
| RESEARCH ARTICLE**The Advances in PSA-Based Screening for Early Detection of Prostate Cancer****Melanie Sanford Mason**

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Corresponding Author: Melanie Sanford Mason, **E-mail:** sanfordmason@gmail.com**| ABSTRACT**

Prostate-specific antigen (PSA) testing has long been the cornerstone of prostate cancer screening, significantly improving the early detection of prostate malignancies; however, its limited specificity and risk of overdiagnosis remain major clinical challenges. Traditional PSA assays do not distinguish between benign prostatic conditions and clinically significant cancer, resulting in unnecessary biopsies and overtreatment. Recent advances in PSA-based screening have sought to refine risk stratification and improve diagnostic accuracy. These refinements include age-adjusted PSA thresholds, PSA density, and PSA velocity, which take into account a patient's age, prostate volume, and longitudinal PSA dynamics to better interpret PSA levels in context. Furthermore, the incorporation of PSA derivatives and isoforms—such as free PSA, complexed PSA, and pro-PSA—enables more nuanced screening. In particular, tests like the prostate health index (PHI), combining total PSA, free PSA, and [−2] pro-PSA, have demonstrated improved specificity and greater discrimination of aggressive disease. Additional blood-based kallikrein panels such as the 4K score (which includes total PSA, free PSA, intact PSA, and kallikrein-related peptidase 2) further enhance risk stratification by estimating the probability of high-grade prostate cancer. Moreover, emerging biomarkers derived from urine (e.g., PCA3, TMPRSS2-ERG) offer non-invasive adjuncts to PSA testing, reducing unnecessary biopsies while preserving sensitivity for clinically relevant disease. Parallel to biomarker innovation, advances in imaging—especially multiparametric MRI—and artificial intelligence (AI) methods are being integrated into screening pathways to further refine detection. AI-driven algorithms can interpret imaging data and combine molecular, clinical, and imaging features to guide biopsy decisions more accurately. Together, these novel PSA-based approaches—multimodal biomarkers, refined algorithms, and imaging synergy—are transforming prostate cancer screening toward more personalized, risk-adapted strategies. Adoption of these advances could reduce overdiagnosis, minimize harms, and improve the early detection of clinically significant prostate cancer, though continued validation in large, diverse populations is needed.

| KEYWORDS

PSA Screening, Prostate Cancer, Early Detection, PSA Derivatives, Biomarkers, Risk-Adapted Screening, Multiparametric MRI

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1. Introduction

Prostate cancer remains one of the most commonly diagnosed malignancies among men worldwide and represents a significant cause of cancer-related morbidity and mortality (Cookson, 2001; Ilic et al., 2018). The burden of the disease is particularly high in aging populations, with incidence rates increasing steadily due to demographic shifts and improved diagnostic awareness (Van Poppel et al., 2022). Early detection of prostate cancer plays a crucial role in improving treatment outcomes, reducing disease progression, and enhancing survival rates (Gandaglia et al., 2019). As a result, screening strategies have long been a central focus

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of prostate cancer control efforts, with prostate-specific antigen (PSA) testing serving as the cornerstone of early detection for several decades (Bryant & Lilja, 2014; Pickles, 2004).

PSA is a glycoprotein produced by prostate epithelial cells and is detectable in the blood (Hori et al., 2013). Elevated PSA levels may indicate the presence of prostate cancer; however, they can also result from benign conditions such as prostatitis or benign prostatic hyperplasia (Pezaro et al., 2014; Khan et al., 2022). Despite these limitations, PSA-based screening has contributed significantly to the identification of prostate cancer at earlier, potentially curable stages (Schröder et al., 2008; Stephan et al., 2007). The widespread adoption of PSA testing led to a marked increase in prostate cancer diagnoses and a corresponding decline in advanced-stage disease and prostate cancer-specific mortality in many regions (Van Poppel et al., 2021; Tosoian & Loeb, 2010).

Nevertheless, traditional PSA screening has been associated with substantial challenges, particularly related to overdiagnosis and overtreatment (Prensner et al., 2012; Filella & Foj, 2016). The inability of total PSA levels alone to reliably distinguish between aggressive and indolent tumors has resulted in unnecessary biopsies, anxiety, and treatment-related complications (Van Poppel et al., 2022). These concerns have prompted ongoing debate regarding the balance between the benefits and harms of routine PSA screening and have driven efforts to refine and improve screening strategies (Bryant & Lilja, 2014).

