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OPTIMIZING PROSTATE CANCER DIAGNOSTICS: CAN BIOMARKERS DECREASE THE BURDEN OF OVER-INVESTIGATION?

Mikołaj Kurczyński *(Corresponding Author, Email: inversusikjam@gmail.com)*
Central Teaching Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
ORCID ID: 0009-0005-6484-6229

Aleksandra Suszczyńska
"UNIDENT" Dental Clinic, Dąbrowa Tarnowska, Poland
ORCID ID: 0009-0009-0923-8529

Angelika Wiatr
Central Teaching Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
ORCID ID: 0009-0002-0202-4535

Ksenia Jakubiak
Central Teaching Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
ORCID ID: 0009-0003-0291-9942

Julia Witkowska
Central Teaching Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
ORCID ID: 0009-0008-6106-9665

Ewa Wojtanowska
Central Teaching Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
ORCID ID: 0009-0007-4813-9473

Aleksandra Pietrucień
Medical Center of Pabianice, ul. Jana Pawła II 68, 95-200 Pabianice, Poland
ORCID ID: 0009-0000-5777-3301

Monika Krasoń
Central Teaching Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
ORCID ID: 0009-0000-5571-9440

ABSTRACT

The foundation of current prostate cancer diagnostics still remains the interpretation of total PSA (tPSA) results, but it is an imperfect test due to its low specificity and diagnostic ambiguities in patients within the "gray zone," meaning patients with a result of (2.0/4.0–10.0 ng/mL). This fact leads to many cases of "overdiagnosis" and an excess of unnecessarily performed biopsies. This article summarizes the diagnostic value of blood-based biomarkers and tests (PHI, 4Kscore, Stockholm3) as well as urine-based ones (SelectMDx and ExoDx). These tests achieve high AUC values (0.76–0.88) and a high negative predictive value (up to 98%) in detecting clinically significant prostate cancer (csPCa, GG ≥ 2), underscoring their advantage over traditional methods. Combining them with multiparametric MRI allows for a 30–65% reduction in unnecessary biopsies while maintaining high oncological safety for the patient. Despite promising results, the high costs of individual tests, lack of reimbursement, and absence of full standardization in international urological guidelines remain a continuous challenge and a hurdle to their introduction into daily practice.

KEYWORDS

Prostate Cancer, Biomarkers, Biopsy, Multiparametric MRI (mpMRI), Prostate Health Index (PHI), 4Kscore, Stockholm3, ExoDx, SelectMDx

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Introduction

The contemporary approach to prostate cancer is changing; the PSA test is no longer the only known marker of prostate diseases, but rather opens the way toward a personalized and multi-stage diagnostic pathway.

The PSA test has been widely used for many years, but it is characterized by low specificity, which brings with it the overperformance of unjustified magnetic resonance imaging (mpMRI) scans and biopsies in patients with low-grade malignancies.

The overperformance of unnecessary examinations creates a clear need for a new and effective patient triage system. Multiparametric magnetic resonance imaging (mpMRI), which has improved the detection of clinically significant prostate cancer, is unfortunately also associated with inter-observer variability, a high rate of ambiguous PI-RADS 3 results, and high costs.

