clinical algorithm is clearly supported by our findings, particularly through the analysis of ROC and DCA curves. In summary, when used alone, SelectMDx provides the highest diagnostic accuracy.

Conversely, we observed that combining it with other methods did not enhance performance but, in fact, led to a slight decrease. This observation was further confirmed by the DCA analysis, which demonstrated that SelectMDx, when used as a standalone test, delivers the greatest clinical benefit and is most effective in reducing unnecessary biopsies. This conclusion is also supported by data published by Pepe and collaborators (2020), who compared the efficiency of SelectMDx and mpMRI in clinical contexts of active surveillance and reached similar conclusions [6].

In conclusion, this study demonstrates that the SelectMDx test is a highly useful tool in determining which patients with intermediate PSA levels truly require a biopsy. With high sensitivity and an excellent ability to exclude cases without aggressive cancer, SelectMDx can significantly reduce the number of unnecessary biopsies — an essential aspect of a modern and balanced clinical practice.

Study 2: Evaluation of the Diagnostic Performance of the SelectMDx Molecular Test in Detecting Clinically Significant Prostate Cancer in an Eastern European Cohort

Introduction

his study represents the first retrospective clinical analysis conducted in Romania — and indeed across Southeastern Europe — aimed at evaluating the performance of the SelectMDx test within a specific regional population.

It is important to emphasize that results obtained in different demographic or healthcare contexts cannot be directly extrapolated, which highlights the need for regional validation studies.

Variations in healthcare systems, screening practices, and genetic backgrounds can influence test outcomes and diagnostic pathways.

Study Objectives

In this second study, we aimed to analyze several key parameters considered essential to understanding the diagnostic value of the SelectMDx test, as follows:

1. To assess the sensitivity and negative predictive value (NPV) of SelectMDx in identifying clinically significant prostate cancer within a Romanian population;
2. To evaluate test performance in specific clinical subgroups frequently encountered in urological practice - particularly in patients with PI-RADS $\leq$ 3 lesions and PSA < 10 ng/mL, where biopsy decisions are often challenging;
3. To explore how SelectMDx might be integrated into a personalized diagnostic algorithm, adapted to the realities of the Romanian healthcare system.

The primary goal was to assess the performance of SelectMDx in a representative clinical setting for Southeastern Europe, focusing on its ability to detect clinically significant prostate cancer.

We also examined the efficiency of SelectMDx as an independent tool and in association with PI-RADS scores, in order to determine whether hybrid diagnostic models provide additional value.

Results

Given the heterogeneous presentation of prostate cancer and the need for precise risk stratification, a detailed analysis of SelectMDx performance was conducted across subgroups defined by clinical and paraclinical features.

Patients with Negative Digital Rectal Examination (DRE)

Among the 82 patients with a negative DRE, 46 (56.1%) had a positive SelectMDx result.Of these, 22 patients (47.8%) were subsequently diagnosed via ultrasound-guided transrectal biopsy with clinically significant adenocarcinoma.

In contrast, among the 36 patients (43.9%) with a negative SelectMDx, only two cases (5.6%) showed histopathologic confirmation of aggressive disease. The test therefore demonstrated excellent performance in this context:

Sensitivity: 91.7%

Specificity: 57.1%

NPV: 94.4% ($p < 0.001$)

Thus, SelectMDx proved highly effective in ruling out aggressive prostate cancer in patients lacking clinical suspicion on DRE, offering significant support for biopsy decision-making.

Patients with PI-RADS ≤ 3 on mpMRI

Among the 65 patients with PI-RADS ≤ 3 lesions — considered inconclusive or low suspicion — 31 (47.7%) had a positive SelectMDx result.

Of these, 8 patients (25.8%) were later confirmed by biopsy to have clinically significant cancer. In contrast, of the 34 patients (52.3%) with negative results, only one (2.9%) was diagnosed with significant cancer. This supports the test's value in equivocal imaging contexts.

Performance metrics in this subgroup:

Sensitivity: 88.9%

Specificity: 58.6%

NPV: 97.1% ($p = 0.002$)

These findings reinforce SelectMDx as an effective rule-out tool, minimizing the risk of missing clinically significant tumors in PI-RADS 3 or ambiguous mpMRI lesions.

