

REVIEW ARTICLE

A multimodal framework for early detection, risk assessment, and biomarker-guided therapy in prostate cancer: Considerations for sub-Saharan African populations

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Abstract

Prostate cancer remains a major global public health concern, with rising incidence rates worldwide, especially in sub-Saharan Africa. Traditional screening modalities, which rely solely on prostate-specific antigen concentration measurement and digital rectal examination (DRE), have shown poor sensitivity and specificity. Hence, this review critically evaluates emerging multimodal diagnostic strategies, including environmental risk assessment, new cytological and immunohistochemical biomarkers, and genomic profiling, to improve early detection and enable precision therapy for prostate cancer. We examine current information on polycyclic aromatic hydrocarbons as environmental risk indicators, the optimization of post-DRE urine cytology, cytological examination of expressed prostate secretions, and the clinical usefulness of biomarkers such as *ERBB2*, *CDK12*, *BRCA2*, and *ATM*. Specific attention is paid to the African background, where unique genetic and environmental factors necessitate the development of tailored diagnostic algorithms. This integrative approach provides a theoretical framework for developing comprehensive diagnostic pathways that can enhance early detection rates and deliver individualized treatment in resource-constrained environments. Although the target population of this review is sub-Saharan Africans, the principles and frameworks presented have broader applicability to other low- and middle-income nations facing similar challenges.

Keywords: Prostate cancer; Biomarker discovery; Immunohistochemistry; Genomic profiling; Sub-Saharan Africa; Polycyclic aromatic hydrocarbons; Implementation science; Precision oncology

1. Introduction

Prostate cancer is the second most commonly diagnosed malignancy and the fifth leading cause of cancer death among men worldwide.¹ Prostate cancer represents a significant and growing burden in sub-Saharan Africa, with incidence and mortality rates exceeding those observed in many Western populations.² The most populous country in Africa, Nigeria, has an age-standardized incidence of 24.4–114.6 per 100,000 men, with substantial geographic disparities.³ The causes of the disproportionate mortality among African populations are multifactorial and include factors such as late presentations, inadequate screening facilities, genetic predispositions, and possibly unique environmental exposures.

The existing diagnostic modalities include measurement of serum prostate-specific antigen (PSA) concentration, digital rectal examination (DRE), and transrectal ultrasound-guided biopsies.⁴ Nevertheless, the specificity of PSA screening is not fully reliable, as PSA levels are also elevated in benign prostatic hyperplasia, prostatitis, and other non-cancerous conditions, leading to overdiagnosis and unnecessary biopsies.⁵ In addition, the traditional screening standards cannot identify clinically significant cancer in men with PSA levels lower than threshold values, especially in African men with different PSA kinetics.⁶

The need for greater diagnostic accuracy has also spurred research into multimodal methods that incorporate environmental risk assessment, liquid biopsy techniques, state-of-the-art immunohistochemistry (IHC), and genomic profiling. Industrial emissions, especially polycyclic aromatic hydrocarbons (PAHs), biomass burning, and environmental carcinogens have become influential factors in prostate carcinogenesis, particularly in the rapidly urbanizing African environment.⁷ At the same time, new developments in molecular pathology have revealed genomic changes, such as breast cancer gene 2 (*BRCA2*), ataxia telangiectasia mutated (*ATM*), cyclin-dependent kinase 12 (*CDK12*), and human epidermal growth factor 2 receptor (*HER2*; *ERBB2*) mutations that can alter the prognosis and choice of treatment.⁸

This review critically analyzes the scientific basis for integrating environmental exposure assessment, non-invasive cytological sampling, IHC biomarkers, and genetic profiling into a unified diagnostic model. Although our main focus is on populations in sub-Saharan Africa, especially Nigeria, the described methodology, implementation plans, and the concept of precision medicine have broader applicability to other resource-limited environments worldwide. The focus on population-specific characteristics provides a blueprint for

adapting precision oncology strategies to meet the needs of diverse genomic backgrounds and healthcare systems. Notably, this review focuses primarily on molecular, cellular, and biomarker-based methods; a detailed description of clinically relevant imaging modalities, such as multiparametric magnetic resonance imaging (mpMRI), is outside the scope of this review. We also consider methodological issues peculiar to Africans and clarify their implications on clinical implementation in resource-constrained healthcare systems.

2. Polycyclic aromatic hydrocarbons and prostate cancer

2.1. Exposure pathways and mechanisms of polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons are a category of organic substances that occur as a result of the partial burning of materials that contain carbon.⁹ The United States Environmental Protection Agency has listed 16 PAHs as priority pollutants due to their ubiquitous environmental occurrence and proven carcinogenicity. Vehicular emissions, industrial processes, tobacco smoke, grilled food, and biomass burning are all considered primary sources of exposure, and they are especially relevant in sub-Saharan Africa, where wood and charcoal are the most commonly used sources of domestic energy.¹⁰

Polycyclic aromatic hydrocarbons are procarcinogenic compounds; their effects are mediated by cytochrome P450 enzymes, which metabolize them into reactive diol epoxides, which, in turn, form DNA adducts. The process induces mutation in oncogenes and tumor suppressor genes, including *TP53* and *RAS*.¹¹ Moreover, PAH metabolites generate reactive oxygen species, causing oxidative DNA damage and chronic inflammation, characteristic of prostate carcinogenesis.¹² Some PAHs also have endocrine-disrupting effects and thereby disrupt androgen receptor signaling pathways, which are pivotal to prostate biology.¹³

Recent mechanistic studies have also revealed other mechanisms by which PAHs promote prostate cancer. High-molecular-weight PAHs, such as benzo[a]pyrene, cause epigenetic changes, including aberrant DNA methylation of tumor suppressor genes and histone modifications that change chromatin accessibility.¹⁴ Such epigenetic alterations may persist for several years after exposure, thereby continuing the multistep process of carcinogenesis. Additionally, exposure to PAHs is associated with systemic inflammation and increased levels of C-reactive protein and interleukin-6, which promote a pro-tumorigenic microenvironment.¹⁵ Mechanistic connections between

environmental exposures and molecular changes provide a biological rationale for integrating PAH biomarkers into comprehensive risk-assessment frameworks.

2.2. Epidemiological data linking polycyclic aromatic hydrocarbons to prostate cancer

Epidemiological studies have demonstrated an association between occupational PAH exposure and increased prostate cancer risk. A systematic review by Moradpour *et al.*¹³ reported an increase in the incidence of prostate cancer in employees in aluminum production, coal gasification, and coke production industries, where workers are exposed to high levels of PAH. These results are supported by the literature on biomarkers that monitor urinary PAH metabolite levels, indicating that they correlate positively with prostate cancer risk, especially for high-molecular-weight PAHs (e.g., benzo[a]pyrene).¹⁶

In African settings, very few studies have investigated the associations of PAH and prostate cancer despite the large exposure load. Nsonwu-Anyanwu *et al.*¹⁷ found high urinary concentrations of PAH metabolites in urban and rural areas, with concentrations, in turn, dependent on proximity to industrial facilities. The oil refining and gas flaring processes in Port Harcourt, one of the largest petrochemical hubs in the Niger Delta region of Nigeria, have very high levels of environmental PAHs.¹⁸ These environmental conditions lead to the need for an integrated exposure assessment in prostate cancer epidemiology among African groups.

However, some decisive limitations need to be considered in the existing evidence base. A majority of studies that found a relationship between PAH and prostate cancer are cross-sectional or retrospective case-control studies, which have limitations in proving causality. Prospective cohort studies that utilize longitudinal exposure to PAH and the outcome of prostate cancer are limited, particularly in the African populations. In addition, exposure misclassification is a serious problem because of temporal changes in PAH exposure and the comparatively short half-lives of urinary metabolites (hours to days). Most studies have not adequately accounted for confounding factors such as socioeconomic status, occupational coexposures, and lifestyle factors. These constraints highlight the necessity of prospective studies with repeated measurements of exposure to PAH biomarkers and complete accounting for confounding factors before PAH biomarkers can be included in clinical risk stratification algorithms with confidence.¹⁹

2.3. Analysis of urinary polycyclic aromatic hydrocarbon metabolites in clinical practice

Urinary biomonitoring is a non-invasive method for

assessing recent exposure to PAHs and their metabolites, including 1-hydroxypyrene.²⁰ The identification of multiple PAH metabolites enables high-sensitivity, high-specificity analysis of urine samples using advanced analytical methods such as gas chromatography–flame ionization detection, gas chromatography–mass spectrometry, high-performance liquid chromatography–fluorescence detection, and liquid chromatography–tandem mass spectrometry (LC-MS/MS).¹⁶

Polycyclic aromatic hydrocarbon exposure assessment would aid in risk stratification, identifying men with prostate cancer who require intensified monitoring or early therapeutic intervention. However, clinical implementation requires methodological standardization of sample collection time, metabolite choice, and exposure time.²¹ Longitudinal studies involving correlations of urinary PAH metabolic levels with incidence and aggressiveness of prostate cancer are urgently needed to determine the causality and the clinically significant levels of exposure.

