Emerging biomarkers in prostate cancer diagnosis and treatment: Insights into genetic, RNA and metabolic markers (Review)

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Abstract. Prostate cancer remains one of the most prevalent malignancies and a major cause of cancer-related mortality among men worldwide. Despite widespread use of prostate-specific antigen testing, current diagnostic approaches suffer from low specificity and limited ability to distinguish between indolent and aggressive disease, resulting in overdiagnosis and overtreatment. Advances in molecular biology, genomics and metabolomics have led to the identification of novel biomarkers that have potential for improving the precision of prostate cancer diagnosis, prognosis and therapy. The present review provides a comprehensive overview of emerging prostate cancer biomarkers, including genetic (such as *BRCA1/2*, *HOXB13* and *PTEN*), RNA-based (such as PCA3 and miRNAs), metabolic (such as citric acid and polyamines) and methylation markers (such as *GSTP1*, *APC* and *RASSF1A*). These biomarkers not only enhance diagnostic accuracy but also facilitate risk stratification, prediction of therapeutic response and real-time disease monitoring through liquid biopsy technologies. Moreover, integrating multi-omics data with artificial intelligence and machine learning may further improve early detection and personalized treatment strategies. Overall, the development and clinical implementation of these biomarkers represent a transformative step toward precision medicine in prostate cancer, enabling earlier diagnosis, optimized therapy selection and improved patient outcomes.

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1. Introduction

Prostate cancer (PCa) is a major public health burden in men: In 2022, there were ~1.47 million new prostate cancer cases globally, making it the second most common cancer in men, and it accounted for ~4.1% of all male cancer mortalities worldwide. In the United States alone, ~313,780 new cases and 35,770 mortalities from prostate cancer are projected in 2025 (1,2). Early and accurate diagnosis is pivotal to improving clinical outcomes, yet the disease often progresses silently in its initial stages. Conventional screening approaches-such as serum prostate-specific antigen (PSA) testing and digital rectal examination-have long served as cornerstones of early detection (2). However, their limited specificity and inability to distinguish indolent from aggressive disease frequently result in overdiagnosis, overtreatment and associated morbidity (3). These shortcomings highlight a need for novel biomarkers that enable more precise disease characterization, risk stratification and individualized treatment planning (4).

Recent advances in genomics, transcriptomics and metabolomics have revolutionized biomarker discovery, unveiling new molecular signatures that bridge laboratory research and clinical application (5). Genetic alterations such as mutations in *BRCA1/2*, *HOXB13* and *PTEN*, as well as *TMPRSS2-ERG* gene fusions, have been associated with PCa initiation, progression and therapeutic resistance (6,7). These genetic insights not only enhance the understanding of tumor biology but also aid in identifying high-risk patients, predicting treatment response and guiding precision interventions such as *PARP* inhibitor therapy (8).

Parallel to these genomic developments, RNA-based biomarkers-including prostate cancer antigen (PCA) 3, microRNAs (miRNAs; such as *miR-141* and *miR-375*) and long non-coding RNAs (lncRNAs)-have emerged as promising tools for non-invasive diagnosis (9). Detection of these RNA molecules in urine, blood or exosomal (exo) fractions

notably improves diagnostic accuracy when used alongside PSA testing, thereby minimizing unnecessary biopsies (10). The advent of liquid biopsy, encompassing circulating tumor DNA (ctDNA) and exo RNA analysis, further enhances real-time disease monitoring. This approach enables dynamic assessment of tumor burden, therapeutic response and the emergence of resistance-associated mutations in key genes such as androgen receptor (AR) and *BRCA1/2* (11,12). In addition to genomic and transcriptomic markers, metabolic biomarkers provide valuable insights into PCa pathophysiology. Metabolites such as citrate, polyamines and sarcosine reflect the distinct metabolic reprogramming that occurs during malignant transformation (13). Their quantification in biofluids-including serum, urine and prostatic secretions-offers complementary diagnostic information and helps differentiate benign prostatic hyperplasia from malignant disease (14).

Collectively, these discoveries mark a paradigm shift in PCa management. The integration of genetic, RNA and metabolic biomarkers into diagnostic workflows has the potential to transform routine screening, prognostic evaluation and therapeutic decision-making. The present review synthesizes current evidence on emerging biomarkers in PCa, emphasizing their translational relevance, diagnostic performance and clinical feasibility. The present review also discusses persistent challenges, such as biomarker validation, inter-population variability and the harmonization of multi-omics data-and explores future directions, including artificial intelligence (AI)-assisted liquid biopsy interpretation and multi-omics integration for advancing precision oncology (Fig. 1) (15).

2. Protein biomarkers in PCa

PSA. PSA, encoded by the *KLK3* gene, is a glycoprotein predominantly secreted by the epithelial cells of the prostate gland (16). While its primary physiological role is the liquefaction of semen, its high organ specificity has established it as a cornerstone biomarker in the screening and diagnosis of prostate diseases (17). In the serum, PSA exists primarily in three molecular forms: Free PSA (f-PSA), which constitutes 10-30% of the total PSA (t-PSA); PSA complexed with α1-antichymotrypsin and PSA complexed with α2-macroglobulin. The latter two are collectively termed complexed PSA (18).

Free-to-total PSA ratio (f/t PSA). f/t PSA provides key diagnostic information beyond t-PSA levels alone (19). In patients with PCa, the proportion of f-PSA is markedly lower compared with those with benign conditions such as benign prostatic hyperplasia. The f/t-PSA ratio is calculated as follows (20): f-PSA/t-PSA=free PSA concentration (ng/ml)/ total PSA concentration (ng/ml).

An f/t PSA ratio <0.15 is associated with an increased risk of malignancy and is a key factor in recommending prostate biopsy, thereby improving diagnostic specificity (21,22). This metric is particularly valuable within the diagnostic 'gray zone' of t-PSA (4-10 ng/ml) (23). A ratio >0.25 typically suggests a benign etiology, whereas a ratio <0.15 warrants further invasive assessment (24,25). Notably, when t-PSA >10 ng/ml, biopsy is generally indicated regardless of the f/t PSA ratio (26). A large multicenter study demonstrated that incorporating the f/t PSA ratio into clinical decision-making

reduced misclassification by ~43%, underscoring its utility in enhancing diagnostic accuracy (27).

Emerging strategies seek to integrate the f/t PSA ratio with other clinical parameters, including patient age, family history and racial background, to develop multivariate predictive models (28,29). These refined algorithms promise to further personalize PCa risk stratification and support early intervention strategies (30).

