https://doi.org/10.22465/juo.255000120006
pISSN: 2951-603X eISSN: 2982-7043
Journal of Urologic Oncology 2025;23(1):4-13

REVIEW ARTICLE

JUO
OPEN ACCESS
JOURNAL OF UROLOGIC ONCOLOGY

Delivering on the Promise of Precision Oncology in Prostate Cancer: Prediagnostic Strategies, Postdiagnostic Applications, and Future Directions. A Narrative Review

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Received January 15, 2025
Revised March 14, 2025
Accepted March 18, 2025

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Precision oncology offers a transformative approach to managing localized prostate cancer (PCa) by tailoring interventions to the biological characteristics of the disease. This strategy addresses critical challenges such as overdiagnosis, overtreatment, and the underutilization of advanced diagnostics. Despite the advancements, barriers such as tumor heterogeneity, patient variability, high costs, and limited accessibility impede widespread adoption of new technologies and risk assessment tools. Looking ahead, innovations in biomarker discovery, artificial intelligence, and machine learning hold promise for further refining risk prediction, treatment selection, and active surveillance protocols. By addressing these challenges and advancing precision tools, precision oncology can transform the management of localized PCa, enabling personalized care that minimizes overtreatment while ensuring optimal outcomes.

Key Words: Precision oncology, Prostate cancer, Diagnosis, Management

• **Grant/Fund Support:** This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
• **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

Despite advancements in prostate cancer (PCa) treatment, the disease exhibits significant variability both within and between patients. In recent years, the diagnosis and management of PCa has been transformed by the discovery of various clinical, historical, and genetic biomarkers aimed at personalizing approaches to the disease. With the integration of a growing number of tools that contribute information about disease biology and prognosis, treatment personalization is becoming increasingly feasible.

Emerging prediagnostic tools, including early-life prostate-specific antigen (PSA) levels, single nucleotide polymorphisms (SNPs), and blood- and urine-based biomarkers can improve long-term risk prediction [1-3]. Advanced imaging modalities including multiparametric magnetic resonance imaging (MRI), further enhance disease diagnostic by identifying areas of clinically significant PCa (csPCa) and can facilitate the avoidance or targeting of prostate biopsy [4,5]. In addition, postdiagnostic tools can

enhance risk stratification and optimize treatment decisions. Genomic classifiers provide insights that extend beyond traditional clinical parameters, informing decisions about suitability for active surveillance, and may have clinical utility in selecting candidates who may or may not benefit from additional therapy. Similarly, in the advanced and metastatic setting, molecular profiling can reveal deleterious mutations, such as DNA repair gene alterations, which aid in guiding adjunctive therapies. Additionally, molecular imaging including prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging improves regional and distant staging accuracy and helps guide the planning of radiation and surgical interventions [6]. Together, these advancements are reshaping the contemporary approach to PCa care, enabling more personalized approaches to diagnosis and treatment.

Precision oncology holds significant promise in transforming the management of localized PCa by refining risk stratification, optimizing treatment strategies, and minimizing overtreatment. However, despite the advancements, several important barriers to its effective implementation remain. These include the still uncertain approach to managing inter-patient, intra- and intertumor heterogeneity, high costs, and limited access. Moreover, despite considerable promise, high levels of evidence regarding real-world effectiveness of precision oncology strategies have not been developed. Continued research and innovation are essential to overcome current limitations and achieve equitable implementation of these advanced tools in clinical care. This review explores the current landscape of prediagnostic and postdiagnostic strategies in precision oncology for localized PCa, highlighting advancements and future directions.

PREDIAGNOSTIC STRATEGIES IN PRECISION ONCOLOGY

1. Risk Prediction

The PSA blood test is typically the first and most consistently utilized biomarker for routine risk assessment prior to PCa diagnosis. However, its use in screening has been controversially attributed to associations with overdiagnosis and overtreatment. Emerging evidence suggests that measuring PSA levels early in life (before age 50) may mitigate these risks by improving the identification of men at higher risk for aggressive cancer while minimizing the harm associated with detecting indolent cancers. Since prostate carcinogenesis often begins in the fourth and fifth decades of life, baseline PSA levels measured at younger ages may offer greater predictive accuracy for aggressive disease [7]. Despite its utility, PSA testing has limitations when used in isolation. At a cutoff level of >4 ng/mL, its specificity and sensitivity range from 20%–40% and 70%–90%, respectively. Low specificity arises because benign conditions such as benign prostatic hyperplasia and prostatitis can elevate PSA levels, contributing to false-positive results and unnecessary biopsies [8].