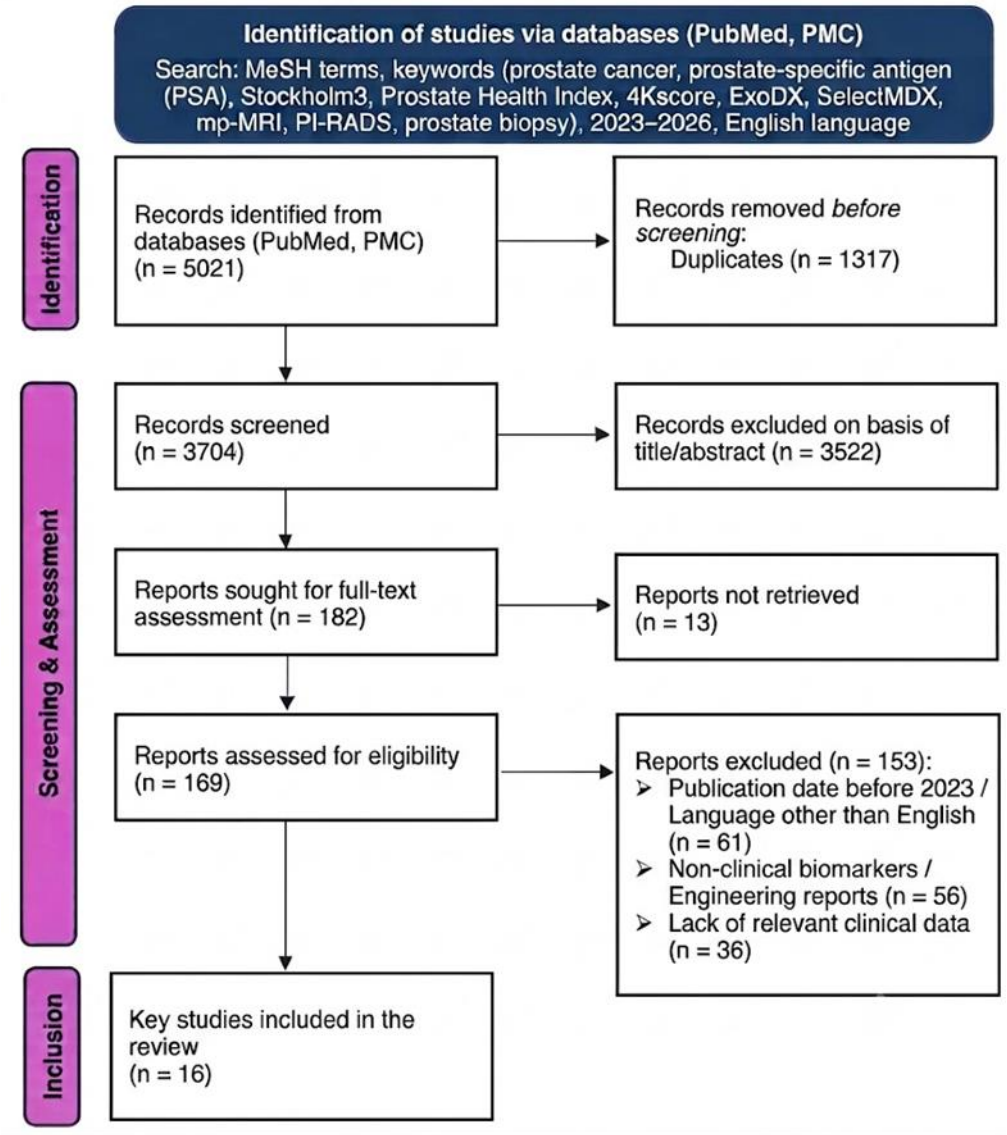
In recent years (i.e., 2023–2026), urine-based markers and tests (ExoDx and SelectMDx) and blood-based ones (PHI, 4Kscore, Stockholm3) helpful in detecting prostate cancer are starting to play an increasingly important role in the modern diagnostic process of clinically significant prostate cancer. These tests select patients during the diagnostic process and limit the number of biopsies, which are associated with dangerous complications for the patient, while also reducing the performance of unnecessary multiparametric MRI scans, thereby increasing availability for patients who need it more urgently.

This review aims to analyze and summarize current knowledge regarding the latest diagnostic solutions based on the detection of serum and urine biomarkers, which can contribute to patient triage and isolate those with clinically significant cancer, while reducing the stress and discomfort associated with invasive procedures for patients who do not require them. At the same time, biomarkers may in the future contribute to lowering healthcare costs associated with "over-investigation," meaning overdiagnosis.

Methods

This review paper was created based on research and review papers located in the PubMed and PubMed Central (PMC) databases. The selection of the searched papers focused on the latest achievements, measurable effects, and utility in clinical practice and the diagnosis of prostate cancer (PCa). The literature search was based on a combination of MeSH terms and keywords such as: prostate cancer, prostate-specific antigen (PSA), Stockholm3, Prostate Health Index, 4Kscore, ExoDX, SelectMDX, multiparametric MRI (mp-MRI), PI-RADS, and prostate biopsy.