The financial and technical resources required for PAH metabolite analysis are a major limitation for implementation in resource-constrained environments. The instrumentation may require more than US\$200,000 for liquid chromatography–tandem mass spectrometry, with recurring costs for maintenance, reagents, and skilled personnel. Pragmatic options could include developing partnerships with regional reference laboratories, focusing on sentinel surveillance among high-exposure groups (e.g., petrochemical workers in Port Harcourt), or simply starting with simpler exposure assessment instruments, such as occupational history questionnaires and residential proximity mapping to industrial sources, and developing analytical capacity progressively.²² Strict cost-effectiveness evaluation of PAH biomonitoring in regular prostate cancer screening and screening of high-risk groups is still needed in African healthcare settings.

3. State-of-the-art cytological prostate cancer detection

3.1. Post-digital rectal examination urine cytology and cell block preparation

Detecting biomarkers in urine after DRE is a minimally invasive technique that leverages prostate massage to release cells and secretions into the urine.²³ Conventional voided urine cytology, however, has low sensitivity for detecting prostate cancer due to limited cellular yield and challenges in sample preservation. Nonetheless, the recovery of prostatic cells is higher after DRE urine collection, thereby improving diagnostic quality.²⁴

Urine cell block, prepared by concentrating cellular material, allows histopathological and immunohistochemical analysis and molecular testing similar to that of tissue biopsies.²⁵ This is done through centrifugation, fixation in either neutral-buffered formalin or alcohol-based preservatives, and paraffin embedding, producing sections that can be stained in various ways. Cell blocks are better at preserving cellular architecture than standard cytological smears. The morphological evaluation of nuclear pleomorphism, nucleolar prominence, and architectural patterns indicative of malignancy is also possible with cell block preparations.²⁶

Several recent studies have supported the use of post-DRE urine cell blocks for detecting prostate cancer. According to McKiernan *et al.*,²⁷ the sensitivity of urine cell morphology combined with molecular markers was 72–84% in the detection of clinically significant cancer. The methodology shows particular potential for serial monitoring, in which active surveillance programs do not require repeated invasive biopsies.²⁸

The evidence must be interpreted cautiously due to several notable methodological flaws. Post-DRE urine cytology, by itself, has a sensitivity of 40–60% and a specificity of 70–85%.²⁹ Cellular adequacy is of great importance to performance, with up to 20–30% of samples considered inadequate due to poor cellularity, hematuria, or poor preservation. The inter-observer variability remains a challenge: kappa coefficients for distinguishing benign from malignant cells range from 0.60 to 0.75, indicating moderate agreement.³⁰ Furthermore, the majority of validation studies were conducted in Western cohorts, with limited evidence in African populations, where anatomical differences in the prostate, infectious burden, and inflammatory milieu may affect test performance. The post-DRE urine cytology, therefore, must be considered a supplemental, but not independent, diagnostic modality, to be applied as part of a multimodal assessment. [Table 1](#) outlines the overall diagnostic performance of cytological and biomarker methodology.

3.2. Expressed prostate secretion cytology

Expressed prostatic secretions (EPS) represent a direct sample of prostate ductal contents enriched with epithelial cells and secretory products.³¹ EPS cytology enables evaluation of cell atypia, inflammatory infiltrates, and the presence of pathogenic agents in relation to chronic prostatitis, a risk factor for prostate cancer.³²

Cytology analysis of the EPS samples includes cellular and nuclear morphology, chromatin distribution, and nuclear cytoplasmic ratios. The characteristic features of malignant cells are usually nuclear enlargement at the

expense of the cytoplasm, hyperchromasia, irregular nuclear shapes, and large nucleoli.³³ Nevertheless, high-grade prostatic intraepithelial neoplasia and invasive carcinoma cannot be differentiated on cytology alone, as this requires molecular markers.³⁴

Post-DRE urine analysis and EPS cytology should be used together to increase diagnostic yield by providing complementary sampling of various prostate compartments. EPS mostly includes central zone material, whereas post-DRE urine samples include peripheral zone cells where most cancers originate.³⁵ Uniformity in the method of cytology sample collection and cytological benchmarks is vital to clinical uptake and utility.

Collection of expressed prostatic secretions faces practical challenges in daily clinical practice despite its theoretical merits. The process requires aggressive prostate massage, which may cause pain to patients and is time-consuming, usually taking 5–10 min, on average, per patient. Adequacy rates of samples differ (50–80%) depending on the operator's technique and patient-related factors such as prostate size, inflammatory status, and previous interventions.³⁶ Moreover, most medical education programs in Africa lack standardized guidelines for collecting EPS, a crucial capacity-building gap that needs to be addressed before the technique is introduced on a large scale. Therefore, EPS cytology will most likely become feasible in specialized centers with dedicated cytology services, but not in the general, resource-constrained environments. Strong cost-effectiveness studies comparing EPS cytology with traditional tissue biopsy are urgently needed to inform implementation strategies in the African context.

3.3. Multiparametric magnetic resonance imaging

Although this review focuses mainly on molecular and cytological diagnostics, it is important to recall the well-established role of mpMRI in modern pathways for detecting prostate cancer. mpMRIs are highly sensitive (85–95%) and moderate specificity (70–85%) in relation to clinically significant prostate cancer (Gleason ≥ 7), and are utilized in high-resource settings in risk stratification and MRI-targeted biopsy guidance.³⁶ A combination of mpMRI with PSA-based screening and molecular biomarkers now forms the standard of care in most developed nations, and it has been suggested to reduce the detection of clinically insignificant malignancies and improve the identification of aggressive pathology.

Nevertheless, there exist substantial obstacles to the implementation of mpMRI in sub-Saharan Africa, such as a lack of 3-Tesla MRI scanners (approximately less than 50 in Nigeria with a population of 220 million), a

lack of trained genitourinary radiologists (which is highly disadvantageous), high overall costs (per scan, which is 300–800 US dollars, equivalent to approximately 3–8 months of minimum wage), and a lack of standardized reporting systems, such as the Prostate Imaging Reporting and Data System with associated training programs.³⁷ These limitations mandate the application of other diagnostic methods, focusing on molecular- and cytological-based techniques that can be easily applied in a resource-constrained environment with limited laboratory infrastructure. With the development of imaging infrastructure and declining costs, a combination of mpMRI/ multimodal molecular approach, as proposed in this review, will be a significant leap forward in diagnostic algorithms in African populations. Until then, the tiered approach introduced in this review emphasizes diagnostic modalities that can be introduced using the existing resources and, at the same time, develop the capacity for more advanced imaging.

4. Immunohistochemical biomarkers in prostate cancer

4.1. *ERBB2*

ERBB2 (HER2/neu) is a gene associated with cell proliferation and differentiation that encodes a receptor tyrosine kinase. Although *ERBB2* amplification and overexpression have been proven to be important targets of therapy in breast and gastric cancers, its role in prostate cancer has become a subject of growing interest.³⁸ *ERBB2* amplification is found in approximately 2–5% of primary prostate cancers, with greater rates in castration-resistant prostate cancer (CRPC) and metastatic disease.³⁹

ERBB2 amplifications are associated with aggressive histology, higher Gleason scores, and a poor clinical prognosis.⁴⁰ Mechanistically, *ERBB2* activation can bypass androgen receptor signaling, contributing to treatment resistance. Recent clinical trials have also investigated HER2-targeted therapies, including trastuzumab and pertuzumab, in CRPC with *ERBB2* amplification and have shown initial efficacy.⁴¹

Standardized scoring systems modified for breast cancer protocols are used to assess the intensity of membranous staining and the percentage of positive tumor cells in IHC of HER2.⁴² A positive HER2 status can be used to identify patients with prostate cancer who are eligible to receive HER2-targeted therapies. Nevertheless, clinically relevant expression thresholds and predictive cutoffs need to be further defined after validation across various populations, including African populations with poorly described *ERBB2* prevalence.

The analysis of HER2 as a biomarker shows that the existing body of evidence on prostate cancer has numerous limitations. Unlike breast cancer, where HER2 IHC is a well-standardized technique with established scoring scales (0, 1+, 2+, 3+) and strong predictive capabilities for therapy response, no consensus exists on scoring procedures, cutoff points, or clinical utility in prostate cancer.⁴³ Its low frequency in *ERBB2* amplification (2–5% in primary tumors) further reduces its usefulness as a screening biomarker. However, higher *ERBB2* levels in CRPC (10–15%) and association with metastatic disease highlight the potential benefits of using it to select patients with advanced-stage disease.⁴⁴

The anti-HER2 therapy trials conducted in prostate cancer have not achieved significant response rates (10–30% objective response) even in cases with *ERBB2* amplification, which is significantly lower than the 40–60% response rates observed in HER2-positive breast cancers.⁴² This decreased activity can be due to inherent variations in tumor biology, decreased levels of *ERBB2* in prostate cancer compared with breast cancer, or inappropriate combination regimens. Notably, studies investigating *ERBB2* have never directly examined prevalence, expression patterns, and therapeutic response in African populations, a significant knowledge gap that limits the uptake of evidence. *ERBB2* testing, therefore, should currently be considered exploratory (Tier 3) rather than standard of care and should be performed only for metastatic CRPC patients in centers where targeted therapies and clinical trial opportunities are available. Table 1 shows the classification of implementation tiers.

