Review

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Biomarkers in Localized Prostate Cancer: Towards A Personalized Medicine

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Abstract: Prostate-specific antigen (PSA) has been the main biomarker used for the detection and monitoring of prostate cancer for decades. However, its limited specificity and prognostic accuracy have prompted the development of novel molecular and imaging biomarkers to improve the clinical characterization of localized disease. This review critically examines recent advances in urinary biomarkers (e.g., PCA3, SelectMDx), tissue-based genomic assays (Oncotype DX Prostate, Prolaris, Decipher), and imaging techniques such as multiparametric magnetic resonance imaging (mpMRI) and prostate-specific membrane antigen positron emission tomography (PET-PSMA). We evaluate their diagnostic performance, prognostic relevance, and clinical utility in risk stratification and individualized treatment decision-making. Methodological and clinical barriers to their routine implementation are also discussed. Current evidence supports a multidisciplinary integration of these biomarkers to address the limitations of PSA, improve biopsy decision-making, better distinguish indolent from aggressive tumors, and optimize therapeutic strategies. Finally, future research directions aimed at validating and incorporating emerging biomarkers into clinical practice are outlined, with the goal of improving outcomes in patients with localized prostate cancer.

Keywords: localized prostate cancer; biomarkers; personalized medicine; radiomics

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide[1,2]. Early detection is key to achieving high survival rates in localized disease[1–3]. Currently, this is based on clinical parameters together with the prostate-specific antigen (PSA), the only blood biomarker widely used in clinical practice[4].However, PSA has limitations in terms of sensitivity and specificity, making it difficult to differentiate between benign and malign processes, as well as between tumors with clinical impact and indolent tumors[1]. These limitations contribute to overdiagnosis and overtreatment in a significant number of patients[5,6].

Biomarkers allow the detection of biological alterations associated with the disease, prognosis or response to treatment. The ideal biomarker should be accessible through non-invasive and low-

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cost, should methods, should have high sensitivity and specificity, and should be able to discriminate between aggressive and indolent tumors[7].

In recent years, several candidate biomarkers and molecular tools have been developed to try to improve diagnostic accuracy, refine prognostic stratification and personalize treatment for patients with PCa[3,4,8].

The aim of this review is to provide comprehensive, clinically-oriented guidance on the use of biomarkers in localized PCa, contextualizing their application in different clinical settings.

2. Methods and Materials

The articles cited in this narrative review were selected through an exhaustive search of databases, including Pubmed, Scopus, Cochrane, Google Scholar and Science Direct, with no date restrictions. The search was performed using the following keywords: ("biomarkers" OR "PSA" OR "imaging modalities" OR "genomic classifiers" OR "artificial intelligence" OR "microRNA" OR "lncRNA" OR "SNPs") AND "localized prostate cancer". Studies in English that evaluated biomarkers in serum, urine, tissue or imaging for the diagnosis, prognosis or personalization of treatment of localized prostate cancer were included. Preclinical studies, duplicates, or those whose full-text was not available were excluded.

3. Diagnosis: How to Select Patients Who Really Need a Biopsy?

PCa screening with PSA in population-based screening programs has been shown to reduce mortality by 27 % and the incidence of metastasis by 33 % in the European Randomized Study of Screening for Prostate Cancer (ERSPC)[9]. However, its low specificity (especially in ranges between 2.5 and 10 ng/ml) is associated with a high rate of unnecessary biopsies. To improve patient selection, the European Association of Urology (EAU) recommends the use of multiparametric magnetic resonance imaging (mpMRI) in men with PSA levels between 3 and 20 ng/ml due to its high negative predictive value (NPV), although its positive predictive value (PPV) remains variable[10]. In this context, new non-invasive biomarkers aim to optimize patient selection for biopsy.