Patients Without a Family History of Prostate Cancer

Among the 116 patients without known family history, 60 (51.7%) had a positive SelectMDx result. (Figure 12.2). Of these, 28 (46.7%) were confirmed with clinically significant cancer by histopathology..

Among the 56 patients with negative test results, only 3 were found to have clinically significant cancer. In this subgroup, the SelectMDx test demonstrated a sensitivity of 90.3%, a specificity of 56.4%, and a negative predictive value of 94.6% ($p < 0.001$).

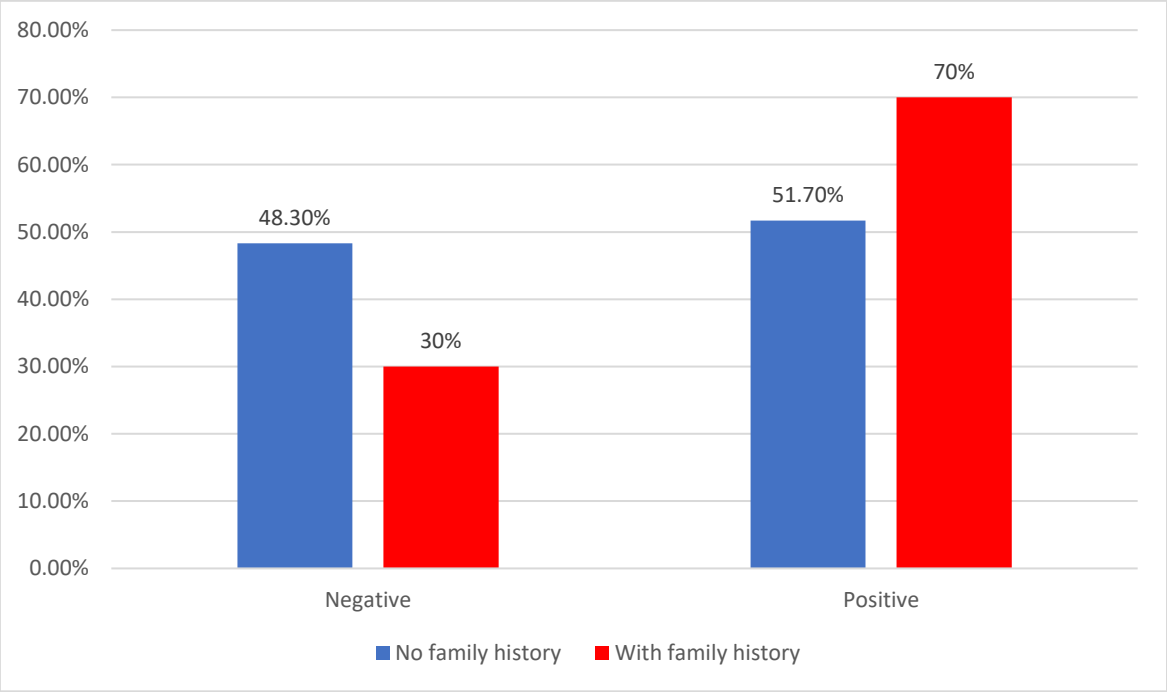

Figure. 12.2. Distribution of patients according to family history and SelectMDx test result

Patients with a positive digital rectal examination (DRE)

Among the 44 patients with suspicious DRE, 27 (61.4%) tested positive for SelectMDx, and 21 (77.8%) of them were confirmed with clinically significant cancer.

Of the 17 patients with negative tests, 5 still had aggressive disease confirmed histologically. In this clinical context, the SelectMDx test achieved a sensitivity of 80.8%, a specificity of 50.0%, and a negative predictive value of 70.6% ($p = 0.016$).

Patients with Positive Family History

Among the 10 patients reporting a positive family history, 7 had positive SelectMDx results, and 5 were confirmed with clinically significant cancer.

The 3 patients with negative results showed no evidence of malignancy on biopsy. In this high hereditary risk category, the SelectMDx test demonstrated a sensitivity of 100%, a specificity of 40%, and a negative predictive value also of 100% (p = 0.034).

