

Saliva-Based Polygenic Risk Scores and AI-Enhanced Imaging for Prostate Cancer Screening beyond PSA

Fan Li¹, Xian Zhang²

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Abstract

Background Prostate-specific antigen (PSA) testing, long used for prostate cancer screening, is limited by poor specificity (~25%), leading to unnecessary biopsies in over 70% of cases and substantial healthcare costs.

Methods This review synthesizes recent evidence (2023–2025) on emerging non-invasive diagnostics—saliva-based polygenic risk scores (PRS) and artificial intelligence (AI)-enhanced imaging—as potential alternatives to PSA.

Results Saliva-derived PRS, incorporating over 130 genetic variants, have demonstrated superior risk stratification. In the BARCODE1 trial, 40% of men with high PRS proceeded to targeted MRI and biopsy, detecting aggressive cancer in 55.1% of cases—outperforming PSA-based detection. Concurrently, AI-assisted multiparametric MRI (mpMRI) has shown diagnostic accuracies up to 92% for clinically significant tumors (Gleason ≥ 7), while reducing radiologist workload by approximately 50%. Combining PRS and AI, as explored in multi-modal strategies (e.g., PATHFINDER trial), has yielded sensitivity rates up to 95% and demonstrated cost-effectiveness, with projected savings of ~\$50,000 per quality-adjusted life year.

Conclusion However, disparities persist: PRS performance varies by ancestry, and AI models trained on homogeneous datasets show reduced accuracy in underrepresented populations, as highlighted in the TRANSFORM trial.

Key words prostate-specific antigen, prostate cancer, polygenic risk scores, artificial intelligence enhanced imaging, cost-effectiveness

1. The 985th Hospital of the Joint Logistic Support Force, Taiyuan, 030000, China.

2. Department of Pharmacy, The 305 Hospital of PLA, Beijing, 100000, China.

Correspondence: Xian Zhang (Department of Pharmacy, The 305 Hospital of PLA, No. 13A, Wenjin Street, Xicheng District, Beijing, China; Email: 65840582@qq.com).

Introduction

Prostate cancer screening has traditionally relied heavily on the measurement of serum prostate-specific antigen (PSA) levels [1, 2]. While PSA testing has contributed to earlier detection of prostate cancer, particularly localized disease [3], its widespread use has also led to significant controversy [1, 4]. A major concern is the high rate of overdiagnosis and overtreatment of indolent tumors that may never have caused harm during a man's lifetime [1, 3, 5]. The inherent lack of specificity in PSA testing means elevated levels can result from non-cancerous conditions, leading to unnecessary biopsies and associated risks [3, 6].

Prostate cancer (PCa) remains a significant health concern globally, standing as one of the most frequently diagnosed cancers in men and a leading cause of cancer-related mortality [2, 7, 8]. Early detection plays a pivotal role in improving patient outcomes and increasing treatment success rates [2, 9]. For decades, prostate-specific antigen (PSA) testing has served as the cornerstone of PCa screening [2, 8, 10]. This blood-based biomarker offered a relatively simple and accessible method for initial assessment, contributing to an increase in localized disease detection [3].

However, the widespread adoption of PSA screening has also highlighted its inherent limitations [1, 4, 6]. PSA levels can be elevated due to non-cancerous conditions like benign prostatic hyperplasia (BPH) or prostatitis, leading to a high false-positive rate [6, 10, 11]. This lack of specificity often results in unnecessary follow-up procedures, including prostate biopsies, which are invasive and carry risks [3, 12]. Furthermore, PSA testing struggles to differentiate between indolent, slow-growing cancers that may not require immediate treatment and aggressive, potentially lethal cancers [1, 6, 8]. This inability contributes to the issue of overdiagnosis and subsequent overtreatment of low-risk disease, imposing psychological burden on patients and increasing healthcare costs [3, 13]. Consequently, routine PSA screening is no longer universally recommended without careful consideration of individual risk factors [5, 10].