1) SNPs and long-term risk assessment

SNPs have been used to predict an individual's susceptibility to diseases, response to therapies, and risks associated with environmental exposures. Age-specific genetic scores can apply to PCa risk assessment, informing screening strategies and identifying men at higher risk for developing metastatic or fatal disease. For example, Pagadala et al. [9] developed a polygenic hazard score (PHS290) to predict the likelihood of developing aggressive cancer at younger ages. In a study involving 590,750 men (median age, 69 years), men with higher PHS290 scores had significantly elevated risks of any PCa (hazard ratio [HR], 5.20), metastatic PCa (HR, 4.89), and fatal PCa (HR, 4.42). Black men had higher average PHS290 scores and PCa incidence compared to non-Hispanic White men, but those with low PHS290 scores had similar risks as the average non-Hispanic White population. These findings underscore the potential clinical application of genetic risk stratification in early PCa decision-making. For example, integrating polygenic risk scores could enhance early detection and prevention efforts in higher-risk groups. Studies suggest that men with high genetic risk or a family history of cancer account for the majority of early PCa deaths, with lifestyle modifications potentially preventing up to one-third of these cases [10] (Table 1).

2) STHLM3: a comprehensive risk prediction model

The Stockholm3 (STHLM3) test is an advanced biomarker panel combining plasma protein biomarkers, genetic

Table 1. Performance characteristics of prediagnostic tests

	Components of each clinical model	Total prostate cancer discrimination
Polygenic hazard score (PHS) [9]	• Genetic dosages of 290 single nucleotide polymorphisms	C-index of 0.688 (95% CI, 0.685–0.690)
Stockholm 3 test (S3M) [11]	• Plasma protein biomarkers (total PSA, free PSA, ratio of free/total PSA, hK2, MIC1, and MSMB) • Genetic markers (score of 254 single nucleotide polymorphisms) • Prostate exam (digital rectal examination, and prostate volume) • Clinical variables (age, first-degree family history of prostate cancer, and a previous biopsy)	AUC of 0.75 (95% CI, 0.73–0.77)
Prostate Health Index (PHI) [12]	• Blood levels of Total PSA, Free PSA, and [-2]proPSA	AUC of 0.71 (95% CI, 0.69–0.75)
4-kallikrein score (4Kscore) [13]	• Blood levels of Total PSA, Free PSA, Intact PSA, and Human kallikrein 2	AUC of 0.82 (95% CI, 0.79–0.85) *for Gleason ≥ 7 cancer
ExoDX Prostate Intelliscore (EPI) [14]	• Urine RNA expression levels of ERG, PCA3, and SPDEF	AUC of 0.77 (95% CI, 0.71–0.83) *for Gleason ≥ 7 cancer
SelectMDx (MDxHealth) [15]	Urine RNA expression levels of HOXC6 and DLX1	AUC of 0.85 (95% CI, 0.83–0.88) *for Gleason Grade ≥ 2 cancer

CI, confidence interval; AUC, area under the curve; C-index, concordance index; PSA, prostate-specific antigen; RNA, ribonucleic acid.

polymorphisms, and clinical variables to improve the detection of csPCa. In a prospective study involving 59,159 men aged 50–69 years, Ström et al. [11] demonstrated that the STHLM3 model outperformed PSA as a screening tool by reducing unnecessary biopsies while maintaining high sensitivity for csPCa detection. An updated version of the STHLM3 test, incorporating the HOXB13 genetic marker, further enhanced predictive accuracy and is increasingly adopted as a reflex test for men with PSA levels ≥3 ng/mL.

3) Integration of family history and germline genetic testing

Integrating family history with germline genetic risk has also become integrated in precision oncology approaches to PCa. Approximately half of PCa risk may be attributed to inherited factors, including pathogenic variants in high-risk genes such as BRCA1/2 and HOXB13. Men with these mutations face a two- to tenfold increase in lifetime PCa risk compared to the general population, particularly if a first-degree relative was diagnosed with PCa before age 65.