Inclusion criteria were English-language articles published from 2023 to 2026. Studies on non-clinical biomarkers, engineering reports without clinical validation, and duplicates were excluded. Sixteen full-text articles were ultimately selected.



Blood biomarkers

PHI – Prostate Health Index

Use of PHI (Prostate Health Index) is a multiparametric algorithm developed to increase the diagnostic specificity of the traditional PSA (Prostate-specific Antigen) assay.

The index includes:

- tPSA (total PSA)
- fPSA (free PSA fraction)
- p2PSA ([-2]proPSA isoform)

What is the p2PSA isoform? It is a proteolytically stable precursor of free PSA, whose expression is significantly more frequently demonstrated in neoplastic tissues than in benign prostatic hyperplasia (BPH).

Formula:

$$\mathrm{PHI} = \left(\frac{\mathrm{p2PSA}}{\mathrm{fPSA}}\right) \times \sqrt{\mathrm{tPSA}}$$

allows for determining the ratio of the concentration of markers associated with malignant changes relative to components occurring in benign conditions; this reflects qualitative biological changes of the cancer independently of the gland volume itself.

The PHI test is intended for the diagnosis of men aged ≥50 years with a negative digital rectal examination (DRE), whose tPSA concentration falls within the so-called "diagnostic gray zone" (most commonly defined as 4.0–10.0 ng/mL). As recent clinical reports indicate, the PHI test is also useful in patients with persistent PSA elevation in whom multiparametric MRI (mpMRI) showed no focal lesions (PI-RADS <3) or in whom a previous fusion biopsy yielded a negative result despite existing clinical doubts (Jeon et al., 2025).

What diagnostic advantage does the PHI test have over traditional markers?

In cohort studies, the PHI test demonstrates a significant advantage over classic markers (tPSA, %fPSA) (Zhong et al., 2026). In the general diagnostic population, the ROC (AUC) for PHI in detecting prostate cancer (PCa) reaches high values (approx. 0.85 vs. 0.75 for tPSA), and in detecting clinically significant cancer (csPCa, clinically significant prostate cancer, Gleason score ≥ 3+4), the AUC value increases to approximately 0.88. Importantly, PHI maintains a stable predictive value at an AUC level of approx. 0.78 in the PSA "gray zone," where the efficacy of regular tPSA drops sharply (AUC < 0.60). Values in the range of 40–45 are accepted as optimal cut-off points for the patient population, ensuring high sensitivity with balanced specificity (Jeon et al., 2025; Zhong et al., 2026). When PHI density (PHID, PHI/prostate volume) is additionally incorporated into the PHI test, it correlates even more strongly with the presence of cancer in multivariate analyses.

The use of PHI allows for limiting overdiagnosis and reduces the number of unnecessary biopsies by 30–40% while maintaining 90% sensitivity for csPCa. Integrating low PHI values with ambiguous findings on mpMRI (PI-RADS 3) enables the safe deferral of biopsy in favor of active patient surveillance (Hatakeyama et al., 2026).

The lack of a universal cut-off point for different ethnic groups, the influence of inflammatory states and medications (e.g., 5-alpha-reductase inhibitors) on distorting results, as well as the requirement for strict pre-analytical standardization of p2PSA are among the main limitations. The PHI index holds recommendations from leading urological societies and FDA approval as a key pre-biopsy triage tool.

4Kscore

The 4Kscore test is a test performed on peripheral blood. It is used to determine the individual risk of developing clinically significant prostate cancer (≥ 2 according to the ISUP/Grade Group classification). This modern test panel consists of 4 plasma kallikreins: - total PSA (tPSA), - free PSA (fPSA), - intact PSA (iPSA), - human kallikrein 2 (hK2) (Scuderi et al., 2023).

