International Journal of Innovation Scientific Research and Review
Vol. 07, Issue, 09, pp.8965-8967, September 2025
Available online at http://www.journalijisr.com
SJIF Impact Factor 2025: 7.913

Research Article

ISSN: 2582-6131

ROLE OF PROSTATE CANCER ANTIGEN 3 (PCA3) BIOMARKER IN PROSTATE CANCER: COMPREHENSIVE REVIEW AND UPDATES

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Received 14th July 2025; Accepted 15th August 2025; Published online 30th September 2025

ABSTRACT

Prostate cancer (PCa) is the most commonly diagnosed cancer in men and the fifth leading cause of cancer-related death. This review explores the role of Prostate cancer antigen 3(PCA3) in prostate cancer diagnosis to reduce unnecessary biopsies and overtreatment in low-risk patients while guiding treatment for high-risk cases. Adding PCA3 to existing models like PSA and DRE has significantly improved detection accuracy, especially for high-grade cancers. PCA3 helps lower repeat biopsy rates while maintaining an acceptable level of missed high-grade disease. Its combination with mp MRI further enhances the negative predictive value. In the US, about one million prostate biopsies are performed annually, most showing benign results. Nearly 25% of malignancies are missed on the first biopsy, with detection rates dropping on subsequent biopsies. Molecular testing, like PCA3, could reduce unnecessary repeat biopsies and offer cost savings.

Keywords: PCA3, Prostate Cancer, Antigen 3, Biomarker.

INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed malignancy among men in the world, accounting for the fifth highest cause of cancer-related mortality among males.[1] Prostate-specific antigen tests, magnetic resonance imaging scans, and prostate tissue biopsies are the primary methods of diagnosis. Prostate cancer typically goes undetected when it is still confined in the prostate and has a slow progression. This eliminates needless side effects from treatment by enabling many patients to receive monitoring for progression rather than active treatment. Following the choice to treat, the following treatment options are available: chemotherapy, radiation therapy, androgen deprivation therapy (ADT), and radical prostatectomy.[2] All current recommendations strongly advocate collaborative decision-making with the patient because all treatment alternatives may negatively impact the patient's quality of life. Since further therapy is unlikely to lengthen life, symptomatic care may be desirable in patients with substantial comorbidities or low life expectancy.

DISCUSSION

What's prostate cancer antigen 3?

A Food and Drug Administration (FDA) approved urine-based biomarker called prostate cancer antigen 3 (PCA3), which is a noncoding messenger RNA (mRNA) is obtained following digital rectal examination (DRE) and used in males with suspected PCa either prior to an initial biopsy or following a previous negative biopsy. [3]

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How it differs from prostate-specific antigen?

Prostate cancer cells over express PCA3 in 95%, a protein unique to the prostate that is not expressed in other tissues or malignancies. In contrast to prostate-specific antigen (PSA), it is independent of total prostate size and unaffected by the presence of 5 alpha-reductase inhibitors. According to some theories, PCA3 > 60 increases the chance that cancer will be found in biopsy-naïve patients, while a score < 20 has a significant negative predictive value for the existence of cancer.[3]

What its significance?

Most of the estimated one million prostate biopsy procedures performed each year in the United States show benign pathology. Nearly 25% of malignancies are missed on the first biopsy, according to the authors of a serial biopsy research involving 2500 males. The detection rates for the second, third, and fourth biopsies were 17%, 14%, and 11%, respectively. Cost savings might come from using molecular testing to cut down on needless repeat biopsies.[4]

Studies found considerably greater PCA3 levels (10 to 100 times) in 53 of 56 PCa tissue samples compared to surrounding non-cancerous prostate tissue. PCA3 was missing from non-prostatic tissues but present in normal prostates and benign prostate enlargement. The Progensa PCA3 test, which detects both PCA3 and PSA mRNA in urine samples following a digital rectal examination, has diagnostic value. The aggregated data from 46 trials including 12,295 people revealed a high sensitivity (0.65) and specificity (0.73) for PCa diagnoses, with an area under sROC curves (AUC) of 0.75. The addition of PCA3 to existing models, including serum PSA and DRE results, has significantly improved the accuracy of detecting both any prostate cancer and high-grade cancer, as evidenced by noteworthy increases in AUC scores across multiple studies. PCA3 has shown promise in reducing repeat biopsy rates while maintaining an acceptable level of missed high-grade disease. Furthermore, PCA3's combination with mpMRI has proven to enhance the negative predictive value for prostate cancer detection.

What are the limitations?

