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Review Article

Advancements of Differentiative Biomarkers for Malignant and Non-Malignant Prostatic Diseases: Inclusive Review

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ABSTRACT

The walnut-sized prostate gland is subjected to three main disorders, including prostatitis, Benign prostate hyperplasia (BPH), and prostate cancer (PCa). In many cases, discrimination between PCa and other conditions is critical, which may lead to a false diagnosis or prognosis in addition to inaccurate therapeutic responses. Additionally, screening with conventional markers such as total Prostate-Specific Antigen (PSA) and/or digital rectal examination (DRE) often leads to overdiagnosis and overmanagement of PCa. Developing advanced screening tools for prostatic diseases remains a challenging dilemma. New molecular approaches and insights are continuously studied by utilizing genomics, proteomics, and the extraction of various microRNAs (miRNAs), often through AI-aided models. All of these methodologies are targeting the reduction of unnecessary biopsies in addition to improving the specificity and sensitivity of diagnostic markers and paving the way for newer non-invasive screening, prognostic, and investigative tools, accompanied by more reliable biomarkers. PSA isoforms and indices, including Prostate Health Index (PHI), Prostate-Specific Antigen Density (PSAD), PSA Velocity (PSAV), and 4K score, are effective when combined with other tools such as multiparametric magnetic resonance imaging (mpMRI). The present review article aims to provide inclusive synopses of recent advances in the field of prostate disorders by introducing non-invasive alternative differentiation tools and more reliable screening molecular markers that can be applied in regular medical practices.

1. Introduction

Prostate diseases, including prostatitis, PCa, and BPH, are a major health problem affecting men globally (He, 2023). PCa is the most aggressive and multifaceted disease, while BPH is a predominant non-cancerous enlargement disorder that affects the prostate gland. Prostatitis or prostate infection/inflammation could be chronic, which is the most prevalent category, or the uncommon acute prostatitis (Clapp, 2002). Moreover, a rare subtype of chronic inflammatory condition called granulomatous prostatitis is responsible for around 3.3% of all benign inflammatory prostate cases (Crocetto et al., 2020). Prostatitis may comprise 25% of all office appointments made to the urological clinics complaining about the genital and urinary systems globally (Khan et al., 2017). PCa is one of the most predominant forms of tumors, and its incidence rate has increased in recent years worldwide. Furthermore, it is the second most common malignancy in men and the fifth commonest reason

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of overall cancer mortality (Siegel et al., 2023). In American males, PCa is the most frequently detected nonskin malignancy and the second leading cause of cancer passing (Wender et al., 2019). PCa cases appear to be typically asymptomatic during their initial phases, and are occasionally diagnosed lately, thereby they do not obtain effective therapy (Bevacqua et al., 2022). Basically, the prostate gland is under the influence of androgens. As a result of the onset of hypogonadism among the aging male population, the likelihood of prostatic diseases is growing; subsequently, the prevalence of both BPH and PCa rises with age (Welén and Damber, 2022). During the course of their development, PCa cells undergo a series of genetic and epigenetic alterations that are indicative of unchecked growth and biochemical transition (Martin et al., 2012), making them acquire the potential for angiogenesis, abnormal proliferation, avoidance of apoptosis, anoikis resistance, metastasis to secondary sites, and androgen independence (Begemann et al., 2018; Malagobadan and Nagoor, 2019).

As these pro-oncogenic pathways and important signaling molecules, including androgen receptor pathway, are currently being studied at the molecular and cellular level, one would anticipate the discovery of novel markers indicating particular tumor properties in individual patients, for instance, Blessin et al, studied the automation of a nuclear antigen, the Ki-67 labeling index evaluation in PCa by deploying AI and fluorescence immunohistochemistry and they concluded that the Ki-67 Li can be a potent predictive parameter in PCa that is now valid in routine medical practice. Once this effective technology is applied to individual tumors, it is projected that a tailored level of analysis of such a bioindicator will have a significant impact on how clinicians identify early PCa and intervene to stop the development of a severe illness (Blessin et al., 2023).

Presently, the supplementary investigative procedures for prostatitis, BPH, as well as PCa largely comprise DRE, ultrasound, X-ray, tissue biopsy, including transrectal ultrasound scan (TRUS) biopsy for pathological investigation and microarray expression profiling, assessment of lower urinary tract activity, prostatic fluid, computed tomography (CT), and magnetic resonance imaging (MRI) inspection. Blood markers include free and total PSA. High specificity and sensitivity serum markers are not yet available, and those that are have considerable drawbacks (Tidd-Johnson et al., 2022; He, 2023).

In recent years, the development of many alternative markers with improved specificity and sensitivity has been on track to play a vital role in supporting the diagnosis of prostatic illnesses. Consequently, the diagnosis and management of PCa and distinguishing it from other prostate conditions must be continuously improved due to its devastating global growth. PCa detection tools are constantly evolving, and the need for stratification techniques to improve early detection of clinically relevant PCa and decrease overdiagnosis and overtreatment is generally acknowledged. To find the optimal test for individualized treatment, direct analyses of biomarkers and risk calculators are central (Porzycki and Ciszkowicz, 2020). The aim of the current review is to provide inclusive outlines of recent advances in the field of prostatic diseases by presenting non-intrusive alternative differentiation tools and more accurate molecular markers that can be applied in regular clinical practices. The sampling methods for detection and risk stratification in suspected PCa patients are explained in the flowchart below (Fig. 1).

2. Literature Review

2.1. Methodology

The current review article is completed by conducting a literature search of PubMed, Google Scholar, and other well-respected databases to retrieve all applicable studies. The search terms (Prostate Biomarkers, Benign prostate hyperplasia, Prostatitis, screening tools, Prostate cancer) were used to explore all relevant research. All linked cross-sectional, prospective, and retrospective-

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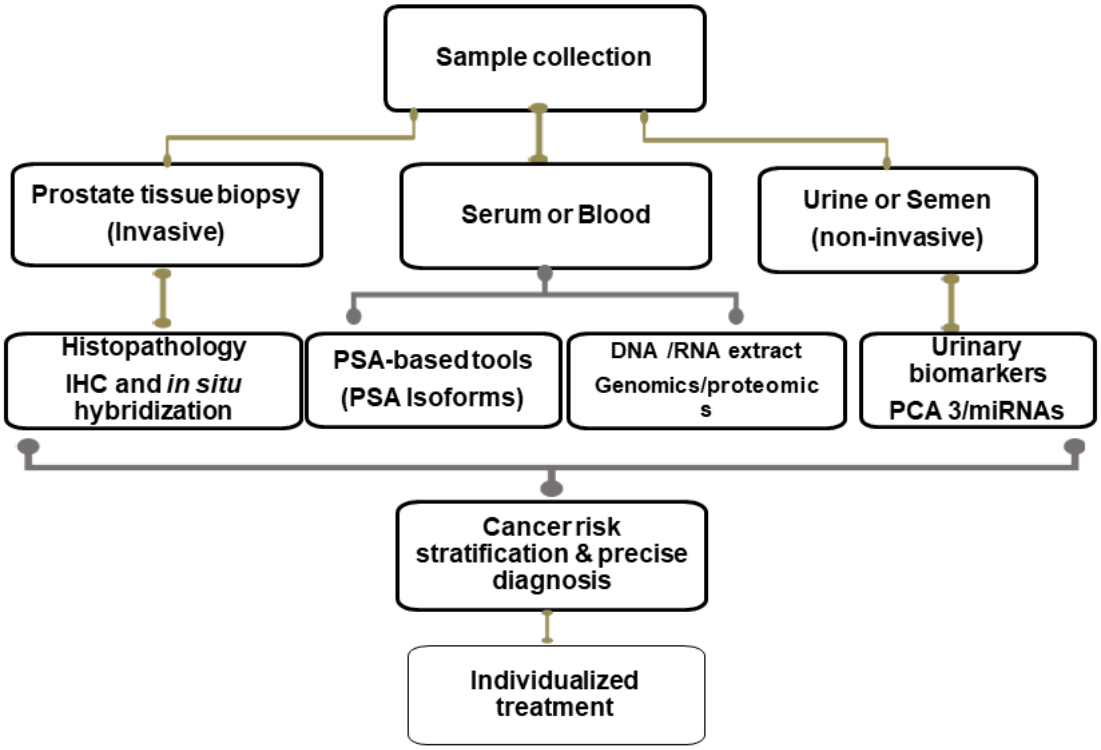

Figure 1. The available sampling approaches for diagnosing and risk stratification in PCa.

studies were included. Case studies with fewer than five patients were excluded from the analysis.

