Evolving role of biomarkers beyond prostate-specific antigen in refining prostate cancer screening: From blood-based tests to urinary and genetic markers (Review)

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Abstract. Prostate-specific antigen (PSA) screening reduces prostate cancer (PCa) mortality but is limited by overdiagnosis and poor specificity for clinically significant disease. These limitations drive the need for more accurate biomarkers to distinguish aggressive cancers from indolent lesions. The present review examined advanced blood-based markers, including PSA isoforms, liquid biopsy components and the Prostate Health Index; urinary biomarkers, such as PCa antigen 3, transmembrane protease serine 2-v-ets erythroblastosis virus E26 oncogene homolog fusion and the MyProstateScore 2.0 panel; and genetic markers ranging from high-penetrance germline mutations to polygenic risk scores. It further explored the integration of these biomarkers with multiparametric MRI, risk-calculator models and health-economic evaluations to optimize screening pathways. Future directions involve multi-omic profiling, artificial intelligence and novel biosensing technologies. The present review aimed to provide a comprehensive and balanced perspective on emerging biomarkers that are reshaping personalized PCa screening.

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Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen; csPCa, clinically significant prostate cancer; tPSA, total PSA; fPSA, free PSA; PHI, Prostate Health Index; mpMRI, multiparametric magnetic resonance imaging; PCA3, prostate cancer antigen 3; TMPRSS2:ERG, transmembrane protease serine 2-v-ets erythroblastosis virus E26 oncogene homolog fusion; MiPS, Mi-Prostate Score; MPS, MyProstate Score; EPI, ExoDx Prostate (IntelliScore) score; NPV, negative predictive value; CTCs, circulating tumor cells; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; GSTP1, glutathione S-transferase pi 1; PRS, polygenic risk score; DDR, DNA damage repair; EV, extracellular vesicle

Key words: PCa, screening, biomarkers, prostate-specific antigen isoforms, liquid biopsy, urinary biomarkers, genetic markers

Contents

1. Introduction

Globally, prostate cancer (PCa) remains a major cause of male cancer morbidity and mortality, with an estimated 1.47 million new cases and 397,000 deaths worldwide in 2022. The age-standardized incidence rate varies considerably across regions, from ~29.4 per 100,000 globally to 9.7 per 100,000 in China and exceeds the estimated number of new cases (313,000) in the United States in 2025 alone. These findings underscore the substantial public health burden of PCa and the need for optimized early detection strategies (1). The introduction of prostate-specific antigen (PSA)-based screening fundamentally altered the landscape of PCa management, catalyzing a shift toward earlier diagnosis. Extensive long-term follow-up data from pivotal randomized trials, notably the European Randomized Study of Screening for Prostate Cancer (ERSPC), have consistently confirmed that organized PSA testing results in a marked reduction in PCa-specific mortality (2-4). This

mortality benefit stands as the foundational justification for PSA screening. Nevertheless, this achievement is intrinsically coupled with notable and enduring drawbacks, predominantly characterized by high rates of overdiagnosis and the consequent overtreatment of indolent, low-risk tumors (5,6). Analytical models estimate that a considerable fraction of screen-detected cancers, especially those classified as Gleason Grade Group 1, may remain clinically silent and never progress to cause morbidity or mortality within the natural lifespan of the patient. This leads to a cascade of unnecessary diagnostic biopsies, therapeutic interventions and associated patient anxiety and iatrogenic morbidity (7,8). Furthermore, the poor specificity of PSA for clinically significant PCa (csPCa) results in a high number of negative biopsies, exposing men to procedural risks without benefit (9,10). This diagnostic inefficiency underscores a critical clinical need to refine the screening pathway by improving the discrimination between aggressive cancers requiring intervention and indolent lesions that can be safely monitored.

The quest to mitigate these harms has driven the evolution of PCa screening from a unilateral PSA-based approach towards more nuanced, risk-adapted strategies. Contemporary paradigms emphasize shared decision-making, informed by an individual's risk profile (11,12). This shift acknowledges that a 'one-size-fits-all' screening policy is suboptimal. Research has focused on identifying factors that modulate screening outcomes, including age at initiation and cessation (13,14), ethnic disparities (15,16) and the impact of comorbidities or medications (17,18). Concurrently, the integration of multiparametric magnetic resonance imaging (mpMRI) into the diagnostic pathway has marked an advance, notably improving the detection of csPCa while reducing the detection of low-risk disease (19-21). However, MRI is a resource-intensive tool, and its optimal deployment requires effective triage (22,23). This context highlights the limitation of PSA as a standalone gatekeeper and fuels the demand for more precise, ancillary tools.

Consequently, the development and validation of novel biomarkers beyond total PSA (tPSA) have become a central research imperative. These biomarkers aim to enhance specificity, enable improved risk stratification and ultimately reduce unnecessary procedures by providing a more accurate molecular portrait of individual risk. Promising avenues include refined blood-based assays such as the Prostate Health Index (PHI) and the 4Kscore, which leverage PSA isoforms and kallikreins (24,25); urinary biomarkers such as PCa antigen 3 (PCA3), transmembrane protease serine 2-v-ets erythroblastosis virus E26 oncogene homolog fusion (TMPRSS2:ERG), and multiplexed mRNA panels (26-28); and genetic markers ranging from high-penetrance germline mutations for targeted screening (29) to polygenic risk scores (PRS) for population risk refinement (30). The evolving evidence suggests that these tools, especially when combined within risk-calculator models (31) or used in sequence with mpMRI (32,33), can notably improve the positive predictive value of screening. Economic evaluations increasingly support the cost-effectiveness of biomarker-guided pathways, suggesting long-term savings by averting low-yield procedures (14,23,34).

Despite this progress, the field faces challenges. Numerous novel biomarkers require further validation in prospective, population-level screening cohorts to avoid spectrum bias and prove generalizability (35). Issues of assay standardization, accessibility and integration into clinical workflows remain barriers to widespread adoption (36). Furthermore, health inequities in screening access and outcomes persist, necessitating tailored approaches. The present review aimed to critically synthesize the current evidence on these novel biomarkers, moving from blood-based to urinary and genetic markers. It evaluated their diagnostic performance, clinical utility in refining the screening-diagnostic pathway and role within emerging multimodal, personalized screening frameworks. By examining both the consistent benefits and the divergent results across studies, the present review sought to provide a comprehensive and balanced perspective on the tools poised to define the next era of PCa early detection.

2. Blood-based biomarkers: Refining the serum signature

The inherent limitations of tPSA have catalyzed a notable evolution in serum-based diagnostics, shifting focus towards more refined assays that improve specificity for csPCa. This evolution is characterized by a strategic shift in focus towards more refined assays designed to improve specificity for csPCa. These advanced blood tests aim to achieve a dual objective: Reducing the burden of unnecessary prostate biopsies and providing a more accurate stratification of individual patient risk. They accomplish this by either leveraging the differential biological properties of various molecular forms of PSA or by detecting novel, non-PSA tumor-derived signals circulating in the bloodstream (Fig. 1). This section critically evaluates the two primary categories of advanced blood-based biomarkers: i) Refined PSA isoforms and derivatives, which represent the most mature and clinically integrated tools; and ii) novel liquid biopsy components, including circulating tumor cells (CTCs), cell-free DNA (cfDNA) and methylation markers, which hold promise for future screening paradigms but require further validation.

