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PRACA POGLĄDOWA
REVIEW

Prostate cancer biomarkers: Review, clinical availability, and importance in reducing unnecessary biopsies

Biomarkery raka prostaty – przegląd, dostępność kliniczna i znaczenie w ograniczaniu niepotrzebnych biopsji

Przemysław Kubicki[1], Hanna Raś[2], Maria Greniuk[3], Katarzyna Jankowska[1]

[1]4. Wojskowy Szpital Kliniczny z Polikliniką SPZOZ we Wrocławiu / 4th Military Clinical Hospital in Wroclaw, Poland
[2]Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii, Wrocław / Lower Silesian Center for Oncology, Pulmonology and Hematology, Wroclaw, Poland
[3]Jan Mikulicz-Radecki University Clinical Hospital, Wroclaw, Poland

ABSTRACT

INTRODUCTION: Prostate cancer is one of the most common cancers diagnosed in men, especially in older age groups. Although prostate specific antigen (PSA) remains the most widely used screening tool, its low specificity often leads to unnecessary biopsies and treatment of harmless conditions. This review aims to present and compare the currently available prostate cancer biomarkers, focusing on how they can help reduce the number of unnecessary biopsies by improving the accuracy of diagnosis.

MATERIAL AND METHODS: A thorough analysis of the literature on key biomarkers was conducted: total PSA, percentage of free PSA (%fPSA), Prostate Health Index (PHI), 4-Kallikrein score (4Kscore), prostate cancer gene 3 (PCA3), Select Molecular Diagnostics test for prostate cancer risk assessment (SelectMDx), and ExoDx Prostate IntelliScore (EPI). Data regarding their sensitivity, specificity, diagnostic cut-off values, and real-world use were reviewed. Their availability and costs in Poland and across Europe were also examined.

RESULTS: While traditional PSA testing is highly sensitive (~93%) and can detect most cases of cancer, it lacks precision (~20% specificity), often flagging non-cancerous conditions. Newer tests are more reliable: %fPSA improves specificity up to 40%; PHI offers a balance of 75% sensitivity and 69% specificity; 4Kscore can reach up to 90% sensitivity and 76% specificity. Other tests, such as PCA3, SelectMDx, and EPI, also show promising results. These tools help doctors better identify which patients are truly at higher risk of aggressive prostate cancer and which can safely avoid a biopsy. However, their high price and limited reimbursement in public healthcare systems – especially in Poland – remain major obstacles.

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Address for correspondence: Przemysław Kubicki, 4. Wojskowy Szpital Kliniczny z Polikliniką SPZOZ, ul. Rudolfa Weigla 5, 50-981 Wrocław, e-mail: przemyslaw.m.kubicki@gmail.com

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CONCLUSIONS: Modern biomarkers significantly improve the accuracy of prostate cancer detection compared to PSA alone. They can help many men avoid unnecessary and invasive procedures. Combining these tests with clinical evaluations and imaging may further improve diagnosis. To make them more widely available, we need more research, better funding, and official clinical recommendations.

KEYWORDS

prostate cancer, biomarkers, PSA, PHI, 4Kscore, PCA3, SelectMDx, ExoDx, unnecessary biopsies, diagnostic ccuracy

STRESZCZENIE

WSTĘP: Rak prostaty jest jednym z najczęściej diagnozowanych nowotworów u mężczyzn, zwłaszcza w starszych grupach wiekowych. Chociaż antygen specyficzny dla prostaty (*prostate specific antigen* – PSA) pozostaje najczęściej stosowanym narzędziem do badań przesiewowych, jego niska swoistość często prowadzi do niepotrzebnych biopsji i leczenia stanów niegroźnych dla zdrowia. Celem przeglądu jest przedstawienie i porównanie dostępnych biomarkerów raka prostaty, ze szczególnym uwzględnieniem tego, w jaki sposób mogą one przyczynić się do zmniejszenia liczby niepotrzebnych biopsji poprzez poprawę dokładności diagnozy.

