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Literature Review

A Comparative Review of PSA, PSMA PET, and PCA3 Biomarkers in Prostate Cancer Diagnosis: Effectiveness, Cost, and Safety Analysis

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Abstract

Prostate cancer is the third most common urological cancer among men in Indonesia, with an incidence rate of 14.8 per 100,000 population in 2012. PSA has been a cornerstone of diagnosis, however its low specificity in distinguishing prostate cancer from other urological malignancies, is followed by study of other biomarkers such as PSMA and PCA3. PSMA and PCA3, either as a single marker or in combination with PSA, has the potential to enhance diagnostic accuracy, aid in risk assessment, and support treatment decision-making. The overall diagnostic accuracy, as indicated by the AUC integrating sensitivity and specificity, shows that PCA3 and PSMA have higher AUC values compared to PSA. Combining PSA with PSMA, PCA3, or both demonstrated promising potential for prostate cancer diagnosis when compared to PSA alone. PSA shows slightly higher sensitivity, supporting its role as a screening tool, while PSMA PET offers better specificity than conventional imaging for detecting advanced prostate cancer, albeit at a higher cost. Meanwhile, PCA3, a urinary biomarker, surpasses PSA in specificity, effectively reducing unnecessary biopsies with a safer, non-invasive approach. PSA remains the standard diagnostic biomarker for prostate cancer screening. Its low specificity may result in unnecessary biopsies. Other biomarkers like PSMA and PCA3 may be more appropriate for specific patient situations than PSA, with PCA3 being the least invasive procedure and PSMA PET being the most expensive. A multimodal approach combining PSA with PSMA or PCA3 shows significantly higher accuracy than PSA alone, improving diagnostic chances and reducing the risk of overdiagnosis.

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1. Introduction

The prostate is an accessory organ of the male reproductive system located below the bladder, primarily functioning to contribute essential secretions to semen to sustain sperm viability[1]. Globally, around 10 million men are currently affected by prostate cancer, with approximately 700,000 cases being metastatic[1]. In Indonesia, prostate cancer is the third most prevalent urologic cancer among men, with the age-standardized incidence rate rising from 10.6 per 100,000 men in 2008 to 14.8 per 100,000, according to GLOBOCAN 2012 data[2]. The projections by the American Cancer Society regarding prostate cancer in the United States for 2024 indicate approximately 299,010 new cases and around 35,250 fatalities attributed to the disease. The period from 2007 to 2014 witnessed a significant decrease in annual prostate cancer diagnoses, which aligned with reduced screening due to alterations in screening guidelines. However, starting from 2014, there has been an overall 3% yearly rise in incidence rates and approximately a 5% annual increase specifically for advanced-stage prostate cancer[3].

Prostate cancer is defined by the abnormal division of cells within the prostate gland, leading to irregular growth of the gland[4]. Over 95% of prostate cancer cases are adenocarcinomas, mainly of acinar origin, with a smaller portion arising from ductal cells. Nearly 80% of prostate adenocarcinomas originate from luminal or, less frequently, basal epithelial cells within the peripheral zones, which constitute over 70% of prostate tissue[1]. Risk factors for prostate cancer include high-fat diet, physical inactivity, obesity, excessive alcohol intake, and exposure to certain chemicals. A family history of prostate cancer, especially with onset at younger age, also heightens risk. Furthermore, certain genetic mutations in genes like BRCA1, BRCA2, and HOXB13 are linked to hereditary prostate cancer in some instances[5]. In the early stages of prostate cancer, patients typically remain asymptomatic. Mortality associated with prostate cancer are largely due to metastasis, where cancerous cells spread to areas such as the pelvic and retroperitoneal lymph nodes, spinal cord, bladder, rectum, bones, and brain[4]. Data from the 2022 Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute suggest that prostate cancer survival rates vary by the extent of metastasis. For localized prostate cancer, where the cancer remains at the primary site, the 5-year relative survival rate is approximately 100%. Similarly, regional prostate cancer, which has spread to nearby tissues or lymph nodes, also has a 5-year survival rate of nearly 100%. However, if the cancer has metastasized to distant tissues, the 5-year relative survival rate drops significantly to around 34%[6].

The diagnosis and treatment strategies for prostate cancer underwent significant changes in 1979 with the discovery of prostate-specific antigen[7]. While serum levels of prostate-specific antigen (PSA) is widely used for diagnosis, it is present not only in prostate cancer but also in normal prostate tissue and benign prostatic conditions[8]. PSA has low specificity in detecting prostate cancer, with accuracy ranging from 25% to 40%, leading to a high negative biopsy rate of up to 75%[4]. This emphasizes the urgent need for the development of alternatives to PSA testing, that can optimize diagnostic accuracy of prostate cancer.

Furthermore, there is an urgent need for more accurate tests to identify patients with aggressive and potentially life-threatening prostate cancer. In the diagnosis of prostate cancer, there is no single examination used. Digital rectal examination (DRE), prostate biopsy, and prostate-specific membrane antigen (PSMA) scanning are performed to measure the likelihood of prostate cancer indications[9]. Prostate-specific membrane antigen (PSMA) is a promising biomarker that offers greater specificity than PSA in detecting prostate cancer[10]. PSMA is a 100 kDa non-soluble type II transmembrane glycoprotein expressed on the apical surface of endothelial cells. It functions enzymatically as a carboxypeptidase in prostate tissue and as a folate hydrolase, playing a role in the utilization and metabolism of folic acid. PSMA targeting is still considered the main biomarker in the most sensitive detection of prostate cancer[11,12].PSMA is a membrane protein whose expression increases with androgen deprivation and correlates with cancer aggressiveness, while PSA is a secretory protein involved in semen liquefaction, with levels decreasing in response to androgen deprivation, making it useful for monitoring disease progression. However, PSMA is not entirely specific to the prostate, as it is also expressed in various non-prostatic solid tumors, including urothelial, renal, gastrointestinal, and breast carcinomas. Nevertheless, its expression levels

in these tissues are lower compared to those in prostate tissue[8].