PSA isoforms and derivatives. PSA circulates in the bloodstream in multiple molecular forms, and assays that quantify specific isoforms have consistently demonstrated superior cancer specificity when compared with the measurement of tPSA alone. Among these, the PHI and the 4Kscore test have emerged as the most extensively validated and clinically established tools. Both integrate traditional clinical parameters with novel serum measurements to generate a personalized, quantitative risk assessment.

PHI. The PHI is a sophisticated mathematical algorithm that combines the serum levels of tPSA, free PSA (fPSA) and the proenzyme precursor isoform [-2] proPSA, the latter being more notably associated with malignant prostatic tissue. Numerous studies have validated its superior diagnostic accuracy over tPSA and %fPSA alone, particularly in the diagnostic 'gray zone' (PSA 2-10 ng/ml). Meta-analyses and large prospective cohort studies consistently report that PHI notably improves specificity for csPCa (Gleason Grade Group ≥2, intermediate- or high-risk disease) while maintaining high sensitivity, thereby potentially avoiding 20-30% of unnecessary biopsies (37-39). For instance, a multicenter European and Asian study highlighted the need for population-specific PHI reference ranges but confirmed its robust diagnostic performance across diverse settings (40). Furthermore,

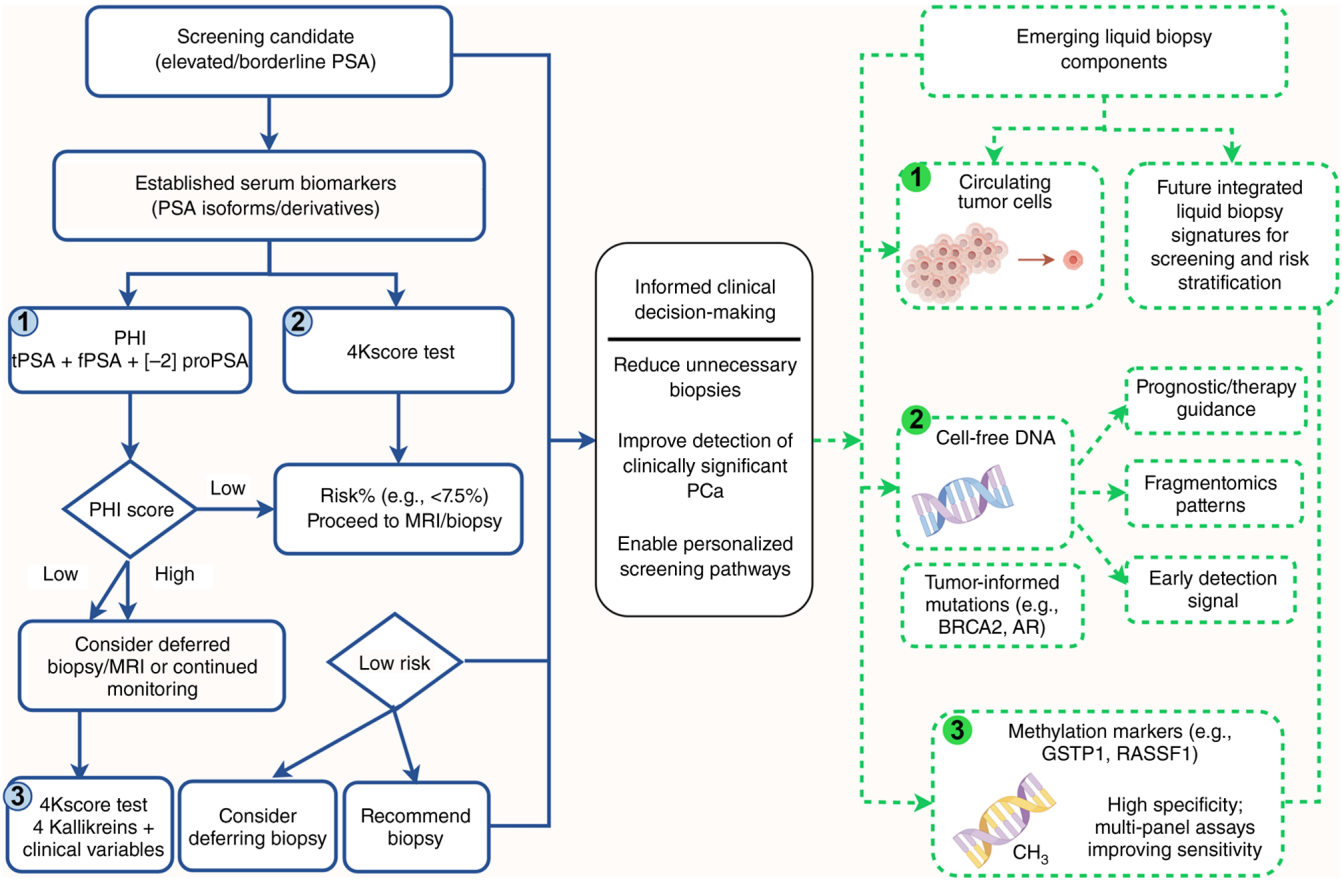

Figure 1. Evolving landscape of blood-based biomarkers in PCa screening: From PSA derivatives to liquid biopsy. This figure illustrates the progression and integration of advanced blood-based biomarkers into a potential screening-diagnostic pathway for PCa. It compares established biomarkers such as the PHI and 4Kscore, which refine risk using PSA isoforms, against emerging liquid biopsy components (circulating tumor cells, cell-free DNA and methylation markers). The pathway highlights how these tools can triage patients, reduce unnecessary procedures, and guide personalized clinical decisions. This evolving landscape signifies a shift from volume-based PSA testing towards molecularly-informed, precision screening strategies. Thus, blood-based biomarkers (PHI, 4Kscore and liquid biopsy) improve risk stratification, reduce unnecessary biopsies, and support personalized screening decisions. This figure was created using the online graphic design website Figdraw (www.figdraw.com). PCa, prostate cancer; PSA, prostate-specific antigen; tPSA, total PSA; fPSA, free PSA; PHI, Prostate Health Index; GSTP1, glutathione S-transferase Pi 1; AR, androgen receptor; RASSF1, Ras association domain-containing protein 1.

PHI demonstrates prognostic value, predicting pathological outcomes at radical prostatectomy and grade reclassification during active surveillance (41-44). Cost-effectiveness analyses suggest that PHI-guided biopsy strategies can be economically favorable by reducing low-yield procedures (45,46). Notably, PHI has been evaluated as an effective 'gatekeeper' to mpMRI; for example, a PHI threshold can stratify men to undergo MRI or proceed directly to biomarker-guided decision-making, optimizing resource utilization (47-49).

4Kscore. The 4Kscore test measures serum levels of four kallikreins (tPSA, fPSA, intact PSA and human kallikrein 2) and combines them with clinical variables (age, digital rectal exam findings, prior biopsy status) to calculate the percentage risk of detecting csPCa on biopsy. Its development and validation, including data from the ERSPC and the STHLM3 study, have shown it to be a powerful tool for pre-biopsy risk stratification (50,51). The primary utility of the test lies in its ability to identify men with a low risk (<7.5%) of csPCa, for whom biopsy can be safely deferred (52,53). Prospective trials, such as the PROBASE screening study, have incorporated the 4Kscore to guide biopsy decisions in men with elevated PSA, demonstrating its practical application in reducing overdiagnosis (50). Recent data from the GÖTEBORG-2 screening trial reaffirmed its performance as a reflex test, notably outperforming tPSA in csPCa detection (24). However, discussions continue regarding the optimal risk threshold for clinical action, and the development of '4Kscore density' (adjusting for prostate volume) is being explored to further refine its predictive power (54,55).