Patients with PI-RADS ≥ 4 on mpMRI

In the group of 61 patients who presented with PI-RADS 4 or 5 scores—corresponding to imaging lesions considered at high risk for malignancy—40 patients (65.6%) had a positive SelectMDx test result. Among these, 30 patients (75%) were subsequently diagnosed with clinically significant prostate cancer. Conversely, among the 21 patients (34.4%) who tested negative, 6 cases (28.6%) were confirmed to have aggressive tumors.

For this category, the SelectMDx test demonstrated a sensitivity of 83.3%, a specificity of 36.4%, and a negative predictive value of 71.4% (p = 0.004).

Advanced analysis of the SelectMDx test performance and clinico-biological correlations

At the same time, we observed that serum PSA levels were significantly higher among patients with a positive SelectMDx test result. Specifically, the median PSA value in this group was 7.1 ng/mL (IQR: 4.2–10.1), compared to 5.14 ng/mL (IQR: 4.09–7.00) in the negative test group (p = 0.012; Table 12.3). This difference supports the premise that SelectMDx tends to express its predictive potential more clearly in the presence of a mildly altered biochemical context.

Table 12.3. Comparison of PSA values according to prostate cancer presence

Cancer	**Mean ± SD**	**Median (IQR)**	**Mean rank**	**p***
Absent (p<0.001)**	7.17 ± 4.44	5.7 (4.25-8.85)	63.60	0.962
Present (p<0.001)**	7.32 ± 5.02	6.4 (3.45-8.69)	63.26	

***Mann-Whitney U Test, **Shapiro-Wilk Test**

Discussion

The results of this second analysis reinforce that SelectMDx has real potential as a non-invasive risk stratification tool, particularly in clinical scenarios where traditional markers (like PSA) lack specificity**.**. To fully establish its clinical value, larger multicenter studies are needed, incorporating diverse populations and defining region-specific thresholds. Given that this study provides the first validation of SelectMDx in Romania, a logical next step is a prospective multicenter trial across Southeastern Europe. Such

transnational validation would strengthen data robustness and facilitate broader clinical integration within European diagnostic algorithms.

While this study offers significant insight into SelectMDx utility in the Romanian population, several methodological limitations must be acknowledged — particularly sample size and single-center design.

In conclusion, our data strongly support the clinical utility of the SelectMDx test in Romanian practice.

Its performance in optimizing biopsy indication, especially in intermediate-risk cases, suggests that SelectMDx may become a cornerstone in precision medicine for urologic oncology.

Study 3: SelectMDx – A Complementary Molecular Tool in Optimizing Diagnostic Management of PI-RADS 3 Lesions Identified by mpMRI

Results

Among patients with PI-RADS 3 scores (n = 40), a statistically significant association was observed between SelectMDx results and the presence of clinically significant prostate cancer.As illustrated in Figure 13.1, 57.1% of patients with a positive SelectMDx result were diagnosed with prostate cancer, compared to only 18.2% of those with a negative result ($p = 0.031$). Conversely, cancer absence was confirmed in 81.8% of patients with negative results, highlighting the potential role of SelectMDx in ruling out malignancy and reducing unnecessary biopsies, thereby emphasizing the negative predictive value (NPV) of

SelectMDx in equivocal imaging lesions.