Additional biomarkers, like Prostate Cancer Antigen 3 (PCA3), have been introduced to improve the accuracy of prostate cancer diagnosis through non-invasive methods. The PCA3 test, which measures the concentration of long non-coding RNA (lncRNA) in the patient's urine, has been discussed in various studies and shows promising results in detecting both malignant and non-malignant prostate conditions. Its potential to accurately identify prostate cancer with high specificity offers an advantage over traditional methods, reducing the need for unnecessary biopsies and improving early detection[13].

2. Method

We reviewed the contemporary peer-reviewed publications for articles related to the sensitivity, specificity, cost, and safety of PSMA and PCA3 tests as complementary diagnosis tests of PSA in diagnosing prostate cancer. We searched electronic databases such as Pubmed, Science Direct, Springerlink All Journal, and others, using the following keywords in various permutations: PSA, PSMA, PCA3, and Prostate Cancer.

3. Results

Prostate-specific antigen (PSA)

Prostate-specific antigen (PSA), also known as human kallikrein-related peptidase 3 (hK3), is a 33 kDa glycoprotein belonging to the kallikrein family of serine proteases. It is primarily secreted by epithelial cells of the prostate and has chymotrypsin-like enzymatic activity. PSA plays roles in various biological processes, including male fertility, cell proliferation regulation, and angiogenesis inhibition. The gene encoding PSA, *KLK3*, is located on chromosome 19 and is regulated by steroid hormones via androgen receptor-mediated transcription. While initially believed to be exclusively expressed in prostatic tissue, PSA has since been detected in other tissues, with at least 13 alternative splicing variants identified[14].

Clinically, the serum PSA test, combined with digital rectal examination (DRE), is widely used for prostate cancer screening, with a PSA level of 4 ng/mL commonly used as the threshold for recommending a biopsy[14]. Determining the optimal serum PSA cutoff value for the early detection of prostate cancer is a complex issue. Studies have evaluated the performance of various PSA cutoff levels across different age groups, focusing on sensitivity, specificity, positive predictive value, and the percentage of organ-confined cancers detected. One study suggested an upper limit of 4 ng/mL for men aged 60 to 69 years. However, this conclusion was based on a limited sample size of only 10 men who underwent biopsy to validate the proposed threshold. Another study examining men aged 50 to 59 years with normal digital rectal examination findings indicated that lowering the PSA cutoff from 4.0 to 3.5 ng/mL would have led to a 45% increase in the number of biopsies performed, highlighting the trade-offs between early detection and potential overdiagnosis[14].

Screening is conducted on men aged 40 to 75 without a history of prostate cancer, using a blood sample for analysis. PSA levels in the bloodstream may increase in conditions such as benign prostatic hyperplasia, prostatitis, perineal trauma, or following ejaculation and sexual activity. If the screening results are normal, the patient may undergo screening again after two years. However, if PSA levels are elevated, the patient should be referred for a multidisciplinary prostate evaluation.[15,16]