2.2. Prostate Tissue Biopsy

During a prostate biopsy using a biopsy needle or through surgery, prostate tissue is removed. A sample is checked pathologically to see if cancer or other abnormal cells are present in the prostate tissue architecture, as well as tissue microarray protein expression profiling (Rubin et al., 2002). The gold standard for diagnosing PCa is still a prostate biopsy. But the difficult process of choosing patients for prostate biopsies is influenced by the growing use of prebiopsy imaging (Streicher et al., 2018). Several techniques can be used to perform a prostate biopsy, and each of them is presently used with unique advantages and disadvantages; transrectal ultrasound (TRUS), the most typical and reliable method, which is accomplished through the rectum. Another method is the transperineal (TP) biopsy approach, in which the skin between the scrotum and the rectum is used for this procedure. The transurethral method, in which a flexible tube with a viewing instrument called a cystoscope is used for this procedure through the urethra. The prostate gland is typically examined using ultrasound, which is also used to direct the biopsy needle. Conventionally, biopsy is achieved for three overall indications: unusual DRE, increased PSA > 4 ng/ml, and clinical doubt of PCa (Shariat et al., 2008; Streicher et al., 2018). Adversely, TRUS biopsy is an invasive procedure and can cause complications, including bleeding, pain, and infection (Shariat and Roehrborn, 2008). Also, TRUS biopsy without prior mpMRI leads to over-detection of clinically non-significant indolent tumors and under-detection of clinically significant disease by missing tumors in specific areas that are hard to visualize by TRUS alone (Noureldin et al., 2010). Though the risk of infection complications may be decreased by transrectal prostate biopsy or transperineal prostate biopsy with fewer biopsy cores (Tops et al., 2022). Moreover, mpMRI can be used as a triage test, which might allow men to avoid pointless TRUS biopsy and increase diagnostic precision (Ahmed et al., 2017; Kasivisvanathan et al., 2018). Since PCa is a diverse

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illness, a solitary biopsy of the prostate, even if it was able to find a focus of cancer, is often insufficient for an inclusive valuation of the disease due to inability to identity the clonal source of metastatic disease in primary PCa, since cancer cells arise in different parts of the prostate as a result of DNA mutations that happen by chance at different times (Erickson et al., 2021). Undervaluing the cribriform PCa pattern, which is present in both intraductal carcinoma (IDC) and invasive cribriform carcinoma (ICC), is another challenge for needle biopsies. This aggressive histological subtype is linked to the development of fatal disease. A small percentage of needle biopsies with high-grade malignancy revealed cribriform PCa. Severe diagnostic criteria enabled the identification of cribriform patterns and the generation of a large set of agreement cases for standardization (Egevad et al., 2023). Lastly, the decision to go ahead with prostate biopsy is complicated and constantly changing; it should be based on an expert uroradiologist's subjective assessment or patient-specific characteristics.

2.3. The Era of PSA as a Blood Biomarker

The US Food and Drug Administration (FDA) approved the PSA (human kallikrein 3, hK3) in 1986 for the monitoring of men with PCa. A critical study conducted in 1994 showed that a 4.0 ng/mL PSA cutoff was useful for choosing patients for biopsy. Subsequently, it was approved for use in identifying PCa in men over 50 (Catalona, 2018). Our capacity to identify, treat, and monitor patients has been transformed by PSA testing. Also, PSA testing resulted in histrionic surges in the incidence of the disease in Australia and other Western nations (Catalona et al.,1993; Brawley et al, 2009). Since serum PSA screening was announced 36 years ago, PCa diagnosis and treatment have been guided by this biomarker. These PSA-driven incidence increases have mostly been in lower-grade and stage tumors, indicating an increased detection of PCa from the pool of sub-clinical tumors. Along with its use in screening, PSA levels in combination with specific clinical and pathological features are broadly used in evaluating the risk of recurrence (prognosis) in patients with recently diagnosed PCa. Overall, an approximate linear association occurs among PSA levels at initial diagnosis and outcome, i.e., the higher the PSA level, the worse the outcome (Duffy, 2020). PSA presentation varies by ethnicity, and many researchers have found higher PSA levels among African American men (Ankerst and Thompson, 2009). Reza et al concluded that the age-specific reference range of PSA in Iranian men was different with other races (Reza et al., 2021). Yet, PSA has proven controversial as a screening test due to several inherent limitations, since it is a very sensitive but fairly non-specific and imprecise screening tool, as both benign and malignant processes will elevate the marker (Nogueira et al., 2009; Saini, 2016; David and Leslie, 2022). Biologically, PSA is a serine protease enzyme formed exclusively by columnar epithelium of prostatic tissue, and Pro-PSA is the intracellular proenzymatic version of PSA. After cellular manufacture, pro-PSA goes through the basal and endothelial cell sheets prior to entering the prostatic ducts, where it is transformed to active PSA, lastly penetrating the capillaries to reach the systemic circulation (Mikolajczyk et al., 2002; David and Leslie, 2022). After undergoing proteolysis, a tiny percentage of this active PSA enters the bloodstream and stays unbound, turning it into inactive or "free" PSA. When active PSA enters the bloodstream, it quickly attaches itself to circulating protease inhibitors (Catalona et al.,1993; Muhammed and Waheed, 2013). Still, the use of PSA in early detection of PCa is challenging due to the high false positive frequency caused by BPH; therefore, it is not considered independently diagnostic or prognostic in PCa (Bickers and Aukim-Hastie, 2009). The Serum contains PSA in a variety of molecular forms, all of which lack enzymatic activity. These forms fall into two broad types: free PSA (i.e., unbound, inactive PSA) and complexed PSA (i.e., bound to serum protease inhibitors) (Lilja et al., 2000). A significant amount of PSA is found in the bloodstream as a compound with alpha 2-macroglobulin (PSA-A2M) and alpha-1-antichymotrypsin (PSA-ACT). Alpha 1-

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antitrypsin also exists in trace concentrations. The free form (fPSA) contains any remaining PSA (Christensson et al., 1993).

Men are currently screened for PCa using the main PSA-ACT form. Levels of 4.0 ng/ml or higher are strong indicators of the possibility of PCa (Catalona et al., 1993). However, raised blood PSA levels have also been attributed to BPH and prostatitis, leading to a huge fraction of false positive screening outcomes (Catalona et al., 1993). A probable solution to this problem comprises the estimation of fPSA levels (Muhammed and Waheed, 2013). Preliminary studies have proposed that the percentage of free PSA is lower in patients with PCa than in those with BPH (Lilja et al., 1991). Recently, some studies demonstrated that the free to total PSA (tPSA) ratio can solitary be utilized in rare situations to stratify the risk of PCa (Lima et al., 2019). The proportion of PSA-ACT is enlarged in PCa (Lilja, Piironen, and Rittenhouse, 2000). Thus, the measurement of fPSA in combination with tPSA can improve the specificity of PCa screening, particularly in men with elevated serum tPSA, which would afterward reduce unnecessary prostate biopsies with negligible effects on cancer detection rates (Etzioni et al., 2004). Lastly, due to the enormous rise in PCa marker research and the arrival of multiple alternative molecular markers that outperform PSA in terms of sensitivity and specificity, the usage of tPSA alone for screening PCa is currently discouraged.