BRCA2 mutations are associated with more aggressive disease and poorer outcomes, while *HOXB13* mutations have been implicated in hereditary PCa. Germline testing allows clinicians to tailor screening strategies and treatment decisions, particularly for individuals with a strong family history or high genetic risk. Current recommendations are to initiate PCa screening at age 40 for men of African descent, those with germline pathogenic variants, or those with multiple family members diagnosed with metastatic PCa.

4) Blood-based biomarkers (PHI, 4Kscore)

The limitations of PSA have led to the development of novel blood-based biomarkers aimed at improving the risk assessment for csPCa, reducing unnecessary biopsies, and guiding personalized treatment strategies. The Prostate Health Index (PHI) is a blood-based assay that uses a combination of proPSA, free PSA, and total PSA into a single score to predict the likelihood of PCa on biopsy. Studies have demonstrated that PHI outperforms total PSA alone in distinguishing between benign conditions and clinically significant PCa, thereby aiding in decision-making regarding the need for a biopsy [12].

The 4Kscore test measures 4 kallikrein protein levels in the blood, total PSA, free PSA, intact PSA, and human kallikrein 2, to estimate the risk of high-grade PCa. Clinical validation has shown that the 4Kscore can reduce unnecessary biopsies by providing a more accurate risk assessment of aggressive PCa [13].

5) Urine-based biomarkers (ExoDX, SelectMDx)

Urine-based biomarkers have also emerged as valuable risk assessment tools. ExoDX Prostate Intelliscore (EPI) analyzes urinary exosomal RNA expressions of 3 genes (*ERG*, *PCA3*, and *SPDEF*) to predict the presence of high-grade PCa. EPI has been shown to distinguish between low-risk and high-risk PCa, supporting its use in guiding biopsy decisions [14]. As for SelectMDx, another urine biomarker that incorporates mRNA levels of the biomarkers HOXC6 and DLX1 in urine

https://doi.org/10.22465/juo.255000120006

with clinical factors of age, PSA, prostate volume, and digital rectal examination findings to assess the risk of high-grade PCa. SelectMDx may help identify men at increased risk for aggressive PCa, thereby improving patient selection for biopsy and reducing unnecessary procedures [15].

2. Advanced Imaging Modalities in Diagnosis

1) Multiparametric MRI for clinically significant PCa

Multiparametric MRI (mpMRI) has revolutionized PCa diagnosis, serving as a cornerstone in detecting, risk stratifying, and managing csPCa. Combining T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging, mpMRI offers detailed insights into prostate anatomy, cellular density, and vascularity, significantly improving diagnostic accuracy [16].

The introduction of standardized reporting systems such as Prostate Imaging Reporting and Data System (PI-RADS) has further advanced mpMRI's utility. In particular, mpMRI/transrectal ultrasonography fusion-guided biopsy, where mpMRI images are fused with real-time ultrasound, has significantly improved the detection of csPCa compared to traditional systematic biopsies. The fusion biopsy approach is now recommended by most centers with availability of MRI in patients with clinical suspicion of PCa, even after a negative systematic biopsy. Despite its benefits, mpMRI is limited by cost, availability, reliance on contrast agents, and the need for specialized expertise in interpreting imaging results, which can restrict access for some patients. Addressing these barriers remains a critical focus for expanding access to precision diagnostic tools [17].

POSTDIAGNOSTIC APPLICATIONS IN LOCALIZED DISEASE

Risk stratification and treatment decisions has conventionally relied on clinicopathological factors such as PSA, Gleason score, and TNM staging. However, standard clinical tools alone may misclassify long-term cancer risks in a substantial proportion of patients with PCa [2,18]. Integrating genomic classifiers and molecular profiling into clinical practice could provide more accurate risk stratification, enabling more personalized treatment strategies and significantly improved patient outcomes.

1. Precision Risk Stratification for Localized PCa

1) Expression based genomic classifiers to refine risk categorization beyond traditional clinical tools

Genomic classifiers available in the United States market include Decipher, Oncotype DX, and Polaris have emerged as tools to redefine the management of localized PCa. These tests use RNA extracted from prostate biopsy samples to analyze the gene expression levels associated with key biological pathways, including cell differentiation, proliferation, structure, androgen signaling, and immune response [19]. By measuring the activity of these pathways, genomics classifiers algorithmically combine these expressions to calculate a risk score representing the tumor's aggressiveness. For example, Decipher is reported as a continuous risk score ranging from 0 to 1, associated with the probability of adverse events including metastasis risk. This score can be further stratified into low-, intermediate-, and high-risk diseases, providing a more nuanced risk stratification. In a meta-analysis of 5 studies that assessed the performance of Decipher, the combined cohort showed that the incidence metastases rates were 5.5%, 15.0%, and 26.7% ($p<0.001$) for the low, intermediate, and high-risk groups, respectively [20]. In a multivariable analysis adjusting for clinicopathologic variables, Decipher remained a statistically significant predictor of metastasis (HR, 1.30; 95% confidence interval, 1.14–1.47; $p<0.001$).