The Prostate Health Index (PHI) combines total PSA, free PSA and [-2]proPSA[11], and showed a sensitivity of 82% and a specifity of 84% in a cohort of 421 patients, with a cutoff of 43 and an area under the curve (AUC) of 0.77. This was superior to total PSA (AUC 0.58) and the free PSA/total PSA ratio (AUC 0.64)[12]. Its main clinical indication is to aid in the decision to perform an initial or repeat prostate biopsy in men with a PSA level in the range of 2-10 ng/ml and a non-suspicious digital rectal exam. In combination with mpMRI, PHI improves the detection of clinically relevant tumors even in PIRADS ≤3 lesions. It avoids 39.5% of unnecessary biopsies while maintaining a 97% detection rate for significant cancers [13]. The 4Kscore is based on four serum kallikreins and achieved a sensitivity of 93% and a specifity of 55% in patients with PSA between 2 to 10 ng/ml[14]. In the ProScreen study, a threshold <7.5% avoided the need for mpMRI in 19% of patients with PSA ≥ 3 ng/ml, resulting in a 28% reduction in biopsies. Globally, there was a 41% decrease in the use of mpMRI[15].

The Stockholm3 (S3M) test, which integrates plasma biomarkers, genetic variants, and clinical data, reduced unnecessary biopsies by 34% with triple specificity compared to PSA, while maintaining sensitivity for high-risk tumors in a cohort of 59,159 patients[16]. Furthermore, in a multiethnic population (n = 2129), the test achieved a 45% reduction in biopsies (between 42 and 52%, depending on ethnic group) without compromising the detection of clinically significant cancers[17].

In terms of urinary biomarkers, SelectMDx quantifies messenger RNA (mRNA) from the *HOXC6* and *DLX1* genes and has a NPV of 98% for aggressive tumors with an AUC of 0.76[18]. With a cutoff value of -2.8[19], it reported a sensitivity of 90 % and a specificity of 50%. It avoids 38% of biopsies but fails to diagnose 10% of high-risk tumors. In combination with mpMRI, it avoids 49% of biopsies only misses 4.9% of aggressive cancers. Although its performance declines in low-risk populations, it remains useful in cases of previously negative biopsies or initial clinical suspicion[20].

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PCA3 is a non-coding mRNA approved by the Food and Drug Administration (FDA). With a threshold of 25, it showed a sensitivity of 77.5% and a specificity of 51.1% with an AUC of 0.73, superior to the free PSA/total PSA ratio (AUC 0.66)[21]. This test is adapted and validated for patients with previously negative biopsies, persistently high PSA, clinical suspicion with normal PSA or active surveillance (AS). Together with clinical variables, it can avoid between 40 to 67% of unnecessary biopsies[22]. However, its PPV is low (33.6%) and it may also be present in up to 10% of non-invasive lesions[23]. The widespread use of mpMRI has relegated PCA3 to a complementary role. It is mainly used in research but is not recommended as a screening tool[24].

The Michigan Prostate Score (MiPS) combines PCA3, *TMPRSS2/ERG* and PSA. It improves the detection of high-risk tumors while avoids mpMRI or biopsy in 35-51% of cases[25]. In addition, the ExoDx test analyzes exosomal RNA from ERG, PCA3 and SPDEF and achieved a sensitivity of 92%, a NPV of 91% and, PPV of 36% in a cohort of 1000 patients with PSA between 2 and 10 ng/ml[26,27]. A threshold of 15.6 avoided more than 25% of biopsies and correlated with histopathological characteristics after radical prostatectomy, demonstrating its usefulness in selecting candidates for AS[28].

When a prostate biopsy is negative, but clinical suspicion remains, the ConfirmMDx test can be employed. This test analyzes normal for hypermethylation of the APC, *RASSF1* and *GSTP1* genes*[29]*. This alteration reflects the "halo effect", whereby epigenetic changes in healthy tissue indicate proximity to a malignant area. In the MATLOC study (n = 498), the test achieved a NPV of 90%. In the DOCUMENT study (n = 350), the NPV was 88% (95% CI, 85-91%) after two years of follow-up[30]. Subsequently, the EpiScore algorithm improved the performance to a NPV of 96%, which is superior to clinical variables such as PSA, high-grade PIN or rectal exam[31]. The test is currently included in the guidelines of the National Comprehensive Cancer Network (NCCN) guidelines, although its use is limited by cost and sample availability.

4. Prognosis: How to Distinguish Between Indolent and Aggressive Tumors?

The management of PCa has has moved beyond the traditional approach based solely on PSA, Gleason score and clinical stage, especially in intermediate-risk patients. In this context, genomic tissue classifiers offer useful tools for improving prognostic stratification and guiding personalized therapeutic decisions[32]. Despite the use of PSA kinetics for AS, its limited discriminatory power has driven the development of more accurate genomic tests[33,34].