4.2. *CDK12*

CDK12 controls transcription elongation and RNA splicing and is essential for gene expression in the DNA damage response (DDR) pathway.⁴⁵ Biallelic *CDK12* deregulation is found in about 3–7% of primary prostate cancer and 5–10% of CRPC metastases, with a distinct molecular subtype.⁴⁶

The genomic features of *CDK12*-deficient tumors include focal tandem duplications, high tumor mutational burden, and neoantigen load.⁴⁷ These cancers have distinct immune checkpoint inhibitor vulnerabilities, making them more sensitive to these agents as they express immunogenic neoantigens.⁴⁸ In addition, synthetic lethal interactions between *CDK12*-mutant prostate cancers and DDR deficiencies suggest a favorable response to poly(ADP-ribose) polymerase (PARP) inhibitors.⁴⁹

Detection of *CDK12* loss is challenging in IHC due to the limited specificity of available antibodies and variable expression patterns. Next-generation sequencing (NGS)-

based molecular testing is the preferred method for detecting *CDK12* alterations.⁵⁰ However, cost-effective alternatives could be explored in resource-limited settings involving IHC-based surrogate markers or targeted sequencing panels. Determining *CDK12* status can guide treatment options, especially regarding immunotherapy and eligibility for a PARP inhibitor.

4.3. *BRCA2*

The *BRCA2* tumor suppressor gene, which encodes a protein required for the homologous recombination DNA repair pathway, has germline mutations occurring in 1–2% of all prostate cancer cases and 5–6% of metastatic prostate cancer.⁵¹ Men with a germline *BRCA2* mutation have a very high risk of prostate cancer (relative risk 5–8), are diagnosed earlier, and present with more aggressive phenotypes.⁵²

BRCA2-mutant prostate cancer has distinctive histopathologic characteristics such as intraductal carcinoma patterns, high tumor grades, and increased potential for metastasis.⁵³ Notably, *BRCA2* loss confers sensitivity to platinum chemotherapy and PARP inhibitors through synthetic lethality. The PROfound trial demonstrated superior radiographic progression-free survival with olaparib compared to androgen receptor pathway inhibitors in *BRCA1/2*-mutated metastatic CRPC.⁵⁴

Assessment of *BRCA2* protein expression and loss of nuclear staining may indicate biallelic inactivation.⁵⁵ However, definitive molecular characterization requires germline and somatic mutation testing using sequencing. Current guidelines recommend that genetic testing should be offered to all males with metastatic prostate cancer, and considered for high-risk localized disease to identify those who may benefit from PARP inhibitor therapy and inform eligibility for cascade family testing.⁵⁶

BRCA2 mutation spectra in African populations differ from those in European and Asian populations, with specific founder mutations in certain ethnic groups.⁵⁷ A comprehensive characterization of *BRCA2* variants

5. Genomic profiling

The modern narrative of using genomic profiling in the framework of prostate carcinoma introduces a critical point of intersection of genetic determinism and therapeutic responsiveness. The *ATM* and *BRCA2* genes are central to this framework, with aberrations having important prognostic and predictive implications. By mapping the expression patterns and mutational landscapes of these loci, researchers can enhance mechanistic understanding of DDR pathways to inform precision-based interventions.

in Nigerian populations remains limited, underscoring research gaps and priorities for operationalizing precision oncology.

5.1. *BRCA2*: Tier 1 genomic evidence and implementation challenges

BRCA2 is the most clinically validated biomarker discussed in this review and can reasonably be classified as Tier 1 (ready to use). Evidence from phase 3 trials has shown substantial clinical benefit from PARP inhibitor therapy in *BRCA2*-mutant metastatic CRPC, with hazard ratios for radiographic progression-free survival ranging from 0.34 to 0.49 compared with standard therapy.⁶³ The PROfound trial⁵⁴ reported a 66% reduction in the risk of disease progression in patients with *BRCA1/2* alterations treated with olaparib. Current guidelines from the National Comprehensive Cancer Network, the European Association of Urology, and the European Society for Medical Oncology recommend germline *BRCA2* testing for patients with metastatic prostate cancer and consideration of testing in selected men with high-risk localized disease or a strong family history.

In African settings, however, implementation faces certain issues that need to be addressed. First, there is a high rate of variants of uncertain significance (VUS) (up to 40% of variants discovered in the African population). Second, there are acute shortages in genetic counseling services, with fewer than 50 certified genetic counselors on the African continent. Third, the costs of germline (US\$1,500–2,000) and somatic testing (US\$2,000–3,000) exceed the annual healthcare budgets of many patients. Fourth, the availability of PARP inhibitors (olaparib, rucaparib, niraparib) in most African countries is inadequate due to regulatory status, cost, and supply chain challenges. Strategic options to overcome these barriers include forming regional testing consortia to leverage economies of scale; developing task-shifting models where clinical laboratory scientists, oncology nurses, and physicians can offer simple genetic counseling under the supervision of genetic specialists through telemedicine; collaborating with pharmaceutical access programs to lower the costs of drugs; and contributing African genomic data to international databases like ClinVar and Human Heredity and Health in Africa (H3Africa) to improve variant classification. *BRCA2* testing can be prioritized despite challenges encountered during its implementation, given strong evidence of clinical utility.

5.2. *CDK12*: Genomic evidence and therapeutic implications

Although the mechanistic rationale for *CDK12* as a therapeutic biomarker is strong, its preclinical validation is

Table 1. Diagnostic performance metrics and implementation readiness classification of multimodal prostate cancer biomarkers

Biomarker/Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Evidence level	Implementation tier	Cost range (USD)	Key limitations	References
Cytological methods									
Post-DRE urine cytology (alone)	40–60	70–85	45–65	75–85	Level 2–3	Tier 2	\$50–150	Variable cellular adequacy (20–30% inadequate); inter-observer variability ($\kappa = 0.6–0.75$)	29,58,59
Post-DRE urine + molecular markers	72–84	80–92	70–85	85–95	Level 2	Tier 2	\$300–600	Requires molecular testing infrastructure; limited African validation	24,28
EPS cytology	45–70	65–80	50–75	70–85	Level 3	Tier 2	\$75–200	Variable adequacy rates (50–80%); operator-dependent; patient discomfort	36,60
Urine cell block with IHC	65–80	75–88	68–82	80–90	Level 2–3	Tier 2	\$200–400	Requires histopathology infrastructure; limited standardization	25,26
Immunohistochemical biomarkers									
ERBB2/HER2 (IHC)	60–75 ^a	85–92 ^a	15–25 ^b	95–98 ^b	Level 2–3	Tier 3	\$150–300	Low prevalence (2–5% primary; 10–15% CRPC); lack of standardized scoring; limited therapeutic validation	43,44,61
BRCA2 protein loss (IHC)	50–70	80–90	65–80	75–88	Level 2–3	Tier 2	\$150–300	Cannot distinguish germline vs. somatic; requires sequencing confirmation	55,62
Genomic/molecular biomarkers									
BRCA2 germline testing	98–100	98–100	85–95 ^c	99–100	Level 1	Tier 1	\$1,500–3,000	High VUS rate in African populations (30–40%); requires genetic counseling	56,57,63,64
BRCA2 somatic testing	95–98	96–99	80–92 ^c	98–100	Level 1	Tier 1	\$2,000–4,000	Requires adequate tumor tissue; high cost	54,63

(cont'd...)

Table 1. (Continued)

Biomarker/Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Evidence level	Implementation tier	Cost range (USD)	Key limitations	References
ATM mutation testing	95–98	95–98	70–85 ^c	96–99	Level 1–2	Tier 2	\$2,000–4,000	Therapeutic response lower than <i>BRCA2</i> ; mono vs. biallelic distinction challenging	65,66
<i>CDK12</i> mutation testing	96–99	97–99	65–80 ^c	98–100	Level 2	Tier 3	\$3,000–5,000	Low prevalence (3–7%); limited therapeutic validation; requires comprehensive NGS	67,68
Multi-gene DDR panel (NGS)	90–95	92–96	75–88	95–98	Level 1–2	Tier 2	\$3,000–5,000	High cost; requires bioinformatics; VUS interpretation challenges	69,70
Environmental biomarkers									
Urinary PAH metabolites	55–75 ^d	60–78 ^d	45–65 ^c	70–85 ^c	Level 3–4	Tier 3	\$200–500	Temporal variability; causality not established; requires LC-MS/MS infrastructure	19,22,71
Combined multimodal approaches									
PSA + cytology + <i>BRCA2</i>	85–92	88–94	82–90	90–95	Level 2	Tier 1–2	\$2,000–3,500	Combined cost; requires multiple platforms	72,73
Comprehensive multimodal (all parameters)	88–95	90–96	85–92	92–97	Level 2–3	Tier 2–3	\$4,500–8,000	High cost; implementation complexity; limited validation in LMICs	74,75