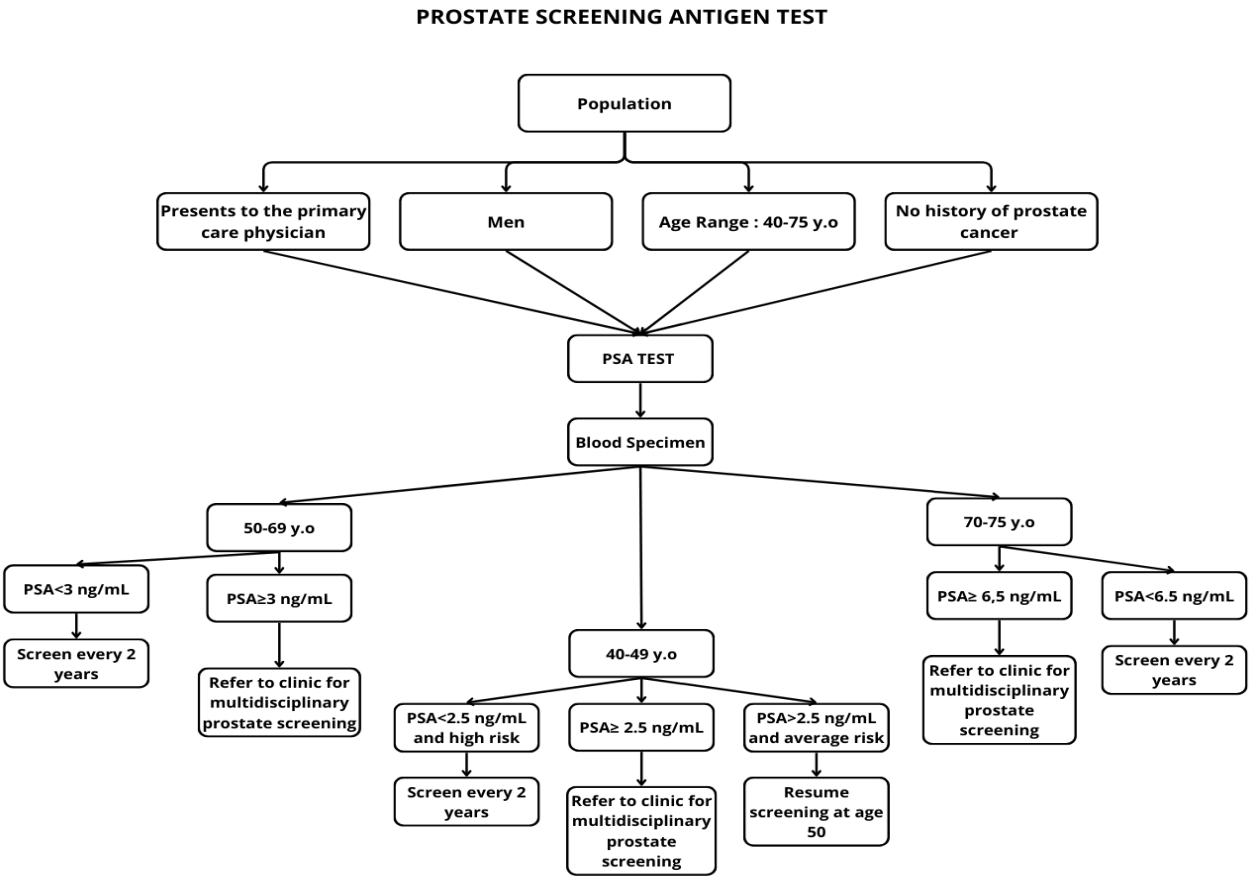

Figure 1. Prostate Screening Antigen Test Mechanism.

Prostate-Specific Membrane Antigen (PSMA)

Prostate-Specific Membrane Antigen (PSMA) is a type II membrane protein originally characterized by the murine monoclonal antibody (mAb) 7E11-C5.3 and is expressed in all forms of prostate tissue, including carcinoma. The PSMA gene is located on the short arm of chromosome 11 in a region that is not commonly deleted in prostate cancer. PSA and PSMA differ in several key aspects. PSA is a secretory protein involved in semen liquefaction and is commonly used as a serum marker for prostate cancer, with levels decreasing in response to androgen deprivation, making it useful for monitoring disease progression and treatment response. In contrast, PSMA is an integral membrane protein with enzymatic functions, and its expression increases with androgen deprivation, correlating with cancer aggressiveness.

While reverse transcriptase polymerase chain reaction (RT-PCR) can detect PSMA in serum, its accuracy has not been validated for screening or clinical decision-making[15]. Leveraging PSMA biomarker, advancements in imaging technology have led to the development of PSMA PET scans, which combine the sensitivity of PET imaging with radioactive tracers that specifically bind to PSMA. These newer PET scans, which utilize tracers such as radioactive sodium fluoride, fluciclovine, choline, or carbon acetate, have shown promise in detecting prostate cancer in various parts of the body. PSMA PET scans, in particular, have become increasingly adopted in many centers due to their precision, although some applications are still under study. This innovation marks a significant step forward in prostate cancer diagnosis and staging[3].

A trial involving men with high-risk localized prostate cancer compared conventional CT and bone scans with PSMA PET-CT for detecting metastases. PSMA PET-CT was 27% more accurate and more effective in identifying

metastases in pelvic lymph nodes and distant areas, including bone compared to bone scintigraphy, with lower radiation exposure. It also led to changes in treatment plans for 28% of patients, compared to 15% with conventional scans[18,19]. Approximately one-third of high-risk prostate cancer patients initially assessed using PSMA PET-CT imaging exhibit lymph node spread. Among these patients, about half display metastases solely in regional pelvic lymph nodes, while the remainder show metastases in both regional and distant lymph nodes[20].

68Gallium-PSMA PET-CT has shown high accuracy in detecting and staging prostate cancer, it demonstrated an overall sensitivity of 0.97 and specificity of 0.66, making it a reliable rule-out test for prostate cancer. Unlike other PET tracers such as F18-Choline and C11-Choline, which can be affected by androgen deprivation therapy (ADT), 68Gallium-PSMA PET-CT uptake is independent of metabolism and ADT, directly targeting androgen receptors. This makes 68Gallium-PSMA PET-CT a more reliable diagnostic marker for prostate cancer, particularly in cases where PSA levels are low or unreliable. Additionally, 68Gallium-PSMA PET-CT does not show variability with changes in Gleason's score and is easier to synthesize using a generator system, unlike F18-Choline or C11-Choline, which require a cyclotron. PSMA PET-CT is essential for detecting prostate cancer lymph node metastases before lymphadenectomy. While 18F-Choline PET-CT was previously the standard imaging method for detecting metastases, 68Gallium-PSMA PET-CT has recently been introduced as a superior alternative. The current study shows that 68Gallium-PSMA PET-CT offers better diagnostic accuracy than 18F-Choline PET-CT, with a lower detection threshold for tumor deposits[21].