2) Implications for active surveillance versus definitive treatment selection

The integration of genomics classifiers with traditional clinicopathologic factors may enhance the precision of decision-making in localized PCa. A deeper understanding of a cancer's potential for metastasis or recurrence after treatment can lead to individualized treatment. Active surveillance, a period of close disease monitoring, is increasingly used for patients with low-risk PCa. Genomic classifiers may provide additional prognostic information to select individuals at higher or lower risks for disease progression. Currently, actionable thresholds for the selection of active surveillance versus immediate treatment among otherwise

low-risk patients based on genomic results have not been validated [21]. However, their use has increased in clinical practice [22].

2. Role of Molecular and Genomic Profiling

1) Identifying actionable mutations in localized disease settings

Awareness of germline genetic alterations that contribute to PCa pathogenesis have growing roles in clinical management. DNA damage repair genes including, *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, and *ATM*, play a role in aggressive disease progression, and may be identified in up to 20% of patients with advanced or metastatic disease [23,24]. These genes are involved in single- and double-strand repair encoding proteins involved in homologous recombination, mismatch repair, and base excision repair. Inactivating mutation in DNA repair can result in genomic instability, resulting om copy number and structural variants that result in cancer progression. In addition to DNA repair genes, the androgen receptor (*AR*) gene has been identified in its role of fueling aggressive PCa and resisting hormonal therapies. Alterations of the *AR* gene through high-level copy number or gain-of-function mutations cause an overactivation of the AR pathway, leading to uncontrollable cancer growth [25]. While androgen deprivation therapy treatments can interfere with the AR pathway early in the disease course, this subtype of PCa often becomes resistant to this treatment and progresses to castration resistance prostate cancer (CRPC) [26,27]. While these genomic alterations contribute to tumor progression and therapy resistance, they also represent actionable targets for treatment. Molecular profiling enables the identification of these mutations, allowing clinicians to tailor adjunctive treatments targeting these mutations.

2) Molecular profiling to guide treatment strategies

Molecular profiling has an increasing role in identifying adjunctive treatment strategies in advanced PCa. PCa with BRCA 1/2 mutations can be targeted with poly(ADP-ribose) polymerase (PARP) inhibitors [28-30]. For example, in a randomized, double-blind, phase 3 trial, patients with metastatic CRPC (mCRPC) were randomized in a 1:1 fashion, with the first group receiving talazoparib, a PARP inhibitor, plus enzalutamide, AR blocker, and the second group receiving a placebo plus enzalutamide as first-line therapy [31]. The primary analysis showed that the talazoparib and enzalutamide group did not reach median radiographic progression-free survival (rPFS). In contrast, the enzalutamide and placebo group reached median rPFS at 21.9 months (HR, 0.63; p<0.0001). In another randomized, double-blind, phase 3 trial, patients with mCRPC were randomized in a 1:1 fashion, with the first group receiving olaparib, a PARP inhibitor, plus abiraterone, and the second group receiving placebo plus abiraterone as first-line therapy. Median rPFS was significantly longer in the abiraterone and olaparib group compared to abitaterone and placebo group (24.8 months vs. 16.6 months; HR, 0.66; p<0.001) [32]. These findings highlight the expanding role of PARP inhibitors with AR pathway blockers in improving rPFS for mCRPC patients with BRCA 1/2 mutations.