CTCs and cfDNA. Beyond PSA derivatives, the analysis of tumor-derived material in blood, known as liquid biopsy, represents a frontier in oncology. While its most established role is in advanced, metastatic disease, its potential for early detection and screening is under intense investigation.

Current role in advanced disease and emerging potential in early detection. In metastatic castration-resistant PCa, the enumeration of CTCs and analysis of cfDNA are validated prognostic tools and can guide therapy by identifying actionable genomic alterations (for example in BRCA1/2 and androgen receptor) (56-59). The clinical utility in this setting is well-documented for monitoring treatment response and understanding resistance mechanisms (60,61). However, their application in early-stage, localized disease is challenged by the low abundance of tumor-derived material in the bloodstream. Studies have confirmed that levels of cfDNA and CTCs are

markedly lower in patients with localized PCa compared with those with metastatic disease (62,63). Despite this limitation, highly sensitive detection techniques are beginning to exhibit clinical potential in localized disease. For example, specific fragmentation patterns of cfDNA (fragmentomics) or the presence of tumor-informed mutations can detect localized cancers with promising sensitivity (64-66). Research indicates that the detection of circulating tumor DNA (ctDNA) in patients with clinically localized disease is associated with a higher risk of rapid biochemical recurrence, suggesting its prognostic, if not yet diagnostic, potential in early stages (46,63).

Methylation markers in blood. DNA methylation is a common and early event in prostate carcinogenesis. Hypermethylation of gene promoters, such as glutathione S-transferase Pi 1 (GSTP1), is notably specific for PCa tissue. Detecting these methylated DNA sequences in plasma or serum cfDNA is therefore a promising diagnostic strategy. Technical feasibility has been demonstrated in multiple studies, showing that methylated GSTP1 can be detected in the blood of patients with PCa with high specificity, albeit with variable sensitivity that is often associated with tumor stage and volume (67-69). The challenge for screening applications is achieving sufficient sensitivity for low-volume, organ-confined disease. To address this, efforts have been focused on generating multi-gene methylation panels. Assays analyzing a combination of methylation markers (for example GSTP1, Ras association domain-containing protein 1 and APC) have shown improved sensitivity for detecting localized PCa compared with single markers (70,71). More advanced approaches use tissue-informed, genome-wide methylation profiling of cfDNA to identify cancer-specific signatures, even distinguishing aggressive histologic subtypes such as neuroendocrine differentiation (72,73). While these epigenetic blood tests require rigorous validation in screening populations, they represent a compelling direction for developing highly specific, non-invasive screening tools.

3. Urinary biomarkers: A non-invasive window to the prostate

The pursuit of non-invasive diagnostic tools has positioned urine as a uniquely valuable biofluid for PCa detection. Urinary biomarkers, originating from prostatic fluid or exfoliated cells, offer a direct molecular snapshot of the prostate gland while circumventing the need for blood draws or invasive procedures (74,75). The present section critically examines the evolution and clinical evidence for key urinary biomarkers, which aim to refine the decision for prostate biopsy by improving the prediction of csPCa (76,77) (Table I). The discussion progresses from single, well-established markers to sophisticated multi-analyte panels, highlighting their diagnostic performance and integration into clinical pathways.

PCA3. PCA3 is a long non-coding RNA that is markedly upregulated in PCa tissue compared with benign prostate cells, offering inherent cancer specificity (78). Its measurement in post-digital rectal exam (post-DRE) urine captures RNA released from prostate cells, providing a quantifiable PCA3 score.

The primary clinical utility of PCA3 has been established in the repeat biopsy setting for men with a prior negative biopsy. Meta-analyses confirm that a PCA3 score can help discriminate between patients who may benefit from a repeat biopsy and those who can be safely monitored (76). A landmark study by Newcomb *et al* (79) within the Canary Prostate Active Surveillance Study prospectively evaluated PCA3 in an active surveillance cohort. This study provided notable evidence that PCA3 scores were associated with the risk of pathological grade reclassification. By demonstrating its potential to monitor disease progression in men opting for surveillance, this research expanded the role of PCA3 beyond diagnostic triage to encompass risk stratification within management pathways. However, its performance for primary screening or initial biopsy decision-making is more limited. While PCA3 demonstrates good specificity, its sensitivity for detecting csPCa, particularly in biopsy-naïve men, is often considered insufficient as a standalone test. This limitation is attributed to variable RNA stability and the moderate association of the test with tumor aggressiveness. Consequently, PCA3 is frequently integrated into multivariable risk models or combined with other markers to enhance its predictive accuracy.

TMPRSS2: ERG gene fusion markers. The TMPRSS2: ERG gene fusion is a seminal genetic alteration present in ~50% PCas, offering high specificity for malignant prostatic epithelium (80). Its detection in urine provides a direct tumor-derived signal. Beyond mere detection, the presence and quantitative level of TMPRSS2: ERG mRNA in urine have been associated with indicators of tumor aggressiveness, such as higher Gleason grade (81).

The clinical strength of TMPRSS2: ERG lies not in its standalone use but in its combination with other biomarkers. This is exemplified by the commercially available Mi-Prostate Score (MiPS) test, which integrates urinary PCA3, TMPRSS2: ERG and serum PSA into a single risk algorithm. A pivotal validation study by Tosoian *et al* (82) demonstrated the robust clinical utility of the MiPS test. In a multicenter cohort of men referred for biopsy, the study showed that MiPS notably improved the prediction of csPCa (Gleason ≥7) compared with standard clinical variables alone (83). Notably, it exhibited a high negative predictive value, effectively ruling out high-grade disease and potentially reducing unnecessary biopsies by 30-40% while maintaining high sensitivity for aggressive cancers. This study underscored the principle that combining markers with complementary characteristics, the sensitivity of PCA3 and the specificity of TMPRSS2: ERG, within a mathematical model yields superior diagnostic accuracy and clearer clinical action thresholds than any single marker.

Multimarker urinary panels. To address the complexity and heterogeneity of PCa, advancements have focused on multiplexed urinary panels that analyze multiple RNA biomarkers simultaneously, aiming for higher diagnostic precision.

SelectMDx is a post-DRE urine test that measures the mRNA expression of homeobox C6 and distal-Less homeobox 1, two homeobox genes involved in oncogenesis, combined with clinical risk factors (84,85). Key validation studies in European biopsy-naïve cohorts have consistently shown that

Table I. Clinical evidence and diagnostic performance of urinary biomarkers in refining prostate cancer biopsy decision-making.