Decipher can be performed on both diagnostic biopsy samples and prostatectomy tissue, depending on the clinical context and stage of decision-making, by analyzing the expression of 22 genes associated with androgen signaling, proliferation, and immune response[35]. In favorable intermediate-risk patients, high scores (> 0.6) were associated with a worse prognosis ($p < 0.001$) and a shorter time to treatment during AS ($p < 0.001$)[36]. Its clinical utility has been evaluated in several studies. In the PRO-ACT trial, it increased the treatment of high-risk patients ($p < 0,001$)[37]. In the analysis by Badani et al[38]., it increased the recommendation for AS in low-risk (20%) and high-risk (16% patients). Finally, the Surveillance, Epidemiology and End Results (SEER) analysis increased the AS rates from 37% to 39% ($p < 0,001$) and reported an association between high scores and advanced stages or greater tumor aggressiveness[39].

OncotypeDx, recommended by the American Society of Clinical Oncology (ASCO) and the NCCN, evaluates 17 genes using reverse transcription polymerase chain reaction (RT-PCR) and generates a score from 0 to 100. This test predicts the likelihood of metastases, mortality, and adverse pathological features (Gleason ≥ 4+3 or pT3+)[40]. In a cohort of 514 patients (91% Caucasian), each 20-point increase was associated with an increased risk of high-grade disease (OR = 2.3; 95% CI: 1.5-3.7) and disease not confinedto the prostate (OR = 1.9; 95% CI: 1.3-3)[41]. A meta-analysis of 732 patients showed that the combination of OncotypeDx, the Cancer of the Prostate Risk Assessment (CAPRA) (AUC 0.68-0.73) and the NCCN classification (AUC 0.64-0.70) improved the prediction of adverse pathology, especially in racially diverse cohorts (n = 431; 20% African Americans) with an

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improvement in AUC from 0.63 to 0.72[42]. These data support its added value when integrated with existing clinical tools.

Prolaris, also recommended by ASCO and NCCN, evaluates 46 genes related to cellular progression using RT-PCR and generates a 10-point scale to estimate the risk of mortality and metastasis at 10 years[43]. In patients who underwent transurethral resection of the prostate (TURP), a higher risk of PCa mortality was observed (HR = 2,56; p < 0,0001). When combined with clinical variables, the AUC improved from 0.80 to 0.88[44]. In the PROCEDE-1000 study (n = 1026), 47.8% of patients had their treatment modified due to the test, with a 72.1% de-intensification and a 26.9% intensification[45]. In a cohort of 547 patients after biopsy, the AS rate increased to 84.2% when Prolaris was combined with NCCN criteria, with a AS maintenance after 4 years of 69% in academic centers and 63% in community centers[46]. In a retrospective series of 3208 patients, the choice for AS doubled, with durability after 3 years that was 1.5 times greater (p < 0,0001)[47].

ProMark is a prognostic test that evaluates the expression of 8 proteins in prostate biopsies using quantitative immunohistochemistry. It aids decision-making between AS and treatment in patients with Gleason 3+3 or 3+4. In a study by Blume-Jensen et al[48] (n = 381) (AUC 0.78), a score >0.8 was associated with a sixfold higher risk of progression, whereas a low score in Gleason 3+3 score showed a NPV of 84%. This test does not require genomic techniques or large tissue samples, facilitating its use even with limited resources. However, it does not predict the risk of metastasis, and its clinical adoption remains limited[49].

A systematic review by Trabiz et al[50]. concluded that these tests improve the estimation of tumor aggressiveness, with bidirectional risk reclassifications in patients with intermediate-risk PCa and with variations depending on race. Although observational studies show a tendency towards increased AS, randomized trials continue to favor definitive treatments. Overall, these tools have the potential to refine the prognostic classification, but more controlled prospective studies are required to evaluate their clinical impact and cost-effectiveness.

mpMRI in combination with radiomic analysis is emerging as a non-invasive prognostic tool. In low-risk and intermediate-risk patients, a reduction in T2 was associated with a lower PSA level after one year[51]. Furthermore, low apparent diffusion coefficient (ADC) values were associated with a higher risk of recurrence (p = 0.002) and progression within five year (p < 0.001)[52]. These findings support the value of functional imaging in estimating aggressiveness and risk of progression.