PSA density (PSAD). PSAD, defined as the ratio of serum PSA concentration to prostate volume (PSAD=t-PSA/prostate volume), refines diagnostic precision by accounting for gland size (31). Prostate volume is typically quantified via transrectal ultrasound (TRUS) or, with increasing frequency, MRI. A PSAD value >0.15 ng/ml/cm^3 is consistently associated with a heightened risk of PCa (32,33). This normalization mitigates the confounding effect of benign gland enlargement, thereby reducing false-positive results (34).

Longitudinal cohort studies have confirmed that an elevated PSAD is a robust predictor of PCa incidence and progression (35,36). Recent evidence indicates that MRI-based PSAD calculations, benefiting from superior soft-tissue resolution, outperform TRUS-derived values (37). Consequently, MRI-calculated PSAD exhibits enhanced diagnostic sensitivity and specificity in discriminating malignant from benign lesions, supporting its integration into modern diagnostic pathways (38).

PSA velocity (PSAV). PSAV measures the dynamic change in PSA levels over time, calculated as the absolute change in PSA per year [PSAV=(PSA$_2$-PSA$_1$)/ΔTime in years] (39). A velocity >0.75 ng/ml per year is considered clinically considerable and suspicious for underlying malignancy (40). PSAV is particularly useful for monitoring individuals with borderline PSA levels and for assessing disease progression in patients' post-treatment (41). A rapid rise in PSA is often associated with aggressive tumor biology and a worse prognosis (42).

The clinical utility of PSAV is being augmented by AI and machine learning (43). Emerging models integrate PSAV with a multitude of clinical, imaging and genomic parameters to achieve more accurate predictions of disease trajectory, thereby aiding in personalized surveillance and therapeutic decision-making (44,45).

Prostate health index (PHI). PHI is an advanced blood test that combines three distinct forms of PSA: f-PSA, t-PSA and a truncated form of kallikrein (KLK)-related protein 4 (k-PSA, also known as hK4). It is calculated using the following formula (46): PHI=(f-PSA)/(t-PSA) x t-PSA √(t-PSA) x k-PSA.

The resulting score stratifies patients according to their risk of harboring clinically considerable PCa, with higher values indicating greater risk (47). The established clinical thresholds guide management as follows: i) A PHI <15 suggests a low likelihood of malignancy, ii) values between 15 and 35 fall into an indeterminate range where adjunctive evaluation with multiparametric MRI (mpMRI) is recommended, iii) a PHI >35 signifies high risk and typically warrants biopsy (48,49). PHI demonstrates superior diagnostic accuracy compared with t-PSA or f/t PSA alone, particularly within the t-PSA gray zone and has been shown to reduce unnecessary biopsies by ~20% (50,51). Prospective validation studies confirm that
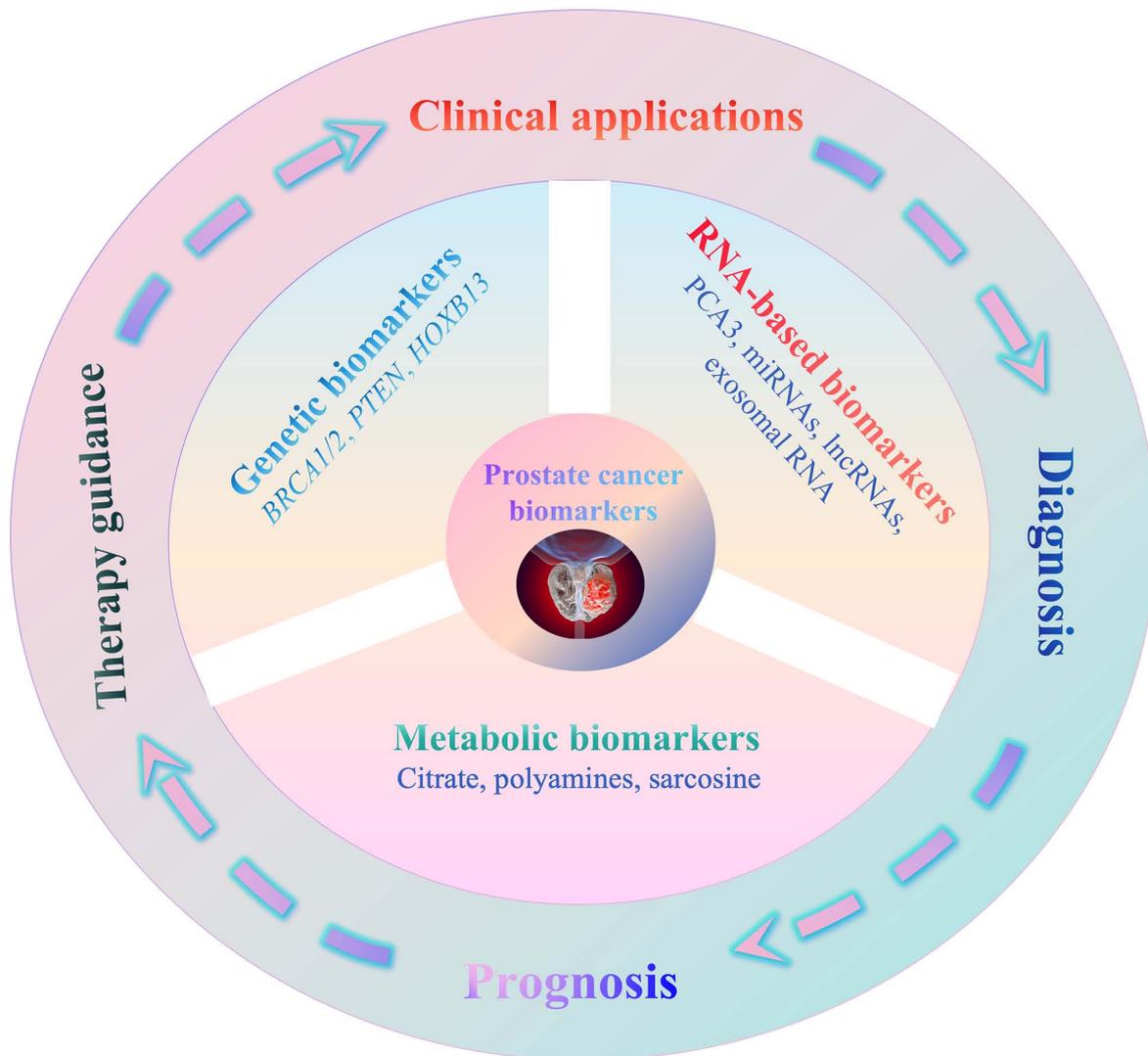
Figure 1. Conceptual framework of emerging biomarkers in PCa. Conceptual framework of emerging biomarkers in PCa, categorized into genetic, RNA-based and metabolic markers, with their corresponding clinical applications in diagnosis, prognosis and personalized treatment. PCa, prostate cancer.