3. Enhancing Treatment Planning With Advanced Imaging

1) PSMA-PET for improved staging accuracy and identification of occult metastases

Advances in imaging have become crucial factors in clinical decision-making and treatment planning for PCa. Conventional imaging methods such as computed tomography (CT) and bone scans possess only modest diagnostic sensitivity and specificity for the detection of metastatic PCa, particularly in earlier phases of the disease [33,34]. Novel imaging modalities, particularly those employing molecular imaging agents, significantly enhance conventional imaging methods. These agents have a high molecular affinity for prostatic tissue, enabling more precise detection of nonlocalized disease and improving the accuracy of staging and treatment planning. One of these agents is gallium-68 PSMA PET-CT, which utilizes radioactive molecules bound to PSMA to identify nonlocalized lesions throughout the body. In a randomized phase 3 trial comparing PSMA PET-CT to conventional CT, PSMA PET-CT had superior accuracy than conventional CT in detecting metastatic lesions (92% vs 65%, p<0.0001) [6]. Additionally, PSMA PET-CT demonstrates greater specificity and sensitivity than CT (38% vs. 85%) and specificity (91% vs. 98%).

https://doi.org/10.22465/juo.255000120006

In addition to gallium-68 PSMA PET-CT, 18F-DCFPyL-PET-CT has shown success in improving detection of nonlocalized prostatic tissue. In a prospective study, 18F-DCFPyL-PET-CT correctly localized 84.8%–87.0% of lesions, resulting in a change of management in 63.9% of patients [35]. Due to the improved detection of prostatic lesions through these molecular imaging agents, the staging has become more accurate, leading to more precise treatment planning.

2) Integration of imaging biomarkers into radiation planning and surgical approaches

The potential clinical role of PSMA-targeted agents extends beyond initial diagnosis into guidance for surgical and radiation-based treatment. For surgical treatment, PSMA-targeted radiotracers, such as 99mTc-PSMA, enable intraoperative image guidance, providing a detailed roadmap to identify prostatic lesions for resection while preserving healthy tissue. In a systemic review of 29 studies, PSMA-targeting agents have a median specificity of 98.9% and sensitivity of 84.8%. Outcomes demonstrated a decline of PSA level of >90% in 22.0% to 100% of patients and biochemical recurrence rates ranging from 50.0% to 61.8% of patients [36]. These results show the potential viability of introducing PSMA-target agents into surgical planning; however, long-term oncological data needs to be further evaluated in surgeries utilizing PSMA-targeted radiotracers.

A direct therapeutic role has also been established with PSMA radioligands such as lutetium-177 (177Lu)–PSMA-617 target PSMA-expressing cells and beta particle radiation to them and the surrounding microenvironment. In a randomized, phase 3 trial, patients with mCRPC were randomized in a 2:1 fashion, with the first group receiving 177Lu–PSMA-617 with standard care and second group receiving standard care. Median rPFS was significantly longer in 177Lu–PSMA-617 with the standard care arm than the standard care arm (8.7 months vs. 3.4 months; HR, 0.40; p<0.001) [37].

4. Active Surveillance and Precision Oncology

Prostate MRI, and its commonly used PI-RADS scores is another means for enhancing disease personalization. Beyond initial disease staging, the degree of MRI lesion visibility appears to have prognostic significance in the setting of active surveillance. In patients on active surveillance, repeat MRI showing an upgraded or persistent upgraded PI-RADs score of 4 and 5 was associated with Gleason grade group (GG) ≥2 disease on subsequent tissue biopsy [38-41]. Moreover, lower PI-RADS scores have been associated with lower odds of reclassification to higher grade disease. By integrating PI-RADS scores with other clinicopathologic factors, such as PSA levels, more comprehensive measures of disease risk may personalize the management of early stage PCa.

Other imaging and biomarker modalities have the potential to better predict outcomes of AS. There is emerging enthusiasm for a role of PMSA-PET increased accuracy in detecting metastatic lesions in primary or recurrent disease, it has been hypothesized that PMSA-PET could predict clinically significant disease with patients on active surveillance. In a small retrospective study, 60% of patients who had concerning features on PSMA PET also had concerning features on final pathology after prostatectomy [42]. These findings may suggest a future role for PSMA-PET in earlier stage disease.

CHALLENGES IN PRECISION ONCOLOGY FOR LOCALIZED PROSTATE CANCER

1. Tumor and Patient Heterogeneity

1) Advances in precision oncology

The genomic diversity of primary PCa within primary PCa withing patients presents significant challenges in accurately predicting prostate-specific mortality rates and effective biomarker driven treatments. Løvf et al. [43] analyzed over 89 tumors in 41 different patients, noting genetic distinctly tumor foci within the prostate. Specifically, they found that 76% of pairwise compared foci had no common mutations at all. Boutros et al. [44] analyzed over 74 patients and found no shared copy number aberrations and very few shared single nucleotide variants between disease foci. This genomic variability within primary PCa poses challenges to comprehensively characterize the nature of a given patient's PCa.

