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Precision Medicine in Prostate Cancer: The Role of Molecular Diagnostics and Targeted Therapies

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Abstract

Prostate cancer is a major health problem in the world, and it has been complicated by the fact that the illness is quite heterogeneous. In the past, the use of PSA testing and histopathological grading has been constrained by failure to reliably distinguish between indolent and aggressive cancer. In this review, the concept of a fundamental change in the field of prostate cancer treatment, facilitated by the development of molecular diagnostics, is discussed. We discuss how genomic classifiers, epigenetic assays, and commercially available tests of biomarkers are being integrated to make risk stratification much more precise and tailored treatment decisions. Also, the stage of imaging, especially PSMA-targeted PET, breakthrough is transforming the accuracy of staging. Dynamic monitoring of tumor evolution has now been made possible by the introduction of liquid biopses, which can be used to study tumor-derived signals in the blood in a non-invasive manner. It is these diagnostic advances that are directly leading to a new generation of therapies that are targeted such as PSMA-directed radioligand therapy and drugs that target molecular weaknesses in cancer cells. Although this is a promising development, to achieve the full potential of precision medicine, the various obstacles, including tumor evolution, and clinically-implementation obstacles must be overcome. It is important to note that more efforts should be put to perfect these tools and strategies in the long run to enhance the results and life of men who have this disease.

Key words prostate cancer, precision medicine, molecular diagnostics, biomarkers, genomic profiling, psma, liquid biopsy, targeted therapy

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Introduction

Prostate cancer (PCa) remains a major health issue in men throughout the world, being the second most frequently diagnosed cancer worldwide and the leading cause of cancer-related death. Current global figures point to the large magnitude of this disease, with over 1.4 million new cases and nearly 400,000 cases annually, ranking it as one of the most frequently diagnosed cancers in men in most countries worldwide. The disease exhibits remarkable biological and clinical heterogeneity that contributes in large part to this clinical conundrum [1]. Pathology of PCa is highly variable; while a significant proportion of early-stage tumors are indolent and can be managed by active surveillance, late stage-particularly metastatic castration-resistant prostate cancer (mCRPC)-is difficult to manage and represents the majority of PCa cases [2, 3].

The complex molecular aetiology of PCa is also where its heterogeneity derives the most. The history of PCa tumorigenesis is a complex interaction between genetic events as mentioned and inherited mutations in genes (**Figure 1**) like TMPRSS2-ERG fusions, PTEN loss, hormonal signaling, epigenetic modifications and environmental influences overlayed with non- modifiable risks such as age, race and family history [4-9]. This is also lent support by anatomy, one of the glands in which around 80% of tumours originate in the peripheral zone of the gland, and biologically due to the centrality of androgen receptor (AR) signalling – both within the epithelium and surrounding stroma – for tumour formation and resistance to treatment.

Diagnosis and treatment of PCa has historically relied on serum Prostate-Specific Antigen (PSA) level, digital rectal examination (DRE), and conventional TRUS-guided biopsy through decades. Although they are useful in suppressing the severity of the disease, While effective treatments for death-adder bite exist, these therapies are known to have limitations that have been well described. PSA testing is non-specific and results in over-diagnosis of benign tumors and inappropriate invasive testing [10], whilst TRUS-biopsy is an invasive procedure with associated sampling error that can under-estimate the actual aggressiveness of an individual tumor influencing critical treatment decisions [11, 12]. The diagnostic setting is being improved by the introduction of new imaging modalities (i.e. mpMRI guided biopsy) and molecular tests (PCA3 urine test) that enable us to better find relevant disease [13, 14]. The therapeutic scenario is also heterogeneous, as indeed it is the disease. Treatment varies from active surveillance of low-risk disease, management for localized cancer, including radical prostatectomy or radiation therapy. In advanced and metastatic setting, palliative treatment, such as ADT, 2nd generation ARPIs, chemotherapy and radio-pharmaceuticals can be offered [15, 16]. But among such many large problems one issue this has almost becoming and epidemic is the resistance which develop at last, gradually for a long time as disease progressing in to lethal form

