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Advances and Prospects in Whole-Genome Sequencing Studies of Prostate Cancer

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Abstract Prostate cancer remains a significant clinical challenge due to its complex genetic landscape and the difficulty in predicting disease progression and treatment response. Recent advances in whole-genome sequencing (WGS) have provided deeper insights into the genetic alterations driving prostate cancer, offering new avenues for personalized treatment strategies. This study synthesizes findings from multiple studies that have employed WGS to identify novel driver mutations, potential therapeutic targets, and biomarkers for treatment response in prostate cancer. Key discoveries include the identification of new putative driver genes, such as *NEAT1* and *FOXA1*, and the elucidation of the role of noncoding mutations in disease progression. Integrative high-throughput sequencing has demonstrated the feasibility of identifying clinically actionable mutations within a clinically relevant timeframe, facilitating biomarker-driven clinical trials. Studies have also highlighted the genomic heterogeneity of prostate cancer, with frequent alterations in genes such as *AR*, *TP53*, and *PTEN*, and the presence of actionable mutations in a significant proportion of cases. Additionally, the use of liquid biopsies for WGS has emerged as a promising non-invasive approach to monitor metastatic castration-resistant prostate cancer (mCRPC) and guide personalized treatment. This study underscores the potential of WGS to transform the clinical management of prostate cancer by enabling precision medicine approaches tailored to the genetic profile of individual tumors.
Keywords Whole-genome sequencing; Prostate cancer; Driver mutations; Biomarkers; Personalized treatment

1 Introduction

Prostate cancer (PCa) is one of the most prevalent malignancies affecting men worldwide and is a leading cause of cancer-related mortality, particularly in Western countries (Gudmundsson et al., 2012). The disease exhibits significant clinical heterogeneity, ranging from indolent tumors that may not require immediate treatment to aggressive forms that can be fatal (Baca and Garraway, 2012). Genetic factors play a crucial role in the development and progression of PCa, with both germline and somatic mutations contributing to its pathogenesis (Nakagawa, 2013). Family history is a well-known risk factor, and recent studies have identified numerous genetic variants associated with increased susceptibility to PCa (Schaid et al., 2020).

Whole-genome sequencing (WGS) has emerged as a powerful tool for uncovering the genetic underpinnings of various cancers, including PCa. By providing a comprehensive view of the entire genome, WGS allows for the identification of both common and rare genetic alterations that drive cancer development and progression (Ren et al., 2017; Jaratlerdsiri et al., 2018). High-throughput sequencing technologies have facilitated the discovery of novel mutations, gene fusions, and other genomic aberrations that are critical for understanding the molecular mechanisms of PCa (Roychowdhury and Chinnaiyan, 2013; Liu et al., 2019). These insights have the potential to inform the development of precision medicine approaches, enabling more accurate diagnosis, prognosis, and targeted therapies (Roychowdhury and Chinnaiyan, 2013).

This study synthesizes the latest advancements in prostate cancer (PCa) whole-genome sequencing (WGS) research, highlighting key genetic alterations and their impact on disease progression and treatment. By examining the results of multiple WGS studies, the research provides a comprehensive overview of the genomic landscape of PCa, identifies potential biomarkers for clinical use, and discusses future research prospects in the field. The study

also explores the genetic diversity of PCa among different populations, emphasizing the importance of including diverse racial groups in genomic research to uncover population-specific genetic drivers of the disease.

2 Advances in Whole-Genome Sequencing of Prostate Cancer

2.1 Identification of genetic mutations

Whole-genome sequencing (WGS) has significantly advanced our understanding of the genetic mutations associated with prostate cancer. Key mutations identified through WGS include alterations in genes such as CHD1, BRCA2, and androgen receptor (AR) upstream activator genes. For instance, a study on Chinese prostate cancer patients revealed a high frequency of *CHD1* deletions and mutations in androgen receptor upstream activator genes, which are associated with disease progression (Ren et al., 2017). Additionally, WGS has uncovered 22 previously unidentified putative driver genes, including *NEAT1* and *FOXA1*, which act as drivers through noncoding mutations (Wedge et al., 2018). These findings highlight the complexity and diversity of genetic alterations in prostate cancer, providing new insights into the molecular mechanisms driving the disease.