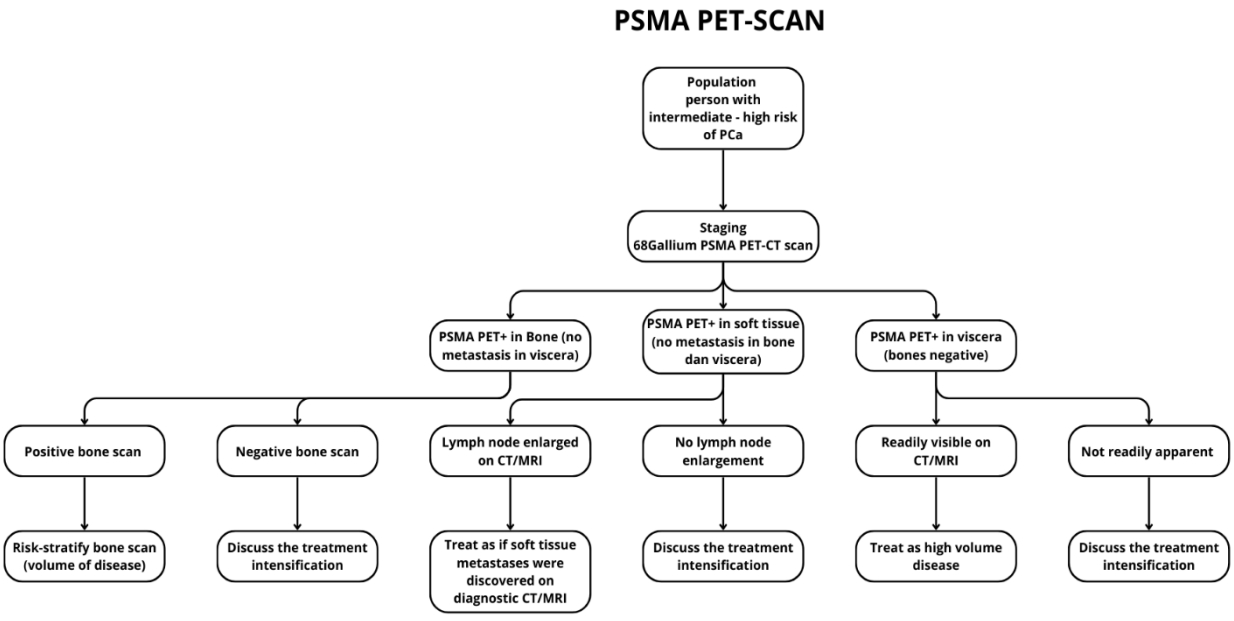

Figure 2. Diagnostic Workflow for PSMA PET-Scan in Prostate Cancer Patient

The diagnostic pathway using 68Gallium-PSMA PET-CT for staging prostate cancer starts with patients at intermediate to high risk. Findings are categorized as PSMA PET-positive in bone, soft tissue, or viscera. Positive bone scans are stratified by disease volume, while negative scans prompt treatment intensification. Lymph node enlargement in soft tissue is treated as metastasis, and its absence leads to further treatment decisions. For visceral metastases, visible lesions on CT/MRI indicate advanced disease, while non-apparent lesions prompt additional treatment discussions. This approach ensures tailored management based on imaging results[22].

Prostate Cancer Antigen

Prostate Cancer Antigen 3 (PCA3), first identified in 1999, is a urine-based biomarker used to predict prostate cancer biopsy outcomes. PCA3 RNA is encoded by a gene located on chromosome 9q21-22, consisting of four exons, with the most common transcript including exons 1, 3, 4a, and 4b. PCA3 is significantly overexpressed in 95% of prostate tumors compared to normal or benign hyperplastic prostate tissue, making it a valuable indicator for prostate cancer detection[4,23,24]. Hessels et al. reported a 66-fold increase in PCA3 expression in prostate cancer tissue compared to normal tissue. This demonstrates the ability of PCR assays to detect small numbers of cancer cells, supporting PCA3 as a potential urinary biomarker for prostate cancer[24]. The first-generation PCA3 test provides qualitative results, while the second generation offers quantitative results by measuring the ratio of PCA3 to PSA mRNA transcripts, thereby accounting for the number of prostate epithelial cells in the urine[25]. The study conducted by Nabok in 2021 demonstrated that electrochemical detection of the prostate cancer marker, long non-coding RNA (lncRNA) PCA3, in a buffer solution using specific redox aptamers yields promising results. Both cyclic voltammetry and impedance spectroscopy methods successfully detected PCA3 concentrations ranging from 1 µg/mL to 0.1 ng/mL. The detection sensitivity was found to be high, and the binding reaction exhibited strong specificity, similar to antigen-antibody interactions. The elevated sensitivity of PCA3 detection is considered sufficient for identifying prostate cancer biomarkers in urine[26].

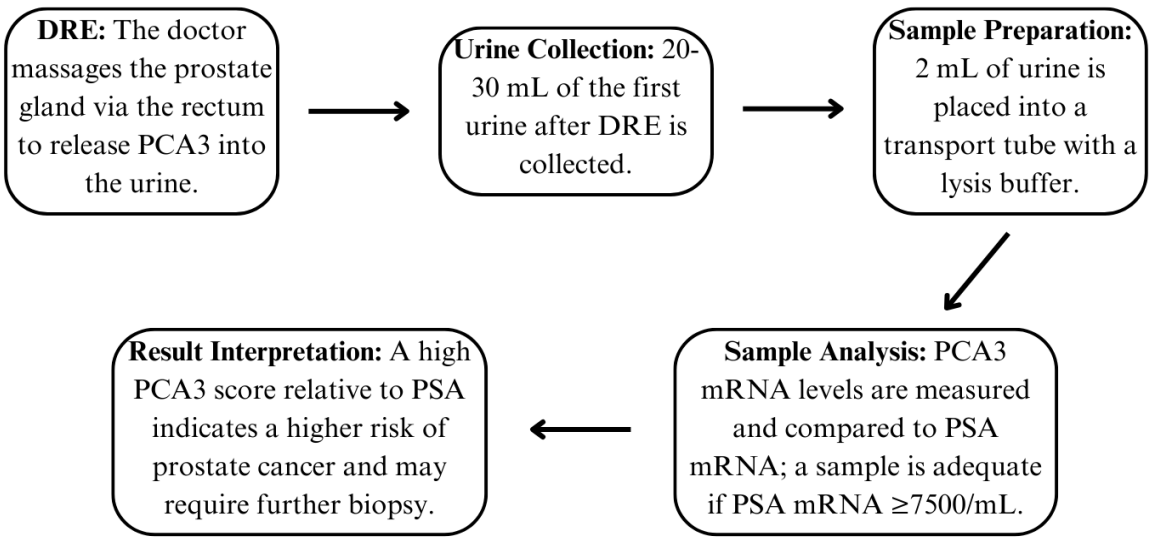

Figure 3. *PCA3 Test Procedure.*

The PCA3 test for prostate cancer begins with a digital rectal examination (DRE) to release PCA3 into the urine. The urine is then collected, and PCA3 mRNA levels are measured and compared to PSA mRNA levels. A high PCA3 score suggests an increased risk of prostate cancer[24,30].