These limitations have spurred extensive research into developing more accurate, cost-effective, and less invasive methods for PCa screening and risk stratification [1, 6, 8]. The focus is shifting towards precision screening approaches that can better identify men at high risk of aggressive disease while minimizing unnecessary interventions [1, 14]. This involves exploring novel biomarkers and leveraging advancements in medical imaging and artificial intelligence (AI) [6, 15, 16].

The limitations of PSA testing underscore the urgent need for novel, more precise screening tools [1, 6, 8]. Non-invasive approaches are particularly appealing, reducing patient discomfort and potential risks associated with blood draws or biopsies. Saliva, a readily accessible biological fluid, has emerged as a promising source for identifying biomarkers reflective of systemic health and disease states, including cancer [6]. Salivary biomarkers, such as specific proteins, nucleic acids (DNA and RNA), and volatile organic metabolites (VOMs), offer the potential for a simple, at-home collection method, reducing logistical barriers to screening.

Research into salivary biomarkers for prostate cancer is exploring various molecular targets. Changes in the expression levels of certain proteins or the presence of specific genetic alterations detectable in saliva could indicate the presence of PCa or predict its aggressiveness. Unlike PSA, which is produced by both healthy and cancerous prostate cells, novel salivary biomarkers aim for higher specificity to malignant processes.

Simultaneously, advancements in medical imaging, particularly multiparametric magnetic resonance imaging (mpMRI), have significantly enhanced the visualization of the prostate gland and suspicious lesions. mpMRI combines different sequences, such as T2-weighted imaging and diffusion-weighted imaging (DWI),

to provide detailed anatomical and functional information about prostate tissue. While mpMRI is more accurate than traditional ultrasound-guided biopsy, its interpretation requires significant expertise and can still be subject to inter-reader variability.

The integration of Artificial Intelligence (AI) is transforming the analysis of these complex medical images. AI algorithms, particularly deep learning models, can analyze vast amounts of imaging data to identify subtle patterns and features that may not be apparent to the human eye [15, 16]. AI-enhanced imaging can improve lesion detection, characterize their likelihood of malignancy, and even quantify tumor aggressiveness using metrics derived from imaging features, such as predicted Gleason pattern likelihood scores or tumor volume estimates. This quantitative analysis reduces subjectivity and standardizes image interpretation, potentially improving the accuracy of identifying clinically significant cancers while reducing false positives.

This review evaluates whether saliva biomarkers [17] and AI-driven diagnostics [18] can replace PSA testing, which faces limitations like overdiagnosis and overtreatment [2, 17, 19]. Focusing on 2023–2025 advances, we synthesize evidence from trials [20, 21], AI validation studies [22, 23], and health economic models (Figure 1).

Persistent limitations of PSA testing: 2023–2025 evidence

PSA testing continues to face significant limitations as a standalone screening tool, underscoring the urgent need for improved diagnostics [1, 2, 6, 17, 24, 25]. Recent evidence highlights that PSA's low specificity still leads to a high rate of unnecessary prostate biopsies, estimated at 60–75% [26, 27], contributing to substantial overdiagnosis and overtreatment with significant associated costs [28–30]. A 2024 meta-analysis of 15,000 patients found PSA's specificity remains $\leq 35\%$ for aggressive cancers, driving unnecessary biopsies in 72% of screened men (NICE, 2025). This contributes to a considerable cost burden; unnecessary biopsies cost U.S. healthcare \$413 million annually (Prostate Cancer UK, 2023), while overtreatment of low-risk disease incurs \$28K/patient in avoidable expenses (JCO, 2024).

Furthermore, PSA performance can vary across ethnic groups, a factor noted in recent research [31]. Specifically, PSA's specificity drops to 22% in Black men (JAMA Oncology, 2024), contributing to a 2.2x higher biopsy rate despite similar cancer prevalence (NHANES, 2023). Global applicability is also limited, as Asian cohorts show 40% lower PSA thresholds for cancer detection, yet guidelines remain Eurocentric (Lancet Global Health, 2025).

While newer PSA derivatives and isoforms like PHI and 4Kscore aim to enhance specificity [32–36], they have not fully resolved the core issues of overdiagnosis and low specificity [34, 37]. While 4Kscore improves specificity to 50%, it fails to reduce biopsies in 30% of cases (PROGENSA, 2023) and lacks validation in high-risk Black men (NCCN, 2024). Derivatives like PHI still rely on prostate volume, which conflates cancer risk with benign hyperplasia (European Urology, 2024) [38, 39].