Author, year	Biomarker (type)	Study design and population	Key findings	Clinical utility and significance	(Refs.)
Rodríguez and García-Perdomo, 2020	PCA3 (lncRNA)	Meta-analysis; biopsy-naïve and prior negative biopsy men	Higher specificity for PCa vs. benign tissue; variable sensitivity for csPCa; useful in repeat biopsy setting	Reduces unnecessary repeat biopsies; limited standalone use in primary screening due to moderate sensitivity for csPCa	(76)
Wendrich and Krabbenborg, 2021	Molecular biomarker test for PCa (interview-based)	Qualitative interview study	Explored perceptions and use of molecular biomarker tests in clinical practice.	Highlights real-world barriers and facilitators to biomarker adoption.	(77)
Newcomb *et al*, 2019	PCA3 (lncRNA)	Prospective cohort (Canary PASS)	PCA3 score associated with grade reclassification risk	Potential role in monitoring disease progression during active surveillance	(79)
Trifunovski *et al*, 2020	TMPRSS2: ERG (gene fusion RNA)	Single-center diagnostic study	Detected fusion transcript in prostate cancer tissue.	Confirms TMPRSS2: ERG as a tumor-specific genetic alteration.	(80)
Warli *et al*, 2023	TMPRSS2: ERG (gene fusion RNA)	Diagnostic validation study	High specificity for PCa; present in ~50% of tumors; quantitative levels are associated with Gleason grade	Often combined with PCA3 in multiparameter tests (such as MiPS) to improve csPCa prediction	(81)
Tosoian *et al*, 2021	Mi-Prostate Score (MPS)-PCA3 + TMPRSS2: ERG + serum PSA	Multicenter validation	Superior prediction of csPCa (Gleason ≥7) compared with clinical variables alone	Reduces unnecessary biopsies while maintaining high sensitivity for high-grade disease	(82)
Lebastchi *et al*, 2020	Mi-Prostate Score (MPS)	Contemporary academic practice study	MPS influenced biopsy decisions, reducing unnecessary procedures.	Supports MPS as a decision aid in clinical practice.	(83)
Rubio-Briones *et al*, 2020	SelectMDx (HOXC6 + DLX1 mRNA)	Opportunistic screening population validation	High NPV for ≥GG2 PCa.	Validates SelectMDx as a rule-out tool in screening populations.	(84)
Hendriks *et al*, 2021	SelectMDx (HOXC6 + DLX1 mRNA)	Prospective European biopsy-naïve cohort	High NPV (>90%) for csPCa; effectively triages men away from unnecessary biopsy	Strong rule-out test; useful as pre-MRI triage tool	(85)
Tutrone *et al*, 2020	ExoDx Prostate (IntelliScore)-exosomal RNA	Prospective validation (PSA 2-10 ng/ml)	EPI score independently predicts csPCa; changes physician biopsy decisions	Reduces unnecessary biopsies in diagnostic gray zone	(86)
Tosoian *et al*, 2024	MyProstateScore 2.0 (MPS 2.0)-expanded gene panel	Development and validation study	High accuracy for csPCa detection, even in PI-RADS 3 MRI cases	Aids in resolving equivocal MRI findings; improves risk stratification	(87)
Tao *et al*, 2023	Urinary EV lncRNA panel	Multicenter diagnostic feasibility study	Novel lncRNA signature improves detection of high-grade PCa	Emerging biomarker with potential for non-invasive risk stratification	(89)

Table I. Continued.

Author, year	Biomarker (type)	Study design and population	Key findings	Clinical utility and significance	(Refs.)
Davey *et al*, 2020	Urinary miRNA panel (exosome-based)	Pilot diagnostic study	miRNA profiles from urinary EVs improve PCa detection accuracy	Promising for early detection and prognostic assessment	(90)
Zhang *et al*, 2023	Urinary miRNA panel	Development and validation study	Developed a miRNA panel for early PCa detection.	Supports miRNA as a non-invasive	(91)

PCa, prostate cancer; csPCa, clinically significant PCa; EPI, Exosome DX Prostate (IntelliScore); EVs, extracellular vesicles; lncRNA, long non-coding RNA; miRNA, microRNA; MiPS, Mi-Prostate score; MPS, MyProstate score; MRI, magnetic resonance imaging; NPV, negative predictive value; PCA3, Prostate cancer antigen 3; PI-RADS, prostate imaging-reporting and data system; PSA, prostate-specific antigen.

SelectMDx possesses a high negative predictive value (NPV), often >90% for high-grade PCa (84,85). The prospective multicenter study by Hendriks *et al* (85) was instrumental in defining its clinical role (85). This study evaluated SelectMDx with or without mpMRI in >500 biopsy-naïve men and confirmed its high NPV. It demonstrated that SelectMDx could effectively identify men at markedly low risk of csPCa, potentially allowing 30-40% of patients to avoid immediate biopsy. This solidified its position primarily as a robust 'rule-out' test to reduce unnecessary procedures.

ExoDx Prostate (IntelliScore) (EPI) analyzes exosome-derived RNA from a first-catch, non-DRE urine sample, evaluating an expression signature to provide an EPI. The prospective validation study by Tutrone *et al* (86) specifically focused on men in the diagnostic gray zone (PSA 2-10 ng/ml), a group where clinical decision-making is most challenging. The study demonstrated that the EPI score independently predicted the likelihood of csPCa and high-grade disease. Notably, it showed that physician biopsy recommendations changed in ~30% of cases based on the EPI score, predominantly leading to a reduction in biopsies for low-risk scores. This study highlighted the practical impact of the test on clinical decision-making in a targeted population.

The evolution of the MyProstateScore (MPS) test exemplifies progress in panel development; initial versions combined PCA3 and TMPRSS2: ERG (82). The comprehensive development and validation study by Tosoian *et al* (87) for MPS 2.0 marked a notable advance (87). MPS 2.0 utilizes an expanded 18-gene panel and was validated across multiple cohorts. A key finding was its excellent performance in men with equivocal MRI findings, a common clinical dilemma. The test accurately stratified risk within this group, helping to resolve uncertainty and guide biopsy decisions. This study underscores the trend towards more complex gene signatures to improve diagnostic accuracy, particularly in challenging clinical scenarios. Other research explores panels of long non-coding RNAs (88,89), microRNAs from urine extracellular vesicle (EV) (90,91) and methylation markers (92), showing promising diagnostic and prognostic potential.

Beyond analytical performance, real-world implementation of urinary biomarkers is markedly influenced by pre-analytical variables. The diagnostic accuracy of PCA3 and TMPRSS2: ERG, for example, is substantially enhanced by a vigorous DRE before urine collection, which exfoliates prostatic cells (78,79). However, the lack of standardization in DRE technique (pressure, duration, number of strokes) introduces notable variability across clinics and studies, potentially affecting test reproducibility and clinical decision thresholds. This variability has been highlighted as a barrier to widespread adoption (77). Sample stability represents another practical hurdle as urinary RNAs degrade over time, and variations in storage temperature, time to processing and the use of preservative buffers can alter measured biomarker levels (86). The ExoDx Prostate test, which uses a first-catch, non-DRE urine sample, was specifically developed to circumvent DRE-related variability (86). Furthermore, differences in urine collection protocols (first-catch vs. post-DRE vs. extended stream) and centrifugation steps affect cellular content and RNA yield. These pre-analytical factors, if not harmonized, limit cross-study comparability and hinder the widespread adoption

of urinary biomarkers in routine practice. Ongoing efforts to develop standardized operating procedures and commercial kits with built-in stabilization are essential to translate these promising markers into reliable clinical tools (36,77).

4. Genetic and polygenic risk markers: Informing inherited susceptibility

The integration of genetic information represents a paradigm shift towards truly personalized PCa risk assessment. Moving beyond phenotypic and demographic factors, genetic and polygenic markers offer insights into an individual's inherent biological susceptibility. These tools hold the promise of refining screening strategies by identifying men at notably elevated risk who may benefit from earlier, more intensive surveillance, while conversely sparing those at genetically lower risk from unnecessary procedures (Table II). This section critically examines the evidence for two primary genetic approaches: High-penetrance germline mutations that define hereditary cancer syndromes and PRS (a quantitative measure that aggregates the cumulative effects of numerous common genetic variants to estimate an individual's inherited risk for PCa) that quantify the aggregate effect of common, low-risk genetic variants across the population.