The multivariate mathematical formula includes the obtained biomarker concentrations and incorporates key patient data, such as age, digital rectal examination (DRE) status, and information regarding a prior negative prostate biopsy.

The result is expressed as a percentage (from 0% to 100%) and reflects the probability of detecting an aggressive proliferative disease.

The target group consists of men who present with an elevated total PSA level (tPSA ≥3.0 or 4.0 ng/mL) or abnormalities detected during a digital rectal examination (DRE). The 4Kscore can be considered a second-line test and can aid in decision-making regarding whether or not to perform a biopsy or an mpMRI (Josefsson et al., 2024).

The test finds particular utility in screened populations and in patients with an ambiguous diagnostic picture.

The negative predictive value (NPV) and sensitivity are high in detecting tumors with a malignancy grade of GG ≥ 2.

The 4Kscore result cut-off points are closely linked to mpMRI findings:

- When the resonance imaging indicates a low probability of the presence of clinically significant cancer (PI-RADS ≥ 2), a 4Kscore result of ≤ 33% is the cut-off point, a safety margin for the patient—when this value is exceeded, there is a sharp increase in the risk of a high-grade lesion (de Almeida et al., 2023).
- In the case of an ambiguous result (PI-RADS 3), the cut-off point drops to a value of ≥8%, which obligates the physician to perform a histopathological examination for verification (de Almeida et al., 2023).

The 4Kscore test, when combined with mpMRI findings, age, and blood tPSA concentration, significantly increases the area under the ROC curve (AUC) from a value of 0.7 to 0.85, indicating the high diagnostic value of this tool.

The primary advantage of the clinical utilization of 4Kscore is its ability to safely limit the number of invasive medical procedures. It has been proven that the implementation of the test allows for reducing the number of performed prostate biopsies by nearly two-thirds in routine practice. Population estimates (e.g., in the USA with approx. 70,000 tests annually) indicate the avoidance of over 45,000 unnecessary biopsies and overdiagnosis by nearly 9,400 cases per year of insignificant, clinically slow-growing cancers (GG1) (Scuderi et al., 2023). Furthermore, the implementation of the 4Kscore test allows for limiting the number of referrals for expensive mpMRI examinations that burden the healthcare system.

Despite its advantages, this test possesses certain limitations. The decision to forgo a biopsy based on low 4Kscore results carries a risk of missing or delaying the diagnosis of a high-grade cancer (GG≥2) in a small percentage of men (estimated at approx. 3,400 cases annually across large populations, the majority of which are tumors of moderate aggressiveness, GG2). Moreover, although 4Kscore exhibits synergy with mpMRI, there is unfortunately still a lack of rigid international guidelines that would explicitly position these two tools within diagnostic algorithms. Currently, this test is treated as a highly useful auxiliary examination that requires individual medical interpretation within the context of the patient's overall risk profile.