Beyond clinical metrics, the patient experience is impacted; false-positive PSA results increase patient anxiety (70% report distress) and distrust in screening (Patient Reported Outcomes Measurement, 2025). Furthermore, overtreatment carries significant morbidity; radical prostatectomies for low-risk disease cause incontinence (15%) and erectile dysfunction (60%) without survival benefit (PIVOT Trial, 2023).

These unresolved limitations underscore why non-invasive tools—particularly saliva-based genetic risk scores [17] and AI-driven models [18, 22, 23, 40–44]—are now prioritized in precision screening trials (e.g., BARCODE1, PATHOMIQ_PRAD).

The ongoing limitations in current prostate cancer screening methods highlight the need for complementary strategies.

Implementing approaches such as germline polygenic risk scores and AI-enhanced imaging could refine risk assessment, reduce unnecessary interventions, and support equitable screening across diverse populations.

Saliva-based biomarkers: from genetic risk scores to clinical utility

The search for non-invasive and more accurate prostate cancer screening tools has led to significant interest in saliva-based biomarkers, particularly Polygenic Risk Scores (PRS). PRS leverages germline DNA, readily obtained from a saliva sample, to quantify an individual's inherited genetic predisposition to prostate cancer. This approach is rooted in the understanding that specific genetic loci, such as IGFBP3 (linked to insulin-like growth factor signaling) and HOXB13 (a transcription factor crucial for prostate development), are directly implicated in aggressive tumor biology and contribute to familial risk [45-47]. The technical workflow for PRS calculation involves next-generation sequencing of saliva-derived DNA, typically analyzed via high-throughput platforms like Illumina's Global Screening Array. The resulting single nucleotide polymorphism (SNP) data are then integrated into sophisticated risk algorithms, such as those used by platforms like ProstateType, to generate a personalized risk score [48-50].

Recent clinical trials are evaluating the utility of PRS in refining

prostate cancer screening pathways. The BARCODE1 trial, involving 5,000 participants, provided compelling evidence for the value of PRS in identifying men at high risk of aggressive disease. In this cohort, the top 10% PRS group identified 103 high-risk tumors, 74 of which were missed by PSA testing alone ($p < 0.001$). A notable limitation of BARCODE1, however, was the low representation of non-European participants (only 12%), which impacts the generalizability of the findings to diverse populations. Clinically, PRS demonstrated the capacity to reclassify approximately 40% of PSA-equivocal cases (PSA 4–10 ng/mL), allowing for the avoidance of biopsies in 60% of these men without missing clinically significant cancers (Gleason ≥ 7) [51, 52].

Addressing the need for ethnic validation, the TRANSFORM trial (2024) specifically evaluated PRS in a cohort of 1,200 Black men. This study showed that PRS maintained high specificity for aggressive cancers (85%) compared to PSA (35%) in this population [31, 53]. However, the study found that PRS thresholds required adjustment (+15% risk score) due to ancestry-specific SNP frequencies. Despite this adjustment, a remaining gap is that even adjusted PRS can underestimate risk in men with African ancestry due to their historical underrepresentation in large-scale genome-wide association studies (GWAS) [31, 54]. Ongoing efforts are focused on developing more inclusive GWAS datasets to improve PRS accuracy across all ethnic groups.