2.2 Insights into tumor heterogeneity

WGS has also provided valuable insights into the heterogeneity of prostate tumors. Intra-tumor and inter-tumor heterogeneity have been extensively studied, revealing significant variations in genetic alterations within and between tumors. For example, a study using targeted next-generation sequencing of advanced prostate cancer identified substantial heterogeneity in genomic alterations, including AR copy number gain, TMPRSS2-ERG fusion, and PTEN loss (Beltran et al., 2013; Bewicke-Copley et al., 2019). This heterogeneity has important implications for treatment and prognosis, as it suggests that personalized treatment strategies may be necessary to effectively target the diverse genetic landscape of prostate cancer.

2.3 Discovery of new biomarkers

The discovery of new biomarkers through WGS has opened up new avenues for early detection and prognosis of prostate cancer. Biomarkers such as PCDH9 and PLXNA1 have been identified as potential prognostic indicators. PCDH9, which is deleted or lost in approximately 23% of tumors, functions as a novel tumor suppressor gene with prognostic potential (Ren et al., 2017). Similarly, the gain/amplification of the *PLXNA1* gene, observed in approximately 17% of tumors, has been shown to promote prostate tumor growth and predict poor survival outcomes (Ren et al., 2017). These biomarkers have potential clinical applications in improving the diagnosis, prognosis, and treatment of prostate cancer.

3 Clinical Applications and Implications

3.1 Personalized medicine

3.1.1 Role of WGS in developing personalized treatment plans

Whole-genome sequencing has significantly advanced the field of personalized medicine by enabling the identification of unique genetic alterations in individual prostate cancer patients. This allows for the development of tailored treatment plans that target specific mutations and pathways involved in the patient's cancer. For instance, WGS has been used to identify mutations in DNA damage response genes, PI3K, MAPK, and Wnt pathways, which can inform the use of targeted therapies such as PARP inhibitors and immunotherapy (Ciccarese et al., 2017; Crumbaker et al., 2020). Additionally, the integration of WGS with other sequencing methods, such as whole-exome sequencing (WES) and RNA sequencing (RNAseq), has been shown to provide a comprehensive mutational landscape that can guide clinical decision-making (Roychowdhury et al., 2011; Nauseef et al., 2023).

3.1.2 Case studies and clinical trials

Several case studies and clinical trials have demonstrated the feasibility and clinical utility of WGS in personalized medicine for prostate cancer. For example, a study involving 34 patients with advanced cancers utilized WGS to identify therapeutically relevant targets, leading to genomic-directed treatments in 10 patients, with preliminary clinical efficacy observed in four patients (Borad et al., 2013). Another study highlighted the use of WGS in a patient with advanced prostate cancer, where the identification of an SPOP mutation and androgen-receptor dependency informed a successful personalized treatment approach (Figure 1) (Armstrong et

al., 2021). These examples underscore the potential of WGS to revolutionize personalized medicine by providing actionable insights into the genetic underpinnings of prostate cancer.

