REVIEW | OPEN ACCESS

Medical Science

The role of prostate-specific antigen density (PSAD) in prostate cancer diagnostics: a literature review with cut-off thresholds and integration with multiparametric magnetic resonance imaging

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To Cite:
Mazurek M, Czuba Z, Świerczyna M, Olecka A, Gałązka F, Orawczak F, Majcherek J, Gałązka J, Kotusiewicz M, Karwowski T. The role of prostate-specific antigen density (PSAD) in prostate cancer diagnostics: a literature review with cut-off thresholds and integration with multiparametric magnetic resonance imaging. *Medical Science* 2026; 30: e40ms3748
doi: https://doi.org/10.54905/disssi.v30i168.e40ms3748

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Peer-Review History
Received: 30 April 2025
Reviewed & Revised: 18/May/2025 to 30/January/2026
Accepted: 16 February 2026
Published: 23 February 2026

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

ABSTRACT

Prostate-specific antigen density (PSAD) is a clinical parameter with diagnostic value in urology. Normalizing PSA concentrations to prostatic volume enables PSAD assessment, providing information beyond that obtainable with total PSA alone, thereby improving specificity and decreasing unnecessary biopsies. The value of 0.15–0.20 ng/mL/cm³ is widely used to limit the risk of significant cancers while avoiding the pitfalls of over-detection. The use of PSAD is considered to have specific diagnostic utility in cases with ambiguous multiparametric magnetic resonance imaging (mpMRI) results, particularly for lesions classified as Pi-RADS score 3. In these conditions, it has repeatedly been shown that imaging may not be sufficient for distinguishing between incurable and clinically relevant prostate cancers. Precise prostate volume measurement is critical because the technique used, such as MRI, transrectal ultrasound (TRUS), or transabdominal ultrasound (TAUS), affects the level of accuracy in subsequent PSAD calculation. It is imperative to note that recent developments in artificial intelligence/machine learning may help improve the reproducibility and standardization of prostate volume measurement. In conclusion, PSAD is an interesting and generally applicable biomarker that improves risk assessment and, above all, biopsy decision-making, especially in the assessment of the borderline prostate. However, there is still a need for province-specific guidelines and further prospective studies regarding the use of PSAD.

Keywords: prostate cancer (PCa); prostate-specific antigen (PSA); prostate-specific antigen density (PSAD); multiparametric magnetic resonance imaging (mpMRI); prostate biopsy.

1. INTRODUCTION

Prostate cancer is the most common malignancy in men worldwide, as well as a major source of morbidity in relation to health. It is currently estimated that the incidence in 2024 will be 1,400,000 cases per year (James et al., 2024). Within the European Union, 335,514 new cases occurred in 2020, with 69,945 deaths due to the malignancy. Poland observed 20,961 new cases in 2022, in addition to 5,625 deaths due to the malignancy, in 2020 (Ferlay et al., 2021). Ageing, as well as variations in the frequency of PSA testing, together with variations in the accessibility of advanced imaging studies, are identified as the main reasons for the increased incidence of prostate cancer cases (James et al., 2024). Due to the high incidence, as well as the strong possibility of overdiagnosis in cases in which cancer is clinically insignificant, there is a definite need for enhanced diagnostic techniques. Using PSA density, in addition to magnetic resonance imaging, there is potential to reduce biopsies and enhance identification of significant malignancies for biopsy in men with higher PSA density, as magnetic resonance imaging studies show more suspicious features (Nordström et al., 2018).

PSA is a parameter that is prostate-specific but is not cancer-specific. Because of that, elevated levels may also result from benign prostatic hyperplasia, prostatitis, or some urologic procedures in terms of generating a high number of false positives and overdiagnosis (Han et al., 2020; James et al., 2024). Within the PSA range of 4 to 10 ng/mL, also considered the "grey zone," diagnostic accuracy is known to reduce to a significant extent, with a diagnostic accuracy of 20-40%, supporting a high proportion of negative biopsy results and overdiagnosis along with unnecessary procedures (Nordström et al., 2018). The MRI-first strategy makes it easier to pick out significant cancer (Boschheidgen et al., 2022). The target biopsy strategies developed in prospective studies, including that of Ahdoot et al., (2020), support targeted biopsy over systematic biopsy. PSAD is calculated as total PSA (in ng/mL) divided by prostate volume (in cm³). This provides a high-value signal with a low denominator to a low-value signal in pre-biopsy risk stratification practices for cases with PSA in the range of 4 to 10 ng/mL and nonspecific mpMRI findings (Wen et al., 2024).