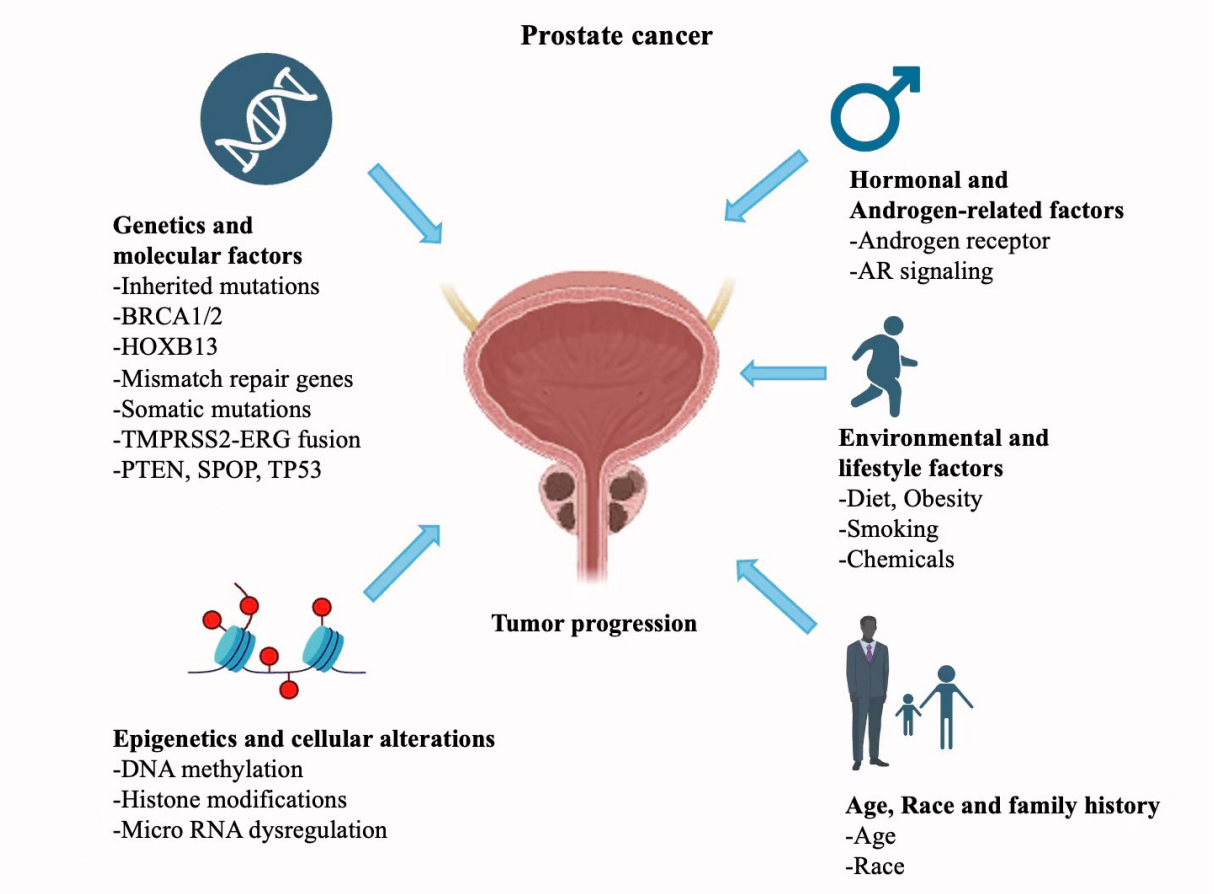

Figure 1. Environmental and molecular factors that drive prostate cancer development. This image shows a schematic complex interaction between genetic mutations, methylation epigenetic mechanisms, hormonal signaling lifestyle factors such as diet and smoking that contribute to the multifactorial nature of prostate cancer origin and spread.

of mCRPC by escaping or detecting novel ways of cheating from endogenous inhibition action of Androgen.

This issue became even more confusing in the last couple of years, when a revolution was being created with molecular diagnostics, with therapeutic targeting that was designed to overcome this and treat for resistance. Novel options in genomic profiling (liquid biopsies as circulating DNA sequencing) and high-level imaging (PSMA-PET) can now provide abundant information on tumor biology and the possibility to accurately risk-stratify patient[s] by dynamic monitoring [17]. In addition, the identification of specific biomarkers such as mismatch repair deficiency and homologous recombination repair defect has an immediate impact on the definition of treatment-induced exposure to relevant target therapies (eg: PARP inhibitors; immunotherapies) [18]. The combination of these molecular tools has led precision medicine to appear as a novel concept for prostate cancer treatment, where therapy is tailored on the basis of the individual patient tumor model [19]. This review will critically review these developments and discuss how the most recent developments in molecular diagnostics combines with new forms of therapies to herald a more efficient and personalized future for management of prostate cancer.

Molecular diagnostics in prostate cancer

Strong and fast progress in molecular diagnostics has revolutionized the spectrum of prostate cancer treatment, enabling a move from a uniform practice in the detection of prostate cancer, prognostication, and management strategies to a more accurate, patient-specific approach [20]. While the conventional methods like PSA test, digital rectal examination (DRE), and systematic TRUS guided biopsy have been an important part, they too are plagued by severe drawbacks: being non-specific and finding it difficult to differentiate between indolent and invasive disease or to predict treatment outcomes [21]. Therefore, genomics, proteomics, and epigenetics studies are extremely valuable now, providing an unprecedented window on tumor biology, and facilitating the development of complex risk stratification models beyond what can be achieved by more traditional parameters alone [22].

The new diagnostic approach uses a multi-faced approach, employing a variety of biospecimens and novel technologies to capture an overall picture of the disease in an individual patient