MATERIAŁ I METODY: Przeprowadzono analizę literatury dotyczącej kluczowych biomarkerów: całkowitego PSA, procentowego udziału wolnego PSA (*percentage of free* PSA – %fPSA), wskaźnika zdrowia prostaty (Prostate Health Index – PHI), testu 4 kallikrein w ocenie ryzyka raka prostaty (*4-Kallikrein score* – 4Kscore), genu raka prostaty 3 (*prostate cancer gene 3* – PCA3), selektywnego testu diagnostyki molekularnej do oceny ryzyka raka prostaty (*Select Molecular Diagnostics test for prostate cancer risk assessment* – SelectMDx) i ExoDx Prostate IntelliScore (EPI). Przeanalizowano dane dotyczące ich czułości, swoistości, progów diagnostycznych i praktycznego zastosowania. Zbadano również ich dostępność oraz koszty w Polsce i w Europie.

WYNIKI: Chociaż badanie PSA jest bardzo czułe (~93%) i pozwala wykryć większość przypadków raka, jego precyzja jest niska (swoistość ~20%), często też wskazuje stany niezwiązane z rakiem. Nowsze testy są bardziej wiarygodne: %fPSA może zwiększyć swoistość diagnostyczną do 40%, w zależności od przyjętego punktu odcięcia; PHI oferuje równowagę między czułością 75% i swoistością 69%; 4Kscore może osiągnąć czułość do 90% i swoistość 76%. Inne testy, takie jak PCA3, SelectMDx i EPI, również dają obiecujące wyniki. Narzędzia te pomagają lekarzom lepiej identyfikować pacjentów, którzy rzeczywiście są narażeni na większe ryzyko wystąpienia agresywnego raka prostaty, oraz tych, którzy mogą bezpiecznie uniknąć biopsji. Jednak wysoka cena testów i ograniczona refundacja w publicznych systemach opieki zdrowotnej – zwłaszcza w Polsce – pozostają istotnymi przeszkodami.

WNIOSKI: Nowoczesne biomarkery znacząco poprawiają dokładność wykrywania raka prostaty w porównaniu z samym PSA. Mogą pomóc uniknąć niepotrzebnych i inwazyjnych procedur. Połączenie tych testów z ocenami klinicznymi i obrazowaniem może dodatkowo wpłynąć na lepszą diagnostykę. Aby stały się one szerzej dostępne, potrzeba więcej badań, lepszego finansowania i oficjalnych zaleceń klinicznych.

SŁOWA KLUCZOWE

rak prostaty, biomarkery, PSA, PHI, 4Kscore, PCA3, SelectMDx, ExoDx, niepotrzebne biopsje, dokładność diagnostyczna

Introduction

Prostate cancer is one of the most frequently diagnosed malignancies in men, particularly affecting societies where the average age of the population is steadily increasing [1,2]. In Poland, prostate cancer is the second most common malignant neoplasm in men (after lung cancer), while in the United States it is now the most frequently diagnosed cancer in men; its incidence almost doubles that of lung cancer [3]. Prostate specific antigen (PSA) measurement is now a standard part of screening, but its limited specificity causes many patients to undergo unnecessary biopsies and experience unnecessary exposure to side effects [4,5]. As a result, only about 25% of men referred for biopsy because of elevated PSA levels have histopathologically confirmed prostate cancer. Therefore, there is increasing emphasis on avoiding unnecessary biopsies and reducing over-diagnosis [5]. In daily clinical practice, the question of how best to qualify patients for biopsy is increasingly being asked. This review was prompted by the need to organize the available knowledge on prostate cancer biomarkers that can support this decision.