2.4. Prostate Health Index (PHI)

The PHI measures tPSA, % free PSA, and the isoform [-2] pro-PSA (p2PSA). The mathematical formula (p2PSA /free PSA) × √ tPSA, is then used to aggregate the levels of these three proteins and generate a score that denotes the probability of detecting PCa at the time of the biopsy (Jansen et al., 2010; Boo et al.,2023). The likelihood of discovering a clinically relevant condition increases with score. According to the PHI scale, a number between 0 and 26.7 indicates a 10% chance of having cancer, while a score over 55 indicates a 50% chance of doing a biopsy and discovering cancer. PHI levels differed significantly between men with and without PCa. Therefore, PHI has been demonstrated to be more effective at detecting PCa, including aggressive PCa, than tPSA and percent free PSA (Duffy, 2020; Yáñez-Castillo et al., 2023). Using PHI in the appropriate demographic could prevent about 30% pointless biopsies. Prior to doing a prostate biopsy on men having a tPSA located amongst 4 and 10 ng/mL, PHI is suggested. PHI appears to be a simple blood test that can diminish the number of pointless biopsies and, in turn, represents a novel choice to reduce the harm while searching to detect PCa (Nordström et al., 2015; Loeb et al., 2015). Lastly, it is important to remember that when it comes to the detection of PHI levels, the optimal conditions for handling and keeping samples before analysis are still unclear. In fact, more research is required to determine whether serum or plasma is the optimum measurement matrix (Duffy, 2020).

2.5. The 4K Score

Four kallikrein peptides are used in the 4K score test: tPSA, fPSA, intact PSA (a type of free PSA), and human kallikrein 2 (hK2). The score is aimed at evaluating the separate risk level percentage (< 1% to >95%) (Zappala et al., 2017). The 4K panel, commercially exists as the 4Kscore test, OPKO Health Inc (Darst, 2020). The 4Kscore can give an individualized risk estimate for PCa by examining these markers. It has been demonstrated to be more accurate by having a higher discriminative capacity for PCa than PSA and DRE (Farha et al., 2022). Also, showed to be superior to traditional PSA testing in predicting the likelihood of aggressive PCA and as a possible useful tool in the decision-making process for confirmatory biopsy, especially in active surveillance management (Borque-Fernando et al., 2019; Duffy, 2020). The 4K score/MRI-based combination tool exhibited the potential to diminish redundant biopsies and decrease recognition of clinically insignificant PCa more efficiently than mpMRI or 4K score alone (Wysock et al., 2020; Wagaskar et al., 2021).

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2.6. Prostate-Specific Antigen Density (PSAD)

The PSAD uses the proportion of serum PSA and prostate volume parameters, i.e., (PSA ÷ prostate volume), and a score can be generated using this measurement factor of the prostate size in relation to the serum PSA level (Chen et al.,2011; Jue et al., 2017). Since an enlarged prostate produces higher serum PSA levels, PSAD can be used as a valuable parameter to assess risk for clinically significant PCa (Omri et al., 2020). Furthermore, PSAD was found to be a valuable tool in discriminating between BPH and PCa (Nath et al., 2020). A PSAD score >0.10–0.15 ng/mL/cc designates a high PCa hazard. Once PSAD at an optimal cutoff of 0.18 ng/ml/cc was considered as the predictor, the PCa detection was found to have a high sensitivity and specificity (77% and 69%, respectively) (Chen et al., 2011). Moreover, PSAD is an important tool for preventing needless biopsies because it is a highly specific test at raised PSA levels (Jue et al., 2017; Nath et al., 2020). The majority of research on PSA density cut-offs has verified that higher thresholds allow for the avoidance of more biopsies, but at the cost of more PCa cases being unnoticed (Jue, 2017). According to Görtz et al, Inclusion of PSAD < 0.1 ng/mL/cc in the plan for biopsy-naive patients with equivocal mpMRI results would permit a decrease in prostate biopsies among 43% of cases at the expense of missing a tiny number 2%, of PCa patients at intermediate risk (Görtz et al., 2021). The earlier studies found that the prostate transition zone volume and transition zone PSA density (TZPSAD) in PCa cases were significantly different in comparison with those in non-cancer cases, and compared to PSAD, the TZPSAD had a greater diagnostic effectiveness (Janane et al.,2012). Similarly, Chang et al. investigated the zonal adjusted PSAD and employed transition zone PSA density (TZPSAD) in conjunction with conventional PSA and PSAD to diagnose PCa in 1038 Taiwanese men whose PSA levels ranged from 4.0 to 20.0 ng/ml. They concluded that TZPSAD showed better PCa detection than serum PSA alone. However, TZPSAD was just as effective as PSAD at predicting PCa, although having a slightly higher cancer specificity. In cases with a serum PSA level of 20 ng/ml, the prostate volume-derived TZPSAD estimate outstripped PSA alone; however, it didn't afford better risk-stratification than PSAD (Chang et al., 2020). Overall, PSAD, when combined with other auxiliary measures, can be used for risk assessment, enhance PCa prediction, and prevent needless biopsies.

2.7. PSA Velocity (PSAV)

PSA Velocity is another PSA-based parameter, which is usually used to detect PCa and predict its development. PSAV is known as an increasing PSA level over time, and it is frequently observed in men who are later detected with PCa (Ankerst, Tangen, and Thompson, 2009). Regardless of PSA level, a biopsy should be performed if there is an annual increase of 0.75 ng/ml (Loeb et al.,2007; Loughlin,2014). Based on solid evidence, the average rate of change in PSA of ≥0.75 µg/l/y significantly increased the ability to differentiate men with BPH from those with PCa (Loughlin,2014). Some studies have explored the effect of age on tPSA and PSAV thresholds and stated that the cut points should be age-adjusted for recommending a prostate biopsy, in addition to prognostic implications of PSA velocity (Moul et al., 2007; Reza et al., 2021). Conversely, a systematic review done by Javaeed et al concluded a conflicting result about the role of PSAV in detecting PCa and expecting progression in active surveillance patients. Though they found evidence that PSAV may have a predictive role in post-treated men (Javaeed et al., 2020).

2.8. Beyond PSA Biomarkers

Despite its limitations, PSA is still a practical, reliable biomarker for tracking disease progression and recurrence. Thus, unless in-person evaluations show otherwise, newly found PCa markers will possibly preserve PSA as a main clinical tool, accompanied by other tests (Prensner et al., 2012). As a PCa diagnostic, prognostic, and screening tool, PSA is currently the focus of a contentious debate; it is crucial to concentrate on additional molecular markers that can aid in clinical outcomes and therapeutic decision-making (Alarcón-Zendejas et

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al., 2022). Over the last decade, a variety of novel serum, urine, and tissue-based PCa markers have been identified through deep sequencing of cell-free DNA (cfDNA) employing modified panels that allow study of PCa-related genes, producing the most advanced results (Porzycki and Ciszkowicz, 2020; Zabegina et al., 2023). The study of PCa and the intracellular signaling systems that control carcinogenesis of the prostate gland has benefited from innovative insights generated by transcriptome and genome research in particular (Ikeda et al.,2019). Other than that, Bioinformatics and artificial intelligence have been used in medicine for monitoring, detecting, diagnosing, and treating patients in order to provide novel clinical predictive models for PCa management (Goldenberg et al., 2019; Li, Huo, and Xo, 2020). As an alternative, numerous research has investigated the potential role of some fluid metabolites, such as urinary fluid exosomes, and the possibility of using them as noninvasive urinary diagnostic and screening markers for PCa (Salciccia et al., 2021; Wang et al., 2022).

2.9. Prostate Cancer Gene 3(PCA3) Urinary-Based Biomarker

Prostate cancer gene 3, one of the most frequently investigated markers, initially called differential display clone 3 (DD3), was primarily pronounced in 1999 (Bussemakers et al.,1999). PCA3, which is also called a Long non-coding RNA (lncRNA), is a non-coding gene expression and a prostate-specific mRNA that is expressed at low levels in healthy prostate tissue but is significantly overexpressed in PCa (Lauer et al., 2023). The test is mainly done through handling of the prostate gland following a DRE, which can release cells into the urethra; thus, sediments from urine will be collected and studied (Ankerst and Thompson, 2009). As a urinary biomarker, PCA3 seems particularly interesting, as they are not excessively intrusive, more specific, effortlessly available, and appropriate for large-scale screening (Durand et al., 2011). However, its prognostic importance remains uncertain as PCA3 has an infrequent genomic association, being present in an antisense track in an intron of the protein-coding gene PRUNE2 (Lauer et al., 2023). Although they are not linked to biochemical recurrence, upregulation of the lncRNA PCA3 and targeted downregulation of the protein-coding PRUNE2 gene in PCa may be early (rather than late) molecular processes in the development of human prostate carcinogenesis (Lauer et al., 2023). PCA3 is androgen-regulated and so forth it aids PCa cell endurance (Ferreira et al., 2012). PCA3 is already considered a PCa biomarker, and it is estimated by the marketable test PROGENSA, approved in 2012 by the FDA, and this test kit appears to have PCa detection sensitivity of 62% and a specificity of 75%, indicating that PCA3 can be one of the molecular markers with clinical effectiveness (Alarcón-Zendejas et al., 2022). The PCA3urine test has confirmed its clinical utility and capacity to forecast the results of biopsies. Additionally, PCA3 is thought to be useful for monitoring patients under active surveillance and for determining when to perform another biopsy. It is necessary to validate its prognostic significance in identifying the characteristics of aggressive malignancy. Proteomic, transcriptomic, and multiplex approaches will likely be combined in future methods to find combinations of several indicators to improve PCa diagnosis and characterization. The therapeutic relevance and prognostic value of the PCA3urine test for biopsy outcomes have been established. Its predictive efficacy in identifying the characteristics of cancer aggression must be validated. PCa diagnosis and characterization will likely be improved by future methods that combine proteomic, transcriptomic, and multiplex tactics to find blends of various markers (Durand et al., 2011). Nevertheless, more research is needed to ensure the clinical value of these technologies, as well as analytical and clinical validity.