Note: Tier 1 indicates ready for implementation (strong evidence base, clinical guidelines support use, therapeutically actionable, feasible in well-equipped tertiary centers). Tier 2 requires local validation (moderate evidence, may require adaptation for African populations, selective implementation in regional reference centers). Tier 3 is in the exploratory/research stage (limited validation, experimental therapeutic implications, primarily for research settings and clinical trials). Evidence level classification: Level 1: Multiple Phase 3 randomized control trials with consistent results; meta-analyses; established clinical guidelines; Level 2: Phase 2 trials; well-designed cohort studies; some guidelines support; Level 3: Retrospective studies; case-control studies; emerging evidence; Level 4: Case series; expert opinion; mechanistic studies. ^aFor detection of *ERBB2* amplification/overexpression in prostate cancer specimens; ^bPPV/NPV for predicting response to anti-HER2 therapy (low PPV reflects low prevalence); ^cPPV/NPV for predicting response to PARP inhibitors or platinum chemotherapy; ^dFor association with prostate cancer risk (not a diagnostic test); ^eFor high versus low exposure groups, causality not established. Cost estimates typically range from 2024 to 2025 (no data from 2026 were found based on the literature search) and vary significantly by region, platform, and volume. African settings may have higher costs due to limited infrastructure and the need for external reference laboratories. Costs include reagents, equipment time, and interpretation but exclude capital equipment purchases. Abbreviations: *BRCA2*: Breast cancer gene 2; CRPC: Castration-resistant prostate cancer; DDR: DNA damage repair; DRE: Digital rectal examination; EPS: Expressed prostatic secretion; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; LC-MS/MS: Liquid chromatography–tandem mass spectrometry; LMICs: Low- and middle-income countries; NGS: Next-generation sequencing; NPV: Negative predictive value; PAH: Polycyclic aromatic hydrocarbon; PPV: Positive predictive value; PSA: Prostate-specific antigen; RCT: Randomized controlled trials; VUS: Variants of uncertain significance.

in its early stages. The linkage between *CDK12* deficiency and immune checkpoint inhibitor response is based on post hoc studies and prospective cohorts of 20–40 patients per study with response rates of 20–40%,⁴⁹ which, however, is considerably higher than the response in unselected groups of CRPC (5–15%), and remains very modest relative to absolute rates.⁷⁶ Prospective trials, e.g., the current IMPACT study,⁴⁶ are tailored to recruit *CDK12*-deficient prostate-cancer patients, but their results are not currently completely available. Consequently, the long-term consistency of the responses and the most appropriate combination of therapies are poorly defined.

The high cost of a comprehensive genomic profiling required to identify *CDK12* abnormalities, between US\$3,000 and 5,000 per sample, is a significant burden in most African environments, which is higher than the per-capita health spending in most African nations per year.^{51,67} In addition, immune checkpoint inhibitors (pembrolizumab, nivolumab) remain inaccessible in sub-Saharan Africa due to their prohibitive prices (around US\$150,000 every year), limited licensing, and the lack of reimbursement. As such, *CDK12* testing must currently be considered a Tier 3 (exploratory) biomarker, most relevant to the research setting, clinical trial enrollments, or patients who have specialized care and can afford more advanced treatments. Given the growing evidence base and increased access to drugs, moving to Tier 2 will be possible.

5.3. DNA damage response evidence in prostate cancer biology

In the cellular environment, the DDR pathway maintains genomic integrity by detecting and repairing DNA damage. Empirical observations show that germline and somatic mutations of DDR genes are both observed in approximately 20–25% of metastatic prostate cancers, making them some of the most common molecular abnormalities identified.⁷⁰ While *BRCA2* has been well-characterized for its role in homologous recombination, the *ATM* kinase extends its effects across multiple aspects of DDR signaling, contributing to cell cycle regulation and the coordination of repair machinery.⁷⁷

ATM mutations are present in 4–6% of primary tumors and 7–10% of metastatic disease cases, and are associated with aggressive phenotypes and worse clinical outcomes.⁷⁸ *ATM* deficiency interferes with homologous recombination repair and thus renders tumors sensitive to PARP inhibitor treatment as well as radiotherapy.^{63,79} Recent studies suggest that *ATM*-mutant prostate tumors might be responsive to ataxia telangiectasia and Rad3-related kinase inhibitors through synthetic lethality mechanisms involving dysregulation of checkpoint kinase.⁸⁰

The therapeutic implications of *ATM* alterations are increasingly recognized, but they require careful interpretation. Although *ATM* deficiency confers sensitivity to PARP inhibitors in preclinical models, the response rate in *ATM*-mutant prostate cancer (15–35%) is significantly lower than that in *BRCA2*-mutant disease (40–60%).⁶⁵ Such an inconsistency may be because monoallelic *ATM* loss, which is more frequent and accounts for about 60% of *ATM*-altered cases, does not completely eliminate the functional capacity of homologous recombination, whereas biallelic *BRCA2* loss causes a total functional impairment. Therefore, the clinical importance of monoallelic versus biallelic *ATM* changes is essential for predicting response to PARP inhibitors. However, this discrimination is difficult with typical sequencing methods, which are not capable of reliably detecting loss of heterozygosity or whether mutations affect both alleles.

Recent evidence suggests that functional assays, including *RAD51* nuclear foci formation assays, which directly measure homologous recombination activity, may be used with genomic sequencing to predict PARP inhibitor activity in *ATM*-mutant tumors.⁶⁶ Such functional assays, however, require fresh or frozen tumor tissue, specialized laboratory infrastructure, and technical expertise, which are not readily accessible, especially in resource-constrained environments. Current evidence supports including *ATM* testing as Tier 2 (local validation and functional correlation are needed) rather than Tier 1, as with *BRCA2*. Patients who have been shown to have biallelic *ATM* loss should therefore be given priority access to PARP inhibitor treatment, and those with monoallelic alterations should be enrolled in clinical trials to better define the therapeutic benefit.

5.4. Methods for gene expression profiling

Gene expression analysis provides quantitative measurements of mRNA transcript abundance, yielding functional genomic data that complements static DNA sequencing data. Common methods include quantitative reverse transcription polymerase chain reaction (RT-qPCR), microarray hybridization, and next-generation RNA sequencing (RNA-seq).⁸¹ RT-qPCR is the modality of choice in laboratories that prioritize cost-efficiency and require high turnaround times, particularly when implementing focused gene panels in low-resource settings. In contrast, RNA-seq provides comprehensive transcriptome coverage, which requires advanced bioinformatics infrastructure and expertise.⁸²

For the detection of *ATM* and *BRCA2* expression, the normalization to reference genes, such as *GAPDH* and *ACTB*, enables inter-sample comparison. A relative

decrease in transcript level might indicate epigenetic downregulation, while an increase in expression might indicate compensatory upregulation or activation of alternative pathways.⁸³ Integration of expression data, mutational status, and protein expression produces a comprehensive molecular description of the tumor phenotype.

Pragmatically, RT-qPCR and RNA-seq have substantial trade-offs, especially under resource-limited conditions. RT-qPCR has a very small initial capital (around US\$15,000–30,000 for thermal cyclers, RNA extractors, and associated equipment), has a quick turnaround time (4–6 hours, from sample to result), and has a small per-sample cost (around US\$20–50 including reagents and labor).⁸⁴ However, it can only identify previously known aberrations in the form of pre-selected gene sets (usually 1,050 genes) and cannot identify new aberrations, including gene fusions, splice variants, and unanticipated changes in expression. RNA-seq provides comprehensive transcriptome coverage, revealing all expressed genes at once (>20,000), fusion transcripts (e.g., *TMPRSS2-ERG*), splice variants, and new alterations. Nevertheless, it demands substantial infrastructure (≥ US\$200,000 for sequencing equipment or the ongoing cost of outsourcing), specialized bioinformatics skills (usually at the master's or PhD level), and additional per-sample costs (about US\$300–800).⁸⁵

To commence the implementation of centers in Nigeria, the following are recommended on a tiered basis: (i) start with RT-qPCR-based targeted panels with a focused strategy on well-established actionable biomarkers (*BRCA2*, *ATM*, *AR*, and the *AR-V7* splice variant) to be integrated with existing molecular pathology infrastructure in major tertiary hospitals in Nigeria, such as Rivers State University Teaching Hospital, Nnamdi Azikiwe University Teaching Hospital, and Jos University Teaching Hospital, among others; (ii) establish partnerships with international and regional sequencing facilities for comprehensive RNA-seq in selected cases (for example, through collaboration with H3Africa network, South Africa sequencing centers, or placement by international equipment manufacturers and reagent producers); (iii) build local RNA-seq capacity through equipment acquisition, training programs, bioinformatics workforce development as resources permit. This strategy balances immediate clinical utility in a resource-constrained setting with pathways to advanced capabilities.