Prostate cancer markers

Classic marker PSA

The classic marker used in prostate cancer diagnosis is PSA. Despite its high sensitivity (93%), it has low specificity. It detects most cases of cancer, but at the same time does not distinguish them well from benign lesions; hence the low specificity: only 1 in 5 positive results is actually cancer [6]. The limitations of this test in differentiating between cancer and benign pro-

liferation of the prostate have prompted the search for more specific indicators.

Percentage of free PSA

Using the percentage of free PSA (%fPSA) to total PSA improves the specificity of diagnosis, especially in patients in the "gray zone" (PSA = 4–10 ng/ml). If the %fPSA falls below 25%, we can expect a sensitivity of up to 95%. Moreover, the specificity compared to classic PSA also increases markedly – sometimes doubling – depending on the population under study [7]. This makes it possible to reduce the number of unnecessary biopsies.

Prostate Health Index

The advent of more advanced diagnostic indices such as the Prostate Health Index (PHI) further supports clinical decisions. The PHI combines three indices: total PSA, free PSA, and the more modern [-2]proenzyme PSA ([-2]proPSA). It achieves a sensitivity of 75% and a specificity of 69% with PHI cutoff values of ≥25–30, depending on the population and algorithm used for a given test, thus outperforming the classic PSA in terms of specificity [8].

4-Kallikrein score

Another advanced tool is the 4-Kallikrein score (4Kscore) test, which combines data from four PSA markers (total PSA, free PSA, intact PSA, and human kallikrein-2 – hK2), along with clinical information such as patient age and digital rectal examination (DRE) score. With a risk threshold of ≥7.5%, this test achieves a sensitivity of 83% to 90% and a specificity of 56% to 76%, depending on the patient's age and baseline PSA level. The 4Kscore has been shown to effectively predict the presence of high-grade cancer (Gleason score ≥7) and significantly reduce the number of unnecessary prostate biopsies [9].

Prostate cancer gene 3

The PCA3 test, based on *PCA3* gene expression in urine after prostate massage, offers an extremely high specificity of up to 87% and a sensitivity of 52%. It is therefore particularly useful in patients referred for subsequent biopsy [10].

Select Molecular Diagnostics test for prostate cancer risk assessment

Newer molecular tests, such as SelectMDx, which assesses gene expression in urine, show a sensitivity of 76.9% and a specificity of 49.6%, indicating their potential use in assessing the risk of clinically significant cancer [11].

ExoDx Prostate IntelliScore

The ExoDx Prostate IntelliScore (EPI) test analyzes RNA from exosomes. Importantly, it does not require prostate massage before sampling. Its sensitivity is as high as 92% and its specificity 53.7%, making it a valuable tool in cancer risk assessment [12].
Sensitivity and specificity data for these tests are shown in Table I and Figure 1.

Table I. Diagnostic performance of selected prostate cancer biomarkers

Marker / Test	Diagnostic threshold	Sensitivity	Specificity	Source
PSA	≥4 ng/ml	93%	~20%	[6]
%fPSA	≤25% (PSA gray zone: 4–10 ng/ml)	~95%	30%–40%	[7]
PHI	25–30	75%	69%	[8]
4Kscore	Risk ≥7.5%	83%–90%*	56%–76%*	[9]
PCA3	PCA3 Score ≥35	52%	87%	[10]
SelectMDx	High-risk result (based on *HOXC6* and *DLX1* expression)	76.9%	49.6%	[11]
EPI	EPI Score ≥15.6	92%	53.7%	[12]

PSA – prostate specific antigen; %fPSA – percentage of free PSA; PHI – Prostate Health Index; 4Kscore – 4-Kallikrein score; PCA3 – prostate cancer gene 3 test; SelectMDx – Select Molecular Diagnostics test for prostate cancer risk assessment; EPI – ExoDx Prostate IntelliScore; *HOXC6* – homeobox C6 gene; *DLX1* – distal-less homeobox 1 gene

*The sensitivity and specificity values of the 4Kscore test vary depending on the patient's age, PSA level, and study population; the test is superior to the classic PSA in predictive accuracy of clinically significant cancer [9].