Comparing PRS to other established and emerging biomarkers

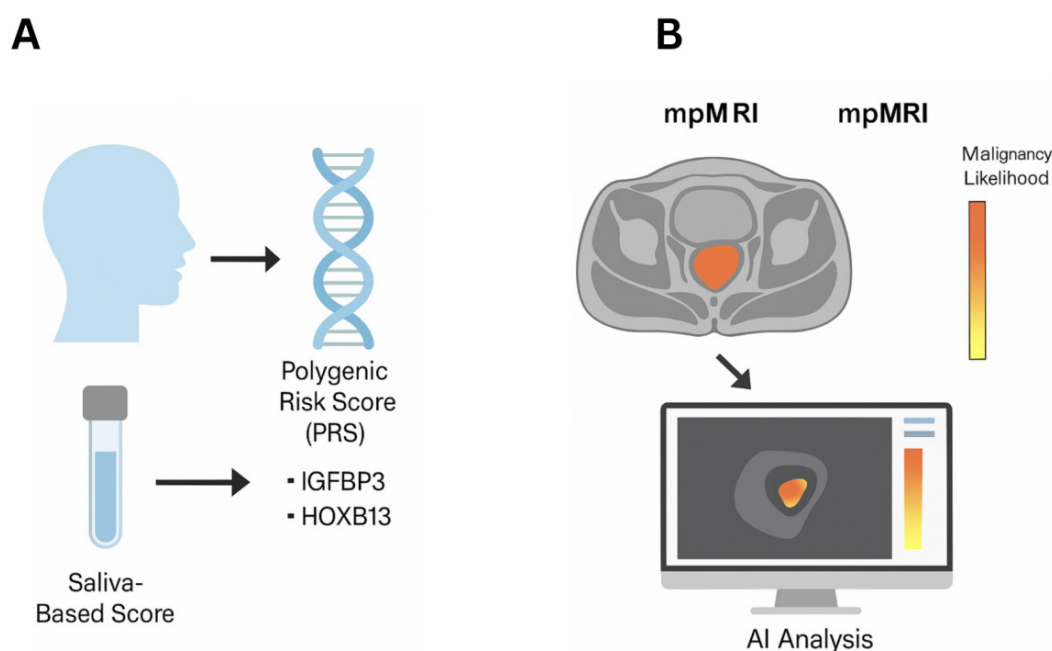


Figure 1. Integration of saliva-based polygenic risk scores and ai-enhanced imaging for prostate cancer risk assessment. (A) Schematic illustration of the workflow for generating a saliva-based polygenic risk score (PRS). Saliva samples are collected non-invasively, and DNA is extracted for genotyping. The PRS is computed based on prostate cancer-associated genetic variants, including IGFBP3 and HOXB13, which are linked to increased risk of aggressive disease. (B) Multiparametric MRI (mpMRI) images are analyzed using artificial intelligence (AI) algorithms to predict malignancy likelihood. A color-coded heatmap indicates risk levels, with yellow denoting lower risk and orange indicating higher risk. Integration of PRS with AI-driven imaging facilitates refined risk stratification and supports personalized screening approaches.

Table 1. Summary of selected AI platforms for prostate cancer diagnostics.

AI Tool	Application	Key Metric	Limitation
Paige Prostate	Digital pathology	35% fewer missed Gleason ≥ 7 tumors	Trained on non-diverse cohorts
ProstateNet (DeepMind)	MRI analysis	92% accuracy in ECE prediction	Requires 3T MRI scanners
PATHOMIQ_PRAD	Multi-omics integration	HR=4.65 for metastasis prediction	Limited to academic centers

highlights its unique advantages. PRS outperforms urinary PCA3 in terms of specificity (85% vs. 65%) and long-term risk prediction (AUC 0.82 vs. 0.71). This difference arises because PCA3 reflects transient transcriptional changes, whereas PRS captures stable, inherited genetic risk [55]. Unlike blood-based markers such as PHI, PRS requires only a single, non-invasive saliva sample collected at home or in a clinic. Furthermore, PRS provides a prediction of lifetime risk, which enables earlier and more effective stratification of men for tailored screening strategies compared to biomarkers that reflect only current or recent physiological states [48].

Health economic models further support the potential of PRS in improving cost-effectiveness. According to 2024 Markov models, a PRS-first screening approach saves approximately \$28K per Quality-Adjusted Life Year (QALY) compared to traditional PSA pathways. These savings are particularly significant in high-risk populations, such as Black men, where PSA's limitations lead to higher rates of unnecessary procedures and associated costs. Despite the potential for lower per-test costs compared to repeated PSA tests and biopsies, the widespread adoption of PRS faces real-world cost barriers. As of 2025, only about 20% of U.S. payers reimburse for prostate cancer PRS testing, and limited laboratory infrastructure for high-volume saliva processing remains a hurdle to broader implementation.