5.5. Clinical application of DNA damage response gene profiling among African populations

A systematic description of DDR gene alterations in

African cohorts of prostate cancer patients offers important clinical and scientific opportunities. Populations of African ancestry exhibit a unique genetic structure, with greater genetic diversity than European populations, leading to distinct mutation patterns and a higher proportion of VUS.⁸⁶ In sub-Saharan African cohorts, such as the study by Jalloh *et al.*,⁸⁷ higher rates of specific DDR pathway alterations have been observed among men of West African ancestry compared to those of European ancestry, though there is limited robust comparative research.

To fill this knowledge gap, multi-center, large-scale genomic studies are required to define population-specific mutation rates, estimates of penetrance, and genotype–phenotype relationships. Accurate interpretation of VUS requires functional assays and allele frequency data in the context of the population being studied. The reference datasets being created by global initiatives (primarily the H3Africa consortium) are supporting variant classification in African populations.⁸⁸ Integrating Nigerian prostate cancer genomic data into these repositories will facilitate the translation of precision medicine throughout the continent.

The interpretation of VUS amongst Africans cannot be overemphasized and is a major obstacle to the equitable application of genomic medicine. Empirical evidence has shown that people of African descent have 2–3 times higher prevalence rates of VUS than those of European descent when variants are measured using standard databases like ClinVar or LOVD, which consist primarily of European data.⁸⁹ In the case of *BRCA2* alone, approximately 40% of the variants detected in African populations are VUS, compared with 10–15% among European populations.⁶⁴ Such a gap is explained by the systematic underrepresentation of African genomes in reference databases, the lack of functional characterization studies of African-specific variants, and the lack of comprehensive family-based studies that would enable segregation analysis to classify variants.

The high frequencies of VUS have practical clinical consequences: patients who harbor VUS are unable to receive clear counseling about their risk of cancer, and are often not eligible to participate in trials with personalized therapies that require pathogenic variants. Relatives are also deprived of cascade testing, which limits prophylaxis. Moreover, VUS creates uncertainty among clinicians and can lead to improper clinical decisions.

Various strategic directions can address the VUS challenge among African populations: (i) systematically submitting identified variants and VUS to public databases, such as ClinVar, LOVD and the *BRCA* Exchange, with associated phenotype data to create African-specific

allele-frequency repositories; (ii) forging collaborations with functional genomics laboratories (such as the H3Africa network or the Evidence-based Network for the Interpretation of Germline Mutant Alleles consortium) to conduct a study of VUS reclassification using assays like homology-directed repair, transcriptional activity assays, and protein expression/ localization studies; (iii) implementing multidisciplinary tumor boards that incorporate genetic counselors and molecular scientists/ pathologists for careful VUS interpretation using American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria adapted for population context; (iv) developing artificial intelligence and machine learning approaches for variant pathogenicity prediction that are specifically trained on diverse populations rather than predominantly European data; (v) participating in international consortia like H3Africa, the African Cancer Genetics Study, and Men of African descent and Carcinoma of the Prostate network to pool data across institutions and achieve sufficient sample size for robust statistical analysis.⁹⁰ These interventions require sustained commitment and financial resources, as well as partnerships within the region and international collaboration, and are essential for precision oncology in Africa.

6. Multimodal approaches: Integrated conceptual framework

6.1. The rationale of multimodal diagnostic strategies

Depending on a single diagnostic parameter has inherent limitations in terms of sensitivity, specificity, and predictive performance. In contrast, the synthesis of complementary streams of information (including environmental exposures [e.g., PAH biomarkers], cytomorphology, protein expression, and genomic changes) to create a complete risk profile and a robust diagnostic algorithm is called multimodal integration.⁷⁴

Assays that combine PSA with supporting biomarkers are of significant value in managing early disease and thereby reducing false positive results and refining the distinction between indolent and aggressive prostate disease conditions. Good examples of successful multimarker tests include the Prostate Health Index (phi) and the 4Kscore, which incorporate PSA isoforms and kallikrein peptides.⁹¹ A further extension of this framework to include environmental risk factors, liquid biopsy markers, and germline risk scores could increase diagnostic accuracy.

The biological basis of multimodal integration is the heterogeneity of prostate cancer, which arises through

distinct pathways driven by germline predisposition, somatic genomic changes, environmental exposures, and endogenous factors, including inflammation and immune responses.¹⁴ This complexity cannot be captured using a single biomarker, regardless of its performance characteristics. Multimodal approaches by combining data of various areas of biology (germline genetics, e.g., *BRCA2*, *ATM*), somatic alteration (e.g., *CDK12*, *ERBB2*), gene expression signatures, protein biomarkers, environmental exposures, and clinical parameters improve the discrimination between aggressive and indolent disease, prognostication accuracy, and the prediction of therapeutic response compared to a single parameter.

6.2. Risk stratification models

Modern risk stratification models increasingly use polygenic risk scores, which aggregate many genetic variants associated with prostate cancer susceptibility.⁹² An African ancestry-optimized polygenic risk score has shown predictive validity, but its performance remains below that of those developed in European populations, largely because African populations are underrepresented in genome-wide association studies.⁹³

Risk prediction accuracy can be enhanced by incorporating environmental exposure data, particularly PAH biomarker data, genetic risk scores, and clinical parameters into these models. Machine learning algorithms that use multimodal data consistently demonstrate higher predictive accuracy than traditional regression approaches.⁹⁴ However, developing these algorithms requires diverse training data to ensure they are applicable across different populations and healthcare systems.

6.3. Precision-guided therapeutic choice of treatment

Multimodal profiling is relevant for informing therapeutic decision-making by highlighting actionable alterations. Alterations in DDR pathways indicate sensitivity to PARP inhibitors, and *ERBB2* amplification suggests possible benefit from HER2-targeted treatments.⁶⁵ Moreover, eligibility for immunotherapy is determined by tumor mutational burden and microsatellite instability status.⁹⁵

Judicious prioritization of biomarkers is critically important in African contexts with limited healthcare resources. Initiating evaluation with cost-effective IHC panels before proceeding to expensive genomic profiling optimizes resource allocation without compromising diagnostic accuracy.⁹⁶ Establishing collaborative networks between Nigerian centers and international reference laboratories may enhance the availability of advanced molecular diagnostics during implementation phases.

6.4. Stepwise implementation strategy for resource-constrained settings

The implementation of multimodal diagnostics in Nigeria and the sub-Saharan African region, in general, must be carried out in a pragmatic, phased approach that balances clinical utility with resource constraints. The tiered strategy presented in Figure 1 outlines a progressive capacity development plan.

Tier 1 should be prioritized in implementation since it embodies diagnostics supported by the strongest evidence base. In the context of this review, Tier 1 encompasses two categories: (a) diagnostics that can be executed alongside current infrastructure in tertiary hospitals, including (i) standardized PSA testing with reflex to free-to-total PSA ratio; (ii) systematic post-DRE urine collection with cell block preparation and basic cytological analysis; and (iii) a full clinical evaluation with family history and occupational exposure documentation; and (b) *BRCA2* germline and somatic mutation testing, which has Tier 1 evidence support (multiple Phase 3 randomized controlled trials, NCCN/EAU/ESMO guideline endorsement) and is therapeutically actionable for PARP inhibitor eligibility. Although *BRCA2* mutation testing requires partnerships with regional or international molecular laboratories and genetic counseling infrastructure that may not yet exist at all centers, its strong evidence base and direct therapeutic implications justify Tier 1 classification. Implementation should be initiated through partnerships with accredited reference laboratories, with progressive development of local sequencing capacity. The category (a) measures can be implemented immediately in significant centers (Port Harcourt, Lagos, Ibadan, Nnewi, Abuja) and further disseminated to secondary centers through training programs, while category (b) can be initiated concurrently through laboratory partnerships.

Tier 2 requires more substantive investment to implement diagnostics with moderate evidence that may require adaptation for African populations, and should prioritize: (i) targeted IHC panels, including *BRCA2* protein expression as a surrogate screening tool and *ATM* protein assessment, to identify candidates for confirmatory genomic testing; (ii) *ATM* mutation testing, which has Tier 1-2 evidence but lower therapeutic response rates than *BRCA2*, requiring local validation and functional correlation; (iii) genetic counseling services through the use of task-shifting models, where trained professionals and oncology nurses undertake counseling via telemedicine under the guidance of a genetic specialist; and (iv) post-DRE urine cytology combined with molecular markers for enhanced diagnostic performance in regional reference centers.

The Society for Cellular Pathology Scientists of Nigeria, the Nigerian Society of Urological Surgeons, and the African Organization for Research and Training in Cancer, in collaboration with the West African Health Organization, should consider negotiating group pricing with the testing diagnostic laboratories and place a broad-based quality assurance program. The estimated timeframe for the implementation of the Tier 2 interventions is two or three years, depending on financial and technical support.

Tier 3 implementation identifies aspirational goals that require significant infrastructure investment; these programs should be determined through multidisciplinary research projects and controlled clinical trials rather than direct large-scale clinical implementation. The major features of Tier 3 are: (i) comprehensive genomic profiling based on the use of extensive gene panels; (ii) systematic PAH biomonitoring in high-exposure populations; and (iii) access to the latest targeted therapeutics in pharmaceutical programs and international clinical trial consortia. It is possible to develop Tier 3 capabilities through strategic partnerships with international oncology centers, active involvement in global clinical trials, and targeted investment in NGS infrastructure and bioinformatics skills, which can be undertaken by a selected number of centers of excellence, potentially five or six centers initially. It is expected that Tier 3 progress will take between five and 10 years, requiring long-term capital expenditure.