2.10. MicroRNAs (miRNAs)

MicroRNAs are a type of minor non-coding supervisory RNAs with 20–24 nucleotides in length that bind to specific target gene transcripts and interfere with their proper translation (Song, Chen, and Song, 2019). Additionally, they control

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messenger RNA post-transcriptional degradation. Due to this epigenetic function, the dysregulation of miRNAs plays a crucial role in the etiology and development of many malignancies, including PCa (Muthamilselvan et al., 2023). MicroRNAs, which were previously thought to be 'junk' RNA, are now widely recognized to be involved in a variety of biochemical and physiological processes (Constâncio et al., 2022). Porkka et al. carried out the first miRNA expression profile in PCa. In order to examine the expression of 319 human miRNAs in PCa cases, they used the oligonucleotide array hybridization approach and discovered 51 miRNAs that were differentially expressed in PCa (Porkka, et al., 2007). Afterward, a large number of platforms have been established for miRNA expression profiling, including Microarray and next-generation sequencing (NGS) technologies. In parallel, qRT-PCR has been recognized as the most appropriate technology to authenticate miRNA expression-profiling results (Casanova-Salas et al., 2012). Numerous biological pathways, including those related to cancer, such as proliferation, apoptosis, the cell cycle, invasion, and migration, depend heavily on miRNAs. Additionally, they may serve as molecular markers for early cancer detection, diagnosis, and prognosis, including PCa. (Bevacqua et al., 2022). In addition to blood, urinary miRNAs, particularly the molecules encapsulated inside extracellular vesicles, can be applied as standard clinical biomarkers for PCa detection (Juracek,2022). The mRNA levels of two genes, HOXC6 and DLX1, which are found to be overexpressed in fierce PCa, are measured using a commercially existing assay called SelectMDx (MDxHealth, Irvine, USA). The mRNA values are quantified following a post-DRE urine sample and normalized to KLK3 mRNA, the gene that encodes PSA. The mRNA values of HOXC6 and DLX1 are then joined into a single RNA value, which is then used, along with known clinical risk factors (patient age, PSAD, and DRE), to determine the percent likelihood of identifying intermediate or higher PCa on initial prostate biopsy (Boehm et al.,2023). To conclude, strong evidence demonstrates the complex nature of the mechanisms underlying the post-transcriptional regulation of miRNAs (Kelly et al., 2018). Though because of their detection, dysregulation, and stability in blood, miRNAs appear to have a lot of potential as a novel marker for PCa in the near future.

2.11. The Role of Artificial Intelligence & Machine Learning in PCa Investigation and Research

Artificial intelligence (AI) is the ability of a computer to conduct cognitive tasks in order to accomplish a certain objective, depending on the provided data, and it is on the way to transform and reshape our healthcare systems (Goldenberg et al., 2019; Castaldo et al., 2021). By spotting patterns and making decisions that previously required human expertise, AI has the potential to improve PCa diagnosis, stratification, and patient classification (Muthamilselvan et al., 2023; Wilson et al., 2024). Moreover, the incorporation of multiple peptides into a machine learning-based biomarker model improves the ability to detect PCa in urine samples without the requirement for prior digital rectal examination, and this multiple-biomarker model has been shown to detect PCa with high accuracy and has the potential to reduce invasive procedures in men who are scheduled for a biopsy (Frantzi et al., 2023). AI and ML will assist medical professionals in providing higher-quality care, and they have the potential to do so in the near future and beyond.

The science of machine learning teaches computers how to create models and learn from massive amounts of data. Using genomic and phenotypic data, ML can improve parts of biomedicine such as cancer screening and prediction, illness diagnosis, prognosis, anatomical imaging, tissue biopsies, tailored treatment, surgical procedures, radiomics, genomics, and transcriptomics (Castaldo et al., 2021; Muthamilselvan et al., 2023; Zhang et al., 2023). Also, it can be used to train machines to identify complicated patterns in sequencing data and radiographic images, distinguishing individual genes

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or sets of genes within expression outlines, as well as certain expression levels that can expect clinical conclusions such as progression, biochemical recurrence, or metastasis (Alarcón-Zendejas et al., 2022). Though the use of chatbots to make diagnoses or propose treatment is the application with the most promise and anxiety. The main concern is that the user with no clinical experience may have difficulty distinguishing between fact and fiction. Regardless of our desire or preference, chatbots will become key tools in the practice of medicine in the future. They, like any good tool, can help us accomplish our jobs better, but if not utilized appropriately, they can cause harm, because the tools are new and difficult to assess using typical approaches (Haug and Drazen, 2023). Lastly, the most frequently utilized prostate biomarkers and their clinical significance are listed in Table 1.

Table 1. Common PCa diagnostic and differentiative bioindicators with their clinical significance.

Biomarker	Sample type	Clinical utility	Significant references
tPSA	Serum	Initial-line screening; high levels prompt biopsy. low specificity: rises in BPH & prostatitis.	David and Leslie, 2022 Wilson et al., *2024*
%fPSA	Serum	Increases specificity over tPSA alone. Help in risk stratification	Etzioni et al., 2004 Lima et al., 2019
Prostate Health Index (PHI)	Serum	Improved discrimination among BPH and PCa within PSA "gray zone"	Duffy, 2020 Yáñez-Castillo et al., 2023
4K Score	Serum	Might decrease needless biopsies by 14-20%. Best diagnostic odds ratio between liquid biomarkers.	Chen et al., 2023 Wagaskar et al., 2021
PCA3	Urine	Non-coding RNA overexpressed in PCa Rises specificity over PSA alone. Better for repeat biopsy choices.	Alarcón-Zendejas et al., 2022 Lauer et al., 2023
SelectMDx (HOXC6, DLX1)	Urine	Distinguishes higher PCa (Gleason ≥7) in men at risk for biopsy or with prior negative biopsy.	Boehm et al.,2023
miRNAs	Blood Urine Semen	Non-coding RNAs. non-invasive early detection and prognosis of PCa.	Bevacqua et al., 2022 Muthamilselvan et al., 2023

3. Discussion

Men around the world continue to struggle with prostatic disorders, and PCa remains the most hostile condition. It is evident that PCa is a heterogeneous disease characterized by diverse clinical performance, from slow to aggressive tumors with lethal expansion. Hence, initial screening and diagnosis of PCa aggressiveness are critical basics for effective patient care (Tanase et al., 2017; Erickson et al., 2021). This review is an attempt to give an overview of multidirectional approaches toward introducing new and innovative markers for prostate disease prognosis and management, especially PCa. Although the earlier markers, such as PSA assisted in an increased detection rate of PCa at earlier stages (Duffy, 2020), uncertainty about the usefulness of PSA screening is apparent and may persist for many years (Duffy, 2011), as it has its own drawbacks, such as a lack of

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specificity, an increase in BPH, and the omission of a significant number of PSA-negative cancers. Conversely, PSA measurement showed higher overall accuracy when combined with other screening tools, such as PSA-derived markers; PHI score, PSAD, and PSAV and 4K score/MRI-based tool (Wagaskar et al., 2021; Tidd-Johnson et al., 2022). Additionally, the PSA positive predicted value (PPV) and overall PCa detection accuracy were dramatically increased by combining the traditional PSA readout with circulating chromosomal conformations (Pchejetski et al., 2023).