Evaluation of PSA, PSMA, and PCA3 Biomarkers for Prostate Cancer Detection

The AUC value represents the overall diagnostic accuracy of a test by integrating sensitivity and specificity across various cut-off points. As shown in **Table 1**, PCA3 and PSMA have higher AUC values compared to PSA. In this study, the AUC values for PCA3 were obtained from both the PCA3 cutoff in urine and the PCA3 score. However, combining PSA and PSMA, PSA and PCA3, or PSMA and PCA3 shows promising potential, significantly enhancing sensitivity and specificity for

prostate cancer diagnosis. PSA demonstrates slightly higher sensitivity compared to other markers, suggesting its superiority as a screening method for prostate cancer.

Table 1. Comparison of Biomarkers for Prostate Cancer Diagnosis

Study	Population	Predictors	AUC (95% CI)	p-value	Sensitivity	Specificity
Gan, 2022[31].	63 PCa patients and 61 controls were enrolled. PCa patients had biopsy-confirmed diagnoses, no prior androgen deprivation therapy, and no cancer history.	PSMA	0.77 (0.69-0.85)	<0.001		
		PCA3	0.78 (0.71-0.86)	<0.001		
		PCA3 and PSMA	0.87 (0.81-0.93)	<0.0001		
Rigau, 2011[32].	The study population consisted of 154 men, 57 (37%) were positive for PCa and 97 (63%) benign controls without cancer.	PSMA	0.74 (0.63-0.86)	0.003	64%	70%
		PCA3	0.61 (0.48-0.74)	0.025	71%	54%
Talesa, 2009[33].	Biopsy showed 46 patients with BPH and 44 with PCa. BPH patients were diagnosed symptomatic BPH, with no prior transurethral manipulation, radiotherapy, acute infection, hormonal therapy before biopsy.	PSA	0.66 (0.54-0.78)	0.005	-	-
		PSMA	0.64 (0.52-0.75)	0.02	-	-
		PCA3	0.68 (0.57-0.79)	0.001	-	-
		PSA and PSMA	0.82	<0.001	-	-
Mahmoud, 2023[8].	The study enrolled 125 subjects: 25 healthy controls, 25 BPH patients, and 75 PCa patients. PSMA and PSCA expression levels were analyzed via quantitative RT-PCR, alongside serum PSA measurement.	PSA	0.94 (0.89-0.98)	<0.001	93%	86%
		PSMA	0.81 (0.73-0.88)	<0.001	83%	80%
		PSA and PSMA	0.96 (0.92-0.99)	<0.001	85%	100%
Cao, 2018 [34].	A retrospective review of 271 men (median age 63) with elevated PSA, strong family history, or abnormal DRE, using PSA (≥4 ng/mL) and PCA3 (≥30 ng/mL) as diagnostic cutoffs.	PSA	0.53 (0.43-0.62)	<0.001	84%	24%
		PCA3	0.70 (0.62-0.79)	<0.001	73%	68%
		PSA and PCA3	0.73 (0.67-0.79)	<0.001	-	-

Ramos, 2013[35].	PCA3 score assessment from post-DRE urine samples before biopsy, compared with PSA levels and biopsy outcomes, using a cutoff score of 35.	PSA	0.57	-	83%	21%
		PCA3	0.77	-	52%	87%

A study revealed that PSMA is significantly overexpressed in the peripheral blood of prostate cancer patients compared to individuals with benign prostatic hyperplasia and healthy controls, highlighting its potential as a biomarker for prostate cancer detection. Tissue analysis further revealed significantly higher PSMA expression in primary prostate cancer compared to benign tissues, with an even greater increase observed in metastatic sites. This overexpression may be linked to PSMA's enzymatic role in producing glutamate and folate from polyglutamated substrates, potentially driven by DNA damage repair gene abnormalities. These defects are associated with an increased need for metabolic precursors, such as folate and glutamate, which are essential for DNA synthesis and repair[36]. High PSMA expression levels were associated with higher Gleason scores, consistent with other studies showing a significant correlation between PSMA mRNA and protein expression and Gleason score, reflecting tumor aggressiveness. This can be explained by PSMA's activation of signaling pathways via G protein-coupled receptors, particularly the metabotropic glutamate receptor (mGluR) on the plasma membrane of prostate cells. PSMA releases free glutamate from vitamin B9 as a glutamate substrate through its zinc metalloproteinase activity and colocalizes closely with two members of the mGluR I family. The upregulation of mGluRs stimulates the phosphorylation of the p110β isoform of phosphoinositide 3-kinase (PI3K), activating the Akt signaling pathway, which plays a crucial role in prostate cancer pathogenesis and progression[37].