Prostate-specific antigen density (PSAD) has a role in biopsy decision-making. The role of PSAD in biopsy decision-making is especially useful in differentiating between benign and significant malignancies in cases of biopsy in PI-RADS 3 lesions, in whom imaging alone is not helpful in making this distinction. Recent literature has suggested cutoffs close to 0.15-0.20 ng/mL/cm³. Use of these cutoffs has been suggested to avoid low-yield biopsies without impairing the identification of ISUP grade ≥2 malignancies (Pellegrino et al., 2024). A value of <0.15 ng/mL/cm³ in PI-RADS 3 lesions can often lead one towards observation or deferral of biopsy, while increased levels are likely to point towards significant malignancies with an increased likelihood of biopsy in these lesions (Pellegrino et al., 2024). However, these determinations are also affected by the imaging technique used in determining the volume of the prostate; MRI-derived volumes are smaller in comparison to transrectal imaging. Hence, for an equal concentration of PSA, with MPMRI, one has an increased PSAD, resulting in possible changes in care in close-liescal diagnostic boundaries (Ahmed et al., 2017; Ye et al., 2024). To possibly reduce changes in classification, in both comparative studies and the use of the risk predictor, one should ideally make one consistent measurement of volume in MPMRI or transrectal sonography for PSAD-driven triage of biopsy in PI-RADS lesions (Straat et al., 2024). Use of cut-offs in the range of 0.15-0.20 ng/mL/cm³ has been helpful in improving positive predictive value with a modest sensitivity loss (Rajendran et al., 2024).

The MRI-first approach is also complementary to PI-RADS and is particularly useful for PI-RADS 3 and above, and remains at the core of the biopsy qualification process (Pellegrino et al., 2024). Uniformity in measuring prostate volume is critical for achieving accurate assessments, as MRI, TRUS, and TAUS often yield different results. Small changes in the volume can affect the PSAD value and push the criterion beyond important threshold values (Ye et al., 2024).

A value of 0.15 ng/ml/cm3 is particularly relevant in men with a prostate gland size of less than 40 cm3. It is also important to consider both PSAD and PI-RADS during decision-making. The use of PSAD categories (<0.10; 0.10-0.15; 0.15-0.20; >0.20 ng/ml/cm3) in combination with PI-RADS levels (1-2, 3, 4-5) is of importance in preventing undue biopsies while still detecting high levels of clinically significant cancers adequately (Tilki et al., 2024). Within active surveillance protocols, PSAD is a useful prognostic indicator for individualized follow-ups on

Aim

This review evaluates the use of PSAD for predicting clinically significant prostate cancer ISUP grade ≥2 in prostate biopsy-referred patients, relative to total PSA, in terms of specific threshold levels, especially around 0.15–0.20 ng/ml/cm², and in terms of mpMRI/PI-RADS-volumes combined, differentiating by either MRI-calculation or by TRUS-calculation within the context of EAU Recommendations in 2025 and current risk algorithms.