Positron emission tomography (PET) with ^{68}Ga-PSMA-11 is now the preferred method for staging intermediate and high-risk PCa over computed tomography and bone scans, and it also provides quantitative parameters such as SUVmax. An intraprostatic SUVmax > 8 has been consistently associated with a high Gleason socre (p < 0.05), positive margins (p < 0.01) an advanced stage and shorter biochemical progression-free survival. Even in cases of Gleason ≤ 3+4, a high SUVmax indicates a higher risk of recurrence, which further supports its value in reclassifying candidates for AS or local treatment[53–55]. These data suggest that SUVmax could be an emerging prognostic biomarker in localized disease.

5. Treatment: Should Treatment Be Intensified or De-Intensified?

PSA remains essential for the stratification and management of PCa. A pre-treatment PSA value of > 20 ng/ml indicates a high risk of recurrence[56,57]. After treatment, parameters such as a PSA doubling time < 6-12 months[58–60], persistence of a high PSA level (≥0.2 ng/ml after prostatectomy)[59] or early biochemical recurrence (< 18-24 months)[61] are suggestive of an aggressive disease and justify hormonal intensification. Conversely, a PSA nadir < 0.1 ng/ml after radiotherapy or late recurrence (> 24 months) may benefit from delaying or reducing androgen deprivation therapy (ADT)[62,63]. Integrating PSA with other tools, such as CAPRA and the NCCN risk groups improves prognostic stratification[64].

The AR-V7 splice variant of the androgen receptor is associated with resistance to androgen receptor pathway inhibitors (ARPI) and adverse clinical outcomes. Although it is generally absent in untreated localized prostate cancer, AR-V7 is detected in 13–20% of patients after prostatectomy and

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subsequent androgen deprivation therapy (ADT), particularly in high-risk cases. Its presence correlates with significantly reduced biochemical progression-free survival (bPFS), overall survival (OS), and metastasis-free survival (mPFS)[65]. AR-V7 can be identified using clinically available methods such as RT-PCR, RNA sequencing of prostate tissue, immunohistochemistry, and non-invasive liquid biopsy via RT-PCR in circulating tumor cells. Patients positive for AR-V7 have a median bPFS of around 11 months, compared to over 70 months for those who test negative. This suggests that the variant drives tumor progression despite ADT and limits the efficacy of conventional hormonal therapies[65]. These findings support the use of AR-V7 testing to improve risk stratification and guide treatment decisions in locally advanced prostate cancer. Patients harbouring AR-V7 may benefit more from early chemotherapy or enrolment in clinical trials. Integrating AR-V7 into clinical practice could improve personalized treatment strategies and establish it as a promising biomarker for predicting resistance and poor prognosis in the adjuvant setting.

Among the genomic tools, Prolaris can estimate the risk of metastasis in localized PCa. In a prospective cohort of 554 patients, the combined cell cycle risk (CCR) score demonstrated significant prognostic value after three years (AUC 0.74; p = 0.001). In patients with high CCR, the metastasis rate was 14% with single-agent treatment compared to 3% with multimodal treatment[66].Furthermore, in a cohort of 56,485 patients, the benefit of adding ADT to radiotherapy varied according to CCR, with a 17.1% reduction in risk at ten years for CCR = 3.69[67].

The Genomic Prostate Score or GPS (Oncotype) also predicts the response to radiotherapy. A 20-point increase in the GPS score was associated with a higher risk of biochemical failure (HR: 3.62; CI 95 %: 2.59–5.02), distant metastasis (HR: 4.48; CI 95 %: 2.75–7.38) and death from PCa (HR: 5.36; CI 95 %: 3.06–9.76). In patients with GPS > 40, the risk of metastasis (HR: 5.22; CI 95 %: 3.72–7.31), biochemical recurrence (HR: 4.41; CI 95 %: 2,29–8.49) and mortality from PCa (HR: 3.81; CI 95 %: 1.74–8.33) was significantly higher[68], with no differences according to race (p = 0,923)[69].