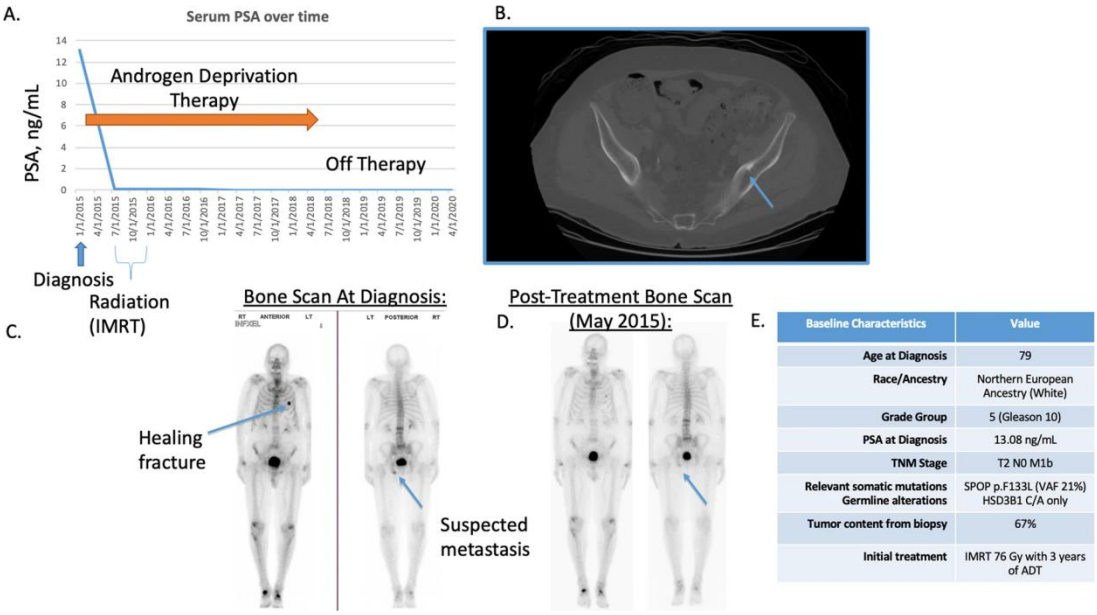

Figure 1 Summary of the patient case and outcomes (Adopted from Armstrong et al., 2021)

3.2 Targeted therapies

3.2.1 Identification of targets for drug development

WGS has been instrumental in identifying novel targets for drug development in prostate cancer. By analyzing the genetic alterations present in prostate cancer samples, researchers have discovered new candidate driver mutations and potential drug targets. For instance, a comprehensive sequencing study identified 22 previously unidentified putative driver genes and several targets of approved and investigational drugs (Wedge et al., 2018). This highlights the potential of WGS to uncover new therapeutic targets that can be exploited for drug development.

3.2.2 Examples of successful targeted therapies

The application of WGS in identifying actionable mutations has led to the development and implementation of successful targeted therapies. For example, the identification of BRCA2 mutations in prostate cancer patients has informed the use of PARP inhibitors, which have shown efficacy in treating these patients (Ciccarese et al., 2017; Crumbaker et al., 2020). Additionally, the discovery of specific gene fusions and amplifications, such as TMPRSS2-ERG and FGFR1, has guided the use of targeted therapies that inhibit these pathways (Roychowdhury et al., 2011; Nauseef et al., 2023). These examples demonstrate the clinical impact of WGS in enabling the development and application of targeted therapies for prostate cancer.

3.3 Predictive and prognostic value

3.3.1 Use of genetic information for predicting disease progression

WGS provides valuable genetic information that can be used to predict disease progression in prostate cancer patients. By identifying specific genetic alterations associated with different stages of cancer development, WGS can help predict the likelihood of disease progression and inform treatment decisions. For instance, the loss of CHD1 and BRCA2 has been identified as early events in the development of ETS fusion-negative prostate cancers, providing insights into disease progression (Wedge et al., 2018). Additionally, the presence of mutations in DNA repair genes has been associated with sensitivity to certain therapies, which can be used to predict treatment response and disease outcomes (Ciccarese et al., 2017; Crumbaker et al., 2020).