Stockholm3

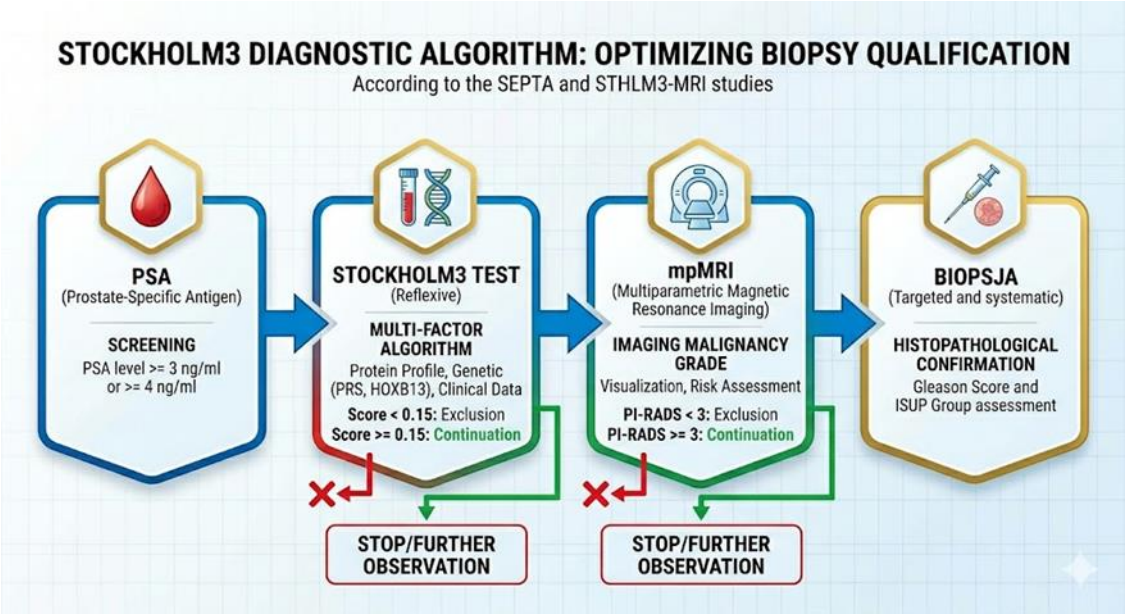
The Stockholm3 (S3M) test is a modern tool based on a multivariate algorithm that refines the risk estimation of developing clinically significant prostate cancer (csPCa, defined as a tumor with a malignancy grade of ≥2 according to the ISUP group / Gleason score ≥ 3+4). The Stockholm3 test consolidates information from 3 independent data panels:

- the first panel consists of clinical data, namely: age, family history (proliferative changes in first-degree relatives), and results regarding previous negative biopsies, if any have been performed (Brooks, 2024),
- the next panel aggregates information regarding plasma protein concentrations: tPSA, fPSA, human kallikrein 2 (hK2), growth differentiation factor 15 (GDF15), and prostate secretory protein 94 (PSP94) (Brooks, 2024),
- the final panel is the genetic profile: the HOXB13 germline variant and a polygenic risk score calculated on the basis of 100 single nucleotide polymorphisms (SNPs) associated with prostate cancer (Brooks, 2024).

The Stockholm3 algorithm is intended for men aged 50 to 74 years who have not been previously diagnosed with prostate cancer, but whose serum tPSA concentration is moderately elevated (≥3 ng/mL or ≥ 4) (Björnebo et al., 2024). It serves as a second-line test that aids in decision-making regarding further in-depth diagnostics (mpMRI, biopsy). Furthermore, the SEPTA study (Vigneswaran et al.) conducted on a group of Black, Asian, and Hispanic patients demonstrated its high reliability and applicability regardless of the patient's ethnic background (Brooks, 2024).

The diagnostic value of the Stockholm3 test significantly exceeds the measurement of tPSA alone. It achieves an area under the ROC curve (AUC) of 0.76, whereas the value for tPSA alone is 0.6. The cut-off point for a Stockholm3 score of ≥0.15 is characterized by a significantly higher positive predictive value (PPV = 28.8%) compared to PSA≥ 3 ng/mL (PPV = 17.6%), while maintaining a similar sensitivity in detecting aggressive forms of the cancer.

Stockholm3 leads to a reduction in performed biopsies by 42% to 52% depending on the cohort, without the risk of missing clinically significant cases (Brooks, 2024). It reduces costs associated with multiparametric MRIs—which burden the healthcare budget—by one-third among men with elevated PSA, which also mitigates the problem of diagnostic ambiguity in regions with limited access to MRI equipment (Björnebo et al., 2024). The final, equally important aspect is the limitation of the detection of clinically insignificant cancers (Gleason 3+3 / ISUP 1), which do not affect the patient's life expectancy but burden them with unnecessary stress and the risk of unnecessary treatment (Björnebo et al., 2024).



The randomized STHLM3-MRI study (Björnebo et al.) showed that the use of the Stockholm3 test combined with biopsy alone (omitting MRI) generates 43% more of these invasive procedures than the optimal pathway with the sequence: Stockholm3 + mpMRI + targeted biopsy; moreover, this results in the detection of a higher number of low-grade cancers (Björnebo et al., 2024). Therefore, this test should not be a substitute for mpMRI, but should rather be treated as a screening tool prior to imaging (Björnebo et al., 2024).