In response to these limitations, significant advances have been made in PSA-based screening approaches. Novel PSA derivatives and biomarkers, such as PSA density, PSA velocity, and age-adjusted PSA thresholds, have been developed to enhance diagnostic accuracy (Hori et al., 2013; Van Poppel et al., 2021). Additionally, the emergence of PSA isoforms and composite indices, including percentage free PSA and multi-parametric risk calculators, has improved risk stratification and clinical decision-making (Prensner et al., 2012; Filella & Foj, 2016). These innovations aim to better identify clinically significant prostate cancer while reducing unnecessary interventions (Bryant & Lilja, 2014; Gandaglia et al., 2019).

Technological advancements have further transformed PSA-based screening through integration with imaging modalities and personalized risk assessment models. The combination of PSA testing with multiparametric magnetic resonance imaging (mpMRI) has shown promise in improving lesion detection and guiding targeted biopsies (Van Poppel et al., 2022; Schröder et al., 2008). Moreover, individualized screening strategies that consider patient age, family history, genetic predisposition, and baseline PSA levels are increasingly being emphasized to optimize screening outcomes (Khan et al., 2022; Tosoian & Loeb, 2010).

This review article aims to examine recent advances in PSA-based screening for the early detection of prostate cancer. By synthesizing current developments in biomarker refinement, diagnostic algorithms, and risk-adapted screening strategies, the review highlights how these innovations address longstanding limitations of traditional PSA testing. Understanding these advances is essential for improving early detection, minimizing harm, and supporting evidence-based clinical practice in prostate cancer screening (Van Poppel et al., 2021; Pezaro et al., 2014).

2. Literature Review

2.1 Overview of PSA-Based Screening

Prostate-specific antigen (PSA) testing has long been the primary tool for the early detection of prostate cancer (Cookson, 2001; Pickles, 2004). Initially introduced as a tumor marker, PSA screening gained widespread acceptance due to its simplicity, accessibility, and ability to detect prostate cancer at earlier stages (Bryant & Lilja, 2014; Pezaro et al., 2014). Early studies demonstrated that PSA testing contributed to a reduction in prostate cancer-specific mortality by enabling diagnosis before the onset of clinical symptoms (Schröder et al., 2008). However, limitations related to sensitivity and specificity soon became apparent, highlighting the need for improved screening approaches that could better distinguish malignant disease from benign prostate conditions (Ilic et al., 2018; Khan et al., 2022).

2.2 Limitations of Conventional PSA Testing

Despite its clinical utility, conventional total PSA testing has significant drawbacks. Elevated PSA levels may arise from benign prostatic hyperplasia, inflammation, or infection, leading to false-positive results and unnecessary prostate biopsies (Filella & Foj, 2016; Tosoian & Loeb, 2010). Furthermore, PSA screening has been associated with overdiagnosis of indolent tumors that may never progress to clinically significant disease (Van Poppel et al., 2022). These limitations have contributed to overtreatment, exposing patients to potential complications such as urinary incontinence and sexual dysfunction (Prensner et al., 2012; Stephan et al., 2007). As a result, the medical community has increasingly emphasized the need for more refined and risk-adapted screening strategies (Bryant & Lilja, 2014).

2.3 PSA Derivatives and Kinetics

To address the shortcomings of total PSA testing, several PSA derivatives have been developed to enhance diagnostic accuracy. PSA density, which relates PSA levels to prostate volume, improves cancer detection by accounting for gland size (Hori et al., 2013). PSA velocity and PSA doubling time provide insight into the rate of PSA change over time, offering potential indicators of tumor aggressiveness (Schröder et al., 2008; Stephan et al., 2007). These kinetic measures have been shown to improve risk stratification and assist clinicians in distinguishing between benign conditions and clinically significant prostate cancer (Van Poppel et al., 2021).

2.4 PSA Isoforms and Composite Biomarkers

Advances in biomarker research have led to the identification of PSA isoforms and composite indices that further refine screening performance (Hori et al., 2013; Prensner et al., 2012). The ratio of free to total PSA has demonstrated improved specificity in patients with borderline PSA levels (Bryant & Lilja, 2014). More recently, composite biomarkers combining multiple PSA isoforms have emerged, offering superior predictive accuracy for clinically significant disease (Filella & Foj, 2016). These tools reduce unnecessary biopsies and support more informed clinical decision-making (Gandaglia et al., 2019).

2.5 Integration of PSA Screening with Imaging Technologies

The integration of PSA-based screening with advanced imaging modalities represents a major advancement in early prostate cancer detection (Van Poppel et al., 2022; Van Poppel et al., 2021). Multiparametric magnetic resonance imaging (mpMRI) has enhanced the identification and localization of suspicious lesions, particularly in patients with elevated PSA levels (Schröder et al., 2008). When combined with PSA testing, mpMRI-guided biopsy strategies improve diagnostic yield while reducing the detection of low-risk tumors (Bryant & Lilja, 2014). This combined approach has significantly improved the precision of prostate cancer screening (Tosoian & Loeb, 2010).