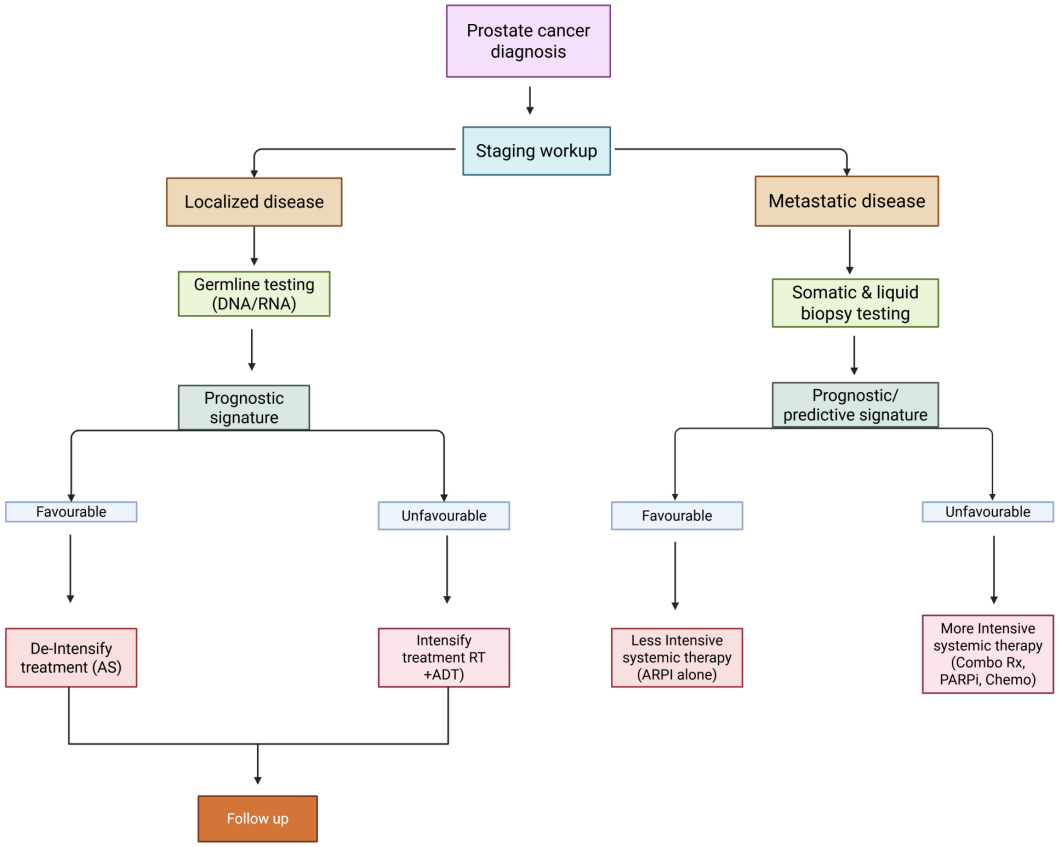

Figure 2. A framework for prostate cancer precision oncology. This schematic charts a biomarker-guided treatment approach through disease stages. In localized disease, germline testing and tissue-based genomic classifiers like Decipher and Prolaris are integrated with familiar clinical tests, including PSA and mpMRI, to improve risk stratification. This stratification informs therapy escalation or de-escalation. Evidence from novel imaging like PSMA-PET is confirmed that identifies metastatic disease, allowing liquid biopsy ctDNA to be used to provide a dynamic molecular profile. If the ctDNA signature is favorable, this approach circumvents aggressive therapy, permitting on-the-fly therapy adjustments in response to the tumor's evolution, but if unfavorable, therapy must be increased using novel agents or channeled into clinical trials.

in the form of a multi-faced portrait. This has enabled next-generation sequencing (NGS) panels to be employed now in order to diagnose both hereditary predisposition to cancer and acquired factors influencing progression and drug resistance [23]. Application of these technologies in the clinical setting has led to commercially available tests like Decipher, Oncotype DX Prostate, and Prolaris that provide validated molecular signatures to help with important decisions, specifically active surveillance versus definitive treatment of localized disease [24-26].

This comprehensive platform, shown in **Figure 2**, provides a formal model for clinical decision-making across the disease continuum from the use of germline and tissue-based genomic classifiers in localized disease to using liquid biopsies to dynamically track disease real-time in metastatic disease settings [27].

Genomic and epigenetic biomarkers: deciphering the molecular blueprint

Multifaceted topography of genomic and epigenetic changes that contribute to the development and resistance to therapy of prostate cancer has revealed by extensive molecular profiling [28]. High-throughput NGS has played a major role in the discovery of key driver mutations that inform treatment choices and prognosis [29]. These include mutations in the tumor suppressor genes like BRCA1 and BRCA2 which predisposes the individual to a considerably elevated risk of aggressive disease, early metastasis and cancer-specific mortality. These technological changes in the homologous recombination repair (HRR) pathway significantly affect the sensitivity to the PARP inhibitors based on the principle of synthetic lethality [30].

Equally, constitutive activation of PI3K/AKT/mTOR pathway by the frequent deletion or mutation of the PTEN tumor suppressor gene in advanced PCa, which facilitates cell survival, proliferation, and resistance to androgen receptor-targeted therapies, is an established biomarker of poor prognosis [31, 32]. The other

Table 1. Commercially available molecular biomarker tests for prostate cancer diagnosis and risk stratification.

Test name	Company / Developer	Biomaterial	Biomarker targets	Primary clinical utility	Key function and outcome	Regulatory status
PHI (Prostate health index)	Beckman coulter	Blood serum	[-2] proPSA, fPSA, tPSA	Initial biopsy	Improves specificity for detecting clinically significant PCa over PSA alone; differentiates PCa from benign conditions.	FDA approved
4Kscore	OPKO health	Blood plasma	tPSA, fPSA, intact PSA, hK2	Initial & Repeat biopsy	Predicts probability of high-grade (Gleason ≥7) PCa; helps avoid unnecessary biopsies in men with elevated PSA.	CLIA certified
PCA3 (Prostate cancer antigen 3)	Hologic	Post-DRE urine	PCA3 mRNA (non-coding RNA)	Repeat biopsy	Overexpressed in >90% of PCa; reduces unnecessary repeat biopsies following a negative initial biopsy.	FDA approved
ExoDX prostate (IntelliScore)	Bio-Techne	Urine	Exosomal RNA (ERG, PCA3, SPDEF)	Initial & Repeat biopsy	Risk score for predicting high-grade PCa upon initial biopsy; minimizes unnecessary procedures.	CLIA certified
SelectMDx	MDxHealth	Post-DRE urine	mRNA (HOXC6, DLX1), PSA	Initial & Repeat biopsy	Identifies men at high risk for clinically significant PCa; used to decide on the need for initial biopsy.	CLIA certified
TMPRSS2-ERG	Various labs	Post-DRE urine / Tissue	TMPRSS2-ERG Gene Fusion	Initial biopsy	Specific marker for PCa; presence associated with higher tumor volume and aggressiveness.	Laboratory developed test (LDT)
MiPS (Mi-prostate score)	Michigan laboratories	Post-DRE urine	PCA3, TMPRSS2-ERG mRNA, PSA	Initial biopsy	Combines serum PSA with urinary RNA markers to predict risk of high-grade PCa.	CLIA certified
ConfirmMDx	MDxHealth	FFPE tissue	DNA Methylation (GSTP1, APC, RASSF1)	Repeat biopsy	Detects an "epigenetic field effect"; identifies men with a negative biopsy who are at low risk for occult PCa, reducing unnecessary repeat biopsies.	CLIA certified