PHI effectively identifies aggressive PCa, improving patient selection for invasive procedures (52,53).

The integration of PHI with mpMRI represents a powerful diagnostic synergy. This combined model enhances detection confidence for clinically considerable cancer while minimizing overtreatment (54). Furthermore, ongoing research into ethnicity-specific PHI thresholds highlights the importance of personalized diagnostic standards to optimize accuracy across diverse populations (55,56).

The KLK family. KLK family comprises 15 secreted serine proteases (*KLK1-KLK15*) clustered on chromosome 19q13.4. These enzymes share structural similarity, characterized by a conserved catalytic triad of histidine, aspartic acid and serine residues (57-59). KLKs participate in diverse physiological processes, including skin desquamation, neural plasticity and inflammation (60-62). For instance, *KLK1* cleaves kininogen to generate bradykinin, thereby modulating vascular tone, permeability and inflammatory signaling (63). *KLK5* and *KLK7* regulate keratinocyte differentiation and desquamation, with aberrant activity implicated in psoriasis and atopic dermatitis (64,65).

Among all KLKs, *KLK3* (a PSA) is the best-established biomarker for PCa (66). Nevertheless, increasing evidence highlights that other family members, particularly *KLK2*, act synergistically with *KLK3* to promote prostate tumorigenesis and reshape the tumor microenvironment (67,68). Dysregulation of the KLK proteolytic network facilitates cancer progression by enhancing tumor invasion, angiogenesis and metastasis (69).

Transcriptomic analyses demonstrate distinct expression patterns of multiple KLKs in prostate carcinoma compared with benign tissue, underscoring their combined diagnostic and prognostic potential (70,71). *KLK2*, sharing ~78% sequence identity with *KLK3*, is also AR-regulated and activates pro-PSA by cleaving its pro-peptide (72). Due to its highly restricted expression profile, *KLK2* has emerged as an attractive therapeutic target (73). Several innovative platforms are currently in development, including: i) Radioligand therapies delivering cytotoxic payloads selectively to KLK2-expressing cells (74), ii) bispecific T-cell engagers redirecting cytotoxic lymphocytes toward KLK2-positive tumor cells (75); and iii) chimeric antigen receptor T-cell therapies engineered to

recognize KLK2 on the cancer cell surface (76). Promising clinical candidates from companies such as Johnson & Johnson and EpimAb Biotherapeutics have advanced into Phase I trials, representing an encouraging step toward precision immunotherapy in PCa (77,78).

3. Nucleic acid biomarkers in PCa

Nucleic acid biomarkers, encompassing DNA- and RNA-based alterations, have emerged as powerful tools for the diagnosis, prognostic stratification and treatment selection of PCa (79). Their analysis, particularly through non-invasive liquid biopsies, offers a real-time snapshot of tumor genetics and dynamics (80).

DNA-based markers: Gene mutations and chromosomal abnormalities
BRCA1/2 genes. Mutations in the *BRCA1* and, more importantly, *BRCA2* genes are associated with hereditary PCa (81). Carriers face a 2-3-fold increased lifetime risk of developing the disease and are more likely to present with aggressive tumor phenotypes (82). Genetic testing for these mutations is key for identifying high-risk individuals, guiding genetic counseling and implementing intensified screening protocols (such as more frequent PSA monitoring or MRI) for early detection (83).

HOXB13 gene. *HOXB13* gene, located on chromosome 17q21.3, encodes a transcription factor key for prostate development and homeostasis (84,85). The G84E germline mutation (c.250G>A) is an autosomal dominant risk allele, found in 5-10% of familial PCa cases, with a higher prevalence in European and North American populations (86-89). Carriers have a 2-3-fold increased PCa risk, a cumulative risk of <42% by age 70 and are associated with higher-grade tumors, increased postoperative recurrence and worse outcomes, particularly in metastatic castration-resistant prostate cancer (mCRPC) (90-93).

PTEN, TP53 and ATM genes. Somatic mutations in key tumor suppressor genes drive PCa progression. *PTEN* loss, occurring in 30-40% of localized cancer types and more frequently in mCRPC, hyperactivates the PI3K-AKT pathway, promoting tumor invasiveness and resistance to androgen deprivation therapy (94-96). *TP53* mutations, rare in localized disease but present in 30-40% of mCRPC, induce genomic instability and chemoresistance (97-99). *ATM* mutations, involved in DNA damage repair, are found in 10-15% of mCRPC cases and influence sensitivity to *PARP* inhibitors and platinum-based chemotherapy (100-102). Co-mutations, such as *PTEN/TP53* or *ATM/BRCA2*, are common in advanced disease and associate with aggressive clinical behavior and distinct therapeutic vulnerabilities (103-106).

TMPRSS2-ERG fusion gene. *TMPRSS2* gene, located on chromosome 21q22.3, encodes a transmembrane serine protease under AR regulation (107). It is predominantly expressed in prostate epithelial cells, where it contributes to extracellular matrix remodeling and signal transduction (108). The *ERG* gene, situated nearby on 21q22.2, belongs to the ETS transcription factor family and is normally expressed in hematopoietic cells but not in healthy prostate tissue (109).

In PCa, intrachromosomal rearrangements such as inversions or translocations within the 21q22 region can fuse the *TMPRSS2* promoter with the ERG coding sequence, creating the TMPRSS2-ERG fusion gene (110). This fusion places ERG expression under AR control, leading to aberrant ERG overexpression in prostate epithelial cells and promoting tumorigenesis (111).

The TMPRSS2-ERG fusion occurs in 40-60% of sporadic prostate cancer types, representing the most frequent gene rearrangement in PCa (112). Its prevalence increases to 50-70% in familial and early-onset (≤55 years) cases (113). Fusion-positive tumors are often associated with higher Gleason scores (≥7), elevated PSA levels and increased risk of lymph node and bone metastases, as well as castration-resistant progression (114,115). However, the independent prognostic value of TMPRSS2-ERG for overall survival remains controversial, as it may depend on co-occurring genomic alterations (116).