High-penetrance germline mutations: Implications for targeted screening. A total of 10-15% of PCas exhibit a marked hereditary component, often driven by pathogenic variants in high-penetrance genes involved in DNA damage repair (DDR) and other notable pathways (93,94). The most clinically established among these are mutations in BRCA1 and BRCA2, which are notably associated not only with breast and ovarian cancers but also with an increased risk of aggressive PCa. Carriers of BRCA2 mutations face a markedly elevated lifetime risk of PCa (estimated 2- to 8-fold higher than non-carriers), earlier age of onset and a greater likelihood of developing high-grade, metastatic disease (93). Similarly, mutations in homeobox B13, particularly the G84E variant, are linked to hereditary PCa, especially in families of European descent (95). Other relevant genes include those involved in mismatch repair [MutL homolog 1, MutS homolog (MSH)2, MSH6 and post meiotic segregation increased 2] associated with Lynch syndrome, a hereditary cancer predisposition syndrome that increases the risk of several malignancies, including PCa. Men with Lynch syndrome, particularly carriers of MSH2 mutations, have a notably elevated risk of developing PCa, often with earlier onset and more aggressive features, which underscores the importance of tailored screening in this population (93,96). Other relevant genes include ataxia-telangiectasia mutated, checkpoint kinase 2 and partner and localizer of BRCA2 (97-99). The evidence for these genes derives primarily from large case-control studies and meta-analyses, with prospective validation for mismatch repair genes from the IMPACT screening study. These genetic markers are already integrated into clinical practice through guideline-recommended germline testing panels (for example NCCN guidelines) and are being translated into targeted screening protocols for high-risk populations (100).

The clinical imperative lies in identifying these mutation carriers to implement targeted screening and management strategies. Evidence from prospective studies supports this approach. For example, the international IMPACT study prospectively evaluated PSA screening in men with known pathogenic mutations in mismatch repair genes (such as MSH2, MSH6) (96). Interim results demonstrated a higher incidence of PCa in carriers compared with non-carrier controls, with a notable proportion being intermediate- or high-risk disease. This study validates the rationale for tailored screening in this genetically defined high-risk cohort and highlights the importance of identifying Lynch syndrome families for proactive management (96).

Furthermore, the presence of germline DDR alterations, particularly in BRCA2, has marked therapeutic implications in advanced disease, predicting sensitivity to poly (ADP-ribose) polymerase inhibitors such as olaparib and rucaparib (101-103). This dual utility, informing both early detection and treatment selection, underscores the importance of germline genetic testing, especially in men with a strong family history, early-onset disease, or advanced/metastatic PCa (98,100,104). However, challenges persist, including equitable access to genetic counseling and testing, variability in mutation prevalence across ancestries and the need for clear clinical guidelines on who to test and how to manage identified carriers.

PRS: Refining population risk stratification. In contrast to rare, high-impact mutations, the majority of inherited PCa risk is attributed to the combined effect of hundreds to thousands of common single-nucleotide polymorphisms (SNPs), each conferring a markedly small individual risk. A PRS aggregates these effects into a single quantitative measure of genetic predisposition. PRS are developed through genome-wide association studies that identify risk-associated SNPs and their effect sizes, typically derived from large, predominantly European ancestry biobanks (105,106). The predictive power of a PRS is directly related to the number of included SNPs and the ancestral match between the derivation and target populations.

A key application of PRS is to augment traditional risk factors, particularly PSA levels, to improve the prediction of csPCa. Evidence from large cohort studies demonstrates that PRS can independently predict PCa risk and, when combined with PSA, notably improve risk stratification compared with PSA alone. For instance, a study by McHugh *et al* (30) assessed a PRS in a screening context, finding that it could identify men with a risk profile justifying earlier or more intensive screening, while others might defer screening. This prospective assessment highlights the potential of PRS to personalize screening initiation and intensity in a population-based setting. Similarly, data from the STHLM3 trial showed that a risk model incorporating a genetic score (alongside clinical variables and plasma protein markers) could reduce unnecessary biopsies while maintaining sensitivity for high-grade disease (107). The integration aims to create a 'genetically adjusted' risk threshold. For example, a man with a high PRS might warrant biopsy at a lower PSA level, whereas a man with a markedly low PRS could be monitored even with a borderline-elevated PSA.

Trans-ancestry meta-analyses have been crucial in developing PRS that perform better across diverse populations,

Table II. Germline mutations and polygenic risk scores in personalized prostate cancer screening: From high-penetrance variants to population-level risk stratification.

Author, year	Genetic marker/study focus	Study design/population	Key findings	Clinical utility and significance	(Refs.)
McHugh *et al*, 2025	PRS for screening	Prospective assessment within a screening cohort	A PRS could identify men whose risk profile justified earlier/more intensive screening, while others might defer screening, improving screening efficiency.	Demonstrates the potential of PRS to personalize screening initiation and intensity in a population-based setting.	(30)
Nyberg *et al*, 2022	BRCA1 and BRCA2 pathogenic variants	Systematic review and meta-analysis	BRCA2 carriers have a 2-8 fold increased lifetime risk of PCa, earlier onset, and higher risk of aggressive/metastatic disease. BRCA1 association is less pronounced.	Provides evidence for targeted screening and counseling in carriers; informs management guidelines.	(93)
Stastna *et al*, 2024	MRE11, RAD50, NBN (MRN) genes	Systematic review and meta-analysis	Germline pathogenic variants in MRN genes are associated with cancer predisposition, including prostate cancer.	Highlights the role of DNA damage repair genes beyond BRCA in hereditary cancer risk assessment.	(94)
Aoki *et al*, 2025	BRCA2 variants (familial vs. sporadic)	Case-control study (Japanese population)	Identified specific BRCA2 single nucleotide variants more prevalent in Japanese familial patients with PCa compared with sporadic cases or controls.	Highlights population-specific mutation spectra; supports germline testing in familial clusters, especially in non-European ancestries.	(95)
Wokołorczyk *et al*, 2021	PALB2 mutations	Case-control and survival analysis	PALB2 mutations are associated with increased PCa risk and may impact survival.	Adds to the spectrum of moderate-penetrance genes relevant for genetic counseling and risk management.	(97)
Berchuck *et al*, 2022	Germline testing in advanced PCa	Analysis of tumor and germline sequencing	Addition of germline testing to tumor-only sequencing improved detection of pathogenic germline variants in DNA repair genes.	Supports comprehensive germline testing in advanced disease for therapeutic (PARP inhibitors) and familial risk implications.	(98)
Shi *et al*, 2022	Rare pathogenic mutations in guideline-recommended genes	Meta-analysis	Germline rare pathogenic mutations in guideline-recommended genes (BRCA2, ATM, HOXB13) are associated with PCa progression.	Strengthens the link between specific germline mutations and aggressive disease, supporting their use in prognostication.	(99)
Bancroft *et al*, 2021 (IMPACT Study)	Mismatch repair gene pathogenic variants (such as MSH2, MSH6)	International prospective screening study	Interim results showed a higher incidence of PCa in carriers, with a marked proportion being intermediate/high-risk disease.	Validates the rationale for tailored, earlier PSA screening in men with Lynch syndrome-associated mutations.	(96)

Table II. Continued.