Abbreviations: CLIA: Clinical Laboratory Improvement Amendments; DRE: Digital Rectal Examination; fPSA: free PSA; FFPE: Formalin-Fixed Paraffin-Embedded; hK2: human Kallikrein 2; PCa: Prostate Cancer; tPSA: total PSA; TMPRSS2: transmembrane protease, serine 2; ERG: ETS-related gene; PCA3: prostate cancer antigen 3; HOXC6: homeobox C6; DLX1: distal-less homeobox 1; RASSF1: RAS association domain family member 1; APC: adenomatous polyposis coli; GSTP1: glutathione S-transferase pi 1.

common changes in the genome, including the mutations in the SPOP gene, influence the mechanisms of chromatin remodeling and repairs, which again highlight the significance of the full genomic profiling to stratify the risk factors [33].

In addition to the genome, the epigenetic alterations provide important information about the dynamic control of gene expression. These critical pathways may be silenced by aberrant DNA methylation, especially hypermethylation of CpG islands on promoters of tumor suppressor genes, such as GSTP1, to promote tumorigenesis. Histone changes also contribute to the issue and clear patterns of dysregulation are observed in high-grade and metastatic tumors. The promise of these epigenetic alterations is enormous because they serve as early detection biomarkers and prognostic factors since they tend to change morphological appearance which is seen using standard histopathology [34]. Systematic analysis of these changes based on tumor tissue can now be done by commercial genomic and epigenetic panels, which furnish actionable information directing the choice of targeted therapy and surveillance strategies [35].

Advanced imaging and theranostics: the PSMA revolution

Prostate-Specific Membrane Antigen (PSMA) has become a guiding principle in diagnostic image and treatment that constitutes a strong theranostic paradigm. PSMA is a transmembrane glycoprotein that is highly overexpressed in cells of prostate cancer, and the level of expression has a high correlation with tumor aggressiveness, Gleason, score, and transition to metastatic castration-resistant disease [36]. The invention of PSMA-targeted PET images, including those complexed with Gallium-68 (68Ga) or Fluorine-18 (18F), has significantly improved sensitivity and specificity in the identification of not only primary tumors but also metastatic lesions to a higher extent than traditional imaging [37]. PSMA-PET/CT has been shown to be better primary staging in high-risk patients [38], restaging in biochemical recurrence [39], and primary selection of patients receiving PSMA-directed therapies [40]. The modality often identifies occult metastatic disease, which is not detected through conventional imaging, and it, therefore, makes a considerable change to the clinical management of the disease [41]. In addition to diagnostic use, PSMA is the ideal target of therapy. PSMA-guided radioligand therapies, including Lutetium-177 (^{177}Lu)-PSMA-617, cause cytotoxic radiation to PSMA positive cancer cells, limit off target effects, and enhance survival rates in men with end-stage metastatic castration-resistant prostate cancer (mCRPC) [42, 43].

Liquid biopsies and circulating biomarkers: real-time monitoring

The use of liquid biopsy technology is a breakthrough in the cancer monitoring process because it provides a non-invasive view of the tumor behavior and progression [44]. Circulating tumor DNA (ctDNA) is now becoming an exceptionally effective instrument in the era of precision medicine, as it provides an opportunity to measure the response to treatment in real-time, non-invasively, and identify the development of resistance [45]. Tumor fragmented DNA is released into the blood of both primary and metastatic lesions, representing the entire mutational map of the cancer [46]. ctDNA analysis is capable of identifying clinically significant genomic changes [43], identifying the emergence of resistant mutations (e.g., in the androgen receptor), monitoring clonal changes to therapeutic pressure, and prescriptively predicting treatment success well before radiographic evidence of its effect is evident. ctDNA profiling has a significant clinical application in directing therapeutic decisions in advanced or recurrent disease