Quality assurance factors are always at the forefront, regardless of their tier. They need to include: (i) participation in external quality assessment schemes of all diagnostic modalities; (ii) regular testing of proficiency of cytology and IHC interpretation; (iii) high quality assurance of NGS assays with well-characterized reference materials; (iv) standard operating procedures based on international guidelines, e.g. College of American Pathologists, United Kingdom National External Quality Assurance Service, and European Molecular Genetics Quality Assurance Network, although adjusted to local practical realities; and (v) the access to proficiency testing materials and expertise through formal collaborations with recognized quality assurance organizations, such as the African Organization for Research and Training in Cancer and the African Society of Laboratory Medicine.

6.5. Operational integration of multimodal data streams in clinical decision-making

The real benefit of multimodal diagnostics lies in the ability to intelligently integrate dissimilar data streams into the clinical decision-making process. The operational principles of such integration are depicted by the following exemplary clinical scenarios (Table 2).

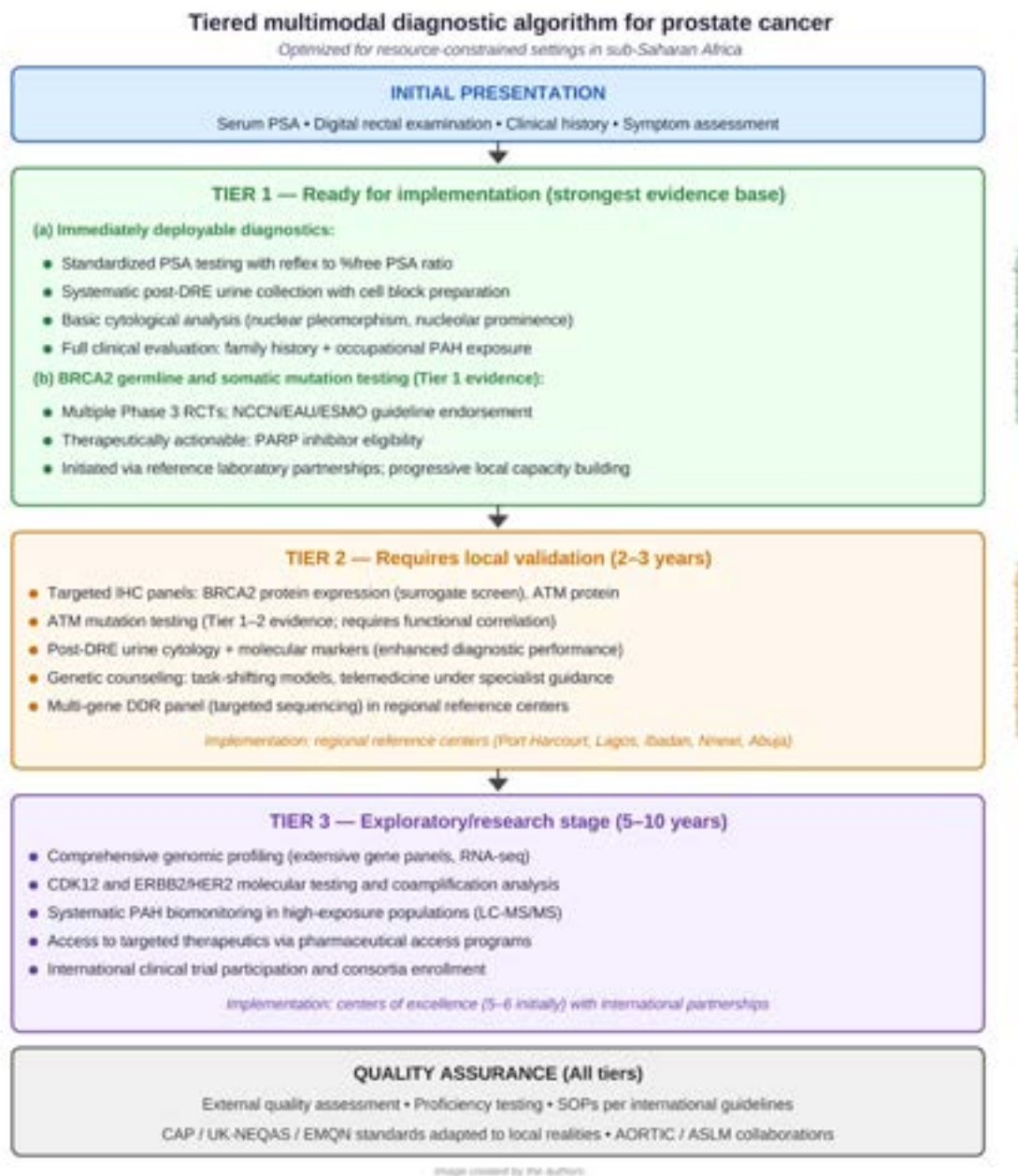


Figure 1. Tiered multimodal diagnostic algorithm for prostate cancer optimized for resource-constrained settings in sub-Saharan Africa. Tier 1 includes immediately deployable clinical and cytological tools, such as percent-free prostate-specific antigen (PSA) measurement, digital rectal examination, and post-digital rectal exam urine cytology block preparation. Tier 2 incorporates validated molecular and genetic diagnostics that require specialized infrastructure, such as breast cancer gene 2 (BRCA2) immunohistochemistry screening, targeted germline/somatic testing, and genetic counseling. Tier 3 represents exploratory or research-intensive approaches that require advanced laboratory capacity and international collaboration, including comprehensive genomic profiling, polycyclic aromatic hydrocarbon (PAH) biomonitoring, *CDK12* and *ERBB2* coamplification, and clinical trials. Image created by the authors using Python 3.12 with Matplotlib v3.10.8.

6.5.1. Clinical case example 1: The environmental–molecular integration in early detection

This section discusses the case of a 58-year-old male petroleum refinery worker with lower urinary tract

symptoms at Port Harcourt.^{97–99} Clinical examination revealed: (i) 25 years of employment in the petrochemical industry with assumed high exposure to PAH; (ii) living near gas-flaring facilities; (iii) PSA level of 8.5 ng/mL with a free/total ratio of 12%; (iv) DRE showing a firm nodule

of the right peripheral zone; (v) post-DRE urine cytology showing atypical cells with higher nuclear-cytoplasmic ratio, more prominence in the nucleoli with sufficient cellular material for cell block IHC; and (vi) urinary PAH metabolite with elevated 1-hydroxypyrene (2.5 µg/g creatinine (>95th percentile for reference population).

A confluence of high-risk environmental exposure, considerable family history, high PSA/low free PSA fraction, abnormal DRE, and abnormal cytology is an indication of a high pre-test probability of clinically significant prostate cancer. With a possible hereditary element being recognized, the following diagnostic and treatment plan was followed:

- (i) *BRCA2* loss screening (IHC of the urine cell block): A positive result showed loss of nuclear *BRCA2* staining on atypical cells.
- (ii) Prostate biopsy to definitively diagnose: A positive result confirming adenocarcinoma with a Gleason score of 4 +3 = 7 (ISUP Grade 3), including an intraductal carcinoma component that raises the suspicion of a *BRCA2*-associated phenotype.
- (iii) Germline *BRCA2* testing: Identified pathogenic *BRCA2* mutation (c.5946delT).
- (iv) Treatment selection: Given the aggressive histology and *BRCA2* mutation, the patient was eligible for definitive treatment; radical prostatectomy versus radiotherapy plus androgen deprivation therapy (ADT) with consideration of platinum-based chemotherapy if metastatic progression occurs, and future eligibility for PARP inhibitors in castration-resistant settings.
- (v) Genetic counseling and cascade testing: First-degree relatives were offered genetic counseling and predictive testing; two brothers identified as mutation carriers and enrolled in an enhanced screening program.

The case is a good example of how environmental risk assessment, cytological methods, IHC screening, and genomic confirmation can be used synergistically to identify high-risk groups, early diagnostic indicators, molecular changes, and specific therapeutic stratification, as well as familial cascade screening.

6.5.2. Clinical case study 2: Molecular profiling of metastatic disease in clinical therapy choices

A 65-year-old patient with metastatic CRPC had disease progression on enzalutamide after 14 months.¹⁰⁰⁻¹⁰⁵ Baseline staging revealed:

- (i) PSA at progression: 45 ng/mL (from nadir of 2.1).
- (ii) Imaging: Multiple new bone metastases on a bone scan, retroperitoneal lymphadenopathy on computed tomography.

- (iii) Prior treatments: Primary ADT (for two years), then enzalutamide for 14 months.