Author, year	Genetic marker/study focus	Study design/population	Key findings	Clinical utility and significance	(Refs.)
Mateo *et al*, 2020	Genomics of lethal PCa	Genomic analysis	Comprehensive genomic profiling reveals alterations associated with lethality and castration resistance.	Provides insights into the molecular drivers of aggressive disease, informing therapeutic strategies.	(101)
de Bono *et al*, 2021	PARP inhibition in mCRPC (TALAPRO-1)	Phase 2 trial	Talazoparib showed antitumor activity in patients with DNA repair alterations.	Supports the use of PARP inhibitors in biomarker-selected patients with mCRPC.	(102)
Mateo *et al*, 2024	Olaparib in mCRPC (PROfound trial)	Phase 3 trial analysis	Olaparib improved outcomes in patients with mCRPC and BRCA1/2 alterations.	Establishes olaparib as a standard therapy for BRCA-mutated mCRPC, linking germline status to targeted treatment.	(103)
Akamatsu *et al*, 2022	Germline testing in Japanese men undergoing biopsy	Clinical utility study	Germline genetic testing identified pathogenic variants in a notable proportion, impacting risk assessment.	Demonstrates the clinical utility and feasibility of germline testing in a non-European population.	(104)
Shore *et al*, 2023	NCCN guidelines for germline testing (PROCLAIM trial)	Prospective trial	NCCN guidelines effectively identified patients with pathogenic germline variants.	Supports the use of established guidelines to select patients for germline genetic testing.	(100)
Conti *et al*, 2021	Trans-ancestry PRS development	Genome-wide association meta-analysis	Identified novel susceptibility loci and developed a PRS with improved cross-ancestry performance, although disparities remain.	Provides a major resource for more equitable genetic risk prediction; underscores the need for diverse representation in genetics research.	(105)
Chen *et al*, 2023	Multi-ancestry PRS and aggressive disease	Meta-analysis within diverse populations	Developed and validated a multi-ancestry PRS. The PRS was associated with aggressive disease, particularly in men of African ancestry.	Addresses critical disparity; PRS may help identify high-risk men for aggressive PCa across ancestries.	(106)
Nordström *et al*, 2021	STHLM3-MRI trial: Combined risk model	Prospective, population-based, randomized trial	A strategy combining a blood-based risk model (including genetic score) with MRI and targeted biopsies reduced unnecessary biopsies while maintaining csPCa detection.	Demonstrates the feasibility and effectiveness of integrating genetic data into a multimodal screening pathway.	(107)

Table II. Continued.

Author, year	Genetic marker/study focus	Study design/population	Key findings	Clinical utility and significance	(Refs.)
Chen *et al*, 2022	Validation of multi-ancestry PRS	Meta-analysis	Validated a multi-ancestry PRS and age-specific risks for PCa across diverse populations.	Confirms the generalizability and potential clinical utility of PRS across different ancestral groups.	(108)
Goss *et al*, 2025	PRS for risk of progression	Retrospective cohort study	A higher PRS was associated with an increased risk of disease upgrading (grade group reclassification) during AS.	Suggests PRS could aid in risk stratification at diagnosis, potentially identifying AS candidates needing closer monitoring.	(109)

AS, active surveillance; PCa, prostate cancer; csPCa, clinically significant PCa; mCRPC, metastatic castration-resistant PCa; NCCN, national comprehensive cancer network; PRS, polygenic risk score.

although performance disparities between ancestral groups remain a concern (105,106,108). Recent advancements also explore the use of PRS to predict disease aggressiveness and outcomes. For example, Goss *et al* (109) demonstrated that a higher PRS was associated with an increased risk of disease upgrading (grade group reclassification) during active surveillance, suggesting its potential role in monitoring strategies. While promising, the widespread clinical implementation of PRS faces hurdles, including standardization of score calculation, integration into electronic health records and clinical decision support tools and ensuring equitable application across diverse patient populations to avoid exacerbating health disparities.

The underrepresentation of non-European ancestry groups in PRS derivation studies remains a notable barrier to equitable PCa screening (105,106,108). Without dedicated efforts to include diverse populations in biomarker discovery and validation, there is a risk that PRS and other genetic tools may inadvertently widen existing health disparities by providing less accurate risk estimates for minority groups (110). Therefore, future research should prioritize trans-ancestry genome-wide association studies, develop ancestry-calibrated risk scores and ensure that clinical validation cohorts reflect the full spectrum of population diversity. Such inclusive approaches are essential to translate the promise of personalized screening into benefit for all men, regardless of genetic ancestry.

5. Integrative strategies and clinical decision-making

The evolving landscape of PCa screening underscores the inadequacy of relying on any single biomarker or imaging modality. The integration of novel biomarkers with advanced imaging techniques and clinical parameters represents a pivotal advancement toward personalized, risk-adapted screening pathways. Such integrative strategies aim to enhance diagnostic precision, optimize resource allocation and ultimately improve clinical decision-making by balancing the detection of csPCa with the reduction of unnecessary procedures. This section examines three key integrative approaches: The combination of biomarkers with mpMRI, the development of risk-calculator models incorporating novel biomarkers and the health-economic evaluation of biomarker-guided pathways (Fig. 2).

Combining biomarkers with mpMRI. The incorporation of mpMRI into the diagnostic pathway has markedly improved the detection of csPCa while reducing the diagnosis of indolent disease. However, mpMRI is resource-intensive and not universally accessible. Consequently, biomarkers are increasingly evaluated as tools to triage patients for MRI or to complement imaging findings, thereby creating a more efficient, sequential diagnostic workflow.

Biomarkers as a 'gatekeeper' to MRI. Using biomarkers to select men most likely to benefit from MRI can reduce unnecessary scans and lower costs. The PHI has been studied extensively in this role. For instance, studies have shown that applying a PHI threshold can effectively stratify men with elevated PSA, where those with low PHI scores may avoid immediate MRI, thereby optimizing healthcare resource utilization (111,112). Similarly, the 4Kscore has demonstrated utility in identifying men at low risk of csPCa, for whom MRI