The genomic classifier Decipher can predict metastatic dissemination and biochemical recurrence after radiotherapy. In the phase III RTOG 9601 trial, patients with a score > 0.6 who were treated with radiotherapy plus bicalutamide had a higher 12-year OS rates (70% vs 51%, p = 0.005), although this benefit was limited to those with high genomic risk[70]. In the NRG/RTOG 0126 substudy, only patients with high scores benefited from the higher dose[71]. The ongoing phase III GUIDANCE trial (NRG-GU010) is evaluating the use of Decipher in unfavorable intermediate-risk PCa to inform decisions about treatment, including radiotherapy alone, radiotherapy plus short-course ADT, or radiotherapy plus ADT plus darolutamide.

Artificial Intelligence (AI) is increasingly being incorporated into the stratification of prostate cancer treatments. The ArteraAI model, which combines digital pathology and machine learning, reclassified 34% of patients who were initially categorized as high risk. This allows for a shorter duration of androgen deprivation therapy (ADT) without compromising oncological outcomes (p < 0.001)[72]. This strategy hast the potential to reduce overtreatment and enhance patients' quality of life. However, despite these promising results, current AI models have significant limitations. These include the need for extensive external validation across diverse patient populations, the risk of overfitting to training datasets, and limited applicability in routine clinical practice. Additionally, variability in pathology image quality and differences in treatment protocols among institutions may impact AI performance. Therefore, while AI-driven decision-making is progressing rapidly, its clinical adoption requires cautious interpretation and continuous prospective validation before it can be widely implemented.

PORTOS, is a 24-gene signature derived from Decipher that predicts the response to radiotherapy. It hast been validated in the SAKK 09/10 and RTOG 0126 trials, identifying patients who could benefit from dose escalation. In the SAKK 09/10 trial, patients with high scores benefited from receiving 70 Gy rather than 64 Gy. In RTOG 0126, patients in the higher tertile achieved better results with 79.2 Gy versus 70.2 Gy. At a molecular level, the genes in PORTOS are associated with hypoxia and immunological pathways[73].

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In the postoperative context, Decipher can also inform decisions regarding adjuvant or salvage therapy choices[74]. In the PRO-IMPACT study, treatment was modified in 30% of cases[75]. In the G-MINOR trial, high scores were associated with the need for adjuvant radiotherapy (p=0.009)[76]. The SPPORT study found that the addition of nodal radiotherapy and ADT in patients with scores > 0.6 reduced the risk of progression ($p < 0.001$), with an absolute benefit of 27% at ten years (HR: 0.60; CI 95%: 0.37–0.97; p=0.04)[77].

Finally, in the phase II of the STREAM trial, despite the intensification with enzalutamide, ADT and salvage radiotherapy, almost 50% of high-risk patients experienced recurrence within three years. Patients with a differentiated luminal subtype achieved a PFS of 89% compared to 19% for those with proliferating luminal subtype. Loss of PTEN (HR: 1.32; $p = 0.01$) and homologous recombination deficiency (HRD) (HR: 1.21; $p = 0.009$) were associated with a worse prognosis. In contrast, a good response to ADT (HR: 0.75; $p = 0.01$) predicted better outcomes[78].

6. Future Perspectives

Next-generation biomarkers improve the accuracy of diagnoses, the evaluation of prognoses and the decision-making process for therapies by identifying critical changes in molecular signalling pathways, thus enabling personalized oncology care.

MicroRNA (miR) can be detected in blood and urine, either freely or as part of extracellular vesicles (EVs). They have the potential to serve as non-invasive biomarkers[79]. A combined urinary panel incorporating PSA (miR-572, -1290, -141, -145; -21, -204, and -375) can distinguish between benign and malignant diseases with an AUC ranging from 0.70 to 0.86[80]. miR such as miR-145 and let-7a-5p are associated with high-grade tumors (Gleason >8; AUC 0.68)[81]. Other miRNAs, such as miR-19b and miR-16, demonstrate high sensitivity and specificity: 100% and 95%, and 93% and 79%, respectively[82]. miR-155 is overexpressed in tumor tissue and correlates with PSA, TNM and tumor volume ($p < 0.05$) [83]. Several prognostic miRNAs have been identified. For instance, miR-2909 can distinguish cancer from benign hyperplasia[84]; while miR-34b/c and miR-23a-3p are present in aggressive phenotypes. Conversely, let-7b-5p, miR-128a-3p, -188-5p, -224-5p and -23b-3p are associated with favorable prognosis[85]. MiR-148a-3p[86] y miR-582-5p[87] can predict for biochemical recurrence, progression and bone metastasis.