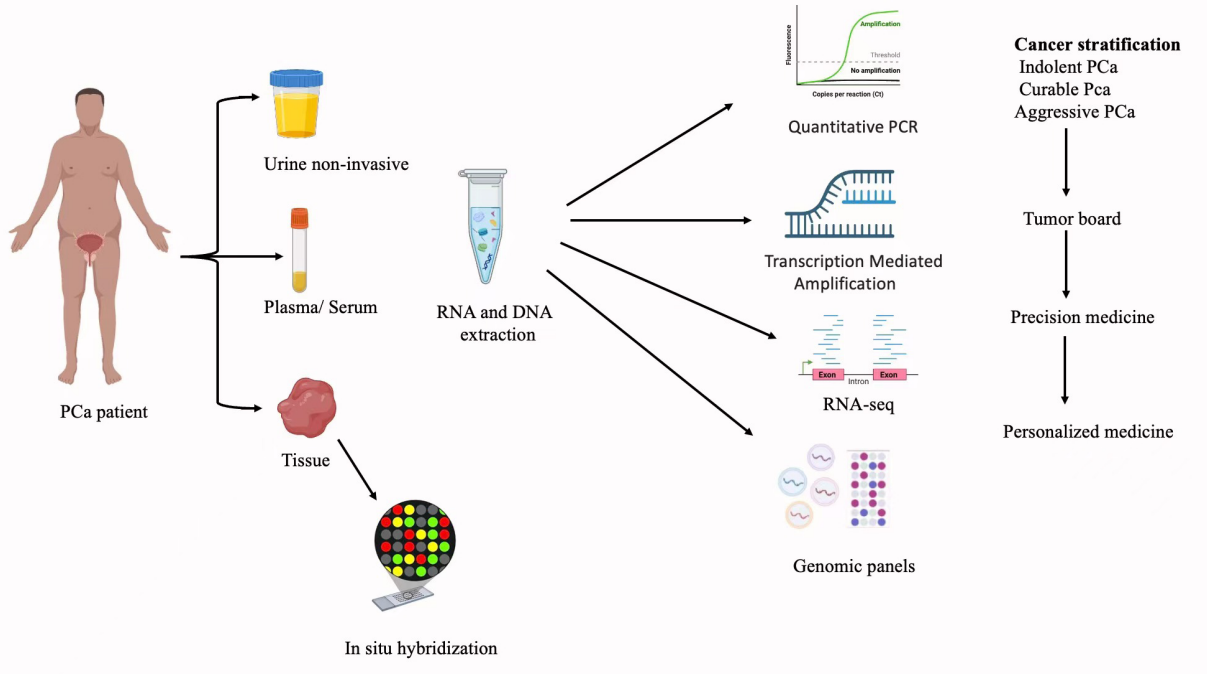

Figure 3. Integrated molecular diagnostic workflow for precision medicine in prostate cancer. Modernization of prostate cancer diagnosis combines utilization of a broad range of biospecimens and molecular techniques such as qPCR, sequencing, and genomic panels. With the help of that, tumors can be classified into three categories: indolent, curable, and aggressive. This combined molecular profiling serves the basis for tumor board discussions, due to which precision medicine options are developed, and personalized treatment schedules suitable for a particular patient are found.

patients where repeated invasive biopsies are not practicable and can be unable to detect tumor heterogeneity. Combining ctDNA analysis with other molecular diagnostics provides an innovative and intensive method of personalizing treatment based on the changing molecular pattern of an individual patient [47]. **Figure 3** shows modern molecular diagnostic workflow combined different types of samples and platforms to stratify tumors and direct personalized clinical management [48, 49].

Commercial biomarker tests for clinical decision-making

One example of molecular discoveries being translated into tools applicable to the clinical setting would be the creation and validation of a number of commercial biomarker tests. These assays have propelled genomic and transcriptomic profiling out of the research to mainstream urological practice with the objective data used to influence key decisions especially in the diagnostic and risk stratification phase of localized disease management [50]. These tests are done on different biospecimens such as blood, urine and tissue as summarized in **Table 1** to answer definite clinical dilemmas.

Urine tests such as PCA3, ExoDX, and SelectMDx are tests that identify PCa-specific RNA transcripts in detecting men at high risk of developing clinically significant disease, thus saving them the bother of undergoing unnecessary invasive procedures. Further predictive value of PSA is created through blood-based tests, such as the 4Kscore and Prostate Health Index (PHI), which adds the predictive value of the related kallikrein proteins [48, 49, 51, 52]. ConfirmMDx is a tissue-based epigenetic test that can be used on histologically negative biopsy cores in the past to identify a "molecular field effect" of occult cancer, to establish whether or not a repeat biopsy should be performed. The combination of these tools with diagnostic algorithms will enable a less risk-focused, more nuanced approach, which directly deals with the shortcomings of PSA and conventional biopsy [53].

Emerging therapeutic strategies

The treatment of prostate cancer has transformed itself on a paradigm shift away being a one-size-fits-all therapy to a precision based oncology paradigm that has been shaped by the convergence of molecular diagnostics and rationally designed targeted therapies [16]. Although conventional therapies such as surgery, radiotherapy, and androgen deprivation therapy (ADT) are still considered the basis, they are often associated with great toxicity and acquisition of therapeutic resistance, especially in the advanced disease [54]. Such adverse effects of treatment, as is described in **Table 2** including functional impairments of local treatment, but also systemic complications of hormone manipulation and chemotherapy [55-57] have been a significant stimulus to the development of more selective biomarker-based approaches capable of producing maximum efficacy and minimum harm.

Biomarker-guided therapies

The most impactful advancements in prostate cancer treatment are those based on molecular profiles. A major challenge in advanced disease is resistance to therapies that target the androgen receptor (AR). **Figure 4** illustrates that castration-resistant prostate cancer (CRPC) cells acquire a wide range of escape mechanisms, including AR splice variants (e.g., AR-V7), androgen production within tumors, amplification of the AR gene, and activation by various ligands [23, 58-63]. AR-V7 in circulating tumor cells (CTCs) has emerged as a reliable liquid biopsy biomarker to guide treatment selection in identifying a group with a lower likelihood of response to next-generation AR-targeted therapies, potentially necessitating taxane chemotherapy sooner [58].

Inhibitors of poly (ADP-ribose) polymerase (PARP), such as olaparib and rucaparib, should be considered among the most effective therapies guided by biomarkers. These are agents that exploit the idea of synthetic lethality in tumors with homologous recombination repair (HRR) deficiencies, particularly in those with mutations in the BRCA1/2 gene [23, 63]. Recent endorsements

Table 2. Spectrum of treatment-related adverse effects in prostate cancer management.