Since the complex nature of prostatic disease requires more breakthroughs in disease screening bioindicators, this fact has prompted researchers to look for more precise and specific bioindicators that can help with not only PCa diagnosis but also successful disease outcome prediction and disease severity stratification (Bickers and Aukim-Hastie, 2009; Bhagirath et al., 2020). Broadly, the investigations for identifying new bioindicators are directed toward the molecular mechanisms that promote severe carcinogenesis, since this transition came as a result of a series of genetic and epigenetic alterations. Thus, the research areas mainly include genomics, transcriptomics, and proteomics. (Martin, 2012; Eickelschulte et al., 2022). While seeking new screening PCa markers, sometimes researchers came up with controversial findings. Cernei et al. concluded that non-proteinogenic amino acid sarcosine shows considerable potential as a non-intrusive molecular marker (Cernei et al., 2013). In contrast, Ankerst et al. concluded that this amino acid should not be further used as a marker for early detection of PCa (Ankerst et al., 2015). Genomic and transcriptomic research has been transformed by next-generation sequencing (NGS). RNA-Seq can find new possible PCa markers since it scans the transcriptome at a single nucleotide resolution, revealing uncharted genomic and transcriptomic domains not unveiled by traditional technologies like microarray (Alkhateeb et al., 2019). The use of miRNAs extracted from urine, blood, and other biofluids, as molecular markers for non-invasive diagnosis, risk stratification, and targeted therapies, is a promising tool if consensus can be reached on the best miRNA detection techniques, sample sources, procedures for collection, storage, and the quantity of biological fluid collected (Angerilli, et al., 2021; Constâncio et al., 2022). However, only a few numbers of miRNAs were found to be reliably linked to disease progression across several studies and datasets, showing their usefulness in predicting prognosis (Rana et al., 2022).

However, their biological importance in the development of PCa is yet uncertain and requires further research. Lastly, in the middle of all these approaches, AI and ML have emerged as promising tools in oncology. AI deployed to predict and automate numerous malignancies, including PCa (Blessin et al., 2023), and subsequently enhancing patient outcomes and healthcare precision and ML has proven to be quite successful at predicting different cancer types. When it comes to cancer prediction, both techniques have outperformed physicians (Huang et al., 2020; Zhang et al., 2023). Besides the great potential of these newly introduced techniques, they remain associated with certain limitations when dealing with real-world data sets, more prospective research must be carried out in order to better grasp the advantages of AI for both cancer patients and urologists (Pai et al., 2020). Finally, the fight to develop novel PCa screening biological indicators is complicated and never-ending, with the goal of developing a highly effective, available, and validated tool that can be applied within various populations worldwide.

4. Conclusions

Prostatic diseases, in particular PCa, remain an international health concern facing males. Despite the fact that tissue biopsy is regarded as the gold standard diagnostic tool, solitary invasive prostate biopsy is insufficient for inclusive evaluation due to the inability to identify a clonal source of metastatic disease in primary PCa. Conventional screening and diagnosing markers such as tPSA show a shortcoming because of their limited specificity and

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sensitivity, which, in many cases, can lead to overdiagnosis and overtreatment of inactive disease. This obstacle displays the ongoing necessity for new auxiliary non-invasive diagnostic, prognostic, and disease stratification bioindicators that could enhance the functionality of traditional tools like tPSA in clinical decision-making through higher sensitivity and specificity. Although PSA-derived markers, including PHI score, PSAD,4k score, and PSAV, showed some diagnostic improvement, especially when combined with other tools such as mpMRI, yet, many questions need to be answered, thus genetic as well as epigenetic studies through the deployment of new technological approaches in genomics, transcriptomics, and proteomics are continuous intensive research areas to reveal novel, easy, and cost-effective biosignatures. MicroRNAs and PCA3, extracted from urine, blood, and prostatic secretions, are promising tools in addition to the latest approaches related to deploying AI and machine learning in prostatic disease research.

Conflict of interest

There is no conflict of interest to this review article.

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References

Ahmed, H. U., Bosaily, A. E. S., Brown, L. C., Gabe, R., Kaplan, R., Parmar, M. K., ... & Emberton, M. (2017). Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. The Lancet 389(10071), pp. 815–822. doi: 10.1016/S0140-6736(16)32401-1.

Alarcón-Zendejas, A.P., Scavuzzo, A., Jiménez-Ríos, M.A., Álvarez-Gómez, R.M., Montiel-Manríquez, R., Castro-Hernández, C., Jiménez-Dávila, M.A., Pérez-Montiel, D., González-Barrios, R., Jiménez-Trejo, F. and Arriaga-Canon, C., (2022). The promising role of new molecular biomarkers in prostate cancer: From coding and non-coding genes to artificial intelligence approaches. Prostate cancer and prostatic diseases, 25(3), pp.431-443.

Alkhateeb, A., Rezaeian, I., Singireddy, S., Cavallo-Medved, D., Porter, L.A. and Rueda, L., (2019). Transcriptomics signature from next-generation sequencing data reveals new transcriptomic biomarkers related to prostate cancer. Cancer informatics, 18, p.1176935119835522.

Angerilli, V., Galuppini, F., Businello, G., Dal Santo, L., Savarino, E., Realdon, S., Guzzardo, V., Nicolè, L., Lazzarin, V., Lonardi, S., Loupakis, F. and Fassan, M., (2021). MicroRNAs as Predictive Biomarkers of Resistance to Targeted Therapies in Gastrointestinal Tumors. Biomedicines, [online] 9(3), p.318. https://doi.org/10.3390/biomedicines9030318.

Ankerst, D.P., Tangen, C.M. and Thompson, I.M. eds., (2009). Prostate cancer screening. Springer Science & Business Media.

Ankerst, D. P. and Thompson, I. M., (2009). The performance characteristics of prostate-specific antigen for prostate cancer screening. In Prostate Cancer Screening (pp. 61-70). Totowa, NJ: Humana Press.

Ankerst, D.P., Liss, M., Zapata, D., Hoefler, J., Thompson, I.M. and Leach, R.J., (2015). A case control study of sarcosine as an early prostate cancer detection biomarker. BMC urology, 15(1), pp.1-4.

© 2026 University of Sulaimani. All rights reserved.

Bhagirath, D., Yang, T.L., Akoto, T., Patel, N., Tabatabai, L.Z. and Saini, S., (2020). MicroRNA-4287 is a novel tumor suppressor microRNA controlling epithelial-to mesenchymal transition in prostate cancer. Oncotarget, 11(51), p.4681.

Begemann, D., Anastos, H. and Kyprianou, N. (2018). Cell death under epithelial–mesenchymal transition control in prostate cancer therapeutic response. International Journal of Urology 25(4), pp. 318–326. doi: 10.1111/iju.13505.

Bevacqua, E., Ammirato, S., Cione, E., Curcio, R., Dolce, V., & Tucci, P. (2022). The Potential of MicroRNAs as Non-Invasive Prostate Cancer Biomarkers: A Systematic Literature Review Based on a Machine Learning Approach. Cancers, 14(21), 5418. https://doi.org/10.3390/cancers14215418

Bickers, B. and Aukim-Hastie, C., (2009). New molecular biomarkers for the prognosis and management of prostate cancer-the post PSA era. Anticancer research, 29(8), pp.3289-3298.

Boehm, B.E., York, M.E., Petrovics, G., Kohaar, I. and Chesnut, G.T. (2023). Biomarkers of Aggressive Prostate Cancer at Diagnosis. International Journal of Molecular Sciences 24(3). doi: 10.3390/ijms24032185.

Boo, Y. et al. (2023). Comparison of Prostate-Specific Antigen and Its Density and Prostate Health Index and Its Density for Detection of Prostate Cancer. Biomedicines 11(7), p. 1912. Available at: https://www.mdpi.com/2227-9059/11/7/1912.

Borque-Fernando, Á. et al. (2019). Role of the 4Kscore test as a predictor of reclassification in prostate cancer active surveillance. Prostate Cancer and Prostatic Diseases 22(1), pp. 84–90. doi: 10.1038/s41391-018-0074-5.