3.3.2 Studies demonstrating prognostic significance

Several studies have demonstrated the prognostic significance of genetic alterations identified through WGS. For example, a retrospective analysis of metastatic prostate cancer patients revealed that most cases harbored

therapeutically relevant alterations, including those associated with PARP inhibitor sensitivity and resistance to androgen pathway targeting agents (Figure 2) (Crumbaker et al., 2020). Another study showed that the integration of WGS with clinical data could identify molecular signatures associated with homologous recombination deficiency and mismatch repair deficiency, which have prognostic implications for treatment response and disease progression (Nauseef et al., 2023). These findings highlight the potential of WGS to provide prognostic insights that can guide clinical management and improve patient outcomes.

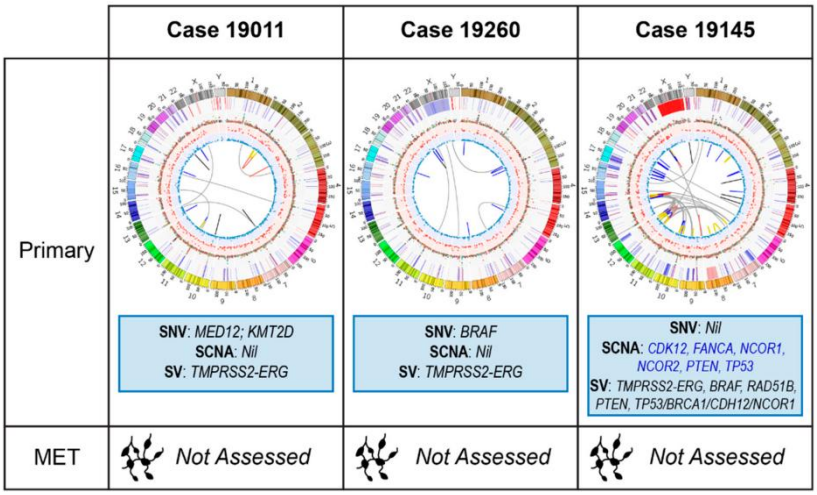

Figure 2 Summary of genomic alterations in primary prostate samples with synchronous lymph node metastases (Cases 19011, 19260 and 19145) (Adopted from Crumbaker et al., 2020)

In conclusion, WGS has emerged as a powerful tool in the clinical management of prostate cancer, offering significant advances in personalized medicine, targeted therapies, and predictive and prognostic value. The continued integration of WGS into clinical practice holds promise for improving the diagnosis, treatment, and outcomes of prostate cancer patients.

4 Challenges and Limitations

4.1 Technical and analytical challenges

Whole-genome sequencing (WGS) of prostate cancer presents several technical and analytical challenges. One significant issue is the difficulty in obtaining sufficient high-quality DNA from metastatic tissues, which are often limited in availability and quality. This is particularly problematic for advanced prostate cancer, where metastatic tissue is crucial for comprehensive genomic analysis (Beltran et al., 2013; Lohr et al., 2014). Additionally, the isolation and sequencing of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) require overcoming the challenges of isolating rare cells and sequencing low-input material, which can lead to incomplete or biased genomic data (Lohr et al., 2014; Sumanasuriya et al., 2021). Furthermore, the complexity of prostate cancer genomes, characterized by a high degree of heterogeneity and the presence of both coding and non-coding mutations, complicates the identification and interpretation of driver mutations and other clinically relevant alterations (Robinson et al., 2015; Ren et al, 2017; Wedge et al., 2018).

4.2 Clinical and ethical considerations

The clinical application of WGS in prostate cancer is fraught with ethical and practical considerations. One major concern is the interpretation and communication of incidental findings, which may have significant implications for patients and their families. The identification of germline mutations, for instance, can reveal hereditary cancer syndromes that necessitate genetic counseling and potential testing of family members (Abida et al., 2017). Additionally, the clinical utility of WGS data is still under investigation, and there is a need for robust clinical trials to validate the prognostic and therapeutic relevance of identified genomic alterations (Beltran et al., 2015). Ethical considerations also include the potential for genetic discrimination and the need for informed consent processes that adequately explain the risks and benefits of WGS to patients (Beltran et al., 2015; Abida et al., 2017).