Molecular profiling results indicated:

- (i) Tissue-based NGS on archival diagnostic biopsy: Biallelic *ATM* loss (germline pathogenic variant + somatic loss of heterozygosity); *BRCA2* wild-type; *CDK12* wild-type; tumor mutational burden: five mutations/Mb (intermediate); microsatellite stable.
- (ii) Germline testing: Confirmed *ATM* germline pathogenic variant (c.5932G>T)
- (iii) Functional assessment (*RAD51* foci formation assay, if available): Reduced *RAD51* foci suggesting impaired homologous recombination.

The presence of biallelic *ATM* loss, in combination with functional evidence of deficiency in homologous recombination, suggests possible sensitivity to PARP inhibitors, although with less frequent responses than in *BRCA2*-mutant disease (estimated 20–30% versus 40–60%). Discussed therapeutic options included:

- (i) PARP inhibitor therapy (olaparib or rucaparib) as the preferred modality given the molecular profile that, although it has modest expected response rates, has a pharmaceutical access program for olaparib.
- (ii) Platinum-based chemotherapy (carboplatin plus docetaxel) as an alternative that can be used, given intermediate tumor mutational burden and microsatellite-stable status.
- (iii) Immunotherapy, which is unfavorable given the intermediate tumor mutational burden and microsatellite-stable status.
- (iv) Conventional chemotherapy (docetaxel alone): Fallback if targeted therapy is unavailable.

The patient was enrolled in a pharmaceutical access program for olaparib, which was closely monitored for response to therapy. Three months after the start, PSA decreased to 12 ng/mL, a 73% drop, and pain also improved, indicating clinical benefit. PARP inhibitors were continued unless the disease progressed.

This case study demonstrates the use of molecular profiling to inform treatment regimen selection and the nuanced interpretation of *ATM* loss, including biallelic loss, and the functional confirmation of loss supports targeted therapy despite lower evidence than for *BRCA2* in advanced disease.

6.5.3. Clinical case analysis case 3: Multimodal monitoring in active surveillance

This section presents the case of a 62-year-old male patient diagnosed with adenocarcinoma of the prostate. Clinical findings included a Gleason score of 3 + 3 = 6 (International

Society of Urological Pathology Grade 1), a PSA value of 6.2 ng/mL, low tumor volume (2 of 12 cores positive, less than 50% core involvement), and a clinical stage of T1c. Active surveillance was selected as the management strategy. The clinical question is how multimodal approaches can be utilized to optimize surveillance while minimizing the need for repeated biopsies. Multimodal monitoring protocol included:

- (i) Serial PSA measurement with 3–6 months intervals, with a stringent computation of PSA kinetics, including doubling time and velocity.
- (ii) A post-DRE urine cytology and cell block examination, performed at six-month intervals, to determine the presence of high-grade cellular morphology.
- (iii) Annual, overall clinical evaluation, which included repeated DRE and systematic symptom evaluation
- (iv) mpMRI conducted at 12 months to assess radiographic progression.

The PSA curve was stable over the 24 months of surveillance (6.2 to 5.8 to 6.5 ng/mL); urine cytology showed unchanged bland cellularity with no features of high-grade cells; and DRE remained unchanged. In this regard, the patient remained under active surveillance, thereby eliminating the risks and financial overheads associated with unnecessary biopsies.

At the 30-month mark, PSA had increased to 9.8 ng/mL (doubling time: 18 months), and urine cytology showed high-grade features, including large nucleoli and irregular nuclear contours. The concordance between PSA kinetics and cytological findings suggests possible disease progression or grade evolution. In this regard, the management plan would involve repeat multiparametric MRI (where available) and/or a diagnostic biopsy. If reclassification to Gleason $3 + 4 = 7$ is confirmed, the patient would exit the active surveillance protocol and transition to definitive therapeutic intervention.

The case demonstrates that longitudinal multimodal surveillance, including the dynamics of PSA and cytology, can help reduce biopsy frequency within the framework of active surveillance without compromising sensitivity to the clinically significant transition, which is especially important in regions where multiparametric MRI is not readily available.

This model of operation shows that multimodal integration is not just additive; it is synergistic, yielding more discriminating information than a single parameter. This individualized clinical decision-making, on a case-by-case basis, is nuanced by risk profiling.

7. Considerations for implementation in the Nigerian setting

7.1. Healthcare infrastructure and laboratory capacity development

Nigerian healthcare systems face significant infrastructural constraints, including a lack of advanced diagnostic testing equipment, unreliable supply of reagents and electricity, and limited specialized staffing in the midst of a teeming youth population.¹⁰⁶ Although baseline infrastructure exist in tertiary centers including those in Nnewi (Nnamdi Azikiwe University Teaching Hospital) and Rivers State University Teaching Hospital, Port Harcourt (representing the regions with the highest and third highest incidence of prostate cancer in Nigeria) where baseline histopathology, requisite molecular biology competence and basic IHC competency are in place, there is a need to embark on extensive capacity building in specialized molecular methods.

Sustainable implementation depends on strategic initiatives, such as promoting South–South collaborations (partnerships with South Africa, Kenya, and other African centers with advanced capabilities), leveraging telemedicine platforms for genetic counseling and pathology consultations, and prioritizing the acquisition of strategic equipment, focusing on multipurpose platforms.⁸⁷ Regional organizations, such as the African Organization for Research and Training in Cancer and its associated networks, play central roles in facilitating knowledge transfer and quality assurance programs.¹⁰⁷

Specific infrastructural priorities of centers in Nigeria include: (i) regional molecular pathology centers, potentially six centers strategically located to serve the six discrete geo-political zones, equipped with PCR, automated IHC platforms, and background sequencing infrastructure; (ii) creation of transport networks linking peripheral centers with regional centers to send specimens to regional centers where advanced testing is possible; and (iii) the development of bioinformatics capability through dedicated training programs with international partners, with the resultant aim of developing local abilities in variant interpretation. Such infrastructure projects require a 3–5-year investment of approximately US\$2–5 million per regional hub, serving a population of 30–50 million people each, and would be a cost-effective long-term investment in enabling precision oncology.

7.2. Environmental and occupational health surveillance systems

The petrochemical industry in Port Harcourt and the industrial mosaic of Nnewi produce distinct environmental

exposure profiles; therefore, they should be systematically monitored. Correlation studies on exposure–disease associations with the environment can be facilitated by harmonizing environmental health monitoring with robust cancer registries. Partnerships with occupational health departments, environmental agencies, and community stakeholders can enhance exposure assessment and support the implementation of public health interventions.¹⁰⁸

Notably, to conduct an environmental surveillance, the following specific recommendations are to be adhered to:

- (i) Conducting sentinel surveillance programs in high-exposure zones, including the Port Harcourt petrochemical industrial area and the Nnewi metalworking districts, which involve a systematic PAH biomonitoring of exposed workers and community residents.
- (ii) Linking environmental exposure data with the prostate cancer registry using unique identifiers, whilst still protecting the privacy of individuals.
- (iii) Implementing occupational exposure registries that document duration and intensity of PAH exposure in relevant industries.
- (iv) Conducting community-based exposure assessment studies using questionnaires, geographic information systems mapping of industrial sites, and biomarker sampling.
- (v) Collaborating with Nigerian environmental agencies (Federal Ministry of Environment, State Ministries of

Environment, and environmental protection agencies) to monitor ambient air and water PAH levels in high-risk areas.

Such surveillance services would provide population-level information to support prevention strategies and individual-level information to support risk stratification in screening programs.

7.3. Genetic counseling and ethical considerations

Germline genetic testing also requires a robust genetic counseling system to obtain informed consent, support proper interpretation of results, and provide psychosocial support. The lack of trained genetic counselors in Nigeria underscores the need to employ task-shifting models and use telegenetics consultations.¹⁰⁹ Ethical systems need to be sensitive to cultural issues related to the disclosure of genetic information, intra-family communication, and data privacy protection.

Culturally sensitive educational resources, combined with community outreach, would increase understanding of the advantages and limitations of genetic testing. It is essential to address existing stereotypes and ensure fair access across different socioeconomic levels to ensure ethical precision medicine practice.¹¹⁰

Particular interventions to overcome genetic counseling gaps encompass: (i) the development of task-shifting models, whereby trained and licensed clinical laboratory scientists, oncology nurses, and medical social

Table 2. Decision integration matrix

Environmental risk	Cytology	IHC/Molecular	Clinical action
High PAH + occupational	Atypical cells	BRCA2 protein loss	Tier 2: Germline testing + enhanced surveillance
Low exposure	Normal cytology	Not indicated	Standard screening protocol
High PAH + family history	High-grade cells	BRCA2 mutation confirmed	Immediate biopsy + aggressive treatment + cascade testing
Moderate exposure	Atypical cells	Normal IHC	Repeat cytology in three months + clinical correlation
Any exposure level	Suspicious cytology	CDK12 mutation + high TMB	Consider immunotherapy eligibility + research trial
High PAH	Normal cytology	Not done	Annual cytology surveillance in high-risk populations

Abbreviations: BRCA2: Breast cancer gene 2; PAH: Polycyclic aromatic hydrocarbon; TMB: Tumor mutational burden.

workers/ clinical psychologists trained in genetics offer basic genetic counseling (discussing the purpose of testing, informed consent, and the interpretation of results) under the guidance of the genetic specialists through telemedicine platforms; (ii) the development of culturally-specific educational resources in the main languages (Ijaw, Yoruba, Igbo, Hausa, and Pidgin English) of Nigeria which clarify the concept of hereditary cancer syndromes, cascade testing, and implications for family members; (iii) the establishment of zonal genetic counseling services co-located with the molecular pathology laboratory hubs that provide both in-person and telemedicine consultations; (iv) the training of oncologists and urologists in basic genetic counseling principles for integration into clinical practice; and (v) partnerships with international genetic counseling programs for training and complex case consultation.