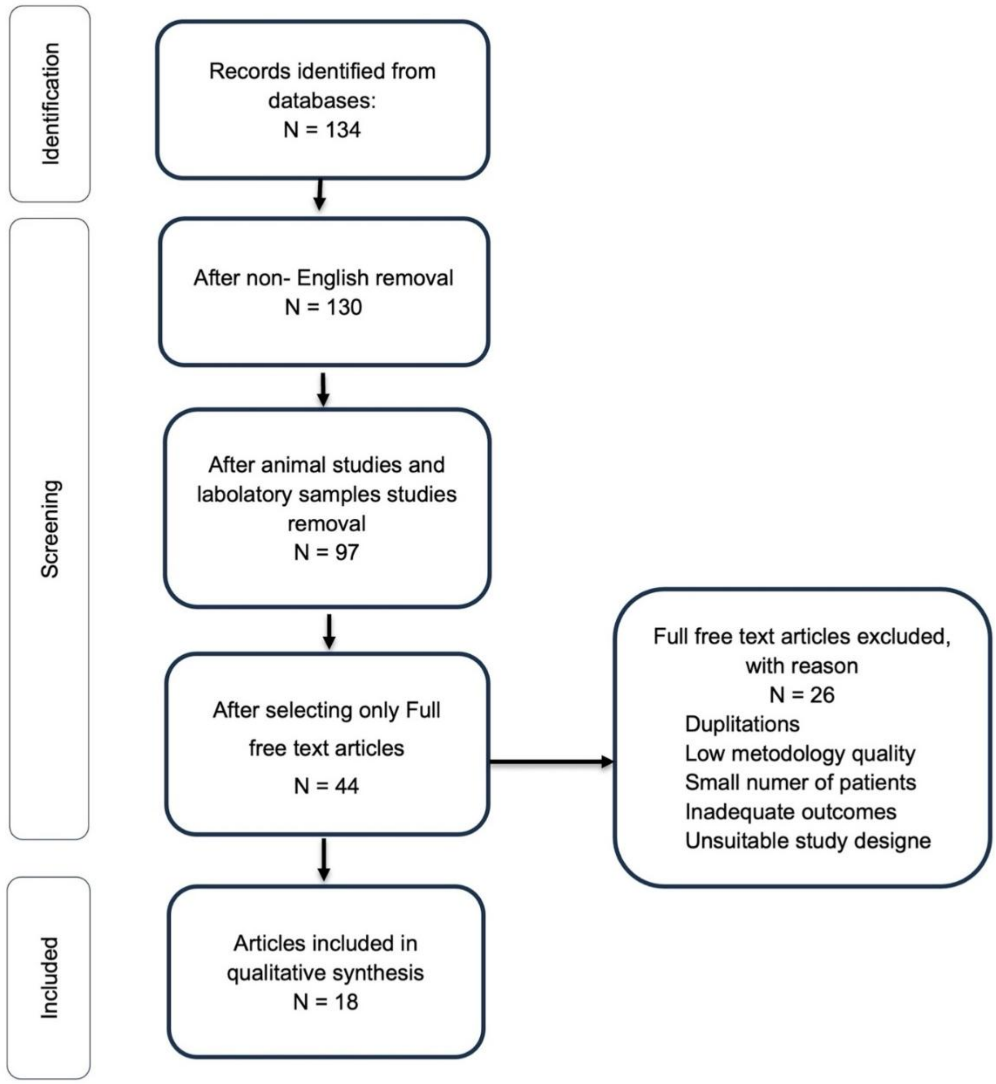

Figure 1. PRISMA flow diagram.

2. REVIEW METHODS

This narrative review integrates the existing knowledge regarding the current use of prostate-specific antigen density (PSAD) in the diagnosis of prostate cancer, particularly concerning the use of threshold values and their combination with multiparametric magnetic resonance imaging (mpMRI) and the PI-RADS system. A literature search was done in three main databases, such as PubMed, Scopus, and Google Scholar, to collect papers concerning the use of PSAD in the diagnosis of significant prostate cancer. In particular, the review focused on studies examining the use of PSAD threshold values and their combination with either mpMRI imaging results and the PI-RADS system. In the literature review, all existing studies to the end of January 2025 have been considered. Moreover, we have used the following keywords: prostate-specific antigen density (PSAD), mpMRI, PI-RADS, and significant prostate cancer (PCa).

In the primary search, 134 papers were identified on the topic under investigation; 130 of them were conducted in English and are therefore considered valid for the analysis. Studies in which the objective was achieved using animal and lab samples have been excluded, and 97 studies have been considered valid based on the analysis objective. Studies where the results of the investigations are not available through access to the full papers have also been eliminated, and 44 studies have been deemed valid based on the requirement of the topic analysis objective. Finally, 18 of the identified 44 studies have been included in the study analysis according to the details mentioned above because the studies about the use of PSAD in significant prostate cancer diagnosis either have been based on duplicate studies, low methodological quality, small study groups, inadequately measured results, or ineffective study design. In the study analysis, the process included evaluating the use of the PRISMA guidelines, as shown in Figure 1.

Peer-reviewed clinical and observational studies, validation studies, and reviews such as systematic reviews, meta-analytic reviews, and narrative reviews were considered, and case reports, editorials, abstracts of presentations, and animal studies were not. We abstracted data from each selected manuscript on the study design, the patients studied, the PSAD thresholds, comparisons with imaging studies, and the authors' conclusions.