Urinary PCA3 demonstrated higher diagnostic specificity and sensitivity than PSA, although no significant difference in AUC was found based on ROC analysis, emphasizing its potential as a noninvasive biomarker for prostate cancer. Urinary PCA3 demonstrated superior diagnostic accuracy for prostate cancer compared to PSA, with an optimal cutoff of ≥9.775 pg/ml (AUC = 0.965, sensitivity = 95.5%, specificity = 95.5%, $p < 0.001$). In contrast, serum PCA3 at a cutoff of ≥5.985 pg/ml (AUC = 0.739, sensitivity = 86.3%, specificity = 54.5%, $p = 0.007$)[38]. With a cutoff of 30 ng/mL, the PCA3 test was able to reduce unnecessary invasive biopsies by 57.4% in the entire study group and by 70.3% in the subgroup with PSA levels in the "gray zone" (4–10 ng/mL)[34]. A PCA3 cutoff of 35 copies of PSA mRNA resulted in 76% specificity and 50% sensitivity, with an AUC of 0.68, and almost no overlap was detected when comparing cancer with BPH, confirming the specificity of the PCA3 score test[39]. Studies focusing exclusively on the combination of PSA and PCA3 are limited, as PCA3 is typically combined with TMPRSS2-ERG in prostate cancer diagnostics. TMPRSS2 is a prostate-specific serine protease regulated by androgenic control, which plays a significant role in prostate carcinogenesis.

The Michigan Prostate Score (MiPS) test, combining serum PSA with PCA3 and TMPRSS2-ERG mRNA levels from post-DRE urine, predicts prostate cancer on biopsy with an AUC of approximately 0.75, improving the sensitivity and specificity of the PSA test. A study of 108 men demonstrated that combining PCA3 and TMPRSS2-ERG increased sensitivity from 63% for PCA3 alone to 73% for both tests[40,41]. Overexpression of TMPRSS2:ERG has been shown to reduce PSMA expression, indicating that androgen ablation in patients with prostate cancer harboring the TMPRSS2:ERG fusion may lead to upregulation of PSMA and improve the effectiveness of therapeutic imaging based on PSMA. A study involving 48 men demonstrated enhanced discriminatory ability when serum PSA, urine PCA3, and TMPRSS2:ERG gene expression were combined in a multivariable

model, yielding an AUC of 0.72 for PSA, 0.65 for PCA3, and 0.77 for TMPRSS2:ERG[42]. The combination of these three tests achieved a sensitivity of 90% and specificity of 80%[43].

Safety Considerations of PSA, PSMA PET, and PCA3 in Prostate Cancer Diagnosis

The safety of PSA testing varies significantly depending on the initial biopsy testing and the sensitivity-specificity of the test. These factors can result in adverse outcomes for patients undergoing the test. The effects of PSA screening can be categorized into three groups: all-cause mortality, prostate cancer-specific mortality, and biopsy-related complications. A study conducted on men aged 50 to 60 years with prior biopsy reported mild adverse events following PSA testing, with the most common being hematuria and hematospermia. Within 30 days after biopsy, 10 participants were prescribed antibiotics for urinary tract infections, and 5 were hospitalized—3 for urosepsis, 1 for pneumonia, and 1 for acute hypertension. No deaths were reported in the study[44]. Similar results were also observed in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial[45]. The incidence rates for prostate cancer were 108.4 and 97.1 (in intervention and control groups) per 10 000 person-years. In the patients follow-up within 13 years, cumulative mortality rates from prostate cancer (in intervention and control groups) were 3.7 and 3.4 deaths per 10 000 person-years, respectively. The all-cause mortality, excluding prostate cancer, observed in this study was 139.13 and 143.67 deaths per 1000 person-years, with 5,783 and 5,982 deaths in the intervention and control groups, respectively. In the intervention group, there were only mild and infrequent PSA-associated complications at a rate of 26.2 per 10,000 screenings, which primarily consist of dizziness, bruising, and hematoma, with the addition of 3 syncope episodes per 10,000 screenings. The diagnostic process itself has higher complications at the rate of 68 per 10,000 diagnostic evaluations after positive screening results on screening, which primarily consist of infection, bleeding, clot formation, and urinary difficulties. Another study analyzed prostate cancer mortality, finding rates of 0.30 and 0.31 per 1000 person-years in the intervention and control groups, respectively. All-cause mortality was 13.74 and 13.51 per 1000 person-years, with 25,459 and 28,306 deaths in each group[46].

Regarding the safety of PSMA PET-CT, no studies reported with post-intervention mortality. However, PSMA PET-CT may still induce several side effects in patients. A multicentre study reported the effects of 18F-rhPSMA-7.3-PET-CT, a type of PSMA PET-CT, in patients with unfavorable intermediate (UIR) to high risk (VHR) prostate cancer[47]. Out of 372 patients screened, 23–37 (7.8–13%) patients had PSMA–positive PLN (pelvic lymph node), while 70 (24%) patients had one or more positive PLNs, non-PSMA related, as observed on histopathology. In 56–98 out of 352 (16–28%) patients who underwent the screening irrespective of surgery, extrapelvic (M1) lesions were observed. No serious adverse events were reported.

Similar results were found in a study evaluating the safety of 68Ga-PSMA PET-CT[48]. No adverse event was reported After 1084 injections of PSMA-11, which is followed by PET-CT-associated 206 intravenous contrast medium or 74 oral contrast medium administrations, and with the addition of 488 furosemide administrations. In a study evaluating PSMA PET-CT with Robot-Assisted Salvage Node Dissection (RASND), 8 patients (23%) experienced Clavien–Dindo grade ≤2 complications. Grade I complications involve deviations from the normal postoperative course without the need for pharmacological or surgical interventions, while Grade II requires pharmacological treatment, blood transfusions, or total parenteral nutrition(49). For the entire cohort, BCR (biochemical reaction)-free survival and clinical recurrence-free survival at a median follow-up of 12 months were 23% and 66%, respectively.