The ethical considerations particular to the Nigerian context include:

- (i) The informed consent procedures should consider the different literacy levels and guarantee the understanding, which may be via visual aids and teach-back techniques.
- (ii) The communication with the family about genetic risk should be culturally sensitive, looking at the extended family structures and the potential effects on marriage opportunities, especially among younger members of the family.
- (iii) The protection of data privacy should address the issue of genetic discrimination in the job market and insurance, but such protection is not yet well established in Nigerian legislation; thus, there is a need to advocate for the policy.
- (iv) Equitable access requires addressing socioeconomic barriers, potentially through tiered pricing, pharmaceutical assistance programs, and public sector subsidies for testing.
- (v) Return of research results from genomic studies requires clear policies about feedback, validation requirements for practical uptake of the findings, and counseling support that would be needed.

8. Future directions and research priorities

8.1. Prospective biomarker validation studies

Validation of biomarkers in Nigerian cohorts would determine the diagnostic performance of integrated multimodal strategies compared with standard procedures. The main endpoints are sensitivity, specificity, positive predictive value, and the potential to reduce unnecessary biopsies. The longitudinal cohorts observed for the changes in biomarkers during active surveillance and treatment

would provide useful information for disease monitoring.

Studies of priority should entail: (i) a prospective, multi-center cohort study evaluating post-DRE urine cytology paired with molecular markers in Nigerian men undergoing prostate biopsy (intended $n = 500$ – $1,000$) to establish sensitivity and specificity in an African population and help identify the optimal combinations of biomarkers; (ii) a case-control study of urinary PAH metabolites comparing prostate cancer cases with age-matched controls in high-exposure (Port Harcourt) versus low-exposure regions to quantify exposure–disease associations; (iii) registry-based study linking germline *BRCA2/ATM* testing results with treatment outcomes to determine predictive value for PARP inhibitor response in Nigerian cohort; and (iv) prospective cohort study of men in active surveillance using serial multimodal assessment (PSA kinetics + urine cytology + clinical parameters) to determine optimal monitoring strategy and reduce biopsy frequency.

8.2. Pharmacogenomics and therapeutic response studies

Understanding the relationship between genetic ancestry and population-specific variations in drug metabolism, efficacy, and toxicity is an essential research topic. Polymorphisms in the cytochrome P450 system, which influence the pharmacokinetics of ADT and chemotherapy, exhibit substantial population variation.¹¹¹ The pharmacogenomic studies of African patients with prostate cancer will serve to determine the best dosing regimen and cancer toxicity management.

Some of the key areas of pharmacogenomic research include the (i) characterization of *CYP17A1*, *CYP3A4/5*, and *UGT2B17* polymorphism frequencies in the Nigerian context and their interaction with the abiraterone and enzalutamide pharmacokinetics and pharmacodynamics; (ii) exploration of *DPYD* variants that influence fluoropyrimidine metabolism to guide the precision dosing of 5-fluorouracil in the event it is used as part of a combination regimen; (iii) evaluation of DNA repair gene polymorphisms (beyond pathogenic mutations) that may modify PARP inhibitor response; (iv) investigation of pharmacogenomics determinants of ADT-related adverse effects including cardiovascular toxicity, bone loss, and metabolic syndrome in African men; and (5) development of Nigeria-specific pharmacogenomics database to enable clinical decision support for precision dosing.

8.3. Research on health disparities

An in-depth analysis of the multilevel factors driving the disparities in prostate cancer in Nigeria, such as

socioeconomic factors, barriers to healthcare access, tumor biology, and environmental exposures, necessitates a trans-disciplinary research model. The development of scalable interventions will be informed by implementation science models for assessing the barriers and facilitators to integrating multimodal diagnostics.

Specific health disparities research questions include:

- (i) Why do Nigerian men present with the disease at a more advanced stage than Western populations? Is that because they do not present at a very early stage, or because the tumor itself has a strong aggressive phenotype, or both?
- (ii) Are genetic factors (e.g., increased rates of DDR pathway changes or unique polygenic profiles) involved in observed outcome differences?
- (iii) What is the impact of socioeconomic barriers on screening uptake and treatment adherence, such as price, travel distance to care, and health literacy?
- (iv) What is the contribution of healthcare system variables (e.g., accessibility of diagnostic services, treatment choices, expertise of specialists) to disparities in outcomes? Are culturally specific interventions, such as community health worker programs, mobile screening teams, and patient navigation, able to reduce disparities?

These questions demand a mixed-methods approach, in which quantitative epidemiologic studies are complemented by qualitative research, as both approaches will shed light on patients' and providers' perspectives.

8.4. Capacity building and training programs

Capacity building entails training personnel in specialized diagnostic methods to equip them to implement the new system. The future of sustainable precision oncology depends on developing a competent workforce across pathology, medical oncology, genetic counseling, and bioinformatics. Training programs, international fellowships, and strategic academic partnerships can be used to increase the human resource capacity. Setting up centers of excellence within institutions in Nigeria can serve as regional centers for diagnostics and training.

Refined capacity building plan should entail:

- (i) Creating formal training programs in molecular pathology and precision oncology at Nigerian schools and teaching hospitals, possibly through international collaborations (for instance, through H3Africa training programs, African Organization for Research and Training in Cancer fellowships).
- (ii) Creating short-term intensive training programs on specific techniques, such as post-DRE urine cytology,

immunohistochemical interpretation, and genetic counseling, which can rapidly increase capacity.

- (iii) Instituting train-the-trainer models so that the initial generation of trainees becomes regional trainers, creating a multiplicative effect.
- (iv) Providing international fellowships for Nigerian clinical laboratory scientists in the molecular and oncology space, as well as oncology clinicians, to gain advanced training in precision oncology with the expectation of return to establish services locally.
- (v) Developing online/distance learning modules for continuing medical education in precision oncology topics.
- (vi) Creating academic–industry partnerships where diagnostic companies provide training on their platforms in exchange for market access.
- (vii) Establishing mentorship programs, such as linking early-career Nigerian investigators with established international precision oncology researchers.

9. Conclusion

Prostate cancer is a complicated disease predisposed by genetic factors, environmental exposure, and molecular heterogeneity. The traditional diagnostic models do not provide high-quality diagnoses that would have ensured successful early diagnosis and personalized treatment, especially in African populations, which are disproportionately affected by the disease. Multimodal approaches that combine environmental risk assessment using urinary PAH metabolites, high-resolution cytological methods such as post-DRE urine cell blocks and EPS cytology, immunohistochemical analysis of *ERBB2*, *CDK12*, and *BRCA2*, and genomic profiling of DDR pathway genes are promising for improving diagnostic accuracy and personalizing therapeutic intervention.

Implementation in Nigerian healthcare requires context-specific adaptations to tackle the limitations of infrastructures, the number of personnel, and the molecular features of the population. The evidence-based incorporation of multimodal diagnostics can be achieved through strategic investment in laboratory infrastructure and research networks, as well as collaborative research aimed at validating the biomarker's performance using African cohorts. These innovations can lead to the reduction of late-stage presentation, better treatment results, and, eventually, fewer deaths due to prostate cancer in sub-Saharan Africa.

The proposed integrated strategy embodies precision medicine principles adapted to resource-constrained settings, demonstrating both feasibility and clinical utility in the overall management of prostate cancer. Future studies

of African-specific genomic backgrounds, environmental risk determinants, and health-system performance optimization measures will further enhance equal access to the latest diagnostics and treatment modalities and, consequently, overcome the existing inequality in access to state-of-the-art prostate cancer care worldwide.

Although the focus of this review is on sub-Saharan African populations, the frameworks and principles outlined are more applicable to global precision oncology implementation. The tiered implementation strategy, with a focus on cost-effectiveness, the incorporation of population-specific genomic characterization, and sensitivity to health-system context, is one of its strengths, making it applicable to other countries in the low- and middle-income sphere, as well as to underserved populations worldwide. In fact, with the global oncology community working toward the realization of health equity and universal access to precision medicine, the solutions outlined in this review (the combination of biological understanding and implementation science with cultural responsiveness) pave the way to applying developments in high-resource countries to diverse healthcare settings. With a long-term focus on capacity building and international cooperation, as well as evidence production in the heterogeneous populations, precision oncology can be a meaningful reality not only to African men with prostate cancer but also to other underserved groups worldwide.

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Conflict of interest

The authors declare that they have no competing interests.

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