3. RESULTS & DISCUSSION

PSAD showed improved prognostic performance compared to total PSA for detecting significant prostate cancer. Although it is an organ-specific marker, its specificity is limited by the effects of benign prostatic hyperplasia, prostate inflammation, or prior urological procedures (Wang et al., 2024). The inclusion of gland size using PSAD has already been shown to improve specificity (Nordström et al., 2018). A large number of studies have shown that PSAD can improve risk stratification over total PSA. The implication is that wider use of PSAD can help minimize the high false-positive rate by reducing unnecessary biopsies (Wang et al., 2024). Researchers suggest that PSAD can serve as a reliable biomarker for csPCA when combined with multiparametric MRI. One of the improvements seen within the PSAD models occurs using a log transformation over total PSA (Pellegrino et al., 2024). Based on recent studies on the prognostic value of PS AD, the European Association of Urology has modified its guidelines to include gland size as a significant component for risk stratification for prostate cancer.

PSAD has since become a critical part of pre-biopsy risk stratification with the intent of complementing rather than replacing total prostate-specific antigen (PSA) testing (Cornford et al., 2024). With the advent of the traditional 0.15-0.20 ng/mL/cm³ values, there was the potential for improving performance beyond PSA testing alone. Some initial data have shown that the 0.15 ng/mL/cm³ value could decrease the rate of low-yielding biopsies with a preservation of high sensitivity for significant cancer (Nordström et al., 2018). Prospective studies and meta-analyses have since reported similar findings. For the best performance in the PSA "grey zone" group, values are best established there. With a 0.20 ng/mL/cm³ threshold, there's potential to improve specificity but also to miss significant cancers (Pellegrino et al., 2023). The 2025 European Association of Urology (EAU) guidelines recommend 0.15 ng/mL/cm³ as the threshold for the general population, with the inclusion of 0.20 ng/mL/cm³ in the context of a large prostate, low clinical risks, or in the case of inconclusive multiparametric MRI results" (Cornford et al., 2024). With the intent of improving the performance of the "grey zone" criteria, the inclusion of PSAD improves the positive prediction of the International Society of Urological Pathology (ISUP) grades 2 or higher with 0.15-0.20, with relatively small effects on reduced positive predictions (Pellegrino et al., 2023).

In the field of mpMRI, the use of PSAD improves the risk stratification, above all in PI-RADS 3 and imaging-negative studies, which can help to decide on a biopsy (Rajendran et al., 2024; Tilki et al., 2024). A useful consideration here is the measurement of the volume, which is important because the value of PSAD is volume-corrected. In this respect, the volumes obtained by MRI are smaller compared to those measured by ultrasound. This can lead to a higher PSAD value given a certain PSA.

PSA Density (PSAD) in the Context of MP-MRI and PI-RADS:

PI-RADS v3 lesions, by definition, are considered to be non-diagnostic or highly equivocal. Also referred to as clinically significant prostate cancer (csPCa), these results range in prevalence rates from low to high teens, which not only pose a significant risk to over- or under-diagnosis but also affect biopsy outcomes in a manner that poses risks to patient care in these contexts (Sheridan et al., 2018). In this regard, PSAD is a triage signal that can be easily obtained from routine laboratory reports. A cut-off point of ≥0.15 ng/mL/cm³ is associated with a high probability of csPCa and is therefore a risk factor that advocates for targeted biopsy in these contexts. Conversely, a value of <0.10 ng/mL/cm³ is associated with a low risk of csPCa and is therefore a risk criterion that advocates for deferment of biopsy in these contexts (Pellegrino et al., 2024). The use of both PI-RADS and PSAD is a risk-calibrated modality that provides improved risk stratification when compared to the use of magnetic resonance alone in these contexts. This risk modality increases the negative predictive value in a magnetic resonance imaging-first strategy for assessing biopsies in PI-RADS v3 cases. Moreover, use of both modalities is associated with low-risk biopsy cases that also lack clinically significant malignancy in these contexts, with biopsy risk similar to that in other contexts (Sathianathen et al., 2020). Use of both modalities is associated with improved risk stratification in this regard compared to their use singularly in these contexts (Rajendran et al., 2024). Another consideration in the use of magnetic resonance in these contexts is that this modality is not very specific in PI-RADS v3 in these contexts, with similar modalities in this regard affecting similar reductions in these tissues in these contexts (Hermie et al., 2019). Use of both modalities in magnetic resonance risk models in these contexts is beneficial in these aspects. This is in that use of similar risk models in these contexts is adjusted with similar modalities that pose risks in these aspects in these regions with similar modalities in this regard (Hagens et al., 2023).