Mechanistically, ERG activation regulates multiple downstream targets, including matrix metalloproteinases and vascular endothelial growth factor, thereby enhancing cell proliferation, invasion and angiogenesis (117). ERG can also repress DNA repair genes such as *BRCA1*, leading to impaired repair capacity and increased genomic instability (118). Notably, *PTEN* deletions co-occur in 30-40% of TMPRSS2-ERG-positive tumors, acting synergistically to drive cancer progression and enzalutamide resistance (119). By contrast, SPOP-mutated prostate cancer types exhibit a markedly lower TMPRSS2-ERG fusion rate (<10%), indicating mutually exclusive oncogenic pathways among PCa molecular subtypes (120).

Recent genomic studies have expanded understanding of TMPRSS2-ERG-associated oncogenesis (121,122). Large-scale genome-wide association studies have identified additional susceptibility loci that may interact with known genes such as *BRCA1/2*, broadening the scope of genetic risk assessment in PCa (123). Furthermore, emerging domestic studies highlight that the TMPRSS2-ERG fusion can regulate PCa cell behavior through modulation of non-coding RNAs, suggesting novel avenues for targeted therapy and improved understanding of PCa pathogenesis (124,125) (Table I).

RNA-based markers: Transcriptional alterations
PCA3. PCA3 is a lncRNA highly overexpressed (10-100 fold) in PCa tissue (126,127). Its level in urine collected after digital rectal examination is quantified as a PCA3 score, which aids in diagnosis, especially within the PSA 'gray zone' (4-10 ng/ml) (128,129). The PCA3 score is calculated using the formula: PCA3 score=(PCA3 copy number/PSA copy number) x100. A score >35 suggests a high probability of cancer, helping to reduce unnecessary biopsies while maintaining high sensitivity (130). Specificity can be affected by prostatitis (131).

Other RNA markers. Expression of ERG mRNA, a product of the TMPRSS2-ERG fusion, and SPINK1 mRNA, often overexpressed in fusion-negative types of cancer, provides complementary diagnostic and subtyping information (132-134). miRNAs such as miR-141 and miR-375 in blood or urine show promise as non-invasive biomarkers (135,136). Panels combining multiple RNA markers (such as PCA3, ERG and miRNAs) have demonstrated superior diagnostic accuracy

Table I. Key genetic biomarkers in PCa: Functions, clinical relevance and therapeutic implications.

Biomarker	Genetic alteration	Clinical significance	Therapeutic implications
BRCA1/2	Germline and somatic mutations	Associated with hereditary and aggressive PCa, higher recurrence and metastasis rates	Predict sensitivity to PARP inhibitors and platinum-based chemotherapy
HOXB13 (G84E mutation)	Missense mutation (c.250G>A)	Increases familial PCa risk 2-3 fold; higher recurrence and therapy resistance	Potential for genetic screening and early intervention in high-risk families
PTEN	Deletions or mutations	Loss leads to PI3K-AKT pathway activation, enhancing tumor invasiveness	PI3K/mTOR inhibitors under investigation
TP53	Missense mutations, deletions	Associated with genomic instability, poor prognosis and chemotherapy resistance	Development of p53 reactivators and immunotherapy
ATM	Mutations (3-15%)	Impaired DNA repair, poor response to standard therapy	Predicts response to PARP inhibitors and platinum therapy
TMPRSS2-ERG fusion	Gene rearrangement (40-60% of PCa)	Early-onset PCa, aggressive features, bone metastasis	May stratify molecular subtypes; potential target for ERG-related therapy

Pca, Prostate cancer; *PARP*, Poly (ADP-ribose) polymerase; *ERG*, Early growth response factor-1.

over single-marker tests (137,138). Furthermore, specific miRNA expression patterns are implicated in modulating the tumor immune microenvironment, suggesting potential for guiding immunotherapy strategies (139,140).

Application in liquid biopsy
ctDNA. ctDNA, released into the bloodstream by tumor cells, provides a non-invasive means to assess tumor genetics and heterogeneity (141-143). Unlike prostate needle biopsies, which are invasive and subject to sampling bias due to tumor heterogeneity, ctDNA testing provides a non-invasive method to detect genetic alterations throughout the body, offering a more comprehensive outlook of tumor characteristics (144,145). This makes ctDNA testing particularly valuable for monitoring patients with castration-resistant prostate cancer or those with inaccessible metastatic lesions (146,147).

In mCRPC, ctDNA analysis enables real-time monitoring of AR mutations (such as T878A and H875Y) that confer resistance to abiraterone and enzalutamide, allowing for dynamic treatment adjustments (148). Of all patients with mCRPC, ~20% harbor mutations in DNA repair genes (such as *BRCA1/2* and *ATM*) detectable in ctDNA, which predict responsiveness to *PARP* inhibitors (149). ctDNA testing offers a non-invasive method to detect these mutations, helping physicians identify candidates for *PARP* inhibitor-targeted therapy (150). Monitoring the abundance of drug-resistant mutations in ctDNA, such as AR mutations, can provide early indications of tumor progression, enabling timely adjustments to treatment regimens (151). ctDNA dynamics also serve as a sensitive marker for minimal residual disease and early recurrence after radical prostatectomy (152,153). Emerging applications include using ctDNA methylation profiles to predict responses

to immunotherapy (154,155), with ongoing clinical trials validating its role in precision oncology (Fig. 2) (156).

Exo l RNA. Exosomes are extracellular vesicles (30-150 nm) that carry nucleic acids, including RNAs, from their cell of origin, reflecting the physiological and pathological state (157,158). In cancer, the RNA profiles in exosomes undergo specific alterations that reflect tissue damage or malignant transformation (159,160). For instance, miR-122 in exosomes from liver cancer cells has been identified as a diagnostic marker for liver cancer, while Aβ-related mRNA levels in exosomes from cerebrospinal fluid can indicate Alzheimer's disease (161).

In PCa, exo RNA holds considerable diagnostic and therapeutic potential (162). RNA secreted by PCa cells may contribute to tumor development, metastasis and progression (163). Certain miRNAs, such as miR-141 and miR-375, show altered expression in urinary exosomes of patients with PCa, which could serve as novel non-invasive biomarkers for early PCa detection (164).

Beyond diagnostics, exosomes are being engineered as therapeutic vehicles for the targeted delivery of siRNA or miRNA to tumor cells, showing efficacy in preclinical models (165). For example exosomes loaded with anti-miR-21 have been used to inhibit metastasis in breast cancer and similar strategies are under investigation for PCa (166,167). Additionally, blocking the release of metastasis-promoting miRNAs (such as miR-10b) in exosomes from tumor cells has been shown to inhibit cancer cell metastasis in lung cancer models, offering a potential strategy for preventing PCa metastasis by interfering with exo RNA function (Table II) (168).