Treatment modality	Common short-term adverse effects	Common long-term adverse effects
Active surveillance/watchful waiting	Haematuria; dysuria; erectile dysfunction; unexplained weight loss	Disease progression; skeletal-related events; cancer-specific mortality
Surgery (Radical prostatectomy)	Erectile dysfunction; urinary incontinence	Persistent erectile dysfunction; chronic urinary incontinence
Radiotherapy	Gastrointestinal irritation (diarrhoea, rectal bleeding); genitourinary symptoms (urgency, haematuria); fatigue	Chronic bowel dysfunction; erectile dysfunction; persistent urinary symptoms; secondary malignancies
Androgen deprivation therapy	Hot flushes; fatigue; reduced libido; cognitive changes; bone pain flare	Osteoporosis; sarcopenia; metabolic syndrome; weight gain; persistent sexual dysfunction
Novel AR-targeted agents		
· Enzalutamide	Fatigue; cognitive impairment; falls; fractures	Persistent cognitive effects; osteoporosis
· Abiraterone	Fluid retention; hypertension; hypokalaemia; hepatotoxicity	Cardiovascular complications
Chemotherapy (Taxanes)	Myelosuppression; peripheral neuropathy; fatigue; alopecia; nausea	Chronic neuropathy; persistent fatigue; oedema

have broadened to encompass a larger spectrum of HRR genes beyond BRCA1/2, and combined strategies using PARP inhibitors with AR-directed treatment are also showing considerable survival benefits in both metastatic castration-resistant prostate cancer (mCRPC) and metastatic castration-sensitive prostate cancer (mCSPC), establishing a new first-line treatment option for a specific group of patients. Regulatory authorizations for several PARP inhibitors in this group characterized by specific molecular traits have been granted thanks to pivotal clinical trials, establishing it as the new standard of care and demonstrating the essential value of extensive genomic profiling [64, 65].

The arsenal for prostate cancer also features immunotherapies, which rely significantly on specific biomarkers. Checkpoint inhibitors like pembrolizumab have shown impressive results, but primarily within a small percentage of tumors exhibiting high microsatellite instability (MSI-H) or a high tumor mutational burden (TMB-H). This has led to tissue-agnostic FDA approvals that highlight a treatment strategy based on molecular phenotype rather than the tissue of origin [66]. These include bispecific T-cell engagers (BiTEs) that focus on PSMA and CD3, along with chimeric antigen receptor (CAR) T-cell therapies aimed at PSMA and NKG2D ligands, both showing initial efficacy in early-phase clinical trials of heavily treated mCRPC.

Targeted and PSMA-directed therapies

The use of prostate-specific membrane antigen (PSMA)-based therapies ranks among the most transformative advances in prostate cancer patient management and generated a new theranostic paradigm. Taking advantage of the promise for diagnosis by PSMA-PET, radioligand therapy uses agents such as Lutetium-177 (177Lu)-PSMA-617 to target radiotherapy to tumor environments and cells over-expressing PSMA [67]. A paradigm-changing phase III study (VISION, TheraP) has shown significantly better overall survival and radiographic progression-free survival in a heavily pretreated mCRPC population, culminating in worldwide regulatory approval. The efficacy of 177Lu-PSMA-617 in the mCRPC prechemo space has now been established by recent studies (PSMAFore), and is under study in metastatic disease hormone sensitive. It is this modality that confers the maximal tumour cell kill and minimum systemic toxicity [43]. The future of RLT lies in the development of more powerful alpha-emitting radionuclides, new PSMA-targeting vectors and tailored dosimetry for a better therapeutic index.

Besides PSMA, other popper agents that have been explored may contribute to the potential for overcoming resistance. Pathway inhibitors of the PI3K/AKT/mTOR pathways, frequently activated by PTEN loss, such as ipatasertib as AKT inhibitors combined with abiraterone have shown benefit in PTEN deficient tumors (major mechanism of resistance when AR is blocked) [68, 69]. There is also growing treatment related gap in t-NEPC, a lethal AR-indifferent state of cancer that needs to be filled by approaches encompassing dysregulated factors such as EZH2 and AURKA commonly observed in this terminal mode of disease [70, 71].