Brawley, O.W., Ankerst, D.P. and Thompson, I.M. (2009). Screening for Prostate Cancer. CA: A Cancer Journal for Clinicians 59(4), pp. 264–273. Available at: http://doi.wiley.com/10.3322/caac.20026.

Casanova-Salas, I., Rubio-Briones, J., Fernández-Serra, A. and López-Guerrero, J.A. (2012). MiRNAs as biomarkers in prostate cancer. Clinical and Translational Oncology 14(11), pp. 803–811. doi: 10.1007/s12094-012-0877-0.

Castaldo, R., Cavaliere, C., Soricelli, A., Salvatore, M., Pecchia, L., & Franzese, M. (2021). Radiomic and Genomic Machine Learning Method Performance for Prostate Cancer Diagnosis: Systematic Literature Review. Journal of medical Internet research, 23(4), e22394. https://doi.org/10.2196/22394

Catalona, W.J., Smith, D.S., Ratliff, T.L. and Basler, J.W., (1993). Detection of organ-confined prostate cancer is increased through prostate-specific antigen—based screening. Jama, 270(8), pp.948-954.

Catalona, W.J. (2018). Prostate Cancer Screening. Medical Clinics of North America 102(2), pp. 199–214. doi: 10.1016/j.mcna.2017.11.001.

Cernei, N., Heger, Z., Gumulec, J., Zitka, O., Masarik, M., Babula, P., Eckschlager, T., Stiborova, M., Kizek, R. and Adam, V., (2013). Sarcosine as a potential prostate cancer biomarker—A review. International journal of molecular sciences, 14(7), pp.13893-13908.

Chang, T.H., Lin, W.R., Tsai, W.K., Chiang, P.K., Chen, M., Tseng, J.S. and Chiu, A.W. (2020). Zonal adjusted PSA density improves prostate cancer detection rates compared with PSA in Taiwanese males with PSA < 20 ng/ml. BMC Urology 20(1). doi: 10.1186/s12894-020-00717-z.

Chen, C. S., Wang, S. S., Li, J. R., Cheng, C. L., Yang, C. R., Chen, W. M., ... & Yang, C. K. (2011). PSA density as a better predictor of prostate cancer than percent-free PSA in a repeat biopsy. Journal of the Chinese Medical Association 74(12), pp. 552–555. doi: 10.1016/j.jcma.2011.10.004.

Christensson, A, Bjork, T and Nilsson, O. (1993). Serum prostate specific antigen complexed to a1-antichymotrypsin as an indicator of prostate cancer. J. of Urol.; 150:100-105.

© 2026 University of Sulaimani. All rights reserved.

Clapp, L. (2002). Prostatitis-The 60 Day Cure Why Most Men Have This Precursor to BPH and Prostate Cancer & an Innovative 10-Step Program for Healing. Available at: www.prostate90fndn.org.

Constâncio, V., Tavares, N.T., Henrique, R., Jerónimo, C. and Lobo, J. (2023). MiRNA biomarkers in cancers of the male reproductive system: Are we approaching clinical application? Andrology 11(4), pp. 651–667. doi: 10.1111/andr.13258.

Crocetto F, Barone B, De Luca L, Creta M. (2020). Granulomatous prostatitis: a challenging differential diagnosis to take into consideration. Future Oncol. 16(13):805-806. doi: 10.2217/fon-2020-0185. Epub 2020 Mar 17. PMID: 32180450.

Darst, B. F., Chou, A., Wan, P., Pooler, L., Sheng, X., Vertosick, E. A., ... & Haiman, C. A (2020). The four-kallikrein panel is effective in identifying aggressive prostate cancer in a multiethnic population. Cancer Epidemiology Biomarkers and Prevention 29(7), pp. 1381–1388. doi: 10.1158/1055-9965.EPI-19-1560.

David, M.K. and Leslie, S.W., (2022). Prostate specific antigen. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557495/?report=printable.

Duffy, M.J. (2011). Prostate-specific antigen: Does the current evidence support its use in prostate cancer screening? Annals of Clinical Biochemistry 48(4), pp. 310–316. doi: 10.1258/acb.2011.010273.

Duffy, M.J. (2020). Biomarkers for prostate cancer: Prostate-specific antigen and beyond. Clinical Chemistry and Laboratory Medicine 58(3), pp. 326–339. doi: 10.1515/cclm-2019-0693.

Durand, X., Moutereau, S., Xylinas, E. and De La Taille, A. (2011). ProgensaTM PCA3 test for prostate cancer. Expert Review of Molecular Diagnostics 11(2), pp. 137–144. doi: 10.1586/erm.10.122.

Egevad, L., Delahunt, B., Iczkowski, K., Kwast, T., Leenders, G., Leite, K., Pan, C., Samaratunga, H., Tsuzuki, T., Mulliqi, N., Ji, X., Olsson, H., Valkonen, M., Ruusuvuori, P., Eklund, M., & Kartasalo, K. (2023). Interobserver Reproducibility of Cribriform Cancer in Prostate Needle Biopsies & Validation of International Society of Urological Pathology Criteria. Histopathology.https://doi.org/10.1111/his.14867.

Eickelschulte, S., Riediger, A. L., Angeles, A. K., Janke, F., Duensing, S., Sültmann, H., & Görtz, M. (2022). Biomarkers for the Detection and Risk Stratification of Aggressive Prostate Cancer. Cancers, 14(24), 6094. https://doi.org/10.3390/cancers14246094

Erickson, A., Hayes, A., Rajakumar, T., Verrill, C., Bryant, R.J., Hamdy, F.C., Wedge, D.C., Woodcock, D.J., Mills, I.G. and Lamb, A.D., (2021). A systematic review of prostate cancer heterogeneity: Understanding the clonal ancestry of multifocal disease. European urology oncology, 4(3), pp.358-369.

Etzioni, R, Seth, F, Peter, H.G, Charles L. K, David F. P, and Meir JS. (2004). Prostate-specific antigen and free prostate-specific antigen in the early detection of prostate cancer: do combination tests improve detection? Cancer Epidemiol Biomarkers Prev; 13(10): 1640-45.

Farha, M.W. and Salami, S.S. (2022). Biomarkers for prostate cancer detection and risk stratification. Therapeutic Advances in Urology 14. doi: 10.1177/17562872221103988.

Ferreira, L. B., Palumbo, A., de Mello, K. D., Sternberg, C., Caetano, M. S., de Oliveira, F. L., ... & Gimba, E. R. P. (2012). PCA3 noncoding RNA is involved in the control of prostate-cancer cell survival and modulates androgen receptor signaling. BMC Cancer 12. doi: 10.1186/1471-2407-12-507.

Frantzi, M., Gomez Gomez, E., Blanca Pedregosa, A., Valero Rosa, J., Latosinska, A., Culig, Z., ... & Carrasco Valiente, J. (2019). CE–MS-based

© 2026 University of Sulaimani. All rights reserved.

urinary biomarkers to distinguish non-significant from significant prostate cancer. British Journal of Cancer 120(12), pp. 1120–1128. doi: 10.1038/s41416-019-0472-z.

Goldenberg, S. L., Nir, G., & Salcudean, S. E. (2019). A new era: artificial intelligence and machine learning in prostate cancer. Nature reviews. Urology, 16(7), 391–403. https://doi.org/10.1038/s41585-019-0193-3

Görtz, M., Radtke, J. P., Hatiboglu, G., Schütz, V., Tosev, G., Güttlein, M., ... & Nyarangi-Dix, J. N. (2021). The Value of PSAD for Prostate Imaging-Reporting and Data System 3 Lesions on mpMRI imaging: A Strategy to Avoid Unnecessary Prostate Biopsies. European Urology Focus 7(2), pp. 325–331. doi: 10.1016/j.euf.2019.11.012.

He, J., Han, Z., Luo, W., Shen, J., Xie, F., Liao, L., Zou, G., Luo, X., Guo, Z., Li, Y. and Li, J., (2023). Serum organic acid metabolites can be used as potential biomarkers to identify prostatitis, benign prostatic hyperplasia, and prostate cancer. Frontiers in Immunology, 13, p.998447.

