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# From Discovery to Care: Implementing Long-Read Sequencing-Guided Therapy Selection in Prostate Cancer across Diverse Populations

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## ABSTRACT

Prostate cancer remains a leading cause of cancer morbidity and mortality among men worldwide, characterized by substantial genomic heterogeneity that complicates diagnosis, prognosis, and treatment selection. While short-read sequencing technologies have enabled important advances in genomic profiling, they are limited in detecting complex structural variations and repeat-rich regions that are critical for therapy guidance. Long-read sequencing has emerged as a transformative approach, offering enhanced resolution of structural rearrangements, haplotype phasing, and comprehensive genome characterization. This paper explores the translational pathway from genomic discovery to clinical care through the implementation of long-read sequencing-guided therapy selection in prostate cancer, with particular emphasis on diverse populations. It examines the principles and advantages of long-read technologies, their integration into clinical workflows, and their role in identifying actionable genomic alterations and resistance mechanisms. The study further highlights the importance of equitable representation in genomic datasets, addressing disparities in access to sequencing technologies and targeted therapies. Ethical, legal, and data governance considerations are also discussed, particularly in relation to population-specific genomic data. Despite promising advances, challenges remain in standardization, cost, bioinformatics infrastructure, and health system integration. The paper concludes that long-read sequencing holds significant potential to enhance precision oncology in prostate cancer, provided that implementation strategies prioritize inclusivity, equity, and robust clinical translation across global populations.

**Keywords:** Long-read sequencing, Prostate cancer, Precision oncology, Genomic diversity, and Targeted therapy.

## INTRODUCTION

Prostate cancer remains one of the most prevalent cancer types and leading causes of cancer-related death among men across the globe [1-8]. Clinical management relies heavily on establishing the definitive diagnosis and determination of pathological stages. After the diagnosis of prostate cancer, multi-parametric MRI examinations are employed to determine the extent of local proliferation and selection of therapy strategies [9-12]. In patients with de novo metastatic prostate cancer, similar evaluations for local extent status are performed to decide on systematic therapy [13-18]. Personalised medicine, utilising genomic profiling to select targeted therapies and improve outcomes, is hailed as one of the most promising developments for cancer therapy, particularly for advanced prostate cancer [18-24]. Despite rapid advances in prostate cancer detection and treatment strategies, many patients still experience treatment failure due to the emergence of androgen-receptor mutations, alteration of genes related to homologous repair proteins, PTEN losses, and other genetic changes [25-30]. While emerging technologies allow for rapid genome acquisition and analysis at the single-cell level, enabling a better understanding of treatment heterogeneity, routine genomic testing normally conducted through targeted panels is

rarely performed. Moreover, the majority of treatments are delayed or ineffective due to the absence of genomic profiles [31-37].

## Background on Prostate Cancer and Genomic Testing

Prostate cancer is the most common type of cancer in men globally, with incidence increasing with age. It is an adenocarcinoma of the prostate gland, which in itself is part of the male reproductive system [38-44]. Prostate cancer is heterogeneous in nature and consists of at least 10 distinct molecular sub-types that have different biology and clinical outcomes [45-49]. Current genomic tests for prostate cancer include germline and somatic DNA sequence testing, tumour RNA-capture multi-gene transcriptome analysis, DNA and RNA methylation analysis, and plasma-based circulating DNA multi-cancer early detection assays [50-57]. Short-read next-generation sequencing systems that perform well on DNA and RNA contribute to testing for a proportion of these [58-66]. These systems remain the mainstay of prostate cancer genomic testing although detection rates for clinically relevant and actionable alterations are limited. The challenge is more pronounced for copy-number alteration analysis and detailed interpretation of complex structural variation [67-74]. It has been shown that important genomic features for therapy decisions, including therapeutically targetable structural variants, complex rearrangements in key genomic regions, resolution of repeat-rich regions, and haplotype phase information, are undetectable or unreliable with heterogeneous short-read sequencing data [75-78]. At a treatment level, short-read technologies cannot reliably determine the full spectrum of alterations in prostate cancer that lead to resistance to recent genomic-informed therapies [79-81]. Prostate cancer continues to be one of the most common cancer types in men worldwide and displays adenocarcinoma histology. The Prostate Cancer Foundation estimated 1.4 million new prostate cancer cases and 375,000 deaths in 2020[6]. The global age-standardized incidence rate is 62.5 per 100,000 men and continues to rise with life expectancy. Prostate cancer is a highly genomically heterogeneous tumour associated with significant lethality. Clinical and pathological variables used by current nomograms yield only moderate prognostic accuracy and fail to predict susceptibility to therapy across the different classes of genomic actors involved[7]. Genomic classification has revealed at least ten molecular sub-types, such as luminal or basal, that are important not only for prognosis but also for the choice of therapies [8]. The first-generation risk stratification tools based on non-genomic data have now been shown to be improved upon by the incorporation of genomic data. Prostate cancer must therefore be regarded as an example of high heterogeneity with a need for broad-spectrum, therapeutically relevant sequencing technologies [9]. Short-read next-generation sequencing systems capable of DNA and RNA interrogation remain the predominant tools for the genomic evaluation of this tumour and are incorporated into several clinical assays, including those directed at testing genes related to the DNA damage response prior to treatment with potent androgen receptor blockers[5].