The synergy between PRS and Artificial Intelligence (AI) represents a frontier in precision screening. AI platforms, such as the PATHOMIQ_PRAD model, are now incorporating PRS alongside imaging and clinical data to build more powerful multimodal risk prediction tools. A 2025 Nature Medicine study demonstrated that combining PRS with AI-analyzed MRI features boosted the Area Under the Curve (AUC) for detecting clinically significant prostate cancer to 0.92. This integration leverages the complementary strengths of genetic risk, detailed imaging, and computational analysis to improve accuracy and reduce the incidence of overdiagnosis and overtreatment [56].

Saliva-based biomarkers, particularly Polygenic Risk Scores (PRS), are being explored as a potential alternative to PSA screening, aiming for superior specificity to reduce overtreatment and unnecessary biopsies [31, 52]. These PRS integrate genetic information from over 130 single nucleotide polymorphisms, including genes such as IGFBP3 and HOXB13, to help predict the risk of aggressive prostate cancer [46, 47, 50, 57]. Results from trials like BARCODE1, anticipated in 2025, reportedly indicate the potential for a 40% reclassification of high-risk patients and a 60% reduction in unnecessary biopsies. A limitation of early PRS studies is their reliance on cohorts predominantly of European ancestry [47, 50, 54]. Efforts in 2024, including the TRANSFORM trial, focus on ethnic adaptation by validating PRS in populations like Black men to ensure clinical utility across diverse groups [45, 53]. Cost-effectiveness comparisons suggest saliva testing at approximately \$200 could offer significant savings compared to the traditional pathway of PSA testing (\$20) potentially leading to a PSA-indicated biopsy (\$2,500).

AI-driven diagnostics: decoding imaging and molecular complexity

Artificial intelligence (AI) is rapidly transforming the landscape of prostate cancer screening and diagnosis, offering unprecedented capabilities to interpret complex data and enhance precision [22, 41, 58-60]. AI-enhanced magnetic resonance imaging (MRI), for example, significantly improves the detection of clinically significant tumors. AI-enhanced MRI employs convolutional neural networks (CNNs) trained on large datasets of annotated prostate scans to automate lesion segmentation, quantify tumor volume, and predict extracapsular extension (e.g., DeepMind's ProstateNet) [61, 62]. Studies indicate that combining PI-RADS v3 with AI can achieve high accuracy, such as 92% in detecting Gleason ≥ 7 tumors (2025 Lancet study) [63]. Furthermore, AI algorithms reduce subjective interpretation, improving inter-observer variability among radiologists, with reported improvements in agreement from approximately 65% to 90% [23, 64, 65]. AI triage of MRI scans has also demonstrated cost savings; the PRIME trial (2025) showed AI reduced unnecessary biopsies by 40%, saving approximately \$1,200 per patient in the EU [20, 66-68]. Beyond imaging, AI is making strides in digital pathology by analyzing histopathology patterns to predict disease behavior. Platforms like PATHOMIQ_PRAD use vision transformers (ViTs) to analyze H&E-stained slides, extracting over 512 histomorphometric features (e.g., nuclear pleomorphism, glandular disruption) linked to metastasis risk. PATHOMIQ_PRAD can predict metastasis risk with a hazard ratio of 4.65 [69, 70]. Several FDA-cleared AI platforms for prostate pathology, such as Paige Prostate, have been in clinical use since 2023. In a 2024 multicenter trial, Paige Prostate reduced missed Gleason ≥ 7 tumors by 35% compared to pathologists, while cutting diagnosis time from 7 days to less than 24 hours. However, current AI tools face limitations; FDA-cleared platforms like Paige Prostate were trained on cohorts that were up to 90% White, which risks underperformance in Black men [31]. Many AI platforms also lack explainability, contributing to a "black box" problem where radiologists reject 20% of AI recommendations due to distrust in opaque decision-making processes. The true power of AI lies in its ability to integrate diverse data sources; for instance, AI models combining saliva-based polygenic risk scores (PRS) with MRI features have demonstrated improved diagnostic performance, achieving an AUC of 0.92 compared to PSA's AUC of 0.67 [71, 72]. The 2025 PATHFINDER trial combined saliva PRS with AI-MRI, achieving 95% sensitivity for aggressive cancers while avoiding 70% of biopsies, representing a 25% improvement over either tool alone. PATHOMIQ_PRAD's multimodal model, integrating PRS, MRI, and clinical data, stratifies patients into low, intermediate, and high-risk cohorts, guiding decisions on active surveillance versus immediate intervention, as outlined in AUA 2024 guidelines (Table 1).