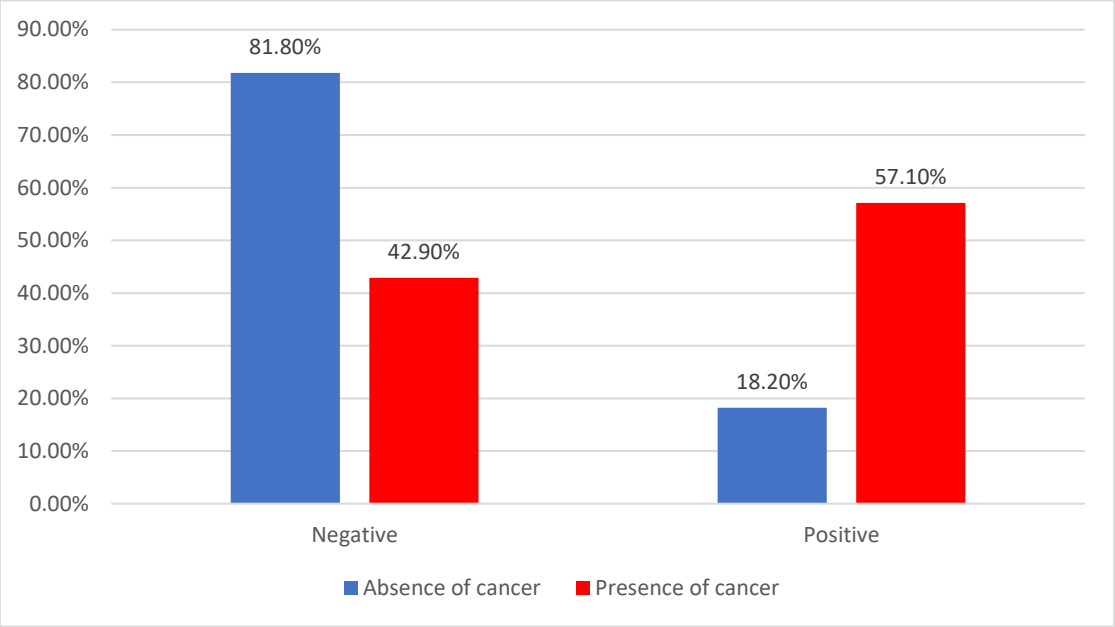

Figure. 13.1 Distribution of patients with PI-RADS = 3 score according to prostate cancer presence and SelectMDx test result

In the subgroup of patients with PI-RADS 3 lesions, the SelectMDx test showed noteworthy diagnostic performance. Specifically, it achieved a sensitivity of 57.14%, a specificity of 81.82%, a positive predictive value (PPV) of 40%, and a negative predictive value (NPV) of 90%. The overall diagnostic accuracy of the test in this setting was 77.5%, suggesting a meaningful ability to rule out clinically significant disease when the result is negative..

Serum PSA levels did not differ significantly between patients with and without cancer (median PSA: 5.3 ng/mL vs. 5.14 ng/mL, p = 0.326).

However, age emerged as a significant differentiating factor.

Patients diagnosed with prostate cancer had a median age of 67 years (IQR: 67–69), significantly higher than those without malignancy (61 years, IQR: 57–66.5; p = 0.012).

This finding suggests that age remains a key variable in oncologic risk assessment, even among patients with equivocal imaging findings.