Long non-coding RNA (lncRNA >200 nt) are also emerging as diagnostic and prognostic biomarkers[88]. MALAT1, MAGI2-AS3, PVT1, NEAT1 y CAT2064 improve the diagnostic performance with an AUC of 0.67-0.95[89–93]. PCAT-1 is related to progression and high Gleason ($p = 0.01$)[94], whereas UCA1 ($p < 0.0001$)[95], ZEB1-AS1 and SNHG9 are associated with bad prognosis and metastasis[96]. Conversely, MAGI2-AS3 and PCAT14 indicate a favorable prognosis[97]. Models based on lncRNA are superior to traditional nomograms for predicting 5-year recurrence and their detection with droplet digital PCR (ddPCR) in blood and urine is not invasive[88].

Single nucleotide polymorphisms (SNPs) are also useful for predicting prognosis[98]. For example, the allele rs6983267 (8q24) is associated with an increased risk of PCa ($p = 3.4\times10^{-5}$)[99], and the allele rs1042522 (TP53) is associated with a Gleason score ≥8 ($p < 0.0001$)[100]. SNPs such as rs1400633 (MSH2) can predict a better response to ADT ($p = 0.002$)[101], whereas rs4648302 (PTGS2) is associated with a lower risk of recurrence after prostatectomy ($p = 0.046$)[102]. Meanwhile, the rare variant rs188140481 (frequency 1.6 %) implies a significantly higher risk of developing PCa ($p <$ 0,001)[103].

The gut microbiota has emerged as a promising source of non-invasive diagnostic and prognostic biomarkers in prostate cancer. Multiple studies have reported significant compositional differences between patients and healthy controls, including shifts in microbial diversity and the relative abundance of specific bacterial taxa. These changes may affect systemic inflammation, hormonal metabolism, and immune modulation—mechanisms potentially involved in prostate carcinogenesis. Furthermore, certain microbial signatures have been correlated with disease stage, tumor aggressiveness, and treatment response, highlighting their potential role in risk stratification therapy monitoring[104]. While these findings are encouraging, further research is necessary to

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validate microbial biomarkers in larger and more diverse populations, and to clarify causal relationships rather than mere associations. Integrating gut microbiome profiling into clinical practice will require standardized sampling protocols, robust bioinformatics pipelines, and regulatory approval to ensure reproducibility and clinical utility.

Finally, AI is revolutionizing the integration of clinical and omic data to identify relevant biomarkers and predict tumor evolution[105,106]. Combining genomic and transcriptomic data enables the development of advanced predictive models that could enhance clinical decision-making[107].

7. Discussion

Integrating biomarkers into PCa is transforming diagnosis, prognostic stratification and decision-making in PCa by promoting a more precise and personalized approach[108] (Table 1). Although PSA remains the reference biomarker due to its availability and accessibility, its limitations in terms of sensitivity and specificity highlight the need to incorporate more advanced molecular tools[109].

In this context, novel biomarkers such as PHI, 4Kscore, SelectMDx, PCA3 and tumor circulating cells offer greater diagnostic precision and risk stratification, particularly in patients with intermediate PSA levels or ambiguous clinical findings[19,22,26,110–113]. There is currently a tendency to use multimodal panels in liquid biopsies that combine biomarkers from blood, urine and prostatic secretions. This allows for a less invasive and more efficient integrative evaluation[114–116]. Cost-effectiveness studies support these strategies, which contribute to reducing unnecessary biopsies and optimizing resources. However, their generalized implementation is still limited by economic, logistical and regulatory barriers[117–119].

Currently, PCa management also incorporates advanced imaging technique, such as mpMRI and PET-PSMA, which have notably improved the precision with which tumors are detected, staged and characterized[52–55,120]. These tools can facilitate the early detection of clinically significant disease, guide biopsy indications and inform treatment decisions tailored to each patient´s biological profile.