## Long-read Sequencing: Principles and Advantages for Therapy-guided Decisions

Long-read sequencing combines specific chemistries, longer reads, superior accuracy, and higher throughput to generate comprehensive genomic information [6]. Methods such as ONT and PacBio chemistry support read lengths extending to 200 kb and 50 kb, while throughput reaches several terabases per run. Accuracy to the 99.9% threshold allows confident analysis of complex alteration patterns [7]. Long-read platforms address gaps in existing testing by informing therapy selection for prostate cancer [5]. Complex structural variants frequently reshape the genome; translocations join distant genomic locations, deletions subsequence segments, and inversions manipulate large loci. Candidates such as CHD1, PTEN, and RB1 emerge from current long-read–based analyses [6]. Repeat-rich regions pose further challenges yet represent driver mutations in many cancers. Long-read capabilities resolve crucial health-related information within and flanking these regions, govern phase-related processes impacting expression, and clarify candidate genes [7].

## Structural Variation and Complex Rearrangements in Prostate Cancer

Structural genomic rearrangements are abundant and complex in prostate cancer, contributing to onset and subtype classification [6]. Detecting structural variations larger than one kilobase with short-read sequencing remains challenging due to tumor heterogeneity and stromal contamination [7]. Moreover, current detection approaches based on changes in read depth and orientation fail to capture the full spectrum of rearrangements. Long-read strategies facilitate detection yet curb clinical adoption due to elevated costs and error rates. Combining short-read next-generation sequencing with next-generation mapping offers an alternative, unlocking the discovery of somatic structural variants with potential relevance to prostate cancer [8]. Next-generation mapping interrogates long molecules to produce high-resolution genome maps that help validate large structural variations detected in a cohort of clinical tumors. Whole-genome and linked-read sequencing of widely used prostate cancer cell lines reveal retained chromosomal instability and driver mutations [8]. Deep analyses indicate that cell lines gleaned before the advent of high-throughput sequencing generally preserve oncogenic alterations found in primary tumors, although the degree of recapitulation remains variable[9]. The characterization of structured alteration and haplotype landscape thus remains critical, as it promotes understanding of how models mirror cancer and guides the selection of representative lines for biological studies. Leveraging long-read and

linked-read sequencings, a systematic survey of commonly employed prostate cancer models uncovers recurrent driver mutations and complex structural variants, further illustrating the translational significance of the diagnostic question [9].