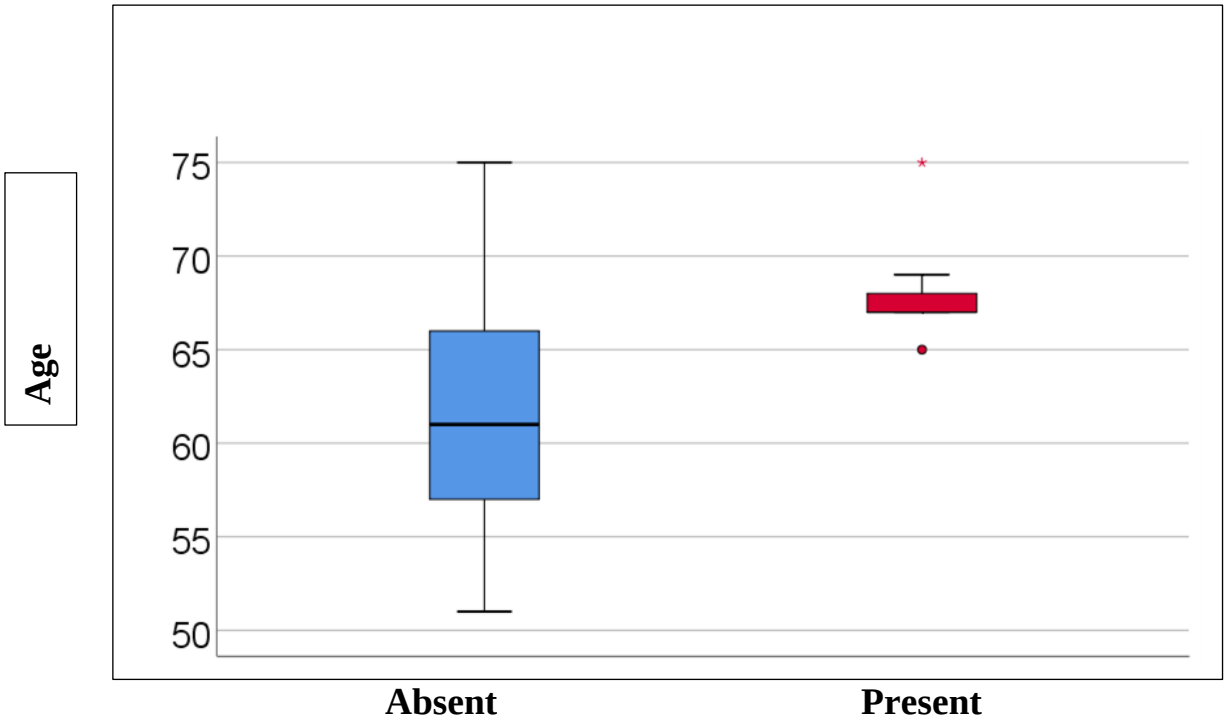

Figure 13.3. Comparison of patient age according to prostate cancer presence among patients with PI-RADS = 3 score

Regarding family history, no statistically significant association was found between familial risk and cancer presence (p = 0.134), though a numerically higher frequency of positive family history was observed among patients with positive SelectMDx results.

Table 13.1. Distribution of patients with PI-RADS = 3 score according to prostate cancer presence and family history

Cancer/ Family History	**Absent**		**Present**		**p***
	Nr.	**%**	**Nr.**	**%**	
No family history	31	93.9%	5	71.4%	0.134
With family history	2	6.1%	2	28.6%	

In the subgroup with negative SelectMDx results, the vast majority (90%, 27/30) were confirmed cancer-free on histopathology.

Notably, none of these patients reported a positive family history of prostate cancer. (Figure 13.4)

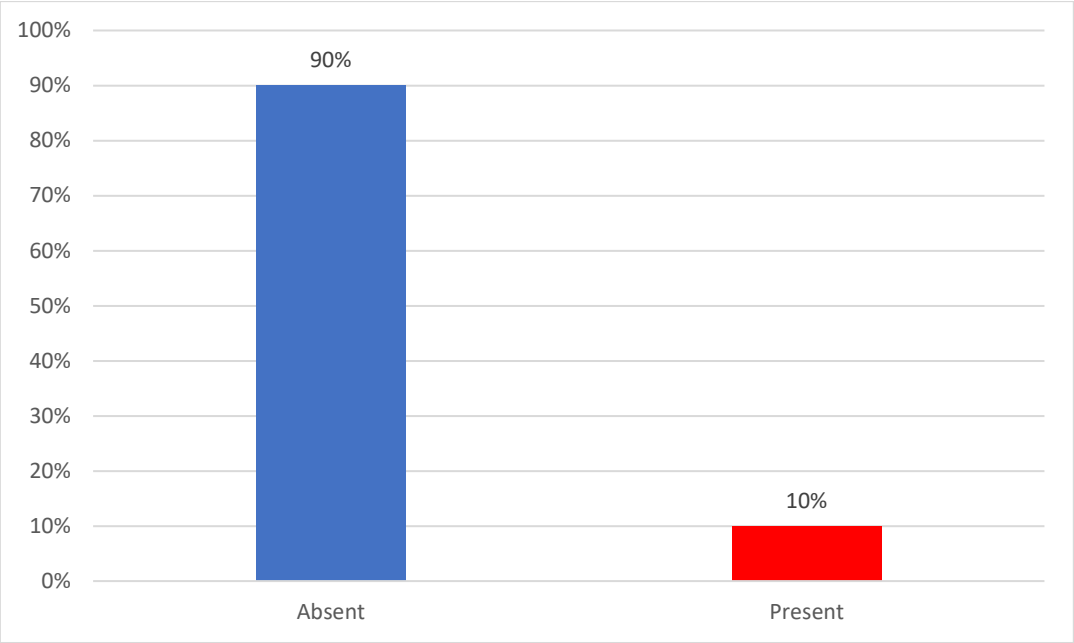

Figure 13.4. Distribution of patients with negative SelectMDx result and PI-RADS = 3 score according to prostate cancer presence

Discussion

Over recent decades, prostate cancer diagnostic strategies have undergone a major paradigm shift, emphasizing the integration of advanced imaging techniques and non-invasive molecular biomarkers to refine clinical decision-making and reduce unnecessary biopsies [7].