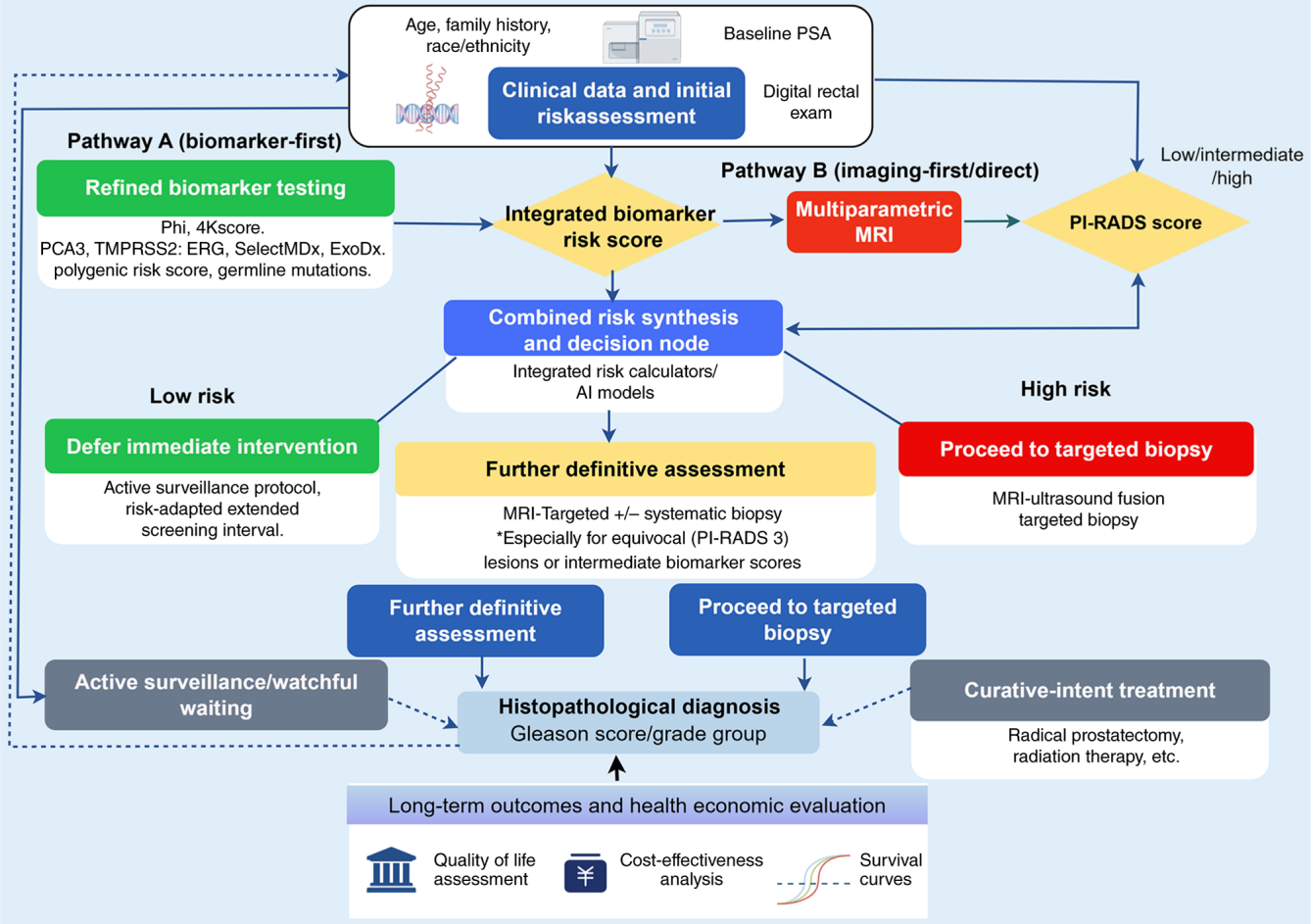

Figure 2. Multimodal, integrated framework for personalized prostate cancer screening and clinical decision-making. This figure outlines a dynamic, biomarker-informed pathway for refining prostate cancer screening. It integrates clinical parameters, novel biomarkers (blood, urine, genetic), and multiparametric MRI within sequential decision nodes to optimize the detection of clinically significant disease while minimizing unnecessary procedures. The framework emphasizes risk-adapted triage, multimodal data synthesis and cost-effective resource allocation, moving toward a personalized screening strategy. Consequently, integrating clinical, biomarker, and MRI data in a sequential, risk-adapted manner enhances detection of clinically significant prostate cancer while reducing overdiagnosis and healthcare costs. This figure was created using the online graphic design website Figdraw (www.figdraw.com). PCA3, prostate cancer antigen 3; PI-RADS, prostate imaging-reporting and data system; PSA, prostate-specific antigen.

might be deferred (113,114). Evaluations, including cost-effectiveness analyses, support the economic viability of such biomarker-first approaches, particularly in screening populations with a low prevalence of csPCa (23,115). Nonetheless, the optimal threshold for these biomarkers remains a subject of ongoing research, as variations in study populations and assay methodologies can influence performance.

Sequential use: Biomarkers to stratify risk, followed by mpMRI for targeted diagnosis. A sequential strategy employs biomarkers for initial risk stratification, followed by mpMRI and targeted biopsy for those at intermediate or high risk. This approach was exemplified in the STHLM3-MRI trial, where a blood-based risk model (incorporating protein biomarkers, genetic data and clinical variables) was used to select men for MRI. This strategy notably reduced the number of MRI scans and biopsies while maintaining high sensitivity for csPCa compared with a standard PSA-based pathway (116,117). Similarly, urinary biomarkers such as SelectMDx and ExoDx Prostate have been evaluated in combination with mpMRI. Studies indicate that these biomarkers can effectively identify men with a low likelihood of csPCa, who may safely avoid immediate MRI or biopsy (118-120). The integration of biomarkers with mpMRI thus allows for a more tailored diagnostic process, potentially enhancing both clinical outcomes and cost-efficiency.

Risk-calculator models incorporating novel biomarkers. Risk-calculator models integrate multiple variables, including clinical parameters, imaging findings and biomarker results, to generate personalized risk estimates for csPCa. These models aim to move beyond binary test results and provide a more nuanced assessment to guide biopsy decisions.

Several validated risk calculators now incorporate novel biomarkers. The rotterdam PCa risk calculator, for example, has been updated to include PHI and the 4Kscore, improving its predictive accuracy for csPCa (121,122). Similarly, the ERSPC risk calculator has been enhanced with kallikrein markers, demonstrating superior performance over PSA alone in predicting biopsy outcomes (122,123). In addition, models incorporating urinary biomarkers such as PCA3 and TMPRSS2: ERG have been developed and validated, showing improved discrimination for high-grade disease (124,125).

The strength of these integrated models lies in their ability to synthesize diverse data sources. For instance, a nomogram combining PHI with mpMRI findings, prostate imaging-reporting and data system score, has been developed and validated in biopsy-naïve men, demonstrating higher diagnostic accuracy than either modality alone (49,126). Similarly, machine learning approaches are being explored to create more sophisticated predictive models that incorporate genomic, proteomic and imaging data (127,128). However, the generalizability of these models can be limited by population-specific factors, such as differences in PSA distribution, genetic ancestry and MRI interpretation standards. Ongoing validation in diverse, prospective cohorts is essential to ensure their widespread applicability.

Cost-effectiveness and health economic considerations. The adoption of novel biomarkers and advanced imaging in PCa screening must be justified not only by clinical effectiveness but also by economic viability. Health economic evaluations are crucial for informing policy decisions and clinical guidelines, particularly in resource-constrained healthcare systems.

Several cost-effectiveness analyses have evaluated biomarker-guided pathways. Studies comparing PHI- or 4Kscore-based strategies with standard PSA testing consistently demonstrate that biomarker triage can reduce the number of biopsies and MRI scans, leading to long-term cost savings (14,129). For example, a microsimulation study based on the STHLM3-MRI trial found that a biomarker-based strategy (using the Stockholm3 test) was cost-effective compared with both PSA screening alone and an MRI-based pathway (23). Similarly, economic evaluations of urinary biomarkers such as SelectMDx and ExoDx Prostate suggest that these tests can be cost-effective by avoiding unnecessary biopsies and reducing overtreatment (14,130).

The cost-effectiveness of mpMRI is notably dependent on pre-test probability. When used as a first-line test in all men with elevated PSA, mpMRI may not be cost-effective due to high upfront costs. However, when preceded by biomarker-based risk stratification (as a second-line test for higher-risk individuals), the combined pathway often proves economically favorable (115,131). Notably, these analyses also highlight the importance of context-specific factors, such as healthcare costs, biopsy complication rates and patient preferences, which can vary markedly across regions and healthcare systems. Key incremental cost-effectiveness ratio (ICER) findings from the cited literature show that PHI-guided biopsy strategies reduce unnecessary biopsies and are generally cost-saving or have ICERs <€50,000 per quality-adjusted life year (QALY) compared with standard PSA testing (45,128). Similarly, the 4Kscore-based approach yields ICERs ranging from cost-saving to ~€35,000 per QALY, depending on the risk threshold applied (13,128). The Stockholm3 test followed by MRI (STHLM3-MRI strategy) was associated with an ICER of €13,600 per QALY vs. PSA alone and was dominant (cost-saving with improved outcomes) compared with an MRI-only pathway (23).