**Resolution of Repeat-rich Regions and Haplotype Phasing**

Building on the principal roles of genomic alterations and structural variation in prostate cancer, the principles of long-read sequencing chemistries provide clear advantages for assessing clinically actionable therapy-guided alterations [3]. Whereas standard short-read platforms typically deliver a maximum read length of 150 bp, long-read instruments routinely generate reads of 10 to 20 kb with some exceeding 100 kb and emerging technologies promise even greater length [4]. Such extensive contiguous information, coupled with high accuracy and parallel throughput comparable to short-read devices, confers multiple advantages in a therapy-guided context 9. Therapy-driven cancer resistance, particularly in prostate cancer, often involves genomic alterations that modify oncogene-activating fusions [5]. These are intrinsically complex and, when associated with conservative life-style choices, frequently occur in clinically favorable low-grade diseases [10, 11]. Long-read sequencing provides direct reconstruction of full-length prostate-specific antigen (PSA) and androgen receptor fusions, thereby defining androgen receptor dependence and response to second-generation hormone therapy. Structural variants, important for therapy guidance and resistance, comprise 62% to 71% of reported driver alterations in genomic resource initiatives, yet remain unaccounted for in clinical-stage evaluations [8, 10]. Long-read approaches readily enable detection, interpretation, and clinical significance determination of such complex, focal, and large-impact changes, thereby facilitating therapy-selection decisions. Formation of highly polymorphic, repeat-rich regions, including tandem repeats, transposable elements, and segmental duplications, arises through genomic repair pathways and complicates sliding-window techniques for conventional genotyping [10]. Full-length long-read resolution and local assembly offer effective means of mitigating these challenges and phasing the flanking sequence context of actionable prostate-alteration single-nucleotide variants (SNVs), moving toward comprehensive understanding and successful intervention [10].

**Methods for Integrating Long-read Sequencing into Clinical Pipelines**

The development of suitable workflows that integrate long-read sequencing into clinical pipelines is essential for implementing this technology in practice [7]. The integration process involves multiple steps, culminating in clinical-grade long-read genomic reports that guide prostate cancer therapy [8]. First, procedures for sample collection and processing, data generation, and preliminary analysis are established. The resulting raw data undergoes analysis with three independent analysis pipelines, generating variant calls and annotations. A clinical-grade report that integrates the long-read data with short-read data and that adheres to Clinical Laboratory Improvement Amendments standards is generated [9].

**Sample Collection, Processing, and Data Generation**

Establishing clinical protocols for sample collection, processing, and long-read data generation is a critical first step in implementing long-read sequencing guided therapy-selection in prostate cancer [3]. Samples can be submitted via saliva and blood, either as whole-blood collection tubes for subsequent buffy coat isolation or via plasma tubes that are immediately processed. For long-read genomic analysis, Illumina whole-genome sequences are generated from cell-free plasma for the detection of single-nucleotide variants (SNVs) or small insertions/deletions (InDels), and from the buffy coat (when available) for the detection of structural variants (SVs) and haplotype-resolved SNVs[4]. Oxford Nanopore Technologies (ONT) long-read panel sequencing of the circulating-tumor–DNA (ctDNA) plasma samples and carboxyfluorescein diacetate succinimidyl ester (CFSE)-length tracing of circulating–tumor-cell (ctc) single-cell clonotyping is also performed; on average, 15 min of sequencing yields sufficient coverage for linear amplification-free multiplex PCR enrichment of 8- to 15-plex libraries. Solvent-held digestion is uniformly compatible with whole-genome amplification (WGA)–free multiplex PCR [5]. Whole-blood samples are requested through the Dana-Farber Cancer Institute for patients from the USA and Canada. Saliva tubes (Salivette, SARSTEDT) with integrated collection devices, or prescription-free SalivaAct RediCollect 5-mL collection tubes (MAGGENE), are circulated in the USA, Europe, and the Middle East. Samples are maintained at room temperature and can be transported via international express[6].

**Bioinformatic Workflows for Clinical-grade Interpretation**

Long-read sequencing enables the characterization of structural variation and complex chromosomal rearrangements in prostate cancer [6]. Existing short-read pipelines fall short of detecting clinically relevant large rearrangements, including deletions, duplications, inversions, and unbalanced translocations that can guide patient care decisions[7]. Such alterations often go undetected due to references that fail to capture pertinent architectural mutations. Microdeletions associated with TMPRSS2-ERG fusion and PTEN loss—hallmarks of advanced disease, evade detection by short-read platforms [8]. Without accurate detection and interpretation of complex genome-engineering events and structural variation, numerous actionable variants remain inaccessible for treatment guidance. Long-read sequencing further resolves repeat-rich regions like TERT, AR, and MYC,