Within this modern framework, the urinary SelectMDx test offers distinct clinical utility, especially in equivocal cases such as PI-RADS 3 lesions detected on mpMRI.

In this cohort, SelectMDx achieved a high negative predictive value (90%), supporting its role as a triage tool to safely exclude malignancy and minimize overdiagnosis and overtreatment.

Although the ROC curve obtained in our study did not reach statistical significance—most likely due to the limited sample size—our estimates for sensitivity and specificity align with multicenter reports that documented AUC values between 0.75 and 0.85 [8].

Interestingly, SelectMDx did not emerge as an independent predictor in multivariate logistic regression, where age was the sole significant factor.

No significant association was found between PSA, prostate volume, or PSA density and cancer presence in this subgroup, raising questions about the clinical relevance of these traditional markers in PI-RADS 3 evaluation.

Despite encouraging findings, several limitations must be acknowledged:

The small sample size of PI-RADS 3 patients limits statistical power;

Cost-effectiveness was not assessed, though it represents an essential factor for clinical adoption.

Overall, SelectMDx appears to be a valuable complementary tool in managing PI-RADS 3 lesions, enabling a more personalized and evidence-based approach.

To confirm these conclusions and establish practical recommendations, prospective multicenter studies with larger cohorts and integrated economic analyses are warranted..

Conclusions and Personal Contributions

Context and Justification

This research was not conceived as a mere academic exercise, but rather arose from a genuine clinical need frequently encountered in urological practice in Romania: how to decide, with greater confidence and fewer risks, when a prostate biopsy is truly indicated. Particularly in situations where the patient falls into a "gray zone" — with PSA values in the intermediate range and inconclusive imaging findings (such as a PI-RADS 3 score) — the decision becomes challenging, often guided more by uncertainty than by solid evidence. In these cases, biopsies are often performed "as a precaution," yet they carry psychological, logistical, and clinical burdens that should not be overlooked.

Through this study, our aim was not only to validate an already established diagnostic tool, but also to integrate it into a local clinical framework, demonstrating that precision medicine can be intelligently and responsibly applied even outside major Western medical centers.

Achievement of Scientific Objectives

In relation to the proposed objectives, we can state that the research has clearly met its goals:

• Objective 1: The evaluation of the sensitivity and negative predictive value of the SelectMDx test within the Romanian cohort confirmed the high performance levels reported in international literature, reinforcing the concept that this test can accurately exclude clinically significant prostate cancer among patients with intermediate risk.

• Objective 2: The analyses performed on clinical subgroups — patients with PSA <10 ng/mL, PI-RADS score ≤3, and no family history — revealed consistent results, demonstrating the applicability of the test even in cases where conventional parameters fail to provide diagnostic clarity.

• Objective 3: The exploration of integrating the test into a diagnostic algorithm tailored to Romanian clinical practice yielded strong conclusions regarding the role of

combining SelectMDx with the PI-RADS score and patient age as a decision-making model for equivocal lesions.

Technical and Economic Advantages and Limitations

Beyond its scientific validation, the results suggest that SelectMDx holds significant potential for current medical practice in Romania:

Advantages:

- Non-invasive and easy-to-perform test;
- Relatively low cost compared to mpMRI;
- Good performance in ruling out aggressive prostate cancers;
- Potential to avoid a substantial number of unnecessary biopsies.

Limitations:

- Moderate specificity — possible risk of false-positive results;
- Limited accessibility in certain centers;
- Requires interpretation in correlation with the clinical profile (age, prostate volume, PSA level).

Unresolved Issues

The research also brought to light several aspects that warrant further investigation:

• The absence of an age- and prostate volume–adjusted standardized threshold;

• The utility of the test in active surveillance remains insufficiently explored;

• Integration into an automated predictive model based on artificial intelligence is not yet available;

• Local cost-effectiveness data are still lacking, despite the economic potential suggested by current findings.