The test is commercially available and is included in European guidelines as a tool supporting clinical decision-making, but the high unit cost of the test and the lack of widespread reimbursement in many healthcare systems remain a challenge.

Data from subsequent rounds of screening (Nordström et al.) indicate a decline in the detection rate of csPCa in repeat examinations (after 2–3 years), concurrent with a false-positive result of the PSA itself. This suggests that it may be justified to extend the intervals to 4–6 years between the first and second examination (Nordström et al., 2024).

Urinary biomarkers

SelectMDX

SelectMDX is a test based on examining the overexpression of the HOXC6 (Homeobox C6) and DLX1 (Distal-Less Homeobox 1) genes, which are typical for highly malignant tumor cells, by directly detecting their mRNA transcripts in urine (Wu et al., 2024). An advanced mathematical algorithm assesses the risk of the presence of a malignant form of the proliferative disease based on a combination of molecular data, clinical data, and classic parameters such as: tPSA, PSA density, prostate volume, age, family history of prostate cancer, and the result of the digital rectal examination (DRE). Together, the above data form a personalized risk score that determines the probability of detecting prostate cancer on the biopsy Gleason scale (Călinoiu et al., 2025).

The target group consists of men with an initial diagnosis of prostate cancer who are qualified for a primary or repeat biopsy after a previous negative targeted biopsy result. The main factor qualifying patients for the SelectMDX test is the so-called "gray zone," meaning tPSA results at a level of 4 to 10 ng/mL, a positive digital rectal examination (DRE), as well as patients with an equivocal, unclear result from a multiparametric magnetic resonance imaging (mpMRI) scan, for example, a PI-RADS 3 score (Soeterik et al., 2025).

Especially noteworthy is the very high negative predictive value (NPV) at a level of 95–98%, which in practice translates into the effective detection of only clinically significant prostate cancer (Gleason ≥7 or ISUP ≥2). The sensitivity of the test is estimated at a level of 93–96%, while the specificity is moderate, in the range of 49–53% (Wu et al., 2024). A high NPV with a negative SelectMDX result provides nearly 100% certainty regarding the exclusion of a malignant lesion and allows for a safe deferral of further invasive diagnostics (targeted biopsy).

Adding the SelectMDX test to the classic PSA assay substantially reduces the number of unnecessary over-performed biopsies by approximately 35–40%. It therefore serves as an additional triage tool that protects

patients with clinically insignificant (Gleason 6) cancer from infectious and hemorrhagic complications associated with biopsy. The test effectively verifies patients with benign prostatic hyperplasia (BPH) or inflammation alongside abnormalities in biochemical tests, which translates into increased savings within healthcare system budgets worldwide and the minimization of biopsy-related stress for the patient (Soeterik et al., 2025).

A limitation of the SelectMDX test is the necessity of an energetic prostate massage during the digital rectal examination, which releases cells and nucleic acids into the urine sample but may cause discomfort for the patient and generate variability between the personnel performing the procedure (Călinoiu et al., 2025). The moderate specificity of the test can yield false-positive results (e.g., in the case of large-volume adenomas), which requires clinical differentiation. The SelectMDX test should not be performed in isolation, but in combination with mpMRI, which together are capable of minimizing the margin of error from 10% (when performing SelectMDX alone) to 5% (with SelectMDX + mpMRI). The test is included in international guidelines as a recommended examination, but as an optional auxiliary biomarker performed before a biopsy, which is due to still high prices and a lack of reimbursement in global medical networks (Călinoiu et al., 2025).

ExoDX

This test, which is a liquid biopsy, represents an advanced diagnostic tool based on the quantitative detection of mRNA molecules such as PCA3 (characteristic of prostate cancer), ERG (a gene transcript indicating an aggressive disease course), and SPDEF (serving as an internal reference gene encoding a transcription factor - sample quality control) (Robaczyńska et al., 2026). These molecules are secreted by tumor cells into the urine within exosomes (Robaczyńska et al., 2026).