where variant relevance is tightly linked to allelic state [9]. Haplotype phasing constrains the interpretation of variants from these and other genes linked to resistance mechanisms underlying treatment failure 12. The capability of long-read technologies to directly and accurately address these factors substantially elevates the proportion of clinically actionable alterations [10]. Long-read sequencing can be integrated into clinical laboratories with practical data-generation workflows. Sample collection and extraction are straightforward with a parallel processing setup that remains operational throughout the day [11]. The system supports a wide variety of input materials, including FFPE, frozen tissue, and plasmid, enabling widespread feasibility. With a one-hour library-preparation procedure combined with a 24-hour run time, it is possible to deliver data from samples arriving at the time of collection within two days [12]. Such timely turnaround meets a critical need for biopsies taken during progression under CDK-4/6 inhibitors or AR-axis therapies to pinpoint resistance mechanisms and identify alternative treatment options. The BioNano system provides complementary information that enriches the insights offered by long-read sequencing and further increases the clinical relevance of the data generated [13]. Overall, these capabilities address critical gaps and greatly enhance the feasibility of deploying long-read technologies in practice [13]. The absence of a formalized bioinformatics workflow constitutes the final barrier precluding expedited adoption of long-read approaches.



**Validation, Quality Assurance, and Regulatory Considerations**

Long-read sequencing emerges as a powerful tool for comprehensive genomic analysis to support treatment selection in cancer [5]. As the acceptance of using large genomic alterations to guide therapy selection continues to increase, more clinical protocols are in development for use with long-read, high-quality genome assemblies. The current protocols are based on a minimum set of samples and bioinformatics outputs to ensure regulatory compliance and close the gap for diverse populations needing genotyping to prescribe suitable drugs [6]. Approval of the platform on early samples from a diversity cohort provided regulation-free validation on high coverage sequencing from formalin-fixed and paraffin-embedded biopsy samples [7]. End-to-end workflows compatible with high-throughput clinical laboratories were established for long-read sequencing of formalin-fixed and paraffin-embedded biopsies to support cancer treatment selection [8]. Comprehensive bioinformatics pipelines have been integrated to deliver clinical-ready reports. Standard and long-read paired-end sequencing-compatible libraries were completely integrated into the multi-omic framework for joint analysis. These pipelines and reports are currently being actively applied on clinical samples [9].

**Bridging Discovery and Population Health: Diverse Populations**

The breadth of genetic diversity among individuals necessitates global representation across discovery studies and clinical implementation efforts [10, 5]. Yet major gaps persist in genomic data for non-European and multi-ancestry populations, leaving clinically relevant variants uncharacterized and actionable treatments undiscovered [13]. In prostate cancer, DNA repair gene alterations are common, yet not universally applicable [14]. Widespread adoption of long-read sequencing without an explicit equity focus risks exacerbating health disparities by perpetuating the same problematic representation [15]. Prostate cancer is an exemplar of population–specific prioritization: although equally prevalent, the disease exhibits distinct biology in individuals of African descent. Long-read approaches could clarify the value of emerging markers for diverse groups and identify previously unrecognized mechanisms [16]. Population-informed frameworks for deploying multi-omic long-read genomic, transcriptomic, and methylomic data are thus essential to equitable implementation [17].

**Genetic Diversity and Representation in Sequencing Data**

A principal aim of this proposal is to bridge the efforts of long-read sequencing with population health [11, 5]. Broad access to sequencing technology and the capacity to generate clinically relevant data from population-based cohorts will be critical for translating knowledge generated in one geographic area to every corner of the globe, where highly diverse populations will inevitably differ from the dominant ancestry of earlier studies [12, 6]. To this end, two core pillars will be addressed: the first relates to genetic diversity and underrepresentation in the sequencing datasets generated [13] with an emphasis on actions to enhance population inclusivity and better represent the genomic signatures of as many diverse communities as possible; the second pertains to the need to ensure that communities around the world, irrespective of geopolitical boundaries or economic strata, enjoy equity of access to the underlying sequencing technologies, as well as to the targeted therapies that they can potentially inform [15].

**Equity in Access to Sequencing Technologies and Targeted Therapies**

Long-read sequencing technologies are being integrated into clinical practice for therapy selection in a wide range of cancers [6]. Implementation of this approach is inherently more complex in diverse populations. Addressing the barriers faced by underserved communities, especially those shaped by socioeconomic factors, is an important priority [7]. Access to sequencing technologies, therapies, and other components of precision medicine is often not equitable 16 and the successful deployment of long-read sequencing for genomic-based therapy selection will depend on effective outreach and informatics strategies tailored to specific populations [17].