The data presented in the table are from selected studies and may vary depending on the study population, the diagnostic criteria used, and the clinical conditions under which they were obtained.

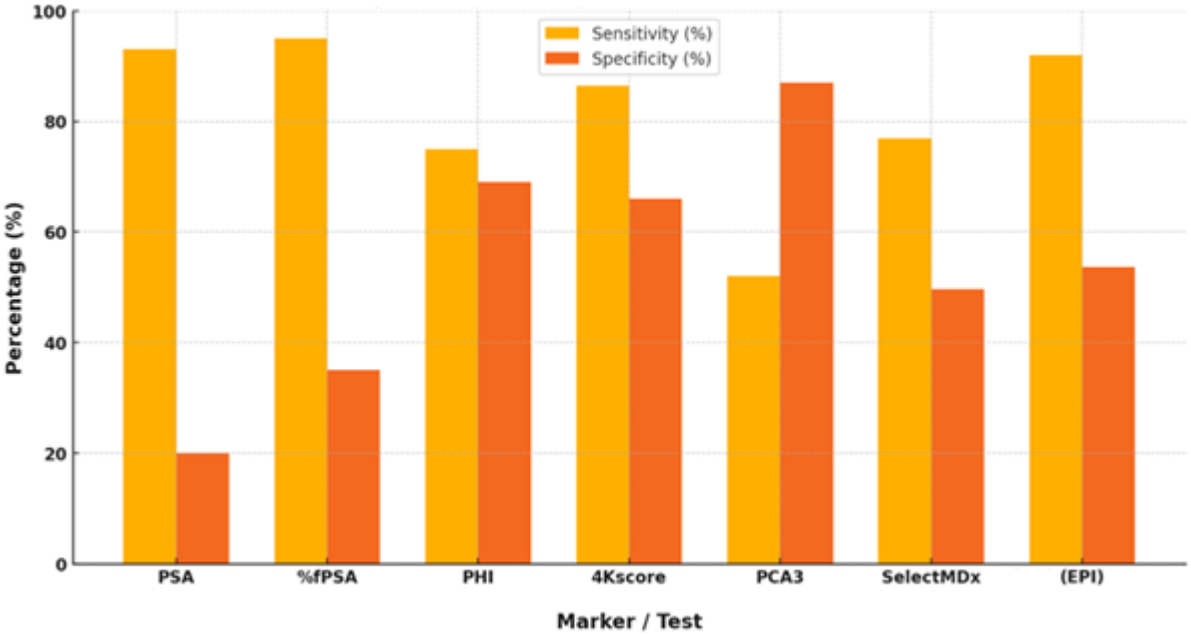

Fig. 1. Sensitivity and specificity of prostate cancer biomarkers. PSA – prostate specific antigen; %fPSA – percentage of free PSA; PHI – Prostate Health Index; 4Kscore –4-Kallikrein score; PCA3 – prostate cancer gene 3 test; SelectMDx – Select Molecular Diagnostics test for prostate cancer risk assessment; EPI – ExoDx Prostate IntelliScore

Discussion

The currently available diagnostic biomarkers help the clinician assess the appropriateness of performing a prostate biopsy, especially in cases of equivocal PSA results. The traditional PSA marker, despite its widespread use and high sensitivity, has very low specificity (~20%), leading to excessive biopsy rates, often in patients without clinically significant cancer [6,7].

In response to these limitations, a number of modern tests have been developed that show improved diagnostic performance – primarily higher specificity while maintaining good sensitivity. Composite tests, such as PHI and 4Kscore, allow more precise risk stratification. Adding PHI to the classic PSA assay significantly improves diagnostic accuracy and avoids up to 30% of unnecessary biopsies [8]. Unlike PSA, which has low specificity, PHI uses a combination of markers; this increases its utility in daily clinical practice [9]. In practice, this means that PHI can more effectively screen out patients with low risk of cancer and avoid many unnecessary biopsies – a huge convenience in a clinician's daily workflow.