The target group consists of patients over 50 years of age presenting with a result in the "gray zone," i.e., tPSA of 2-10 ng/mL(Tutrone et al., 2023). The test is highly helpful in classifying patients for core needle biopsy to confirm or exclude neoplastic disease, as well as in patients with a prior negative biopsy result who present with clinical indications (mpMRI result - PI-RADS 3).

The test has a cut-off point at a level of 15.6 on a scale from 0 to 100 (Tutrone et al., 2023). A result below this value indicates a low risk of developing high-grade prostate cancer (Gleason ≥ 7 or GG ≥2) (Tutrone et al., 2023).

The test is also characterized by a high negative predictive value, i.e., the NPV for ≥ GG2 91%, whereas it is 97% for patients with ≥GG3 - this translates into a safe deferral of the biopsy procedure and the exclusion of clinically significant cancer (Tutrone et al., 2023).

Unlike other urine-based diagnostic tests, ExoDx does not require a prior digital rectal prostate massage, which ensures that the patient experiences no discomfort during the diagnostic process; this also improves the standardization of patient preparation before sample collection (Tutrone et al., 2023). Providing urologists with the EPI result significantly modifies the decision-making proces (Tutrone et al., 2023).

Men with scores <15.6 avoid undergoing a biopsy; long-term studies indicate a 30% reduction in performed procedures compared to the standard diagnostic pathway (Grobholz et al., 2025). Within a 2.5-year follow-up, oncological safety is confirmed, and the time to a potential first biopsy was extended threefold (from approximately 69 to 216 days), with a low rate of missed aggressive cases (Grobholz et al., 2025). On the other hand, the detection rate with a score above 15.6, i.e., in the group of patients at risk for clinically significant high-grade prostate cancer (HGPC), increases by nearly 27%.

The main issue with the test is its relatively low specificity and positive predictive value (PPV), which means that a high test score directs further diagnostic steps but is not synonymous with a definitive diagnosis of high-risk prostate cancer. The high costs of the test and low availability in the European Union are further barriers hindering the introduction of the test as a routine element of the diagnostic pathway (Grobholz et al., 2025).

Discussion

What is the primary challenge of contemporary urological oncology?

It is the low specificity of commonly assayed tPSA, which leads to the over-performance of invasive procedures such as core needle biopsy of the prostate; this exposes the patient to unnecessary complications, while the ultimate diagnosis in these patients is often benign prostatic hyperplasia (BPH) or inflammation. Implementing diagnostic algorithms of multiparametric liquid biomarkers from blood and urine in clinical practice effectively resolves this problem.

Can multiparametric diagnostic tests in blood and urine safely allow for the deferral of verifying an elevated tPSA result via biopsy?

Oncological safety is the key characteristic that permits the introduction of these tests into clinical practice. It is possible to exclude clinically significant cancer thanks to a satisfactory negative predictive value (NPV) at a level of 91-98% and safely defer invasive procedures.

The tests discussed in this paper are characterized by varying efficacy within a PSA range of 4–10 ng/mL, i.e., the so-called "gray zone." The PHI test demonstrates a stable predictive value (AUC approx. 0.78), whereas the efficacy of classic tPSA drops drastically (AUC< 0.60). Conversely, the Stockholm3 and 4Kscore tests combine biology with the patient's history and clinical status-including the results of previously performed biopsies, age, and family history (the Stockholm3 test additionally incorporates the patient's genetic profile-SNPs, HOXB13). An impressive result of a 42-60% reduction in the number of biopsies (depending on the cohort) represents a significant advantage over the PHI test, which reduces biopsies in 30-40% of cases.

SelectMDX and ExoDX, which are urine biomarkers, are also characterized by high efficacy, but there is one specific factor that constitutes a fundamental practical advantage of the ExoDX test-the lack of necessity for a digital rectal prostate massage (DRE). During this procedure, the patient may experience pain and discomfort. This procedure also introduces another serious problem-pre-analytical standardization, which can be hindered by operator manual variability; ExoDX therefore eliminates the human factor, facilitating standardization.