Rigorous integration of patient clinical factors including age and comorbidity also offer improvement and personalization of treatment strategies. Briganti et al. [45] analyzed over 3,838 patients with PCa in a multi-institutional study, finding that older patients and patients with comorbidities were not associated with cancer-specific mortality. However, older age and patients with comorbidities were associated with other-cause mortality. These results suggest that older patients or comorbid patients may not benefit from aggressive treatment including biomarker-guided treatment due to the high risk of dying to other cause. Conversely, younger and healthier patients may benefit biomarker-guided treatment with a curative intent as the cancer-specific mortality rate is higher than other-cause mortality rate for these patients. As a result, these factors should be considered as part of integrative risk stratification strategy and factored into individualized treatment strategies.

2. Barriers to Widespread Implementation

High upfront cost for genomic tests and molecular-based imaging may limit widespread implementation in certain patient populations. Tissue based gene expression testing as well as molecular imaging is associated with substantial direct costs as well as a host of downstream expenditures [46]. Despite studies justifying the long-term cost effectiveness of these diagnostics, these upfront costs could limit accessibility of these advanced diagnostics to individuals with limited resources and/or no insurance coverage. As a result, a discrepancy in usage of advanced diagnostic among patient communities could result in differences of oncological outcomes among these communities.

FUTURE DIRECTIONS IN PRECISION ONCOLOGY FOR LOCALIZED PROSTATE CANCER

1. Innovations in Biomarker Discovery and Validation

Personalized prevention and treatment have been shown to significantly improve patient outcomes, leading to increased utilization of genetic testing and treatment selection based on genetic characteristics in PCa. As a result, the clinical guidelines, including those from the National Comprehensive Cancer Network, now recommend that patients diagnosed with high, very high risk, and metastatic PCa should undergo both germline and somatic genetic testing. The identification of specific mutations may directly influence treatment plans. However, several challenges delay the widespread implementation of these guidelines, including limited access to genetic counselors, difficulties in integrating genetic testing into clinical workflows, high costs, and issues with insurance coverage. Addressing these barriers is crucial to fully realizing the potential of genetic testing in PCa management [47].

2. Future Directions: Role of Artificial Intelligence

Recent advancements in artificial intelligence (AI) and machine learning have been applied to PCa risk stratification from both imaging as well as digital pathology. These include AI-based systems that have demonstrated excellent performance in identifying clinically significance PCa from prostate MRI images. For example, In a recent study of 10,207 examinations, an AI system showed a superior and noninferior area under the receiver operator characteristic curve for the detection of GG 2 or higher disease compared with radiologists [48]. These findings highlight the potential for enhanced imaging tools to integrate into clinical care, with numerous applications including risk stratification at initial diagnosis, personalized treatment planning, and surveillance monitoring.

Applications of AI to digitized pathology are also promising for both streamlining clinical processes but also may enhance predictive and prognostic estimates [49,50]. The Artera AI platform is a clinically available digital pathology tool derived from high resolution scans of prostate slides. In addition to prognostic estimates, the AI predictive model has been used to identify patients with PCa receiving radiation therapy who are most likely to benefit from short-term androgen deprivation therapy [51].

CONCLUSION

Personalization of treatment for PCa has become more attainable with the advancements within the clinical setting

https://doi.org/10.22465/juo.255000120006

before and after diagnosis. While PSA remains a foundational tool, its limitations solicit the integration of more precise approaches. The adoption of genomic classifiers, molecular profiling, and advanced imaging technologies into clinical practice represents a paradigm shift in PCa management, offering more precise risk stratification, personalized treatment strategies, and improved patient outcomes. Despite significant advancements in precision oncology for localized PCa, challenges such as tumor heterogeneity, patient-specific clinical factors, financial barriers, and practical limitations continue to limit its widespread adoption.

NOTES

- **Author Contribution:**

  Conceptualization: ML; Data curation: ML, GMD, PSP; Formal analysis: ML, GMD, PSP; Methodology: ML, GMD, PSP; Project administration: ML; Visualization: ML, GMD, PSP; Writing - original draft: ML, GMD, PSP; Writing - review & editing: ML, GMD, PSP.

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