4.3 Cost and accessibility

The high cost of WGS remains a significant barrier to its widespread adoption in clinical practice. Despite advances in sequencing technologies that have reduced costs, WGS is still expensive compared to other genomic testing methods, such as targeted sequencing or panel-based approaches (Beltran et al., 2013; Imieliński et al., 2017). This cost factor limits accessibility, particularly in resource-limited settings, and raises questions about the cost-effectiveness of WGS in routine clinical care. Additionally, the infrastructure required for WGS, including bioinformatics support and data storage, adds to the overall expense and complexity of implementing WGS in clinical settings (Abida et al., 2017; Imieliński et al., 2017). Efforts to reduce costs and improve the efficiency of WGS are essential to make this technology more accessible and practical for widespread clinical use.

5 Future Prospects and Research Directions

5.1 Technological advancements

5.1.1 Emerging technologies in genome sequencing

The field of whole-genome sequencing is rapidly evolving, with significant advancements in next-generation sequencing (NGS) technologies. These advancements have enabled more comprehensive and detailed analyses of cancer genomes, including prostate cancer. Emerging technologies such as deep WGS and liquid biopsy techniques are particularly promising. For instance, deep WGS of circulating tumor DNA (ctDNA) has shown potential in revealing the clonal architecture and evolution of treatment-resistant prostate cancer, providing insights into the heterogeneity of ctDNA populations compared to metastatic tissue (Herberts et al., 2022; Weiss et al., 2022). Additionally, the development of scalable NGS systems, such as the Oncomine Comprehensive Panel, has facilitated the detection of relevant somatic variants in solid tumors, including prostate cancer, using minimal DNA/RNA from formalin-fixed paraffin-embedded (FFPE) tissues (Hovelson et al., 2015; Liang et al., 2019).

5.1.2 Potential improvements in WGS accuracy and efficiency

Despite the progress, there are still substantial improvements to be made in sequencing technologies, informatics, and computational resources to enhance the accuracy and efficiency of WGS. Current WGS platforms are considered primitive, and there is a need for better integration of multi-omics data, functional data, and clinical-pathological data to fully interpret the diverse cancer genomes and phenotypes (Nakagawa et al., 2015; Nakagawa and Fujita, 2018). Moreover, the feasibility of WGS in routine clinical practice has been demonstrated, but challenges such as low tumor purity and the need for fresh-frozen samples instead of FFPE samples need to be addressed to improve the success rate and turnaround time of WGS (Samsom et al., 2022).

5.2 Integrative approaches

5.2.1 Combining WGS with other omics technologies

Integrative approaches that combine WGS with other omics technologies, such as transcriptomics, epigenomics, and immunogenomics, are essential for a comprehensive understanding of cancer biology. For example, integrating WGS data with RNA-Seq, epigenomics, and clinical-pathological information can help elucidate the functional or clinical implications of unexplored genomic regions and mutational signatures in cancer genomes (Nakagawa and Fujita, 2018; Rubin and Demichelis, 2018). Additionally, ctDNA nucleosome footprinting has been used to infer mRNA abundance in metastatic lesions, demonstrating the potential of combining WGS with transcriptomic data to understand the transcriptomic patterns in prostate cancer (Herberts et al., 2022).

5.2.2 Benefits of integrative cancer genomics

The benefits of integrative cancer genomics are manifold. By combining WGS with other omics data, researchers can identify new genomic alterations and clinically actionable aberrations that could impact treatment decisions. For instance, a multi-institutional clinical sequencing infrastructure for metastatic castration-resistant prostate cancer (mCRPC) identified frequent aberrations in *AR*, *ETS* genes, *TP53*, and *PTEN*, as well as new genomic alterations in *PIK3CA/B*, *BRAF/RAF1*, and other cancer-related genes (Robinson et al., 2015). Such integrative approaches can provide a more comprehensive understanding of the genomic landscape of prostate cancer and facilitate the development of precision medicine frameworks.