Toward a multimodal, personalized screening framework. The future of PCa screening lies in the intelligent integration of clinical, molecular and imaging data within a personalized framework. This multimodal approach acknowledges the biological heterogeneity of PCa and the diverse risk profiles of individuals. Promising directions include the development of composite scores that combine serum, urine and genetic markers (for example polygenic risk scores) with mpMRI findings to provide a comprehensive risk assessment (117,132,133). Artificial intelligence and machine learning platforms are increasingly being employed to analyze these complex datasets, potentially uncovering novel diagnostic signatures and improving predictive accuracy (128,134).

However, the implementation of such integrated pathways faces several challenges. These include the need for standardized assay protocols, equitable access to advanced diagnostics across diverse populations and the seamless integration of multimodal data into clinical workflows and electronic health records. Furthermore, robust prospective validation in population-level screening cohorts is essential to confirm the generalizability and real-world effectiveness of these strategies (35,135). Despite these hurdles, the continued evolution of integrative approaches holds great promise for refining PCa screening, ultimately aiming to maximize the detection of aggressive cancers while minimizing patient harms and healthcare costs.

6. Future directions

The continuous evolution of PCa biomarker research is poised to fundamentally reshape early detection paradigms. Future directions are increasingly focused on overcoming the limitations of single-analyte tests by leveraging technological convergence, advanced analytics and a deeper understanding of tumor biology. The integration of multi-omic data, the application of artificial intelligence, the refinement of liquid biopsy applications for localized disease and the development of novel biosensing platforms represent the most promising avenues. These advancements aim to achieve the ultimate goal of personalized screening: Maximizing the detection of csPCa while minimizing invasive procedures and overdiagnosis.

A primary trajectory involves the comprehensive integration of multi-omic data, encompassing genomics, transcriptomics, proteomics, metabolomics and epigenomics, to construct holistic molecular profiles. While individual biomarker classes (such as urinary PCA3, serum kallikreins, germline mutations) have demonstrated utility, their combined power within integrated models is greater (136,137). Emerging research is exploring novel dimensions of molecular information. For instance, analysis of chromatin conformation changes in peripheral blood cells has shown potential to detect PCa and stratify disease risk groups, suggesting that systemic epigenetic alterations may serve as a non-invasive biomarker (138). Similarly, extensive profiling of EV proteomes is uncovering novel protein cargoes associated with PCa aggressiveness and therapy response (139,140). The validation of multi-gene liquid biopsy signatures, such as the PROSTest which analyzes circulating RNA biomarkers, aims to provide a comprehensive risk assessment from a single blood draw (141,142). The challenge lies in standardizing these complex assays and validating their cost-effectiveness in diverse, prospective screening cohorts to avoid overfitting and ensure generalizability.

Concurrently, artificial intelligence and machine learning are transitioning from supportive tools to central components in biomarker discovery and application. Artificial intelligence algorithms can analyze vast, multidimensional datasets from medical imaging, histopathology and molecular assays to identify patterns imperceptible to human analysis (143,144). In imaging, deep learning models are being developed for automated and accurate segmentation of the prostate gland and its zones on MRI, which is crucial for standardizing quantitative imaging biomarkers (145,146). Beyond image analysis, machine learning is being applied to genomic and transcriptomic data to identify novel biomarker combinations and predictive signatures for diagnosis and prognosis (147,148). For example, explainable artificial intelligence frameworks are being integrated with biosensor data (such as exosomal multi-marker detection) to create transparent and clinically interpretable risk prediction tools (149). However, the divergent results from different artificial intelligence models, often due to variations in training datasets, algorithmic approaches and validation cohorts, highlight the need for rigorous external validation and standardization before widespread clinical adoption (11,12). Furthermore, the successful translation of artificial intelligence-driven biomarker models will require not only explainable artificial intelligence that provides clinicians with interpretable predictions but also prospective clinical trials that assess their real-world performance, impact on clinical decision-making and cost-effectiveness in screening populations.

The refinement of liquid biopsy for early-stage, localized PCa remains a critical frontier. While ctDNA and CTCs are established in advanced disease, their low abundance in localized cancer has limited screening utility (150). Future efforts are directed toward ultra-sensitive detection methods and alternative analytes. Research into fragmentomics, the analysis of cfDNA fragmentation patterns, shows promise for detecting cancer-specific signatures with higher sensitivity for localized tumors (151). Furthermore, novel RNA species in biofluids are gaining attention. Transfer RNA-derived fragments and other non-coding RNAs present in urine or serum are being investigated as stable and cancer-specific biomarkers with diagnostic and prognostic potential (152). Studies also indicate that combining the detection of ctDNA with CTCs in a dual-analyte approach may improve the sensitivity for early cancer detection (153). The consistent finding across studies is that detection of any tumor-derived material in localized disease often associates with more aggressive pathology, reinforcing its prognostic if not yet diagnostic value.

Technological innovation in biosensing and point-of-care testing is another key direction aimed at improving accessibility and rapidity. Novel electrochemical and optical immunosensors are being developed for the sensitive, multiplexed detection of PCa biomarkers such as PSA, PCA3 and novel targets such as six-transmembrane epithelial antigen of the prostate 1 (154,155). These platforms often employ advanced nanomaterials (graphene, MXenes, gold nanoparticles) to enhance signal amplification (156,157). The goal is to create affordable, rapid and user-friendly devices that could be deployed in primary care settings, facilitating wider and more equitable access to refined risk assessment. Additionally, research into capturing and analyzing the glycan structure of PSA (glycosylation) rather than just its quantity may provide notably improved cancer specificity (6,7).

Despite the promising horizons, notable challenges must be navigated. The clinical translation of novel biomarkers and artificial intelligence models require robust, prospective validation in population-level screening studies to minimize spectrum bias and prove real-world effectiveness (122). For multi-gene urinary panels and polygenic risk scores, additional barriers include lack of standardized reimbursement pathways, uncertain regulatory approval processes (FDA clearance for lab-developed tests) and slow clinician adoption due to limited familiarity with complex genomic results and unclear integration into existing clinical workflows. Disparities in biomarker performance across different ancestral groups necessitate the development and validation of tools in diverse populations to avoid exacerbating healthcare inequalities (110). Furthermore, the practical integration of complex multimodal data (imaging, genomics, proteomics) into clinical workflow and electronic health records, along with clear guidelines on interpretation and cost-effectiveness, is essential for adoption (158). Finally, as the biomarker arsenal expands, the ethical implications of genetic risk prediction and the psychological impact of complex risk stratification warrant careful consideration within a shared decision-making framework.

In conclusion, the future of PCa screening biomarkers is intrinsically multimodal and technologically driven. It will likely be characterized by the seamless integration of multi-omic liquid biopsy signatures, artificial intelligence-enhanced image analysis and innovative detection platforms, all feeding into dynamic, personalized risk calculators. Success will depend not only on technological prowess but also on rigorous validation in diverse populations, thoughtful health economic analysis and a commitment to equitable implementation, ultimately forging a pathway that is as precise and patient-centered as it is scientifically advanced.

7. Conclusions

PSA screening remains valuable but is limited by overdiagnosis and poor specificity. Advances in blood, urinary and genetic biomarkers offer improved risk stratification and specificity for csPCa. Integrating these markers with multiparametric MRI and risk-prediction models can reduce unnecessary procedures and enhance screening efficiency. Future personalized approaches will rely on multi-omic profiling, artificial intelligence and novel detection platforms to optimize early detection while minimizing harms.

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LL conceived the review, coordinated the literature analysis and drafted and critically revised the manuscript. LZ and ZL contributed to literature screening, data synthesis and co-drafting of key sections. KC and WR provided intellectual oversight, supervised the overall development of the work and critically revised the manuscript for important content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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