In a cohort study evaluating the efficacy and safety of PSMA PET-CT[49], there are even positive outcomes in the 6 treated patients[50]. The procedure resulted in radiologically stable diseases in 2 patients after 4 cycles and clinical responses such as pain relief, less dyspnea, and less fatigue in 4 patients after 2 or 4 cycles of

PSMA PET-CT. Furthermore, the survival outcome of PSMA PET-CT is also affected by the patients' PSA threshold. Another study[51] reported that the 3-year event-free survival rates is higher in patients with lower PSA threshold, which are 70% for patients with PSA <0.5 ng/mL and 40% for patients with PSA >0.5 ng/mL[51]. The PSA threshold effect was significant in multivariate analyses ($p < 0.001$). In another study, the greater effect of PSA threshold is shown with the overall survival of 1216 patients, with only PSA-associated recurrence of prostate cancer. The restaging PSMA PET-CT precisely predicted the overall survival for patients with PSA >0.5 ng/mL, despite the lower PSA recurrence[52]. Overall, long-term follow-up from similar PSMA PET-CT trials is required to further assess potential quality of life and mortality benefits.

Randomized trials show that PCA3 screening can reduce disease-specific mortality by 21-30%. However, similar to PSA screening, it can lead to false positives, diagnosing clinically insignificant disease, which may result in overtreatment and impact quality of life. The effects of PCA3 screening are categorized into three groups: all-cause mortality, prostate cancer-specific mortality, and biopsy-related complications. A study found that adding PCA3 to PSA testing improves diagnosis accuracy, eliminates unnecessary biopsies, and preserves fewer lives. PSA is more sensitive, while PCA3 is more specific, meaning a higher PCA3 level reduces overdiagnosis and unnecessary biopsies but increases mortality, as higher specificity leads to fewer detections. All-cause mortality was not mentioned in the study. The safety of all three screening methods are summarized in the following **Table 2.**

Table 2. Safety of PSA. PSMA. and PCA3 Screening Methods in Prostate Cancer Diagnosis.

Testing	Study	All-cause mortality (per 1000 person-years)	Prostate cancer mortality (per 1000 person-years)	Screening/biopsy/imaging-related complications
PSA	Hugosson. et al[44].	_	_	Urinary tract infections (10). urosepsis (3). pneumonia (1). and acute hypertension (1)
	PLCO Screening Test study[45].	3.7	139.13	Dizziness. bruising. hematoma. syncope. infection. bleeding. clot formation. urinary difficulties
	Cluster Randomized Trial of PSA[46].	0.3	13.74	Not reported
PSMA PET-SCAN (Imaging)	Surasi. et al.[45]	Not reported	Not reported	Positive pelvic lymph nodes (PLN). extrapelvic (M1) lesions
	Siriwardana. et al.[49].			Clavien-Dindo grade <2 complications. biochemical reaction (BCR)
PCA3 (Biopsy)	Birnbaum. J.K.. et al.[53].	_	22.2-25.4	Not reported
	Pinkhasov. et al.[54].	_	_	Urosepsis. urinary retention. gross hematuria. transient ischemic attack

Cost Analysis of PSA, PSMA PET, and PCA3 in Prostate Cancer Diagnosis

The overall cost for PSA is the lowest compared to other screening methods. There is a slight difference in the price ranges calculated from various sources. Medicare payments measured the costs for PSA by adjusting them to 2009 US dollars while accounting for temporal and geographic variations[55]. The measured average annual cost per person during 2007-2009 was $36, which comprises screening-related and biopsy-related (biopsy, pathology, and hospitalization) expenses, non-bindingly. Biopsy-related costs accounted for the majority of screening costs (72%; $26 per person), while the screening-related cost itself only accounted for 28% ($10 per person) of the overall screening cost[55]. The cost varies according to multiple factors, including referral level, quartiles of screening expenditure, and age. At hospital referral region (HRR) level, the average annual screening cost per person ranged from $17 to $62, with a median of $36. The cost only varied little across quartiles of screening expenditures, which are $9 per person in the 1st quartile and $10 per person in the 2nd, 3rd, and 4th quartiles. There is also an inverse relation between the cost and age ($p<0.001$).

A study conducted in New Zealand assessed the overall cost of PSA in public hospitals during 2010-2011[56]. The unit costs also consist of screening-related and biopsy-related expenses. This study accounted also for the total of future biopsy costs, resulting in about 90 times more expensive biopsy costs compared to the first study. Another study also reported similar results [57], accounting future biopsy costs as well, though the increase is about 40 times from the first study. The summary of PSA costs are listed in **Table 3**.

Table 3. Summary of PSA Screening Costs

Study	Age	Screening-Related Cost (in USD)	Biopsy-Related Cost (in USD)
Ma, et al. 2013[55], (US)	66-74	$43.00	$10.00
	75-84	$31.00	$10.00
	85-99	$14.00	$10.00
	General	$26.00	$10.00
Mean		$28.50	$10.00
Lao, et al. 2013[56], (New Zealand)	General	$6.47	$901.86
Mean		$6.47	$901.86
Martin, et al. 2013[57], (US)	General	$20.30	$408.70
Mean		$20.30	$408.70
Mean Total		**$18.42**	**$440.19**

PSMA PET-CT is one of the most costly imaging modalities, more effective than conventional imaging (CT or bone scan) for initial staging, but more expensive than PSA despite its higher specificity. Based on **Table 4.**, the cost of PSMA PET-CT ranges from $115.98 to $17.955.33, with an average of $5.706.31. This is significantly higher than PSA costs, and the price varies depending on the type of PSMA PET-CT and patient staging. For example, in the US, PSMA PET-CT for critical patients costs $17.955.33, while it costs $1.617 in the initial stage.