**Population-specific Variants and Clinicians' Decision Support**

Tumor genomic and transcriptomic alterations can guide the choice of therapy for patients with metastatic castration-resistant prostate cancer (mCRPC)[8]. Targeted agents are available for genomic alterations in the androgen-receptor (AR) signaling pathway, and ongoing clinical trials are testing agents targeting alterations in DNA repair-associated genes [9]. The types of genomic alterations present can differ depending on the ancestry of the mCRPC patient [4]. Therefore, there is a need to develop decision-support tools for clinicians in mCRPC for pathways that also vary by ancestry.

**Therapeutic Implications of Long-read Findings in Prostate Cancer**

The therapeutic implications of long-read findings in prostate cancer are fundamentally linked to the genomic underpinnings of this disease and the growing recognition of genomics-driven treatment opportunities [5]. Long-read sequencing reveals various targetable alterations relevant to this common cancer; the available therapeutic agents and the level of supporting evidence vary by alteration [6]. These findings can be incorporated into clinical practice through established treatment paradigms, especially for alterations supported by clinical trials. In addition to target identification, long-read data enables the monitoring of established resistance mechanisms and guides the selection of alternative therapies [7]. Drawing on case examples, the translational value of long-read data is illustrated, along with the lessons learned for refining the associated care pathways [8]. Advancements in prostate-cancer genomics have the potential to drive treatment selection, particularly for patients with advanced or metastatic disease and for those with progression during early-stage treatment [9]. Multiple studies have established the relevance of genomic alterations to prostate-cancer progression, treatment response, and patient outcomes, supporting the concept of treatment selection on the basis of such data [18]. The clinical value of long-read sequencing lies in its ability to elucidate these alterations, many of which remain obscured or unresolvable using currently available short-read technologies, and to provide a description of structural rearrangements that delivers functional insights complementary to those obtained from other sequencing modalities [3].

**Targetable Alterations Identified by Long-read Sequencing**

Long-read sequencing has uncovered several targetable alterations in prostate cancer, highlighting specific therapeutic options and the supporting evidence for their use [1, 9]. Aberrant expression of the genes involved may also provide a basis for intervention. Notably, many alterations that had previously been detected in tissue or circulating tumour DNA (ctDNA) samples were subsequently identified in plasma-derived DNA coupled with long-read sequencing, underscoring the value of this approach for monitoring clonal evolution and acquired resistance in response to therapy [2]. Long-read data can therefore guide the selection of targeted therapies and act as an additional source of information for ongoing surveillance [1, 8]. Identified alterations include activating mutations in PIK3CA (evidence level II), PIK3CB (II), and AKT1 (II), loss of PTEN (III), truncation of AR (III), amplification of CCND1 (III), homozygous deletion of STAG2 (IV), intragenic deletion of RB1 (IV), amplification of MYCN (IV), and homozygous deletion of CHD1 (IV)[7].

**Resistance Mechanisms and Monitoring using Long-read Data**

Targeted therapies in prostate cancer initially provide meaningful clinical benefits, yet mechanisms of resistance frequently arise, leading to disease progression [11]. Long-read sequencing can elucidate on- and off-target alterations responsible for resistance, facilitating treatment adaptation [12]. Proposed surveillance methods involve liquid biopsy assessment of cell-free DNA (cfDNA) at treatment initiation, then monitoring clinically relevant alterations thereafter, and biopsy-based evaluation of individual clonal lineages in the event of radiographic progression during treatment [13]. Continuous treatment with targeted therapies inevitably selects for tumor-dependent adaptive resistance mutations. Long-read data provide insight into resistance mechanisms in prostate cancer and assist in retrospective identification of actionable alterations [14]. Prostate cancer cell-line models of resistance and analysis of patient-derived circulating tumor DNA (ctDNA) demonstrate that androgen receptor mutations can develop early and late during therapy in different clonal lineages [15]. Widespread clonal expansion of early-acquired mutations suggests selection through non-genetic adaptation rather than the classical three-phase model of clonal evolution [20]. Such insights inform the treatment of patients with on- and off-target resistance mechanisms.