Moreover, the regulation of exo lncRNA also presents novel avenues for interfering with cancer proliferation and
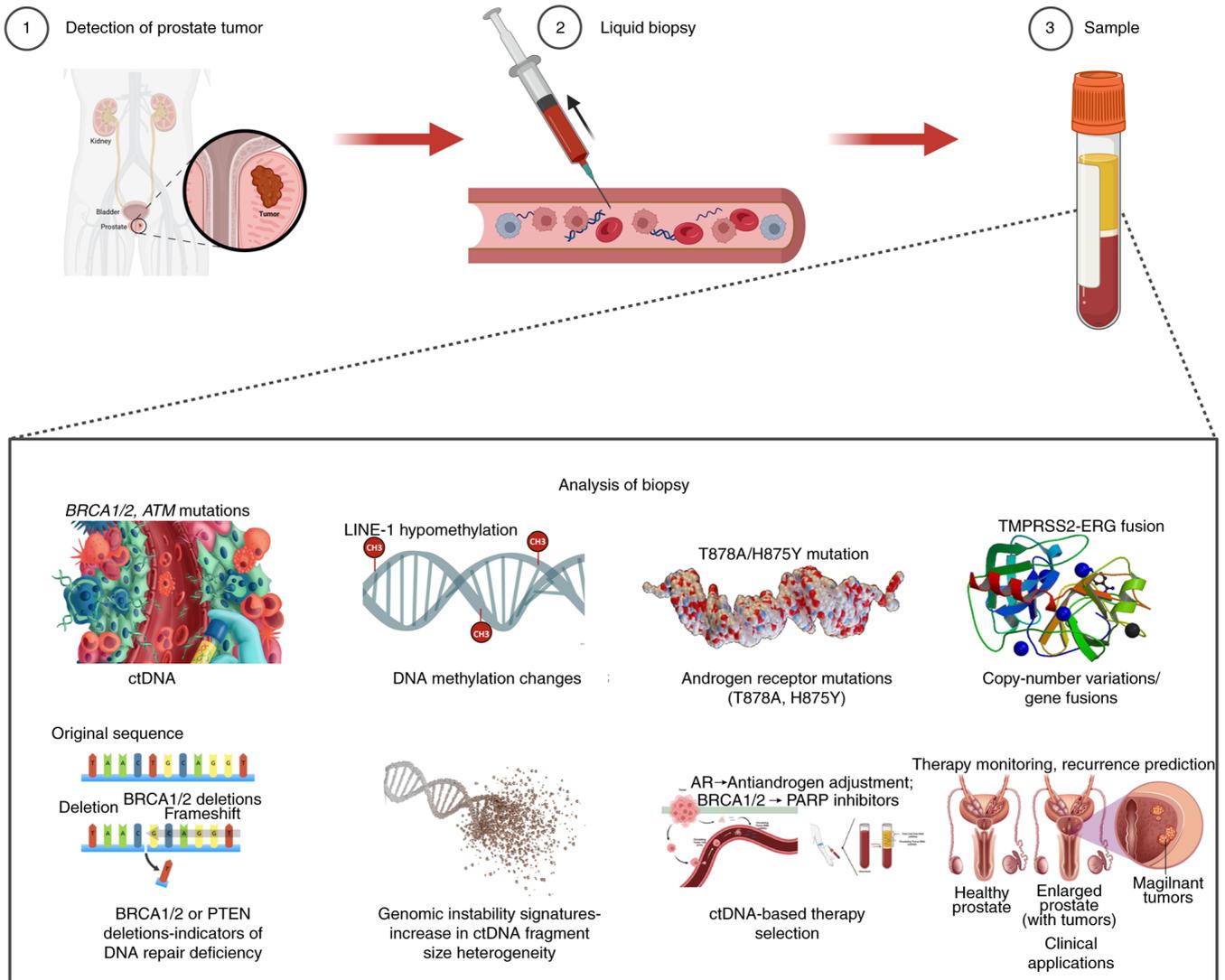
Figure 2. Mechanistic overview and workflow of liquid biopsy in PCa management. Prostate tumor cells release ctDNA fragments into the bloodstream through apoptosis, necrosis and active secretion. These fragments carry characteristic genetic and epigenetic alterations reflective of the primary and metastatic lesions. Following blood collection and plasma separation, ctDNA analysis enables detection of clinically relevant mutations-including *BRCA1/2*, *ATM* and *PTEN* deletions indicative of DNA repair deficiency, AR mutations (*T878A* and *H875Y*) associated with androgen resistance and *TMPRSS2-ERG* gene fusions-along with epigenetic markers such as LINE-1 hypomethylation and patterns of genomic instability. Integrating these molecular signals facilitates ctDNA-based therapy selection, such as adjustment of antiandrogen regimens or the use of PARP inhibitors in DNA repair-deficient tumors. The resulting data support precision oncology through dynamic monitoring of therapy response, prediction of recurrence and stratification of high-risk patients. PCa, prostate cancer; ctDNA, circulating tumor DNA.

invasion (169). In preclinical studies, some researchers have successfully developed exosome carriers specifically targeting PCa cells and loaded them with anti-cancer RNA molecules (170-172). These carriers have demonstrated promising effects in inhibiting tumor growth and metastasis in animal models, providing new hope for targeted PCa therapies (172). Similarly, some studies have analyzed exo RNA profiles at different stages of PCa, revealing that certain RNA characteristics can accurately determine disease stage and prognosis, which can guide clinicians in formulating more precise treatment plans (Fig. 3) (172,173).

4. Other types of biomarkers

Citric acid and polyamines. Citric acid and polyamines have attracted increasing attention as metabolic biomarkers for PCa diagnosis and management (173). Citric acid, abundantly present in prostatic fluid, blood and tissues, serves as an indicator of prostate metabolism (174). Reduced citric acid levels are typically associated with malignant transformation, offering potential diagnostic utility in differentiating benign from malignant lesions (175). The use of magnetic resonance spectroscopy (MRS) enables non-invasive quantification of citric acid, providing valuable metabolic information for clinical decision-making (176). However, its diagnostic sensitivity remains limited when used alone and combination with other biomarkers such as PSA improves accuracy and specificity (177).

Polyamines, such as putrescine, spermidine and spermine-also show association with tumor aggressiveness and metastatic potential (178,179). Elevated polyamine concentrations in serum or urine may indicate enhanced

Table II. RNA-based biomarkers in PCa: diagnostic and prognostic applications.