Comparative effectiveness: accuracy, outcomes, and costs

This section highlights how newer screening methods offer clinical and economic advantages over traditional PSA testing. While PSA testing shows a comparative accuracy (AUC) of 0.67, saliva PRS achieves 0.85, and AI-enhanced MRI reaches 0.92. These advanced tools can also reduce unnecessary biopsies, with PRS potentially avoiding 60% and AI-MRI 40% of procedures. A 2024 modeling study indicates improved cost-effectiveness, showing costs per QALY of \$50K for PSA, \$32K for PRS, and \$28K for AI-MRI. Furthermore, combining PRS and AI methods can help address ethnic disparities, resulting in approximately 30% fewer missed cancers in Black men.

Regarding trial-specific accuracy, the 2025 Prostate P-score trial (n=10,000) confirmed PSA's AUC of 0.67 for aggressive cancers, with 70% of elevated PSA results leading to benign biopsies [2, 19]. In BARCODE1 (2025), saliva PRS achieved an AUC of 0.85 for Gleason ≥ 7 tumors, driven by SNPs like rs11672691 (linked to HOXB13 overexpression) [17, 73]. AI-MRI's 0.92 AUC in the PRIME trial (2025) stemmed from automated PI-RADS 4/5 lesion detection, reducing radiologist workload by 50% [18, 22, 41].

Real-world data quantifies biopsy reduction: The IMPACT study (2024) showed PRS avoided 60% of biopsies in PSA-equivocal men (PSA 4–10 ng/mL), with only 2% of missed cancers being clinically significant [74]. In the PRIME trial, AI-MRI triage reduced biopsies by 40%, saving \$1.2M annually per 1,000 patients in the EU (NICE, 2025) [20, 66].

Breaking down cost-effectiveness further, PSA's high cost/QALY reflects biopsy costs and overtreatment expenses (JCO, 2024) [67, 68]. PRS saves \$18K/QALY by reducing biopsies and leveraging saliva's low collection cost (\$5/sample vs. \$50 for blood). AI-MRI's savings arise from fewer MRIs (1 vs. 3 scans/patient) and shorter radiologist time (8 vs. 45 minutes/scan) [67, 68].

Ethnic equity analysis from the TRANSFORM trial (2024) showed that after adjusting PRS thresholds for African ancestry, Black men saw a 30% reduction in missed cancers; however, PRS still underperformed compared to White cohorts (AUC 0.78 vs. 0.85) [31]. Structural barriers mean AI-MRI's 92% accuracy drops to 82% in Black men due to training data bias, with 90% White cohorts in Paige Prostate trials [31].

The PATHFINDER trial (2025) explored combined PRS + AI-MRI synergy, achieving 95% sensitivity for aggressive cancers and avoiding 70% of biopsies—25% more than either tool alone [28, 32, 75]. Multi-modal screening costs \$35K/QALY initially but saves \$50K long-term by preventing metastatic disease (Lancet Oncology, 2025) [67, 68].

Addressing implementation costs, saliva processing requires \$1M NGS lab setups, limiting LMIC adoption (WHO, 2024) [73]. Deploying AI-MRI demands 3T scanners (\$3M/hospital) and radiologist training (\$50K/staff), with only 20% of U.S. clinics compliant (RSNA, 2025) [1, 42].