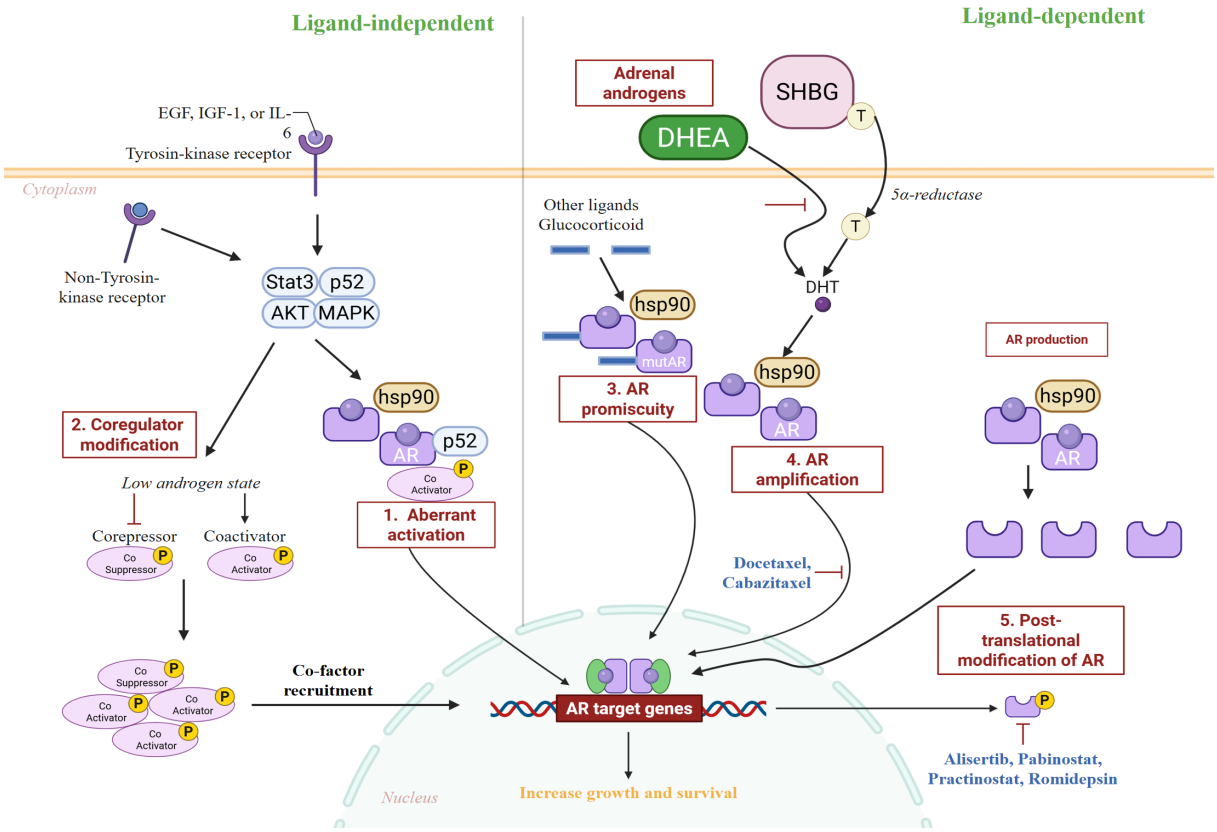

Figure 4. Mechanisms of therapy-induced AR adaptation in prostate cancer. Key molecular adaptations of the AR pathway that facilitate resistance to androgen deprivation therapy. The model highlights how prostate tumors bypass androgen blockade through alternative activation of wild-type AR (e.g., via growth factors, intratumoral androgens), structural alterations to AR itself (e.g., splice variants, mutations), and genomic changes (e.g., amplification). For each mechanism (1-5), corresponding investigational or approved therapeutic interventions are shown.

Combination strategies and future directions

The therapeutic combination is considered as the key in order to make treatment more effective, to avoid resistance and to tackle various tumor heterogeneity [72]. BIG ranks high among such priorities; CO AR-guided therapies combined with PARP, AKT or strong biological synergy within a given tumor — e.g., chemotherapy. Novel practice-changing trials show that AR-pathway inhibitor early intensification plus docetaxel or PARP inhibitor improves survival in mCSPC patients and support this treatment approach. These strategies are designed to overcome androgenic-dependent tumor growth and at the same time set up a resistance escape route, resulting in a more effective anti-tumor response [68, 73-75]. Treatment that is adjusted to the individual patient, based on real-time monitoring of molecular information from circulating Tumor DNA (ctDNA), are adaptive treatment schedules that might optimize personalized therapy.

Longitudinal liquid biopsy would facilitate exploration of treatment cycling toward clinical relevance and manipulation of dynamic tumor biology. Having said this, and despite the promising data generated in such a rapidly expanding field, substantial obstacles remain for both researchers and clinicians in the form of intra-tumor heterogeneity, cancer cell plasticity and lineage switching [76-78], as well as cost and complexity profiles of molecularly targeted therapy. Hence, the future of research should aim for universal detection of biomarkers, multimodal strategic therapy combinations (e.g., RLT plus immunotherapy or PARP inhibitors) and construction of scalable and fair precision medicine model to adapt the dynamic molecular profile in each patient's disease [79].

Challenges and future directions

Although we have witnessed extensive advances and promising technologies in molecular diagnostics and therapeutic strategies, the treatment of prostate cancer is still challenged by formidable obstacles that limit the ability to fully achieve precision medicine. In addition to the factors discussed above, tumor heterogeneity has emerged as one of the most challenging and inherent obstacles, which presents itself across patients (interpatient heterogeneity) and even throughout different regions in an individual's tumor (intratumoral heterogeneity) [80]. The genetic variation in prostate cancer, consist of diverse hormones somatic mutations and hormone-induced gene expression profilesurthermore, it entails all ranges of interaction: complex and long-range chromosomal rearrangements to simple changes (e.g., with bioactive cell active peptides) and coding-sense point mutations. This heterogeneity makes treatment prediction complex, as different tumors of the same subtype can show very different clinical behavior, respond differently to the same therapy and develop distinct mechanisms of resistance during disease progression [81]. It reflects the reality that we have to try different drug types and combinations given every patient's head and neck cancer is unique, meaning one-size-fits-all treatments don't work. Intratumoral heterogeneity also promotes Darwinian evolution; preexisting or treatment-selected subclones may harbor unrestrained growth or resistance mechanisms that allow them to escape initial therapies, leading to progression of disease, metastases, and therapeutic failure. To traverse this complexity, high-resolution molecular profiling at single-cell granularity and regular longitudinal dynamic of tumor evolution with approaches like liquid biopsies repeated in time are necessary.