Biomarker	Type	Sample source	Clinical application	Limitations
PCA3	Long non-coding RNA	Urine (post-DRE)	Improves biopsy specificity in PSA gray zone; PCA3 score >35 suggests PCa	Affected by prostatitis, 70-80% specificity
ERG mRNA	Fusion transcript	Blood, urine	Detects TMPRSS2-ERG fusion, aids in tumor classification	Prognostic value may depend on co-mutations
SPINK1 mRNA	Protein-coding RNA	Tissue, blood	Marker for non-fusion PCa subtype; combined with ERG for classification	Limited standalone use
miR-141, miR-375	MicroRNAs	Serum, urine	Non-invasive biomarkers; associated with tumor stage and metastasis	Require standardization across cohorts
RNA panels (combined)	PCA3 + ERG + miRNAs	Liquid biopsy (blood/urine)	Multi-marker models show higher sensitivity/specificity	Clinical validation needed

PCA3, Prostate cancer antigen 3; ERG, ETS-related gene; SPINK1, Serine protease inhibitor Kazal type 1; TMPRSS2, transmembrane protease, serine 2.
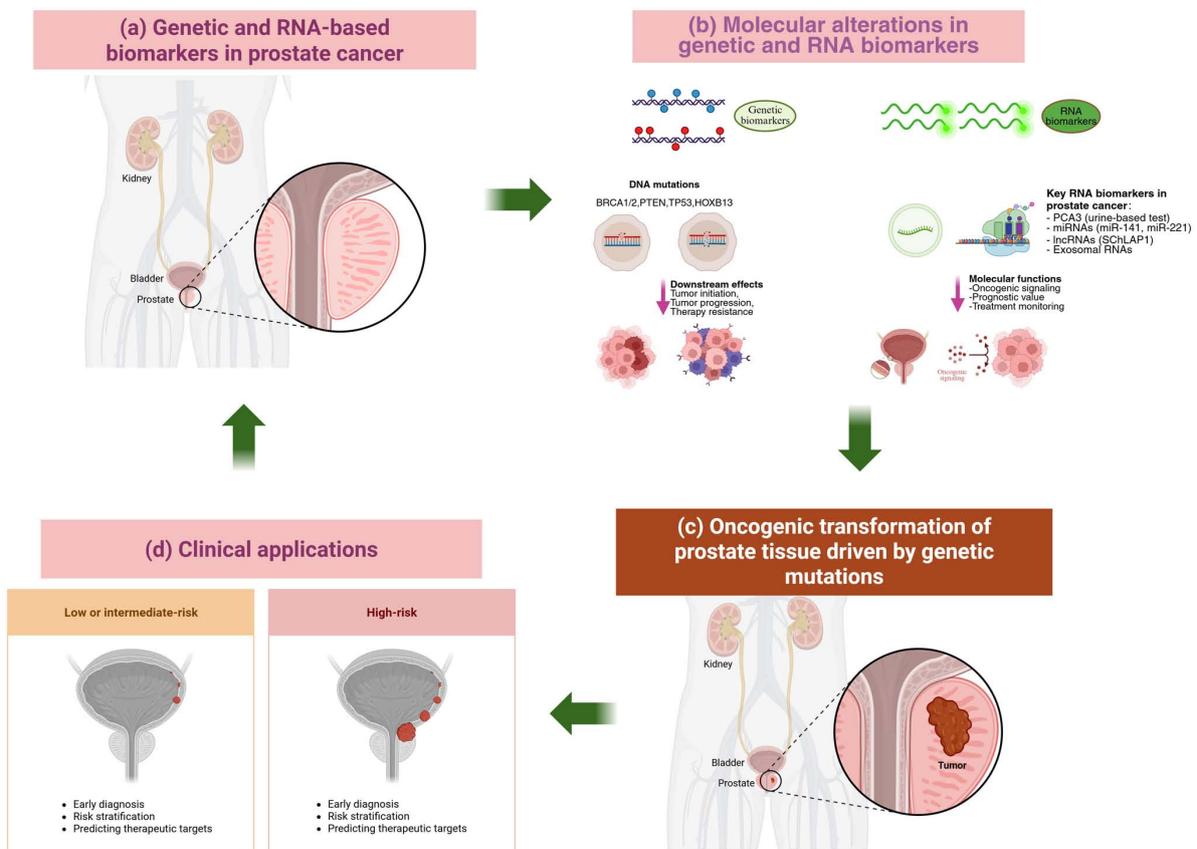

Figure 3. Genetic and RNA-based biomarkers in PCa and their implications for clinical applications. This schematic illustrates representative genetic (such as *BRCA1/2*, *PTEN*, *TP53* and *HOXB13*) and RNA-based (such as PCA3, miRNAs, lncRNAs and exosomal RNAs) biomarkers in PCa. Their downstream effects and molecular functions are integrated into clinical applications, including early diagnosis, disease risk stratification and prediction of therapeutic targets. PCa, prostate cancer.

tumor invasiveness and poor prognosis (180). Monitoring polyamine profiles could therefore assist in predicting disease progression and evaluating treatment responses. Nevertheless, benign conditions such as inflammation can modestly elevate polyamine levels, limiting diagnostic specificity (181).

Table III. Metabolic, protein and epigenetic biomarkers in PCa.

Biomarker	Category	Clinical significance	Diagnostic/therapeutic potential
PSA, f/t-PSA ratio, PSAD, PSAV	Protein (KLK3)	Widely used for screening; improved accuracy in gray zone with ratios/velocity	Still lacks specificity; combined with other biomarkers improves outcomes
PHI	Protein composite (f-PSA, t-PSA, hK4)	Higher accuracy than PSA alone; reduces unnecessary biopsies by ~20%	Threshold may vary by ethnicity; useful with mpMRI
KLK2, KLK family	Serine proteases	Regulate prostate microenvironment; KLK2 synergizes with PSA	KLK2 targeted therapies (bispecific antibodies, RLTs, CAR-T) under trials
Citric acid	Metabolite	Reduced in PCa due to altered mitochondrial metabolism	Detectable by MRS; adjunct to PSA
Polyamines (such as putrescine)	Metabolite	Elevated in aggressive PCa; associated with metastasis risk	Potential for urine-based early detection models
p63, 34βE12	Basal cell markers	Loss indicates adenocarcinoma; combined staining sensitivity >95%	Routine use in biopsy pathology
AMACR (P504S)	Protein (lipid metabolism)	Positive in PCa cytoplasm, with >98% specificity when combined with p63/34βE12	Clinical diagnostic marker
Methylation markers (GSTP1, APC, RASSF1A, PTEN, CDH1, SFRP2)	Epigenetic	Frequently altered; GSTP1 in >90% PCa	Basis for liquid biopsy assays and early detection

PSA, Prostate-specific antigen; f/t-PSA ratio, Free-to-total PSA ratio; PSAD, PSA density; PSAV, PSA velocity; PHI, Prostate health index; KLK2, human kallikrein 2; KLK family, human kallikrein family; p63, protein 63; 34βE12, an antibody that detects high molecular weight cytokeratins; AMACR (P504S), α-methylacyl-CoA racemase, and it is also known by the marker name P504S; GSTP1, Glutathione S-transferase P1; APC, Adenomatous Polyposis Coli; RASSF1A, Ras-association domain family 1 isoform A; PTEN, Phosphatase and TENsin homolog; CDH1, Cadherin 1; SFRP2, Secreted Frizzled-Related Protein 2; KLK3, human Kallikrein 3.