Table 4. Summary of PSMA PET CT Costs

Study	Type of PSMA		Cost (in USD)
Szczesniewski et al.[59] (Spain)	PSMA PET	Initial stage	$5.355.57
	PSMA PET-CT		$6.043.06
Subramanian et al.[60] (US)	[^{18}F]DCFPyL PSMA PET-CT	Initial stage	$1.617.15
Song et al.[58] (Australia)	PSMA PET-CT	Initial stage	$665.04
De Rooij et al.[61] (US)		Initial stage	$115.98
Schwenk et al.[62] (US)	[^{68}Ga]Ga-PSMA-11 PET-CT	Palliative (false)	$4.953.82
		Salvage	$8.614.69
Tien et al.[63] (US)		Palliative to death	$17.955.33
	Mean		$5.706.31

The choice of biopsy test is crucial in PCA3 screening, with three options: TRUS, transperineal, and saturation biopsy. TRUS biopsy may lead to complications, as 2.5% of 1000 patients required hospital admission or an ED visit post-procedure. However, biopsies are typically needed only for early-stage prostate cancers.[54] Optimizing the use of PCA3 to predict patient outcomes can, in fact, reduce the number of unnecessary and uncomfortable future biopsies.[64] Further comparing prostate cancer biomarker screening, we also assessed the cost of PCA3 testing. A study calculated PCA3 assay costs provided by the manufacturer by applying UK costs to resource use obtained from a US study.[65] The estimated cost of the PCA3 testing kit was given as £164.67 (or $175.46) including value-added tax (VAT). A higher cost of £175.11 (or $186.585) has also been used in a scenario analysis of the study. The mentioned cost does not include the cost of a biopsy test prior to the screening. The cost of biopsy which adds to the PCA3 test cost in one-testing also varies as shown in Table 5.

According to the table, we concluded that the price range for PCA3 testing ranges from $543.32-545.445 for transrectal biopsy, $929.631-940.756 for transperineal biopsy, and $1.109.898-1.121.023. This cost did not include the future biopsies for potential complications or fluctuating health conditions in patients. These price ranges are relatively higher than that of a PSA test, but still significantly lower compared to PSMA PET-CT test. The costs of all three screening methods are summarized in the following **Table 6.**

Safety analysis of the three methods shows that PSMA PET-SCAN is the safest option, with no reported all-cause mortality and prostate-specific mortality. We assume that this result is due to no requirements of biopsy test in the procedure, which was a major contributor to adverse effects leading to mortality. Regardless of its lowest risk, PSMA PET-CT has the highest cost, with the mean cost of $5.706.31. As opposed, PSA requires the lowest mean cost of $458.61, even though with a much higher number of adverse effects and mortality risk. Meanwhile, the PCA3 method is the second best option in both safety and cost.

Table 5. Summary of PCA3 Screening Costs

Source	Type of Test	Cost (in USD)	Cost (PSA Included)	
			Lowest	Highest
Transrectal (standard) biopsy				
Department of Health 2013.NHS reference cost LB27Z* in outpatient procedures – urology[66].	Outpatient	$238.68	$414.14	$425.26
National Collaborating Centre for Cancer (NCCC) 2014[67].	Histopathology	$120.18	$295.64	$306.77
Total		**$358.86**	**$534.32**	**$545.45**
Transperineal (standard) biopsy				
Department of Health 2013. NHS reference cost LB27Z in outpatient procedures – urology[66].	Day case	$633.99	$809.45	$820.58
National Collaborating Centre for Cancer (NCCC) 2014[67].	Histopathology	$120.18	$295.64	$306.77
Total		**$754.17**	**$929.63**	**$940.76**
Saturation biopsy				
Department of Health 2013. NHS reference cost LB27Z in outpatient procedures – urology[66].	Day case	$633.99	$809.45	$820.58
National Collaborating Centre for Cancer (NCCC) 2014[67].	Histopathology	$300.45	$475.91	$487.03
Total		**$934.44**	**$1.109.90**	**$1.121.02**

Table 6. Comparison of PSA, PSMA, and PCA3 Screening and Biopsy Costs

Test	Type of Screen	Cost per Test	Biopsy Test Cost	Total Cost
PSA	Single screen at all age	$18,42	$440,19	$458,61
PSMA PET-CT	Single screen at all age	$5.706,31	_	$5.706,31
PCA3(65)	Single screen at all age	$186,59	$358.86 (Transrectal Biopsy)	$545,45
			$754.171 (Transperineal Biopsy)	$940,76
			$934.438 (Saturation Biopsy)	$1.121,02

4. Summary

PSA has been the cornerstone of prostate cancer diagnosis, but its low specificity in distinguishing prostate cancer from other urological conditions has led to the consideration of alternative biomarkers, such as PSMA and PCA3. The overall diagnostic accuracy, as reflected by the AUC integrating sensitivity and specificity, shows that PCA3 and PSMA outperform PSA. Combining PSA with PSMA, PCA3, or both enhances the diagnostic capabilities for prostate cancer compared to PSA alone. PSMA PET is the most expensive diagnostic option, but offers superior specificity for detecting advanced prostate cancer. Meanwhile, non-invasive approach that reduces unnecessary biopsies can be achieved using PCA3 as a urinary biomarker. The inclusion of PSMA and PCA3 biomarkers with PSA significantly enhances prostate cancer diagnosis. This combination improves detection accuracy and reduces unnecessary biopsies, leading to better patient outcomes.

Author's Contribution

All authors have contributed to the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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