Haug, C.J. and Drazen, J.M., (2023). Artificial intelligence and machine learning in clinical medicine, (2023). New England Journal of Medicine, 388(13), pp.1201-1208.

Huang, S., Yang, J., Fong, S. and Zhao, Q., (2020). Artificial intelligence in cancer diagnosis and prognosis: Opportunities and challenges. Cancer letters, 471, pp.61-71.

Ikeda, S., Elkin, S. K., Tomson, B. N., Carter, J. L., & Kurzrock, R. (2019). Next-generation sequencing of prostate cancer: genomic and pathway alterations, potential actionability patterns, and relative rate of use of clinical-grade testing. Cancer biology & therapy, 20(2), 219–226. https://doi.org/10.1080/15384047.2018.1523849

Janane, A., Hajji, F., Ismail, T., Jawad, C., Elondo, J. C., Dakka, Y., ... & Albouzidi, A. (2012). Utilidad y valor predictivo de la densidad de PSA ajustada por el volumen de la zona de transición en hombres con niveles de PSA entre 2 y 4 ng/ml. Actas Urologicas Espanolas 36(2), pp. 93–98. doi: 10.1016/j.acuro.2011.06.025.

Jansen, F. H., van Schaik, R. H., Kurstjens, J., Horninger, W., Klocker, H., Bektic, J., ... & Bartsch, G. (2010). Prostate-Specific Antigen (PSA) Isoform p2PSA in Combination with Total PSA and Free PSA Improves Diagnostic Accuracy in Prostate Cancer Detection. European Urology 57(6), pp. 921–927. doi: 10.1016/j.eururo.2010.02.003.

Javaeed, A., Ghauri, S.K., Ibrahim, A. and Doheim, M.F. (2020). Prostate-specific antigen velocity in diagnosis and prognosis of prostate cancer - A systematic review. Oncology Reviews 14(1), pp. 64–71. doi: 10.4081/oncol.2020.449.

Jue, J. S., Barboza, M. P., Prakash, N. S., Venkatramani, V., Sinha, V. R., Pavan, N., ... & Punnen, S. (2017). Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy. Urology 105, pp. 123–128. doi: 10.1016/j.urology.2017.04.015.

Juracek, J., Madrzyk, M., Stanik, M. and Slaby, O. (2022). Urinary microRNAs and Their Significance in Prostate Cancer Diagnosis: A 5-Year Update. Cancers 14(13). doi: 10.3390/cancers14133157.

Kasivisvanathan, V., Rannikko, A. S., Borghi, M., Panebianco, V., Mynderse, L. A., Vaarala, M. H., ... & Moore, C. M. (2018). MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. New England Journal of Medicine. doi: 10.1056/nejmoa1801993.

Kelly, B.D., Miller, N., Sweeney, K.J., Durkan, G.C., Rogers, E., Walsh, K. and Kerin, M.J. (2015). A circulating microRNA signature as a biomarker for prostate cancer in a high-risk group. Journal of Clinical Medicine 4(7), pp. 1369–1379. doi: 10.3390/jcm4071369.

© 2026 University of Sulaimani. All rights reserved.

Khan FU, Ihsan AU, Khan HU, Jana R, Wazir J, Khongorzul P, Waqar M, Zhou X. (2017). Comprehensive overview of prostatitis. Biomed Pharmacother. 94:1064-1076. doi: 10.1016/j.biopha.2017.08.016. Epub 2017 Aug 16. PMID: 28813783.

Lauer, R. C., Barry, M., Smith, T. L., Thomas, A. M., Wu, J., Du, R., ... & Arap, W. (2023). Dysregulation of the PRUNE2/PCA3 genetic axis in human prostate cancer: from experimental discovery to validation in two independent patient cohorts. 12, p. 81929. doi: 10.7554/eLife.

Li, S., Hou, J. and Xu, W. 2020. Screening and identification of key biomarkers in prostate cancer using bioinformatics. Molecular Medicine Reports 21(1), pp. 311–319. doi: 10.3892/mmr.2019.10799.

Lilja, H, Christensson, A, and Dahlen, U. (1991). Prostate-specific antigen in serum occurs predominantly in complex with alpha-1-antichymotrypsin. Clin Chem 37:1618-1625.

Lilja, H, Piironen, TP and Rittenhouse, HG (2000). Prostate-specific antigen. In Vogelzang NJ, Shipley WU, Scardino PT, Coffey DS eds, Comprehensive Textbook of Genitourinary Oncology. Philadelphia:Lippincott, Williams and Wilkins Publishers: 638–50.

Lima, A. R., Pinto, J., Azevedo, A. I., Barros-Silva, D., Jeronimo, C., Henrique, R., ... & Carvalho, M. (2019). Identification of a biomarker panel for improvement of prostate cancer diagnosis by volatile metabolic profiling of urine. British Journal of Cancer 121(10), pp. 857–868. doi: 10.1038/s41416-019-0585-4.

Loeb, S., Sanda, M. G., Broyles, D. L., Shin, S. S., Bangma, C. H., Wei, J. T., ... & Catalona, W. J. (2015). The prostate health index selectively identifies clinically significant prostate cancer. Journal of Urology 193(4), pp. 1163–1169. doi: 10.1016/j.juro.2014.10.121.

Loeb, S., Roehl, K.A., Catalona, W.J. and Nadler, R.B. (2007). Prostate Specific Antigen Velocity Threshold for Predicting Prostate Cancer in Young Men. Journal of Urology 177(3), pp. 899–902. doi: 10.1016/j.juro.2006.10.028.

Loughlin, K.R. (2014). PSA velocity: A systematic review of clinical applications. Urologic Oncology: Seminars and Original Investigations 32(8), pp. 1116–1125. doi: 10.1016/j.urolonc.2014.04.010.

Malagobadan, S. and Nagoor, N.H. (2018). Anoikis. In: Encyclopedia of Cancer. Elsevier, pp. 75–84. doi: 10.1016/B978-0-12-801238-3.65021-3.

Martin, S.K., Vaughan, T.B., Atkinson, T., Zhu, H. and Kyprianou, N. (2012). Emerging biomarkers of prostate cancer (Review). Oncology Reports 28(2), pp. 409–417. doi: 10.3892/or.2012.1832.

Mikolajczyk, S.D., Marks, L.S., Partin, A.W. and Rittenhouse, H.G., (2002). Free prostate-specific antigen in serum is becoming more complex. Urology, 59(6), pp.797-802.

Moul, J. W., Sun, L., Hotaling, J. M., Fitzsimons, N. J., Polascik, T. J., Robertson, C. N., ... & Albala, D. M. (2007). Age Adjusted Prostate Specific Antigen and Prostate Specific Antigen Velocity Cut Points in Prostate Cancer Screening. Journal of Urology 177(2), pp. 499–504. doi: 10.1016/j.juro.2006.09.063.

Muhammad, S.M. and Waheed, I.I., (2013). Prostate–Specific Antigen (Psa) as a Screening Tool for Benign Prostate Hyperplasia (Bph) and Prostate Cancer (Pca) in Sulaimani Province. Science Journal of University of Zakho, 1(2), pp.486-495.

Muthamilselvan, S., Ramasami Sundhar Baabu, P., & Palaniappan, A. (2023). Microfluidics for Profiling miRNA Biomarker Panels in AI-Assisted Cancer Diagnosis and Prognosis. Technology in cancer research & treatment, 22, 15330338231185284. https://doi.org/10.1177/15330338231185284

Nath, C.K., Barman, B., Phukan, P., Sailo, S.L., Dey, B., Nath, I. and Rajkhowa, P. (2020). PSAD: A Measurement to Differentiate Benign Hypertrophy of Prostate from Prostate Carcinoma. Journal of Laboratory Physicians

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12(01), pp. 44–48. doi: 10.1055/s-0040-1714195.

Nogueira, L., Corradi, R. and Eastham, J.A., (2009). Prostatic specific antigen for prostate cancer detection. International braz j urol, 35, pp.521-531.

Nordström, T., Vickers, A., Assel, M., Lilja, H., Grönberg, H. and Eklund, M. (2015). Comparison between the four-kallikrein panel and prostate health index for predicting prostate cancer. European Urology 68(1), pp. 139–146. doi: 10.1016/j.eururo.2014.08.010.