Integration of PSAD with imaging and clinical factors

The addition of Prostate-Specific Antigen Density (PSAD) to Quantitative Multiparametric MRI (mpMRI) adds improved risk prediction. PSAD analysis is particularly valuable for diagnosing equivocal target lesions. The Apparent Diffusion Coefficient (ADC) decreases with increasing aggressiveness of cancers; hence, a combination of cutoff values of PSAD and ADC values helps to better identify significant cancers. It is also worth noting that adding PSAD analysis helps reduce the number of unnecessary biopsies in biopsy-naive and repeat-biopsy populations (Zhang et al., 2024). A measurement of lesion volume provides critical additional data, such that lesions that are large with low ADC values and high PSAD values are strongly predictive of significant disease, and lesions that are small with high ADC levels and low PSAD values represent lesions of less virulent/intermediate disease (Zhang et al., 2024; Rajendran et al., 2024). Multivariable models that include PSAD, ADC, and gland/lesion volume are better predictors of patient outcomes than PI-RADS alone and are superior in calibration and discrimination. It helps to better identify targeted biopsies and observe lesions by achieving a decrease in overdiagnosis (Hagens et al., 2023). The clinical utility of this benefit is significant for lesions classified as PI-RADS 3.

In biopsy-naïve men, a model including age, PSAD, lesion volume, ADC, and DRE had an AUC of about 0.86 with good calibration, improving upon each variable alone (Zhang et al., 2024). This has been seen in other studies as well, in that adding simple clinical factors (age, gland volume, DRE) to PI-RADS 3 improves identification of clinically significant disease and has been advocated for a step-wise decision model based on the number of risk factors present (Kwe et al., 2024; Hermie et al., 2019). These data are consistent with an MRI-first strategy and current calculator availability. Models including clinical information combined with multiparametric MRI features, together with developed and established risk models (such as the ERSPC), have been suggested to minimize low-yield biopsies while maintaining sensitivity for significant disease, especially in situations of moderate suspicion of cancer on MRI (Sathianathen et al., 2020). Current guidelines have adopted PSAD and PI-RADS as decision calculators, among others, to maximize strategies for invasive testing (Cornford et al., 2024). Large datasets have verified these strategies: in high-volume institutions, the addition of PSAD with parameters of ADC and volume of the lesions, combined with clinical factors, improves patient identification with increased cancer risk in PI-RADS 3 lesions; however, low PSAD places biopsy in the context of safety (Pellegrino et al., 2024).

PSAD Cut-offs

The point of raising the PSAD threshold to 0.20 ng/mL/cm³ is understandable because it increases specificity and positive predictive value at the cost of a small decrement in sensitivity, potentially leading to the underappreciation of a few cases of csPCa (Pellegrino et al., 2023; Cornford et al., 2024). In a selected group of patients with a gland volume above 40 mL and a high-risk profile, this is generally preferred by clinicians (Pellegrino et al., 2023; Cornford et al., 2024). Many studies say that the approach is potentially the best right now. That's why, in MRI-first strategies, PSAD is closely evaluated alongside PI-RADS to inform biopsy decisions, improving risk stratification and avoiding unnecessary biopsies. Such analyses and studies combine the uncertain MRI to generate a more specific probabilistic risk for the patient. For PI-RADS 3 lesions, PSAD < 0.10 ng/mL/cm³ generally supports active surveillance for the very low likelihood of csPCa, while PSAD ≥ 0.15 ng/mL/cm³ suggests a higher likelihood of csPCa for targeted biopsy. These go towards more individualized clinical decision-making. Active patient follow-up should be performed for active surveillance strategies and should actively monitor PSA dynamics, symptoms, and potentially involve repeat MRI evaluation when necessary.