A highly important aspect of the discussion is the comparison of biomarkers and multiparametric MRI. The data presented above (e.g., the STHLM3-MRI study) clearly prove that multiparametric MRI is indispensable, and no marker will displace it on its own. The best and most complete clinical pathway is to use biomarkers as screening tools to qualify patients for the next stage, which is mpMRI, followed by a potential targeted biopsy in high-risk patients. Such a management model reduces the probability of diagnostic error to just 5% (as seen with the combination of SelectMDX + mpMRI) and aids in decision-making during diagnostics when facing equivocal PI-RADS 3 results.

These methods enjoy FDA approval and are included in European guidelines; however, their implementation from a clinical perspective remains a systemic and biological challenge-primarily due to the moderate specificity of the tests (large adenomas can yield false-positive results).

Test results are not indifferent to used medications, such as 5-alpha-reductase inhibitors, and another issue is the lack of a universal cut-off point for the PHI test across different ethnic groups. From an economic standpoint, these tests are very expensive, and healthcare systems do not reimburse them. Regions struggling with limited access to MRI could be unburdened by these tests, but as long as their unit cost remains very high, their role will be limited to commercial diagnostic support tests. Another question is how often these tests should be repeated and for how long a result excluding prostate cancer can allow for safe observation of the patient. Recent reports suggest that to avoid false-positive results resulting from PSA fluctuations, the intervals between subsequent rounds of testing (e.g., for Stockholm3) should be between 4 and 6 years.

Conclusions

Modern blood and urine biomarkers (PHI, 4Kscore, Stockholm3, SelectMDX, ExoDX) have revolutionized the approach to patients whose tPSA result is moderately elevated. They have significantly reduced the number of unnecessarily performed biopsies by 30% up to even 60%, thereby eliminating the overdiagnosis of clinically insignificant tumors, which translates into healthcare savings. A high negative predictive value (NPV) at a level of 91-98% almost certainly guarantees high oncological safety and allows for the deferral of invasive procedures while excluding aggressive forms of the disease. Biomarkers serve as an excellent adjunct to mpMRI imaging within the diagnostic pathway, particularly in the case of equivocal lesions on the PI-RADS 3 scale.

Thanks to tests like Stockholm3 which, by combining several components (polygenic risk profile information, patient clinical data, assaying protein molecules of PSA isoforms and kallikreins, alongside the

result of multiparametric MRI), leads to an increase in diagnostic precision and a reduction of the margin of error to just 5%.

Among urine-based assays such as the ExoDX or SelectMDX tests, patient comfort should also be a significant factor determining the choice of a given test. The ExoDX test holds a practical clinical advantage because it does not require a prostate massage, which in the case of SelectMDX can pose a problem regarding the pre-analytical standardization of the sample.

These tests meet with recommendation and approval from leading urological societies due to their high diagnostic value. However, they cannot yet be fully integrated into daily clinical practice and routine management algorithms due to the current high unit cost of the assays, the lack of reimbursement, the risk of false-positive results in patients with large adenomas or inflammation, and due to the use of certain medications that disrupt the biochemical profile (5-alpha-reductase inhibitors).

Author's Contribution:
Conceptualization: Mikołaj Kurczyński, Ksenia Jakubiak.
Methodology: Aleksandra Pietruceń, Julia Witkowska.
Formal Analysis: Ewa Wojtanowska, Ksenia Jakubiak.
Sources: Aleksandra Suszczyńska, Angelika Wiatr.
Visualisation: Monika Krasoń, Julia Witkowska.
Investigation: Aleksandra Pietruceń, Ksenia Jakubiak
Supervision: Aleksandra Suszczyńska, Angelika Wiatr.
Validation: Julia Witkowska, Monika Krasoń.
Writing – Review & Editing: Mikołaj Kurczyński, Ksenia Jakubiak
Project administration: Ewa Wojtanowska, Ksenia Jakubiak

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