From a therapeutic perspective, abnormal metabolism of citric acid and polyamines represents a promising target for intervention (182). Strategies aiming to restore mitochondrial metabolism or inhibit ornithine decarboxylase, a key enzyme in polyamine synthesis, have demonstrated potential in enhancing endocrine therapy and overcoming drug resistance (182,183). Recent metabolomics-based studies have identified urinary derivatives such as N^1-acetylputrescine, which, when analyzed together with citric acid metabolites, notably improve early screening sensitivity (184,185). Integration of MRS-derived citric acid signals and serum polyamine levels with machine learning algorithms has further enhanced diagnostic precision, particularly for small lesions (186,187). Cross-ethnic studies have revealed distinct metabolic profiles of citric acid and polyamines, suggesting that population-specific diagnostic thresholds may improve biomarker accuracy (188,189). Moreover, emerging evidence indicates that gut microbial metabolites can modulate prostate metabolism by influencing citric acid and polyamine pathways, offering new insights into prostate carcinogenesis and potential microbiota-targeted therapies (189).

p63 and 34βE12. Basal cell markers p63 and 34βE12 are indispensable tools in PCa histopathology (190). In normal glands, basal cells form a continuous layer expressing nuclear p63 and cytoplasmic 34βE12 (191-193). Their absence is a hallmark of adenocarcinoma, reflecting the replacement of normal basal epithelium by malignant cells (194,195).

Compared with p63, which is nuclear and occasionally affected by tissue fixation, 34βE12 provides stable cytoplasmic staining, allowing reliable detection even in suboptimally preserved specimens (196,197). During prostate biopsy evaluation, the concurrent loss of both markers indicates carcinoma, with diagnostic sensitivity >95% and specificity >90% (198-200). When basal cells appear partially positive, additional markers such as PSA or α-methylacyl-CoA racemase are used to confirm malignancy (201,202).

Recent advances combine p63 and 34βE12 immunostaining with AI-assisted pathology, markedly improving interpretive accuracy and reducing observer variability (203,204). Single-cell sequencing and organoid models have further elucidated the dynamic expression of these markers across tumor grades, associating their loss
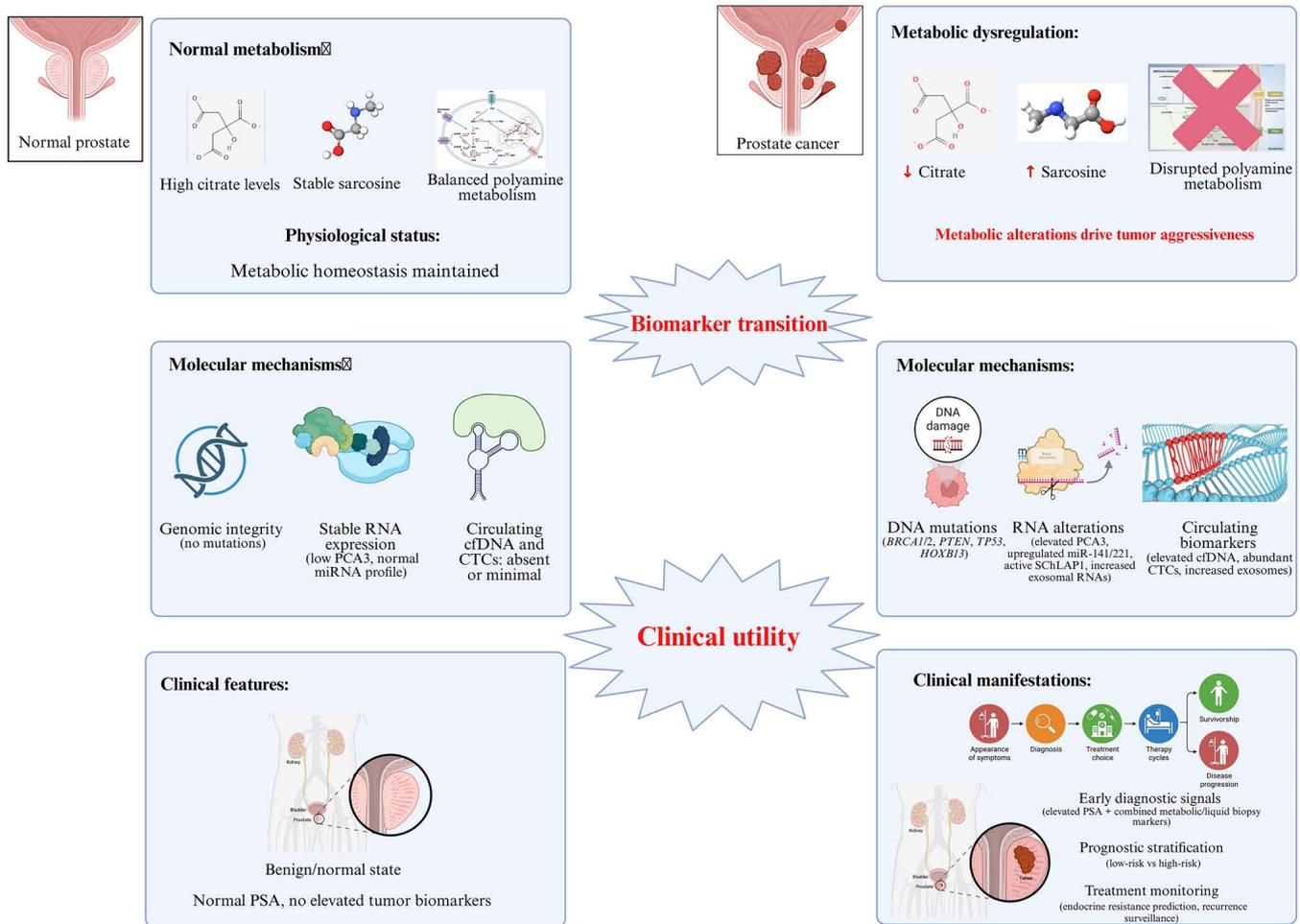
Figure 4. Comparative overview of metabolic, molecular and clinical biomarker profiles in normal prostate vs. PCa. The schematic illustrates the transition from a normal prostate state (left) to PCa (right), highlighting differences across three levels: i) Metabolic status, where normal citrate, sarcosine and polyamine metabolism is disrupted in cancer; ii) molecular mechanisms, with PCa characterized by DNA mutations (*BRCA1/2, PTEN, TP53* and *HOXB13*), aberrant RNA profiles (elevated PCA3, altered miRNAs, active SChLAP1, increased exosomal RNAs) and abundant circulating biomarkers (cfDNA, CTCs and exosomes); and iii) clinical features, shifting from a benign state with normal PSA to detectable early diagnostic signals, prognostic stratification and treatment monitoring. The central axes 'Biomarker transition' and 'clinical utility' emphasize the integration of multi-level biomarkers to support precision oncology in PCa management. PCa, prostate cancer; cfDNA, cell-free DNA; CTCs, circulating tumor cells; PSA, prostate-specific antigen.