Resistance to therapy is a major problem in treatment of patients with prostate cancer. Even with new targeted therapies, immunotherapy and rational combinations, tumors often develop resistance in numerous ways (adaptive) [3, 72]. Changes in the androgen receptor A. Receptor gene amplifications, LBD mutations of the receptor (e.g., F876L) or expression of constitutively active AR splice variants (e.g., AR-V7) can lead to resistance against both traditional androgen deprivation and modern AR-targeted treatments [58, 82]. In addition, the induction and phosphorylation of other survival and growth signaling pathways, including PI3K/AKT/mTOR, MAPK or Wnt/β-catenin, allow tumor cells to acquire resistance during subsequent cycles of initial inhibitory treatment while they proliferate and survive [82, 83]. Additional layers of complexity in therapeutic approaches related to epigenetic plasticity and phenotypic switching, including transformation towards an aggressive treatment-emergent neuroendocrine prostate cancer (t-NEPC) phenotype also frequently occur in rapidly fatal disease [70, 77]. The development of such complex resistance mechanisms highlights the immediate necessity for real-time molecular surveillance within hospital practice to allow rapid recognition of adaptive shifts and prompt adaptation of treatment paradigms [77, 84]. Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) tests are useful for detecting resistance mutations and monitoring tumor evolution non-invasively. Yet, technical limitations concerning low and high-frequency detection, logistics in sample handling as well as acceptable test price prohibit their broad use in clinical routine applications still [85, 86].

Apart from tumor heterogeneity and resistance to drug, the reliable verification and practical application of new type of biomarker are the main obstacles for precision medicine. Discovery phase studies have identified several highly promising biomarkers, across all the genomic -omics (genomic, epigenomic, proteomic, metabolomic) however to become robust useful tools in a clinical setting the discovery-phase findings need widespread prospective multicenter validation trials [87, 88]. This approach is essential to demonstrating the test's analytical validity, clinical sensitivity and specificity, prognostic value and – most importantly- predictive value that can guide decisions about treatment in different populations of patients [89]. In the absence of robust validation, novel markers could be overestimated with regard to their clinical value or a practice may be adopted that does not significantly benefit patients. Furthermore, harmonization of assay-related methods, QC procedures and interpretative criteria is critical for enabling uniformity and consistency between various laboratories and clinical areas [90, 91]. Regulation of companion diagnostics, payer reimbursement strategies, and the harmonization of advanced molecular data with existing clinical decision making processes are a few other critical issues that need to be addressed in an organized fashion to overcome barriers for the integration and use of biomarker-based precision medicine.

In the near future, different strategies and technology developers have a great deal of promise to address those limitations. Creating large, comprehensive panels of integrated biomarkers from multiple omics—genomic, transcriptomic, epigenetic, proteomic and imaging—will yield a more complete picture of the biology of tumors and lead to better risk stratification and informed decisions [92, 93]. Such an "adaptive" or "N-of-1" approach to therapy, wherein real-time molecular data on individual lesions obtained from liquid biopsies is hierarchically integrated into its current treatment, has the potential for improving outcomes over long-term periods by dynamically tailoring interventions to the cancer's evolving local milieu, effectively shifting from a static to dynamic treatment paradigm [94, 95]. Moreover, recent advances in machine learning and artificial intelligence (AI) can enable processing of high-dimensional complex datasets, discovery of hidden predictive patterns, and generation of prospective clinical decision support to an extent that has not previously been possible [96, 97]. This will be crucial, and academia - industry - regulatory

alliances will all need to cooperate in a spirit of partnership if the field is to advance biomarker qualification; promote innovative clinical trial designs, including consideration of adaptive designs; increase access for patients who might benefit from beneficial treatments/diagnostics whether they have unmet medical needs or not [98, 99].

In the end, overcoming the obstacles of tumor heterogeneity, treatment resistance, and biomarker validation is critical to delivering on the possibilities promised by precision medicine in prostate cancer [83, 100]. Although it is an exciting and considerable progress, future development would rely on ongoing scientific discovery and translating sophisticated molecular knowledge into practice with prudence [80, 101]. By addressing these issues collectively, the field can strive for truly personalized care that optimizes survival while minimizing treatment-related toxicity and maximizing quality of life for the patient with prostate cancer [19, 102].

Conclusion

The therapeutic landscape for prostate cancer is undergoing a profound transformation as the treatment paradigm shifts from a one-size-fits-all to a personalized, molecularly-targeted approach. The review also found that advances in molecular diagnotics (tissue based genomic classifiers, PSMA-PET scanning, liquid biopsy) now giv eof an ability to completely characterise tumour biology permitting better risk stratification and monitoring. Ironically, though the diagnosis of prostate cancer has been modernized with advances in imaging technology, the treatment landscape has changed from traditional androgen deprivation to biomarker-based therapy with PARP inhibitors in homologous recombination repair deficient tumors and immune checkpoint inhibitors in high microsatellite instability disease. The most outstanding progress has been made in therapy PSMA-targeted radioligand therapy, a paradigmatic treatment approach in the theranostic revolution interconnecting diagnostic imaging and effective treatment.

But barriers to the full implementation of precision medicine are formidable. Tumor heterogeneity of an extraordinary manner and adaptability potential of cancer cells are the main reasons for unavoidable drug resistance. New biomarkers will only be integrated as validated clinical tools through rigorous prospective validation and standardisation. Dismantling these silos with integrated multi-omics profiling, interpretation of complex information by artificial intelligence, and building capacity for adaptive clinical trials based on liquid biopsy in the context of personalized medicine is the future in clinical genomics. To ensure these novel approaches are accessible to all, academia, industry and regulators need to collaborate. Amidst all these challenges, this field can work towards a distant future where treatment for prostate cancer is truly personalized to achieve the maximal efficacy and minimal toxicity and ultimately with improved long-term outcomes in our patients.

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Ethical policy

Non applicable.

Availability of data and materials

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

Author contributions

Amira Guedouar contributed to the conception of the review, literature screening, data synthesis, and drafting of the manuscript. Enas Roumieh participated in literature retrieval, verification of extracted information, and critical revision of the final manuscript.

Competing interests

The author declares no competing interests.

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None.

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