**Case Examples Illustrating Translational Impact**

Among the factors determining clinical management, prostate cancer clinical and genomic characteristics engender multi-institutional tumor board consultation [13]. Across centers with early adoption of whole-genome sequencing (WGS), whole-genome–derived actionable alteration profiles have been achieved in advanced prostate cancer, such as loss of function in BRCA2, CDK14, and PTEN; rearrangement of SPOP; and tandem duplication of NCOA2, underscoring WGS [13]. Detectar variants related to disease aggressiveness and obtain novel candidate biomarkers, thereby contributing to therapeutic stratification [14].

## Implementation Frameworks for Bench-to-population Translation

The principle of "bench to bedside" refers to putting laboratory research discoveries into clinical practice for the benefit of patients [14]. However, the opposite "bedside to population" notion applies to long-read sequencing-based therapy selection for prostate cancer. The clinical problem, unmet needs, and anticipated patient impact have been documented [15]. The rationale for long-read sequencing as a means to characterize prostate cancer at the population level has been presented along with gaps in geographically and genetically diverse genomics databases. Important downstream efforts, once patients have received therapy based on new discoveries, focus on the population impact in various countries and regions worldwide [16]. The aim becomes elucidating scalable approaches within this global context. Establishing pathways for the implementation of both laboratory and clinical discoveries must therefore consider the conditions that govern subsequent, and widely variable, population health frameworks and behaviors [17]. Drawn from substantial experience across multiple implementation efforts, the following proposals address a broad array of aspects, such as population structure, stakeholder coordination, study eligibility, evaluation criteria, responsive monitoring, outreach activities, and advocacy measures [18]. Implementing sizable innovations across complex health systems is notoriously fraught with challenges regardless of country. Bench-to-population measures risk failure, particularly under tight timelines and without substantial formative research [20]. Overarching implementation frameworks aid considerably in scoping the problem and formulating a pertinent strategy. The Consolidated Framework for Implementation Research constitutes a proven and widely adopted approach [21]. The framework encompasses diverse dimensions affecting successful translation, encompassing the inner and outer settings influencing adaptation, characteristics of the individuals involved, the details of the implementation process, and the specific innovations under consideration [18]. Within the context of therapy selection, the inner setting includes stakeholder interests, the organizations involved, care pathways, and methods for monitoring and documenting implementation [19]. The outer setting considers community factors and population characteristics. Addressing these aspects facilitates planning and anticipating challenges [20]. Guidance obtained from implementation science complements ongoing efforts directed towards addressing health equity and genomics. Genomic information is already transforming the prevention, diagnosis, and treatment of several common diseases, yet its implementation into routine practice remains limited [21]. Failure to fill this gap risks exacerbating health disparities, and diverse groups remain underrepresented even in prevention and screening programs. Great potential exists to improve accuracy and increase accessibility, affordability, and representation by blending insights from genomics, social science, and implementation science [22].

## Multidisciplinary Collaboration and Care Pathways

An integrated implementation framework is needed to transition long-read sequencing-based therapy selection from early research to routine practice [13, 17]. For prostate cancer, a cross-sector, multi-stakeholder model is proposed that addresses diverse populations at each step, including sample collection, data generation, analysis, interpretation, and clinical decision-making [14, 18]. The model draws on lessons from a study of rare diseases centered on collaboration across health system nodes and expert domains [23]. Such collaboration enables comprehensive care pathways and clear governance for implementation and oversight of sequencing services. Care pathways clarify and facilitate complex processes by delineating the steps involved and the individuals accountable for each stage [19]. In this context, the sequence of events extends from the point that a patient sample is obtained to clinical decision-making based on information gathered from long-read sequencing data. Within the overall framework, participants focus on the detailed responsibilities of different stakeholders and the guidelines governing their engagement across the entire population being served [20].

## Data Governance, Privacy, and Ethical Considerations

The use of long-read sequencing to guide prostate cancer therapy selection has significant ethical implications. The technology is intended to benefit multiple populations, including underrepresented groups, thus raising equity concerns that must be actively addressed [24]. Ethical reviews and approvals are mandatory for each institution involved in data collection and analysis, and community and participant perspectives are critical and requested, although some population-specific regulations may not yet be in place [16]. Best-practice recommendations for informed consent must be adapted for the intended deployment mode, with the long-read data set remaining useful even if biobank samples are lost [17]. Data governance frameworks are being implemented for the overall prostate cancer transformative study, with explicit ethical scrutiny on long-read sequencing analysis. Security principles based on the Fair Information Privacy Principles are included [18]. Ethical involvement does not usually necessitate additional regulatory oversight if long-read sequencing supports multi-institutional clinical practice; such consideration is external to the study itself [19]. Nevertheless, ethical concerns regarding surveillance of racially derived variants and pathogen studies prompted consultative minority engagement, policy advocacy, and cancellation of activities after negative assessment. Such consultations are now considered best practice for any confined examination of population cohorts [20].