5.3 Global collaborative efforts

5.3.1 Importance of international research collaborations

International research collaborations are crucial for advancing the field of prostate cancer genomics. Large-scale cancer genome-sequencing projects, such as the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA), have been instrumental in analyzing various cancer genomes, including prostate cancer, to explore genomic alterations and their diversity comprehensively (Nakagawa er al., 2015). These collaborations enable the sharing of data, resources, and expertise, which is essential for tackling the complexity and heterogeneity of cancer genomes.

5.3.2 Examples of global initiatives in prostate cancer genomics

Several global initiatives have made significant contributions to prostate cancer genomics. For example, the ICGC and TCGA projects have focused on exome sequencing to analyze many types of cancer genomes, including prostate cancer, and have provided valuable insights into somatic mutations, copy number alterations, and other genomic features (Nakagawa er al., 2015). Additionally, multi-institutional efforts, such as the study on mCRPC that involved whole-exome and transcriptome sequencing of tumor biopsies from multiple institutions, have identified clinically actionable aberrations and new genomic alterations that could inform treatment strategies (Robinson et al., 2015). These examples highlight the importance of global collaborative efforts in advancing our understanding of prostate cancer genomics and improving patient outcomes.

In conclusion, the future of whole-genome sequencing studies in prostate cancer lies in technological advancements, integrative approaches, and global collaborative efforts. By addressing current challenges and leveraging emerging technologies and international collaborations, researchers can continue to make significant strides in understanding and treating prostate cancer.

6 Concluding Remarks

Whole-genome sequencing studies have significantly advanced our understanding of prostate cancer's genetic landscape. Key findings include the identification of novel driver mutations and pathways involved in disease progression. For instance, new putative driver genes such as *NEAT1* and *FOXA1* have been identified through noncoding mutations, and early events in cancer development like the loss of CHD1 and BRCA2 have been established. Additionally, frequent genomic alterations in genes such as *AR*, *ETS*, *TP53*, and *PTEN* have been observed, with specific mutations enriched in metastatic castration-resistant prostate cancer (mCRPC). Studies have also highlighted the genomic complexity and heterogeneity of prostate cancer across different ethnic populations, identifying unique genetic alterations in Chinese patients. Furthermore, the feasibility of using circulating tumor cells (CTCs) for genomic analysis has been demonstrated, providing a non-invasive method to study metastatic prostate cancer.

The insights gained from WGS studies have profound clinical and research implications. Clinically, the identification of actionable genetic alterations can guide personalized treatment strategies. For example, alterations in DNA damage repair genes such as *BRCA2* and *ATM* suggest potential responsiveness to PARP inhibitors. The discovery of novel therapeutic targets, such as those identified through computational chemogenomic analysis, opens new avenues for drug development and clinical trials. Research-wise, the enhanced understanding of prostate cancer's genomic landscape facilitates the development of precision medicine frameworks, enabling more accurate prognostic assessments and tailored therapeutic interventions. Additionally, the ability to perform genomic profiling using archival FFPE tissue samples broadens the scope of genomic studies, allowing for retrospective analyses and the inclusion of diverse patient cohorts.

The advances in WGS have undeniably transformed prostate cancer research and treatment. However, several challenges remain. The heterogeneity of prostate cancer necessitates comprehensive genomic profiling to capture the full spectrum of genetic alterations. Future research should focus on integrating multi-omics data to provide a holistic view of the disease. Clinically, there is a need to establish standardized protocols for the implementation of genomic findings in routine practice, ensuring that patients benefit from the latest scientific advancements. Additionally, expanding genomic studies to include underrepresented populations will enhance the

generalizability of findings and contribute to global health equity. In conclusion, while significant progress has been made, continued efforts in research, clinical application, and policy development are essential to fully realize the potential of WGS in improving prostate cancer outcomes.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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