The European Association of Urology (EAU) criteria divide PSAD values into < 0.10, 0.10-0.15, 0.15-0.20, and > 0.20 ng/ml/cm³. This method increases the likelihood of significant cancer. These criteria provide a standardized approach for better diagnostics. It is unnecessary to use the same threshold values for all individuals, as the method is influenced by gland size and patient age. In the case of small glands (< 40ml), assessing the values using a threshold of 0.15 ng/ml/cm³ in the presence of an MRI-visible tumor with a PI-RADS of 3 or 4 provides the best assistance. In the case of larger glands (60-80ml), using a threshold of 0.20 ng/ml/cm³ increases specificity and reduces the need for biopsy (Pellegrino et al., 2023). With increased age, the blood level of PSA increases along with the size of the prostate because of benign prostatic hyperplasia. Both of these aspects are addressed in PSAD. It does not fluctuate with age like PSA.

If PSAD is low and MRI does not show any suspicious findings, it is reasonable to wait before doing a biopsy. Calculators that use age, PSAD, MRI results, and DRE can help with this decision (Sathianathen et al., 2020). In a younger group of men with small prostates (below 40 mL), a PSAD between 0.10 and 0.15 ng/mL/cm³ with an MRI-visible lesion may still be an argument to make a targeted biopsy, to avoid missing important disease (Pellegrino et al., 2024; Rajendran et al., 2024). New findings show that this approach aligns with MRI-first algorithms and the current 2025 EAU guidance. The focus here is on context-specific decision making based on the integrated clinical-imaging profile, as opposed to a cut point approach that is at present the gold standard in clinical practice (Cornford et al., 2024). The generally accepted cut points for PSA density, as already stated, should be used to improve the relative specificity of the test above that of the total PSA level, thereby decreasing the number of low-grade biopsies that increase patient risk of serious post-procedure complications. The goal here is to identify the patients likely to truly benefit from the invasive procedure being proposed (Cornford et al., 2024). To clarify PSAD cut-offs, Table 1 briefly summarizes PSAD thresholds with risk stratification and recommended decision directions.

Table 1. Summary of PSAD cut-offs with risk stratification and recommended decision direction

PSAD Cut-off (ng/mL/cm³)	Risk stratification of csPCa	Decision direction
<0.10	Low risk	Defer biopsy, surveillance
0.10-0.15	Intermediate risk	Consider targeted biopsy if other risk factors present
0.15-0.20	Elevated risk	Biopsy consideration
>0.20	Highest risk	Stronger biopsy indication

Artificial intelligence (AI) and machine learning (ML) algorithms

AI and ML have become increasingly important tools for diagnosing prostate cancer, especially when used with MRI and PSAD. They help with image analysis, automatic prostate volume calculations, and more objective, consistent decisions. There is also a great need to ensure the gland volume is accurately measured for accurate PSAD calculations. Deep-learning algorithms have the potential to detect the prostate and mark potential areas with a level of sensitivity comparable to that of experienced professionals. Standardization of measurement methods increases accuracy and reduces variability across all kinds of imaging studies. That’s why AI-based computerized systems use common contour lines across various imaging platforms to standardize MRI and ultrasound, thereby enhancing the accuracy of inter-centre PSAD measurements. ML systems also have the potential to use parameters from routine MRI lesion analysis to determine the probability of the lesion character. If such parameters are used in combination with PSAD and other similar parameters, the likelihood of a correct diagnosis increases, thereby reducing the risk of futile biopsies, particularly for PI-RADS grade 3 lesions, which are primarily based on these parameters. Still, it is a sensible and vision-driven effort to incorporate AI-based parameters into PSAD to achieve uniform diagnosis of prostate cancer.

4. CONCLUSION

PSAD is a proven marker that helps find significant prostate cancer and cuts down on unnecessary biopsies. Using a threshold between 0.15 and 0.20 ng/mL/cm³ gives the best balance of sensitivity and specificity. When PSAD is used alongside mpMRI and PI-RADS, it sharpens risk assessment, especially for PI-RADS 3 cases. It is important to standardise how prostate volume is measured and to include PSAD in AI-based risk models to move prostate cancer diagnosis toward more personalised and evidence-based care.

Abbreviations:

PSA - Prostate-Specific Antigen
PSAD - Prostate-Specific Antigen Density
DRE - Digital Rectal Examination
mpMRI - Multiparametric Magnetic Resonance Imaging
ERSPC - European Randomized Study of Screening for Prostate Cancer
PI-RADS - Prostate Imaging Reporting and Data System
EAU - European Association of Urology

Acknowledgments

The authors have no acknowledgments to disclose.

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Supervision: Mateusz Mazurek

Informed consent

Not applicable.

Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on reasonable request to the corresponding author.

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