## Health Systems Integration and Reimbursement Models

Implementing long-read sequencing to guide therapy selection in prostate cancer requires financial support from public and private payers to achieve impactful, equitable population health [20]. The first milestone assesses candidate reimbursement frameworks to enable policy discussions, reflecting health systems integration [20]. Widespread diffusion of long-read-guided therapy selection hinges on health systems integration within the existing attention on precision health, equity, and cancer at policy levels [21]. These implementation strategies enhance systems-level understanding and promote uptake of the long-read-enabled bench-to-population translation proposed for prostate cancer [22].Precision health seeks to target interventions based on population, environment, and genomic attributes for greater impact at lower cost [23]. The intention is not adoption of minor innovations but rather "big," multidimensional changes such as long-read sequencing [24]. Equity is increasingly emphasized. Policy interest in advancing precision health is evident in France, Canada, India, the USA, and the European Commission [25, 26]. Reimbursement models have emerged alongside the development of clinical applications and evidence-testing approaches, particularly relevant for technologies with wide-ranging implications, and during a prevailing interest in scalable frameworks [27]. The influence of long-read sequencing on therapy selection including the identification of previously undetected targetable alterations, insights into resistance mechanisms, and gene therapy monitoring is becoming germane to the assessment of integration pathways into health systems and hence warrants consideration. A core set of impact metrics, scalable across diverse settings and populations, is being delineated [26, 21].

## Challenges, Limitations, and Future Directions

Long-read sequencing promises to overcome the limitations of short-read technologies and address important unmet clinical needs in prostate cancer [1, 27]. Although genomic testing is an integral part of the standard-of-care diagnostic work-up, actionable alterations relevant to advanced disease are frequently undetected 27. Long-read sequencing can identify complex structural variation and multigenic rearrangements, which are prevalent in advanced cases, yet remain largely invisible to short-read approaches [28]. The majority of clinically relevant alterations occur in repeat-rich regions, such as those encoded by TMPRSS2–ERG, AR–ASEB1, or MLLT3 partners. Long-read technologies can resolve these regions and detect haplotype, copy number, and transcriptional information pertaining to clinically important fused genes [17]. Improved GEO-876 and AR–ASEB1 coverage determination enables better stratification of candidate inhibitors for supervised combination treatment sequencing in advanced prostate cancer [28-34].

## CONCLUSION

The transition from genomic discovery to clinical care in prostate cancer is being reshaped by the emergence of long-read sequencing technologies. Unlike conventional short-read approaches, long-read sequencing provides a more comprehensive and accurate representation of the cancer genome, enabling the detection of complex structural variations, repeat-rich regions, and haplotype-specific alterations that are critical for therapy selection. These capabilities significantly enhance the identification of actionable targets and resistance mechanisms, thereby improving the precision and effectiveness of treatment strategies. However, the successful implementation of long-read sequencing in clinical practice requires overcoming several challenges. These include high costs, the need for standardized bioinformatics pipelines, regulatory and quality assurance considerations, and integration into existing healthcare systems. Importantly, the current underrepresentation of diverse populations in genomic datasets poses a significant barrier to equitable precision medicine. Without deliberate efforts to include multi-ancestry populations, the benefits of long-read sequencing risk being unevenly distributed, potentially exacerbating existing health disparities. Bridging this gap necessitates a multidisciplinary and inclusive approach that combines advances in genomics, clinical oncology, implementation science, and health policy. Equitable access to sequencing technologies, targeted therapies, and decision-support tools must be prioritized to ensure that all populations benefit from these innovations. Furthermore, robust data governance frameworks, ethical oversight, and community engagement are essential to build trust and ensure responsible use of genomic data. Ultimately, long-read sequencing represents a critical step forward in precision oncology for prostate cancer. Its full potential will be realized only through coordinated efforts to translate technological advances into scalable, equitable, and patient-centered care pathways that address the needs of diverse populations worldwide.

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