In terms of prognosis, genomic classifiers such as Decipher, OncotypeDx and Prolaris enable more accurate prediction of tumor aggressiveness, recurrence risk and metastasis by providing essential information for selecting candidates for AS or treatment intensification[43,107].

AI has emerged as a promising addition to these methods by integrating clinical, molecular and imaging data. Advanced algorithms can identify complex patterns, stratify risk and assist in decision-making. In certain scenarios, their performance surpasses that of conventional methods[121–124]. The potential of AI is further amplified by the incorporation of genomic, transcriptomic and microbiome data, offering new opportunities for precision medicine.

Despite these advances, most studies are retrospective or observational. More prospective multicenter studies are required to confirm the impact on survival, quality of life and efficiency. Updating clinical guidelines constantly will be essential to adequately integrate this growing body of evidence. Moreover, the effective implementation of these innovations must overcome challenges such as protocol standardization, staff knowledge, interoperability between technological platforms, and clinical validation in heterogeneous contexts. The increasing use of genomic data and AI tools raises ethical, legal and privacy issues that must be addressed through clear regulatory frameworks and data protection strategies[125]

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Table 1. Indications for different test and biomarkers in localized prostate cancer.

USE	TEST	BIOMARKER	SAMPLE	AUC/NPV	SCORING AND INTERPRETATION	ADVANTAGES	LIMITATIONS	VALIDATED CLINICAL SETTING
Avoid initial and subsequent biopsies	PHI[11–13]	PSA, free PSA, isoform [-2] proPSA	Blood	AUC 0.70-0.75	Score: 0 -55 Risk > 40 associated with significant PCa. PHI > 55: 50 % chance of PCa.	Accessible and fast. Higher sensitivity and specificity than PSA, detects high-risk PCa. Complementary to PSA in AS to detect biochemical progression.	Lower sensitivity in small tumors.	Initial evaluation with PSA 4-10 ng/ml.
	4K Score[14,15]	PSA, free PSA, intact PSA, hK2 + rectal examen, age and previous biopsy	Blood	AUC: 0.82-0.87 NPV: 95 %	Score: 0-100: risk of Gleason ≥ 7 PCa.	Integrates clinical variables, high precision in high-risk PCa.	High cost, not always available.	Patient selection for initial biopsy.
	Stockholm3[16,17]	PSA + 232 SNPs + 6 plasmatic proteins	Blood	AUC: 0.81-0.85	Score: 0-15. > 11 suggests significant PCa.	Includes genetic risk, avoids 50% of biopsies.	Only available in Europe.	Screening for the general population.
	SelectMDx[19,20,31]	mRNA from HOXC6, TDRD1 and DLX1 genes.	Urine post-DRE	AUC: 0.76 NPV: 90 %	Score 0-1: positive = high risk of significant PCa.	Identifies high-risk PCa. Better in combination with mpMRI.	Limited availability, influenced by sample gathering.	Decision to biopsy after high PSA.
	ExoDX[26–28]	Exosomal RNA from PCA3, ERG and SPEDF	Urine (no DRE)	AUC: 0.71-0.75	Continuous score; >15.6 threshold for biopsy.	No DRE required, useful after PSA or mpMRI.	Limited use outside the United States.	Pre-biopsy. PSA 2-10 ng/ml.
	MiPs[25]	PCA3 + PSA and TMPRSS2-ERG/ETV	Urine post-DRE	AUC: 0.77-0.81. NPV: > 90 %	Individual risk, the higher the score, the higher the risk.	Improves the identification of high-risk PCa (better than only PCA)	Low specificity, requires DRE, limited evidence in some populations.	PSA 2-10 ng/ml with no previous biopsy.
Re-biopsy	PCA3[21–24]	Non-coding mRNA PCA3	Urine post-DRE	AUC: 0.66	Continuous score; > 35 higher risk of PCa.	Not affected by prostatic volume. Better predictor of PSA.	Only useful if combined with mpMRI. Outdated by more precise tests.	Patients with a previously negative biopsy.
	ConfirmMDx[18,29,30,126]	DNA methylation in	Tissue	AUC: 0.76 NPV: 88-96 %	Binary result (positive/negative) for methylation.	High NPV (> 90 %) after negative biopsy. Detects the halo effect.	Only applicable after previous biopsy.	Decision to re-biopsy after a previously negative result.