Noureldin, M.E., Connor, M.J., Boxall, N., Miah, S., Shah, T. and Walz, J. (2020). Current techniques of prostate biopsy: An update from past to present. Translational Andrology and Urology 9(3), pp. 1510–1517. doi: 10.21037/tau.2019.09.20.

Omri, N., Kamil, M., Alexander, K., Alexander, K., Edmond, S., Ariel, Z., ... & Azik, H. (2020). Association between PSA density and pathologically significant prostate cancer: The impact of prostate volume. Prostate 80(16), pp. 1444–1449. doi: 10.1002/pros.24078.

Pai, R.K., Van Booven, D.J., Parmar, M., Lokeshwar, S.D., Shah, K., Ramasamy, R. and Arora, H., (2020). A review of current advancements and limitations of artificial intelligence in genitourinary cancers. American journal of clinical and experimental urology, 8(5), p.152.

Pchejetski, D., Hunter, E., Dezfouli, M., Salter, M., Powell, R., Green, J., Naithani, T., Koutsothanasi, C., Alshaker, H., Jaipuria, J., Connor, M. J., Eldred-Evans, D., Fiorentino, F., Ahmed, H., Akoulitchev, A., & Winkler, M. (2023). Circulating Chromosome Conformation Signatures Significantly Enhance PSA Positive Predicting Value and Overall Accuracy for Prostate Cancer Detection. Cancers, 15(3), 821. https://doi.org/10.3390/cancers15030821

Porzycki, P. and Ciszkowicz, E. 2020. Modern biomarkers in prostate cancer diagnosis. Central European Journal of Urology 73(3), pp. 300–306. doi: 10.5173/ceju.2020.0067R.

Prensner, J.R., Rubin, M.A., Wei, J.T. and Chinnaiyan, A.M. (2012). Beyond PSA: The next generation of prostate cancer biomarkers. Science Translational Medicine 4(127). doi: 10.1126/scitranslmed.3003180.

Rana, S., Valbuena, G.N., Curry, E., Bevan, C.L. and Keun, H.C. (2022). MicroRNAs as biomarkers for prostate cancer prognosis: a systematic review and a systematic reanalysis of public data. British Journal of Cancer. doi: 10.1038/s41416-021-01677-3.

Reza, H.S., Ali, Z., Tara, H. and Ali, B. (2021). Age-specific reference ranges of prostate-specific antigen in the elderly of Amirkola: A population-based study. Asian Journal of Urology 8(2), pp. 183–188. doi: 10.1016/j.ajur.2020.03.001.

Rubin MA, Dunn R, Strawderman M, Pienta KJ. Tissue microarray sampling strategy for prostate cancer biomarker analysis. (2002). Am J Surg Pathol 26(3):312-9. doi: 10.1097/00000478-200203000-00004. PMID: 11859202.

Saini, S. (2016). PSA and beyond: alternative prostate cancer biomarkers. Cellular Oncology 39(2), pp. 97–106. doi: 10.1007/s13402-016-0268-6.

Salciccia, S., Capriotti, A. L., Lagana, A., Fais, S., Logozzi, M., De Berardinis, E., ... & Maggi, M. (2021). Biomarkers in prostate cancer diagnosis: From current knowledge to the role of metabolomics and exosomes. International Journal of Molecular Sciences 22(9). doi: 10.3390/ijms22094367.

Shariat, S.F., Karam, J.A., Margulis, V. and Karakiewicz, P.I. (2008). New blood-based biomarkers for the diagnosis, staging and prognosis of prostate cancer. BJU International 101(6), pp. 675–683. doi: 10.1111/j.1464-410X.2007.07283. x.

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Shariat, S.F. and Roehrborn C.G. (2008). Using biopsy to detect prostate cancer. Rev. Urol., 10, pp.262-279.

Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. CA: a cancer journal for clinicians, 73(1), 17–48. https://doi.org/10.3322/caac.21763

Song, C., Chen, H. and Song, C. (2019). Research status and progress of the RNA or protein biomarkers for prostate cancer. OncoTargets and Therapy 12, pp. 2123–2136. doi: 10.2147/OTT.S194138.

Streicher, J., Meyerson, B.L., Karivedu, V. and Sidana, A. (2019). A review of optimal prostate biopsy: indications and techniques. Therapeutic Advances in Urology 11, pp. 1–8. doi: 10.1177/1756287219870074.

Tanase, C.P., Codrici, E., Popescu, I.D., Mihai, S., Enciu, A.M., Necula, L.G., Preda, A., Ismail, G. and Albulescu, R., (2017). Prostate cancer proteomics: Current trends and future perspectives for biomarker discovery. Oncotarget, 8(11), p.18497.

Tidd-Johnson, A. et al. (2022). Prostate cancer screening: Continued controversies and novel biomarker advancements. Current Urology 16(4), pp. 197–206. doi: 10.1097/CU9.0000000000000145.

Tops, S.C., Grootenhuis, J.G., Derksen, A.M., Giardina, F., Kolwijck, E., Wertheim, H.F., Somford, D.M. and Sedelaar, J.M., (2022). The effect of different types of prostate biopsy techniques on post-biopsy infectious complications. The Journal of Urology, 208(1), pp.109-118.

Wagaskar, V. G., Sobotka, S., Ratnani, P., Young, J., Lantz, A., Parekh, S., Falagario, U. G., Li, L., Lewis, S., Haines, K., 3rd, Punnen, S., Wiklund, P., & Tewari, A. (2021). A 4K score/MRI-based nomogram for predicting prostate cancer, clinically significant prostate cancer, and unfavorable prostate cancer. Cancer reports (Hoboken, N.J.), 4(4), e1357. https://doi.org/10.1002/cnr2.1357

Welén, K. and Damber, J.E. (2022). Androgens, aging, and prostate health. Reviews in Endocrine and Metabolic Disorders 23(6), pp. 1221–1231. doi: 10.1007/s11154-022-09730-z.

Wender, R.C., Brawley, O.W., Fedewa, S.A., Gansler, T. and Smith, R.A. (2019). A blueprint for cancer screening and early detection: Advancing screening's contribution to cancer control. CA: A Cancer Journal for Clinicians 69(1), pp. 50–79. doi: 10.3322/caac.21550.

Wilson, T. K., & Zishiri, O. T. (2024). Prostate cancer: A review of genetics, current biomarkers and personalised treatments. Cancer Reports, 7(10), e70016.

Wysock, J.S., Becher, E., Persily, J., Loeb, S. and Lepor, H. (2020). Concordance and Performance of 4Kscore and SelectMDx for Informing Decision to Perform Prostate Biopsy and Detection of Prostate Cancer. Urology 141, pp. 119–124. doi: 10.1016/j.urology.2020.02.032.

Yáñez-Castillo, Y. M., Melgarejo-Segura, M. T., Funes-Padilla, C., Folgueral-Corral, M. E., García-Larios, J. V., Arrabal-Polo, M. A., ... & Arrabal-Martín, M. (2023). Prostate health index (PHI) as an accurate prostate cancer predictor. Journal of Cancer Research and Clinical Oncology. doi: 10.1007/s00432-023-04860-6.

Zabegina, L., Zyatchin, I., Kniazeva, M., Shalaev, A., Berkut, M., Sharoyko, V., Mikhailovskii, V., Kondratov, K., Reva, S., Nosov, A., & Malek, A. (2023). Diagnosis of Prostate Cancer through the Multi-Ligand Binding of Prostate-Derived Extracellular Vesicles and miRNA Analysis. Life (Basel, Switzerland), 13(4), 885. https://doi.org/10.3390/life13040885

Zappala, S.M., Scardino, P.T., Okrongly, D., Linder, V. and Dong, Y. (2017). Clinical performance of the 4Kscore Test to predict high-grade prostate cancer at biopsy: A meta-analysis of us and European clinical validation study results. Reviews in urology 19(3), pp. 149–155. Available at:

© 2026 University of Sulaimani. All rights reserved.

http://www.ncbi.nlm.nih.gov/pubmed/29302237.

Zhang, B., Shi, H., & Wang, H. (2023). Machine Learning and AI in Cancer Prognosis, Prediction, and Treatment Selection: A Critical Approach. Journal of multidisciplinary healthcare, 16, 1779–1791. https://doi.org/10.2147/JMDH.S410301

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