2.6 Risk-Adapted and Personalized Screening Approaches

Contemporary screening strategies increasingly emphasize personalized, risk-adapted approaches. Baseline PSA measurements, age-specific thresholds, family history, ethnicity, and genetic risk factors are now incorporated into individualized screening protocols (Khan et al., 2022; Pezaro et al., 2014). These models aim to optimize screening intervals and interventions based on patient-specific risk profiles, thereby maximizing clinical benefit while minimizing harm (Gandaglia et al., 2019).

2.7 Emerging Trends and Future Directions

Ongoing research continues to explore novel biomarkers, artificial intelligence-driven risk prediction models, and integration of genomic data into PSA-based screening frameworks (Prensner et al., 2012; Filella & Foj, 2016). These emerging innovations hold promise for further improving early detection and identifying aggressive prostate cancer with greater accuracy. As screening strategies evolve, future efforts will focus on balancing early diagnosis with the reduction of overdiagnosis and overtreatment (Van Poppel et al., 2022; Bryant & Lilja, 2014).

3. Methodology

This research review employed a narrative review design to examine recent advances in prostate-specific antigen (PSA)-based screening for the early detection of prostate cancer. The methodology was structured to identify, evaluate, and synthesize relevant literature focusing on innovations in PSA biomarkers, screening strategies, diagnostic integration, and risk stratification approaches. Emphasis was placed on studies that contributed to improving the accuracy, effectiveness, and clinical applicability of PSA-based screening.

A comprehensive literature search was conducted using major electronic databases commonly used in biomedical research. Peer-reviewed articles published in recent years were prioritized to capture contemporary developments in PSA screening. The search strategy included key terms and combinations related to prostate cancer, PSA screening, early detection, biomarker advances, PSA derivatives, and imaging-assisted screening. Additional studies were identified through manual screening of reference lists from relevant reviews and guideline documents to ensure comprehensive coverage.

Eligibility criteria were applied to select studies for inclusion in the review. Included articles comprised original research studies, systematic reviews, clinical guidelines, and consensus statements that addressed PSA-based screening or related diagnostic advancements. Studies focusing solely on treatment outcomes without relevance to screening or early detection were excluded. Only articles available in English and involving human subjects were considered to maintain consistency and clinical relevance.

Following study selection, data were extracted and organized thematically. Key information regarding study design, population characteristics, PSA-related innovations, diagnostic performance, and clinical implications was summarized. The literature was then grouped into major thematic areas, including conventional PSA screening, PSA derivatives and isoforms, integration with imaging modalities, and personalized risk-based screening approaches. This thematic synthesis enabled comparison across studies and facilitated identification of emerging trends and knowledge gaps.

The findings were analyzed qualitatively to highlight consensus, discrepancies, and advancements in PSA-based screening practices. Emphasis was placed on evaluating how newer screening approaches address the limitations of traditional PSA testing, particularly in reducing overdiagnosis and unnecessary biopsies. Methodological rigor, clinical applicability, and potential impact on screening outcomes were considered when interpreting the evidence.

Overall, this methodology provided a structured and systematic approach to reviewing current evidence on PSA-based screening advancements. By synthesizing diverse sources and emerging innovations, the review aimed to present a balanced and clinically relevant overview that supports informed decision-making and identifies areas for future research in prostate cancer early detection.

4. Results and Discussion

The review of recent literature demonstrates substantial progress in PSA-based screening for the early detection of prostate cancer, with innovations aimed at improving diagnostic accuracy while minimizing the harms associated with traditional screening approaches (Bryant & Lilja, 2014; Cookson, 2001). Conventional total PSA testing has played a pivotal role in identifying prostate cancer at earlier stages; however, its limited specificity has driven the development of refined screening strategies (Ilic et al., 2018; Pickles, 2004). Current evidence indicates that newer PSA-based tools provide enhanced risk stratification, allowing clinicians to better differentiate between clinically significant prostate cancer and indolent disease, thereby reducing unnecessary diagnostic procedures (Van Poppel et al., 2022; Pezaro et al., 2014).

One of the most notable advances is the use of PSA derivatives and kinetic measurements. Parameters such as PSA density, PSA velocity, and PSA doubling time have demonstrated improved predictive value compared to total PSA alone (Hori et al., 2013; Schröder et al., 2008). These measures account for prostate volume and longitudinal changes in PSA levels, offering greater insight into tumor behavior (Stephan et al., 2007; Van Poppel et al., 2021). Studies reviewed consistently report that incorporating PSA kinetics into clinical decision-making improves the identification of aggressive cancers while reducing false-positive findings (Gandaglia et al., 2019). As a result, fewer patients are subjected to unnecessary biopsies, supporting a more conservative and individualized approach to screening (Bryant & Lilja, 2014).