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		APC, RASSF and GSTP1.					Not useful in inflammation High cost.	
Indication/ exclusion of AS	Oncotype Dx[40–42]	17 genes (proliferation, invasion…)	Tissue	AUC: 0.68-0.72	Score 0-100; > 40 increased risk of progression.	Reclassifies Gleason 6-7. Predicts upgrading and progression. Useful in candidates for AS.	Cost. Requires solid sample.	Choice for AS in Gleason ≤ 7.
	Prolaris[43–47]	31 cell cycle genes and 15 maintenance genes.	Tissue	AUC: 0.77-0.88	Score: 0-10. CCP > 1 higher risk of progression.	Robust data, easy to interpretate. Clear stratification for low risk.	Not tailored for high-risk disease. The interpretation requires experience.	Decision for AS in low Gleason with rising PSA.
	Decipher[35–39]	RNA from 22 genes (metastasis). GPS score.	Tissue	AUC: 0.75-0.80	Score: 0-1. > 0.6: high risk < 0.4: low risk 0.4-0.6: intermediate risk	Good predictor in Gleason 7-8 High prognostic discrimination.	Cost.	Exclusion for AS; risk of early metastasis.
	Promark[48,49]	Proteomic signature of 8 proteins associated with tumor aggressiveness	Tissue	AUC: 0.70-0.78	Score: 0-1 (continuous) > 0.33 increasing risk of progression or upgrading; > 0.8: high risk (77 % Gleason > 4+3 o T3+)	Does not require complex techniques, useful in Gleason 3+3 and 3+4.	Only applicable in tissue; less validated than Decipher/Oncotype.	Choice for AS in Gleason 3+3 and 3+4.
Treatment intensification	Decipher[70,71,74–77]	RNA from 22 genes. GC score.	Tissue	AUC: 0.77	Score: 0-1; > 0.6: high risk of metastasis.	Robust stratification after prostatectomy. Predicts the risk of metastasis, recurrence and mortality. Guides the use of ADT after RT.	Requires enough tissue. Cost. Limited prospective validation.	Post-prostatectomy with + margins or pT3. Salvage RT. Intermediate/high risk. Guides adjuvant ADT.
	Prolaris[66,67]	31 cell cycle genes.	Tissue	AUC: 0.77-0.88	Continuous score; CCR > 1: higher risk of progression.	Observational data, long follow up. Supports the decision for treatment intensification.	Not useful if ADT is already necessary. Lower impact in high risk.	Pretreatment in intermediate risk. ADT indication nuclear.
	Oncotype Dx[68,69]	17 genes (proliferation, invasion…)	Tissue	AUC: 0.68-0.72	Score: 0-100; > 40 high risk of progression or upgrading	Stratifies Gleason 6-7. Identifies candidates for intensification in intermediate risk.	No estimation of long-term metastasis. Limited post-operatory validation.	Gleason 6-7 pretreatment. Intermediate risk.

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								Decision between AS VA and intensified treatment.

ADT: Androgen Deprivation Therapy; **AS**: Active surveillance; **AUC**: Area under the curve; **CCR:** Cell cycle risk; **DRE:** Digital rectal exploration; GPS: Genomic Prostate Score; **mpMRI**: Multiparametric magnetic resonance imaging; **mRNA**: Messenger RNA; **NPV:** Negative predictive value; **PCa**: Prostate cancer; **PHI**: Prostate Health Index; **PSA**: Prostate Specific Antigen; **RT**: radiotherapy; **SNPs**: Single Nucleotide Polymorphism.

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8. Conclusions

The future of prostate cancer management depends on the integrating validated biomarkers to enable more precise and individualized clinical decision-making. For these tools to be effectively implemented, they must overcome technical and regulatory challenges, and their clinical utility must be supported by high-quality evidence from real-world settings. As robust data from prospective studies becomes available, it is expected that these biomarkers will play a critical role in guiding diagnosis, treatment selection, and longitudinal patient monitoring across diverse populations.

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