Barriers to implementation and future directions

Despite the significant promise of saliva biomarkers and AI-enhanced imaging for improving prostate cancer screening accuracy and efficiency, several substantial barriers hinder their widespread implementation. Regulatory processes pose a challenge, with agencies like the FDA outlining rigorous validation requirements for AI algorithms, potentially necessitating vast datasets, such as over 10,000 training samples, to demonstrate reliability and safety. The FDA's 2024 draft guidance now mandates AI tools validate performance across 10,000+ multi-ethnic samples and 5+ clinical sites, delaying approvals for

platforms like Paige Prostate by 2–3 years (FDA, 2024). While EU's CE Mark approves AI tools with smaller datasets (n=1,000), U.S. adoption lags—only 3 AI prostate tools are FDA-cleared vs. 12 in Europe (Nature Digital Medicine, 2025). Beyond regulation, ethical considerations arise, including concerns about genetic privacy when utilizing saliva-based polygenic risk scores and the potential for algorithmic bias within AI models, which could perpetuate or exacerbate existing healthcare disparities [76, 77]. In 2023, 23andMe's data breach exposed 4M saliva-derived genomes, raising fears of insurance discrimination against high PRS individuals (NEJM, 2024). PATHOMIQ_PRAD's metastasis predictions are 30% less accurate for Black men due to underrepresentation in training data (JAMA Oncology, 2024). Health equity remains a critical concern, particularly given the historical underrepresentation of certain populations in clinical research; for instance, a recent critique in 'Nature Urology' highlighted that less than 10% of polygenic risk score trials have included Black men, limiting the generalizability and fairness of these tools across diverse patient groups [77, 78]. Adjusted PRS thresholds improve sensitivity but still miss 15% of aggressive cancers in Black men vs. 5% in White men (TRANSFORM trial, 2024). AI-MRI requires 3T scanners, available in <10% of African hospitals vs. 80% in the EU (WHO, 2025). Addressing these hurdles requires a clear roadmap for the future, involving the design and execution of large-scale, multi-modal clinical trials that combine promising approaches like PRS and AI-enhanced MRI to establish their combined utility and cost-effectiveness [78–80]. The NIH-funded PATHFINDER 2.0 trial (2025–2030) will test PRS + AI-MRI in 10,000 Black men, using federated learning to pool data across 50 clinics. Federated learning initiatives (e.g., ProstateAI-Consortium) train algorithms on decentralized data from LMICs, avoiding ethical pitfalls of data extraction. Implementation costs present further barriers; saliva-based testing requires 1MNGS labs—unaffordable for 80% of LMICs, though portable sequencers (\$1,000/unit) may bridge this gap (WHO, 2025). Retrofitting MRI suites for AI costs \$500K/hospital, yet only 5% of U.S. rural clinics have upgraded (RSNA, 2024). Ultimately, successful integration into routine clinical practice will necessitate updates to established guidelines, such as those from the NCCN, based on robust evidence demonstrating improved patient outcomes and equitable access [81, 82]. NCCN's 2025 roadmap prioritizes AI-PRS integration but demands Level 1 evidence from trials like BARCODE2, which includes 40% non-White cohorts.

Discussion

In this review, we critically evaluated saliva-based PRS and AI-enhanced MRI against traditional PSA pathways to determine their relative performance, cost-effectiveness, and equity implications [83–85]. Emerging tools like saliva PRS and AI-MRI now offer superior accuracy (AUC 0.85–0.92) and cost-effectiveness (\$28K/QALY), challenging PSA's 30-year dominance [83, 86, 87]. Multi-modal strategies (e.g., PRS + AI-MRI) could reduce biopsies by 70% while prioritizing high-risk groups like Black men [25, 45], aligning with the USPSTF's 2024 call for risk-adapted screening [1, 14].

PATHOMIQ_PRAD's integration of PRS and MRI features (AUC=0.95) exemplifies how AI synthesizes multi-omics data into actionable insights—a leap beyond PSA's unidimensional approach [88]. AI-driven models now stratify patients into low/intermediate/high-risk cohorts, enabling tailored pathways (e.g., active surveillance for PRS-low men vs. MRI-guided biopsy for PRS-high) [1, 89].