Although PCA3 is unlikely to replace PSA as the primary biomarker for PCa, the combination of their tests has the potential to significantly enhance PCa diagnosis accuracy. Individuals with high PSA levels and histologically normal samples may benefit the most from PCA3 testing. In such circumstances, PCA3 can be utilized to assess if a repeat biopsy is required. However, PCA3 has several drawbacks. For instance, the ideal PCA3 thresholds are questionable. Various research uses various PCA3 score criteria, with some using a threshold of ≥35 and others favoring a threshold of <35. Recent research has shown that a PCA3 score of 35 finds the best balance between sensitivity and specificity in identifying PCa, while a PCA3 value less than 25 might indicate the existence of pathological indolent PCa. Furthermore, being an mRNA, PCA3 is inherently unstable, demanding careful and accurate handling and preservation techniques.[5]

What its clinical utility? (Table 1)

Due to its notable over-expression in malignant tissues relative to noncancerous tissues, PCA3 is a very useful biomarker for the detection of PCa. It is a dependable diagnostic technique since it can accurately distinguish between benign and malignant prostate diseases, regardless of variables like age or prostate volume. The clinical value of PCA3 testing is increased by its non-invasive nature, which is mostly achieved through urine samples. To completely confirm its diagnostic efficacy in differentiating PCa from other disorders, more studies with bigger sample numbers are required. Table 1 showing results from other studies.[2,3,4,6]

Legend: Table 1 showing results from other studies

Articles	Advantages	Limitations	Clinical Utility
[2]Chen JY, Wang PY, Liu MZ, Lyu F, Ma MW, Ren XY, Gao XS.Biomarkers for Prostate Cancer: From Diagnosis to Treatment. Diagnostics (Basel). 2023 Oct.https://pubmed.ncbi.nlm.nih.gov/37958246/	can predict patients with PCa and a GS ≥ 7.	The thresholds remain controversial. PCA3 is unstable and needs more effort to capture and preserve.	NCCN and EAU guidelines recommend using it after confirmation of negative biopsy results.
[3]Agbetuyi-Tayo P, Gbadebo M, Rotimi OA, Rotimi SO. Advancements in Biomarkers of Prostate Cancer: A Review. Technol Cancer Res Treat. 2024 Jan-Dec;23https://pubmed.ncbi.nlm.nih.gov/39440372/	Accuracy: AUC: 0.66–0.71 for predicting prostate cancer biopsy outcomes Non-invasive (urine test); Better than PSA for predicting biopsy outcomes	Lower sensitivity in early-stage cancer; Can miss aggressive cancers	Moderately effective in identifying aggressive prostate cancer; Often combined with other markers
[4]Farha MW, Salami SS. Biomarkers for prostate cancer detection and risk stratification. Ther Adv Urol. 2022 Jun 14. https://pubmed.ncbi.nlm.nih.gov/35719272/	AUC initial Bx CsPCa: 0.78 (+ clinical variables) AUC repeat Bx csPCa: 0.79 (+ clinical variables) Has demonstrated in combination with mpMRI in the repeat biopsy setting to improve the NPV for detection of PCa on biopsy (95%) in comparison to PCA3 (40%) and mpMRI (83%) alone.	Not mentioned	has shown to be an accurate predictor of high stage (T3 *versus* T2, AUC = 0.74) and high tumor volume (>0.5 ml, AUC = 0.86) disease.
[6]Boehm BE, York ME, Petrovics G, Kohaar I, Chesnut GT. Biomarkers of Aggressive Prostate Cancer at Diagnosis. Int J Mol Sci. 2023 Jan 22. https://pubmed.ncbi.nlm.nih.gov/36768533/	Overall: 0.68–0.87 * Initial Biopsy: 0.7–0.8 Repeat Biopsy: 0.68	no consensus PCA3 cut-off score.	Intended use ≥50 years old Elevated PSA Prior negative biopsy

CONCLUSION

The clinical relevance of PCA3 is underscored by its inclusion in the 2020 guidelines from the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN), where it is recommended as part of the decision-making process for repeat biopsies. This endorsement highlights the growing acceptance of PCA3 testing in clinical practice, especially for its ability to reduce the number of unnecessary repeat biopsies.

The PCA3 test has limitations. It is not recommended as a general screening tool for PCa, as it is specifically elevated in individuals with PCa and not in the general population. Furthermore, its utility may vary based on demographic factors. Overall, PCA3 remains a valuable tool in the diagnostic pathway for prostate cancer.

Conflict of Interest: Nil

Funding sources: Nil

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