with malignancy progression, recurrence risk and treatment outcomes (205-207).

Methylation markers. DNA methylation represents one of the earliest and most consistent molecular alterations in PCa. Among the numerous genes identified, *GSTP1* promoter methylation is the most extensively validated (208). *GSTP1* encodes glutathione S-transferase, an enzyme involved in detoxification and oxidative defense. Hypermethylation-induced silencing of *GSTP1* occurs in >90% of PCa cases but rarely in benign tissues, making it a highly specific diagnostic indicator (209). Combined detection of *GSTP1* methylation with urinary PCA3 enhances diagnostic specificity >90% (210).

Other genes such as *APC*, *RASSF1A*, *PTEN* and *CDH1* also demonstrate marked clinical relevance (211). *APC* promoter methylation is observed in 50-70% of cases and is associated with tumor progression and lymph node metastasis (212). *RASSF1A* methylation frequently co-occurs with *GSTP1* and helps detect high-grade tumors with greater accuracy (213). *PTEN* methylation activates the PI3K/AKT pathway and

contributes to castration resistance (214), while *CDH1* and *SFRP2* methylation associate with increased invasiveness and disease progression (Table III) (215).

Genome-wide methylation profiling has recently identified novel PCa-related epigenetic signatures with potential diagnostic and prognostic applications (216). Combining methylation markers with genetic and RNA-based assays, particularly in liquid biopsy formats, offers a more comprehensive and non-invasive diagnostic strategy (217). Studies also indicate that non-coding RNAs may regulate methylation marker expression, adding another layer of complexity to prostate tumorigenesis (218,219). These findings highlight the promise of methylation-based diagnostics and their integration into precision oncology (Fig. 4) (219).

5. Conclusion and future perspective

The convergence of genetic, transcriptomic and metabolic biomarkers has fundamentally transformed PCa research and clinical management. Genetic alterations-such as *BRCA1/2*,
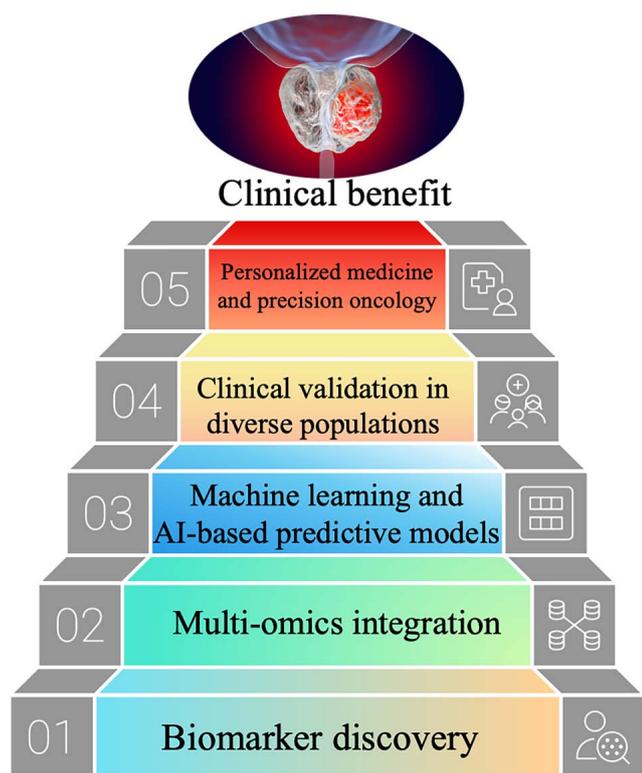
Figure 5. Future directions in PCa biomarker research. This figure illustrates the anticipated future trajectory of PCa biomarker research. Key advancements include the integration of multi-omics approaches (such as genomics, transcriptomics, epigenomics, proteomics and metabolomics), application of AI and machine learning for data interpretation and rigorous clinical validation across diverse patient populations. Together, these strategies aim to enable precision oncology, optimize therapeutic decision-making and ultimately improve patient outcomes. AI, artificial intelligence; PCa, prostate cancer; cfDNA, cell-free DNA; CTCs, circulating tumor cells; PSA, Prostate-specific antigen.

HOXB13 and *TMPRSS2-ERG* fusions-enable precise risk stratification and therapeutic guidance (220). RNA-based biomarkers, including PCA3, ERG mRNA and miRNA panels, have established robust, non-invasive tools for early detection and disease monitoring (221). Metabolic biomarkers such as citric acid and polyamines complement these findings by reflecting tumor aggressiveness and metabolic reprogramming (222). Epigenetic and liquid biopsy markers, particularly DNA methylation (such as *GSTP1* and *APC*) and circulating nucleic acids (ctDNA, exo RNA), are emerging as cornerstones of precision diagnostics (223). Their integration into clinical workflows enables dynamic disease monitoring and individualized therapy optimization (224).

Future research should focus on multi-omics integration-combining genomic, transcriptomic, methylomic and metabolomic data to construct comprehensive biomarker networks (225). Incorporating AI and machine learning will further enhance diagnostic accuracy and predict therapeutic outcomes (226). Additionally, investigating population-specific biomarker variations and tumor microenvironment interactions will be vital for developing equitable, personalized care strategies (227). Ultimately, the continued refinement and clinical validation of these emerging biomarkers will usher in a new era of PCa precision medicine, enabling earlier detection, tailored therapy and improved survival and quality of life for patients worldwide (Fig. 5) (228).

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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