Future Directions

Based on the obtained results, the following directions are clearly outlined:

1. Multicentric validation across other regions of the country;
2. Integrated nomograms and AI models - based on age, prostate volume, PSA density, mpMRI findings, and SelectMDx results;

3. Economic evaluations - adapted to the real conditions of the Romanian healthcare system;
4. Applicability in active surveillance - particularly for low-risk patients;
5. Personalization of decision thresholds - adjusted according to each patient's individual characteristics.

Personal Contributions within the Research

This doctoral thesis represents not merely an applied analysis of a diagnostic tool, but a comprehensive endeavor that brings significant original contributions — with impact both clinically and methodologically. These contributions are neither theoretical nor speculative; they are supported by concrete data, obtained in a real-world clinical setting, and rigorously documented across multiple chapters of the thesis.

Local Validation of the SelectMDx Test in an Eastern European Population

This work represents the first concrete application of the SelectMDx test in a cohort of patients from Romania, investigated within a real-world clinical context rather than an idealized experimental setting.

The results obtained demonstrate that SelectMDx maintains its core performance characteristics — particularly regarding sensitivity and negative predictive value — even in the absence of advanced imaging resources such as state-of-the-art mpMRI, which is not yet available in all healthcare facilities across the country. Thus, SelectMDx not only provides substantial support in assessing oncologic risk but also proves its relevance within a healthcare system facing practical challenges, emerging as a valuable tool for optimizing the diagnostic pathway, especially in regions where imaging infrastructure remains limited.

Development of a Personalized Clinical Algorithm for PI-RADS 3

Within this research, we developed a clinical decision model that integrates three essential parameters: patient age, PI-RADS imaging score, and the molecular SelectMDx test result. This approach was specifically designed to address the challenges faced by the Romanian healthcare system, where resources may be limited and access to high-performance investigations is not always uniform**.**

Imaging–Molecular Synergy for Patient Stratification

This study represents, for the first time in Romania, a concrete demonstration of the effectiveness of combining the SelectMDx molecular test with mpMRI-based imaging assessment in patients with a PI-RADS 3 score — a frequently encountered yet diagnostically challenging category.

Exploring the Role of Clinical Factors in Test Optimization

We identified and demonstrated the significance of factors such as patient age and prostate volume in the interpretation of SelectMDx results. Statistical analysis revealed that age exerts a significant and independent influence on oncologic risk, supporting the concept of a personalized interpretation of test outcomes.

Comparative Analysis of Clinical Subgroups

We performed a stratified analysis of test performance based on clinical parameters such as PI-RADS score, PSA levels below 10 ng/mL, and family history.

Originality and Clinical Impact

All these contributions converge toward a concrete outcome: the definition of a practical, sustainable, and locally adapted solution for improving the diagnostic process of prostate cancer in Romania.

We demonstrated that SelectMDx can become more than a standalone test — it can serve as the core of an intelligent clinical algorithm, in which decision-making is informed and evidence-based, relying not solely on a single serum marker (such as PSA), but on a coherent combination of clinical, imaging, and molecular data.

Institutional context and integration within national research initiatives

This doctoral thesis was carried out within a broader institutional initiative aimed at supporting excellence in research and innovation in the field of healthcare. The scientific activity presented is directly related to the project “Supporting RDI Excellence in the Field of Health and Enhancing the Competitiveness of the ‘Carol Davila’ University of Medicine and Pharmacy in Bucharest to Achieve the Status of European Regional Leader”, conducted under Program 1 – Development of the National Research and Development System, Subprogram 1.2 – Institutional Performance.Within this project, the research was conducted along the strategic direction of the “Health” domain, during the period 03.01.2022 – 14.06.2024, through the dedicated subproject:“The Value of Genetic Tests in the Diagnostic Protocol of High-Risk Prostate Adenocarcinoma (Gleason Score ≥7)”.

This scientific activity has been directly aligned with the objectives of the National Cancer Control Plan of Romania, a strategic document emphasizing the need to promote early diagnosis and the use of modern, non-invasive, and safe technologies — particularly in the field of prostate cancer.

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