The EPI test is distinguished by its high predictive value and the fact that there is no need for prostate massage prior to sampling. It may be particularly useful in a population of patients with borderline PSA results who require a better selection tool. It also has the advantages of simplicity and minimal dependence on clinical data [12].

Among the tests based on urine RNA analysis, PCA3 test and SelectMDx are worth mentioning. PCA3 test achieves high specificity (about 87%) and moderate sensitivity, making it useful especially in patients eligible for repeat biopsy [10]. SelectMDx, with a sensitivity of 76.9% and a specificity of 49.6%, is applicable in assessing the risk of clinically significant cancer and can reduce the number of unnecessary biopsies by up to 50% [11].

It should be noted, however, that the diagnostic performance of the tests varies depending on the population in which they were tested, as well as the accepted definitions of clinically significant cancer, and the PSA level and cutoff point used. There is also a need for greater standardization of sampling techniques, particularly in urine-based tests [13].

Availability and costs

In terms of availability and cost, the price of molecular tests is still a significant barrier to their widespread use. In the US market, the price of a PHI test ranges from ~$72 to $130, depending on the diagnostic center. Urine-based tests, such as SelectMDx (~$500) and EPI (~$760), also have relatively high prices [14]. While there is no data on the costs in Poland, it can be assumed that these tests are only commercially available, with the risk of even higher prices and limited access in the public healthcare system.

Poland compares unfavorably to Western European countries. In Germany, the Netherlands, and Scandinavian countries, PHI and PCA3 tests are in some cases reimbursed or funded through pilot programs. SelectMDx and EPI tests remain largely restricted to the private sector, mainly through health insurance or as paid consumer tests. Despite a growing number of studies confirming their clinical utility, these

biomarkers have not yet been widely integrated into national diagnostic programs, due in part to the lack of clear cost-benefit analysis and formal clinical recommendations in many European countries [13].

The optimal use of biomarkers requires their integration with other elements of the diagnostic process, such as clinical data, per rectum findings, and multiparametric magnetic resonance imaging (MRI). Such an approach can increase the accuracy of detecting clinically significant cancers and reduce the number of unnecessary biopsies, which is both clinically and economically important [15].

Conclusions

Prostate cancer is one of the most common cancers in men. This makes it so important to detect it as early as possible – but at the same time to avoid unnecessary, stressful tests. Until now, the primary tool for diagnosis has been the PSA level in the blood. The problem is that while PSA can detect many cases of cancer, it often produces false positives. As a result, many men end up with a completely unnecessary biopsy.

Fortunately, medicine is moving forward. New tests have emerged – PHI, 4Kscore, PCA3 test, SelectMDx, and EPI – that better distinguish between patients who need further diagnosis and those who can be quietly observed. Not only are these modern biomarkers more accurate, but they also reduce the number of invasive procedures.

However, before they can enter everyday practice for good, they still have to pass several important milestones: they need to be thoroughly tested in different groups of patients, sampling methods need to be standardized, and they need to be evaluated to see if their use really pays off – not only medically, but also financially.

The future of prostate cancer diagnostics will most likely belong to a combination of these tests with modern imaging, such as MRI, and accurate clinical evaluation. This will enable doctors to make faster and more accurate decisions, while helping patients to avoid additional stress and unnecessary procedures. This is a big step toward more precise, safer, and personalized medicine.

Authors' contribution
Study design – P. Kubicki, H. Raś, M. Greniuk
Data collection – K. Jankowska, P. Kubicki
Manuscript preparation – P. Kubicki, H. Raś, M. Greniuk
Literature research – P. Kubicki, H. Raś, M. Greniuk
Final approval of the version to be published – K. Jankowska, H. Raś, M. Greniuk

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