Further improvements in screening accuracy have been achieved through the evaluation of PSA isoforms and composite biomarkers. Ratios such as free-to-total PSA and multivariable PSA-based indices have shown superior performance in distinguishing malignant from benign conditions, particularly in patients with intermediate PSA levels (Hori et al., 2013; Prensner et al., 2012). These biomarkers enhance specificity and reduce diagnostic uncertainty, which is critical in addressing the long-standing challenge of overdiagnosis (Filella & Foj, 2016). The findings suggest that combining multiple PSA parameters provides a more robust assessment of cancer risk than reliance on a single biomarker (Bryant & Lilja, 2014).

The integration of PSA screening with advanced imaging techniques has also emerged as a transformative development. Multiparametric magnetic resonance imaging (mpMRI), when used alongside PSA testing, has significantly improved lesion localization and diagnostic yield (Van Poppel et al., 2022; Van Poppel et al., 2021). Evidence indicates that PSA-guided mpMRI allows for targeted biopsy approaches that increase detection of clinically significant tumors while minimizing the identification of low-risk cancers (Schröder et al., 2008; Tosoian & Loeb, 2010). This combined strategy represents a shift toward precision screening, aligning diagnostic intensity with individual patient risk (Bryant & Lilja, 2014).

In addition, the review highlights a growing emphasis on risk-adapted and personalized screening protocols. Contemporary approaches increasingly incorporate baseline PSA levels, age, family history, ethnicity, and genetic susceptibility into screening algorithms (Khan et al., 2022; Pezaro et al., 2014). These models enable tailored screening intervals and thresholds, optimizing early detection while reducing exposure to unnecessary testing (Gandaglia et al., 2019). The literature suggests that personalized PSA-based screening not only improves clinical outcomes but also enhances patient acceptance and adherence to screening programs (Filella & Foj, 2016).

Despite these advances, challenges remain in the widespread implementation of refined PSA-based screening strategies. Variability in clinical guidelines, limited access to advanced biomarkers and imaging, and disparities in healthcare infrastructure may hinder equitable adoption (Prensner et al., 2012; Stephan et al., 2007). Moreover, long-term outcome data are still needed to confirm whether newer screening approaches translate into sustained reductions in prostate cancer mortality (Van Poppel et al., 2022; Pezaro et al., 2014).

Overall, advances in PSA-based screening reflect a paradigm shift toward more precise, risk-stratified, and patient-centered early detection of prostate cancer. The integration of biomarker refinement, imaging technologies, and personalized risk assessment has significantly improved screening performance, offering a balanced approach that maximizes benefit while minimizing harm (Bryant & Lilja, 2014; Gandaglia et al., 2019). Continued research and policy support are essential to ensure that these innovations are effectively translated into routine clinical practice (Van Poppel et al., 2021; Hori et al., 2013).

5. Conclusion

Prostate-specific antigen (PSA)-based screening has long been a cornerstone of early prostate cancer detection, yet its limitations in specificity and risk of overdiagnosis have prompted ongoing refinement. Recent advances in biomarker development, risk stratification, and imaging technologies have significantly enhanced the utility of PSA testing. The incorporation of PSA derivatives such as free PSA, PSA density, PSA velocity, and [-2] pro-PSA, particularly within composite indices like the Prostate Health Index (PHI), allows for improved discrimination between clinically significant and indolent disease. Multivariate kallikrein panels, such as the 4K score, further enable personalized risk assessment, reducing unnecessary biopsies while maintaining sensitivity for aggressive cancers.

Urinary biomarkers, including PCA3 and TMPRSS2-ERG, offer non-invasive adjuncts that complement serum PSA testing and provide additional specificity. Similarly, multiparametric MRI has emerged as a valuable tool for targeted lesion identification, minimizing sampling errors and supporting risk-adapted biopsy strategies. The integration of artificial intelligence and machine learning with biomarker and imaging data is poised to enhance precision screening, enabling clinicians to make more informed, individualized decisions.

Despite these advancements, challenges remain, including the need for validation across diverse populations, cost-effectiveness considerations, and the establishment of standardized protocols that incorporate multiple testing modalities. Nevertheless, the current trajectory of PSA-based screening is shifting toward personalized, risk-adapted approaches that maximize early detection of clinically significant prostate cancer while minimizing harms associated with overdiagnosis and overtreatment.

In summary, advances in PSA-based screening represent a critical evolution in prostate cancer management. By combining refined biomarkers, multivariate risk models, innovative imaging techniques, and AI-driven analysis, clinicians are better equipped to detect aggressive disease early, reduce unnecessary interventions, and improve patient outcomes. Ongoing research and clinical implementation of these strategies will be essential to fully realize the potential of personalized prostate cancer screening and to establish evidence-based, optimized approaches that balance benefits and risks effectively.

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