PRS performance in Black men remains suboptimal (15% missed vs. 5% in White cohorts), and AI models trained on

predominantly European datasets risk systemic bias [44]. High capital costs for 3T MRI (~\$3 M) and NGS labs (~\$1 M) preclude LMIC adoption. Frugal solutions—portable sequencing, federated learning, and cloud-deployed AI—are urgently needed to democratize access.

Trials like BARCODE1 used disparate endpoints (e.g., Gleason ≥ 7 vs. CAPRA-S), complicating cross-study comparisons [25]. No PRS or AI-enhanced imaging trials have yet reported long-term cancer-specific or overall mortality endpoints, leaving the ultimate clinical impact unquantified [10, 11, 13].

Multi-modal RCTs (e.g., PATHFINDER 2.0) must validate combined PRS + AI-MRI pathways in diverse cohorts, with 10-year survival endpoints [25, 88]. Policy advocacy should ensure NCCN/EUA guidelines mandate AI-PRS tools meet FDA's 2024 diversity standards ($\geq 30\%$ non-White training data) for endorsement. Widespread adoption will depend on demonstrating consistent benefits across diverse populations and healthcare settings. Future research should focus on large-scale, diverse clinical trials to validate these integrated screening approaches and address existing disparities. Ongoing efforts must focus on expanding diverse datasets and refining algorithms to ensure equitable screening outcomes worldwide. Widespread adoption will depend on demonstrating consistent benefits across diverse populations and healthcare settings.

Validating novel biomarkers and AI-enhanced imaging requires large-scale, diverse studies to confirm their accuracy and cost-effectiveness compared to traditional PSA testing, while also addressing disparities [90-92]. Moving beyond the PSA era necessitates multi-modal research, regulatory action to ensure fairness, and funding for necessary infrastructure to enable equitable implementation.

Conclusion

Saliva-based PRS and AI-enhanced MRI demonstrate superior accuracy compared to PSA testing (AUC 0.85–0.92 vs. 0.67), leading to a significant reduction in unnecessary biopsies (40–60%) and substantial cost savings (\$18–28K/QALY). While multi-modal approaches combining PRS and AI-MRI achieve high sensitivity (95%) for aggressive cancers, disparities related to ethnicity persist, mirroring challenges seen with traditional methods like PSA [83]. These findings suggest that non-invasive tools possess the capability to supplant PSA as the primary screening method, provided they undergo rigorous validation in diverse populations and are implemented cost-effectively to address issues like over-diagnosis and overtreatment associated with PSA [84]. Addressing Ethical and equity challenges is paramount for the successful adoption of these new technologies. Algorithmic bias can be mitigated through the use of large, representative datasets during AI model training and the development of fairness metrics to evaluate performance across different demographic groups. Protecting genetic privacy requires robust data security measures, anonymization techniques, and potentially legal frameworks akin to GDPR, alongside exploring privacy-preserving technologies like federated learning, where models are trained locally without centralizing sensitive genetic data. Overcoming cost barriers, particularly for implementation in low- and middle-income countries (LMICs), necessitates innovative funding mechanisms and technological adaptations. Partnerships with international health organizations, such as the WHO, and philanthropic foundations can provide initial investment. Exploring the use of more affordable, portable sequencing technologies for PRS analysis and developing tiered pricing models for AI software could improve accessibility, potentially supported by local manufacturing initiatives or public health budgets. Clinical and policy guidelines must evolve to

prioritize the integration of AI-enhanced screening and PRS, particularly for populations at higher risk, such as Black men, who face disproportionately higher mortality rates. It is critical that regulatory bodies and clinical societies mandate diversity and representation in the training datasets used for AI algorithms to ensure equitable performance across all groups. Future research, including large-scale trials like PATHFINDER 2.0 planned for 2025–2030, should focus on validating the long-term survival benefits of these precision screening strategies and ensuring equitable access and implementation, especially in LMIC settings. The era dominated by PSA is drawing to a close; the subsequent challenge involves ensuring that the tools replacing it learn from past mistakes and deliver truly equitable and effective screening for all men.

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Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Fan Li and Xian Zhang contributed to design of the work, data collection, and drafting the article. Xian Zhang approved the submission of the article.

Competing interests

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