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Prostate Cancer: Genetics, Epidemiology, Diagnosis, Therapeutic Advances, and Emerging Alternative Approaches

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ABSTRACT

Prostate cancer (PCa) remains the second most commonly diagnosed malignancy in men and a leading cause of cancer-related mortality worldwide. Its etiology is multifactorial, shaped by age, ethnicity, environmental exposures, lifestyle factors, and a strong hereditary component, with germline mutations in DNA repair genes such as BRCA1/2, ATM, CHEK2, and HOXB13 playing a pivotal role in susceptibility and disease progression. Advances in molecular biology have revealed profound tumor heterogeneity and the contribution of androgen receptor signaling, epigenetic modifications, and microenvironmental interactions to disease pathophysiology. Screening and diagnostic approaches have evolved beyond conventional prostate-specific antigen (PSA) testing and digital rectal examination (DRE) to incorporate multiparametric magnetic resonance imaging (mpMRI), prostate-specific membrane antigen positron emission tomography (PSMA-PET), and emerging biomarker panels, enabling earlier detection and risk stratification. Treatment modalities range from active surveillance for indolent disease to surgery, radiation, androgen deprivation therapy, and systemic agents, including next-generation androgen receptor inhibitors, chemotherapy, PARP inhibitors, and radioligand therapies. Despite these advances, treatment resistance, adverse effects, and risk of overtreatment persist, driving exploration of complementary strategies such as immunotherapy, phytochemicals, nanomedicine, and gene-based interventions. This review provides a comprehensive synthesis of genetic determinants, epidemiological trends, diagnostic strategies, therapeutic advancements, and alternative approaches to prostate cancer, emphasizing the need for precision medicine and multidisciplinary care to improve survival and quality of life.

Keywords: *Prostate cancer; genetics; diagnosis; biomarkers; treatment strategies; alternative approaches; precision oncology.*

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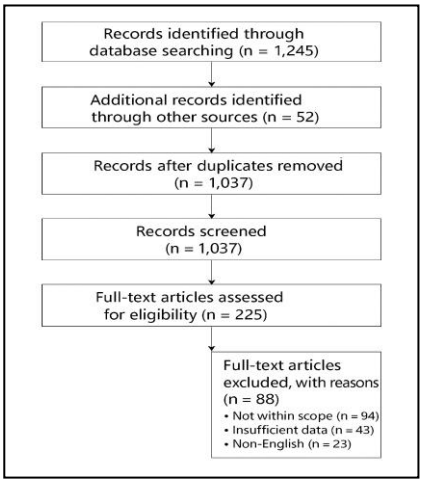
1. INTRODUCTION

Prostate cancer (PCa) remains one of the most significant health concerns affecting men worldwide (1), representing the second most frequently diagnosed solid-organ malignancy after lung cancer and a leading cause of cancer-related mortality (2). Globally, it accounts for over 1.3 million new cases and nearly 360,000 deaths annually, with prevalence particularly high among men over the age of 65 and those of African or Caribbean ancestry. The prostate, an accessory reproductive organ located below the bladder, gives rise to malignancies predominantly in the form of adenocarcinomas, most commonly originating in the peripheral zone (3). The etiology of PCa is multifactorial, shaped by a complex interplay of genetic predisposition, lifestyle factors, and environmental influences. Well-established non-modifiable risk factors include increasing age, family history, germline mutations, and ethnicity, while modifiable risk factors such as obesity, metabolic syndrome, dietary habits, and smoking have also been implicated (4). Genetic studies have provided compelling evidence for hereditary prostate cancer, with particular emphasis on androgen receptor signaling and genetic variants in androgen biosynthesis and metabolism pathways. These molecular insights not only improve our understanding of carcinogenesis but also provide opportunities for biomarker discovery and targeted therapy (5). Diagnosis of PCa typically relies on prostate-specific antigen (PSA) testing, digital rectal examination, imaging modalities, and histopathological confirmation through biopsy (6). Despite advances in screening and early detection, challenges remain regarding the balance between overdiagnosis, overtreatment, and optimal management strategies (7). Current therapeutic options range from active surveillance to surgery, radiation, chemotherapy, and androgen-deprivation therapy. However, significant morbidity, high costs, treatment resistance, and adverse effects continue to underscore the need for safer, cost-effective, and more personalized treatment approaches (8). In this review, we present a comprehensive synthesis of the genetics, epidemiology, diagnostic advances, conventional treatment strategies, and emerging alternative approaches to prostate cancer, aiming to provide a holistic perspective on the current complexities of the disease.

2. METHODS

A comprehensive literature search was conducted using **PubMed, Scopus, Web of Science, and Google Scholar** to identify relevant studies published. The search was restricted to peer-reviewed articles in English, including original research, systematic reviews, meta-analyses, and clinical guidelines. A combination of Medical Subject Headings (MeSH) and free-text keywords was employed to capture the breadth of research on prostate cancer. The primary search terms included *"Prostate cancer," "Prostatic neoplasms," and "Prostate carcinoma."* To address the genetic and molecular dimensions, terms such as *"Genetic susceptibility," "Germline mutations," "Somatic mutations," "DNA repair genes," "BRCA1," "BRCA2," "ATM," "HOXB13," "TP53," "MSH2," "MSH6," "Tumor heterogeneity," and "Genomic profiling"* were applied. Epidemiological and clinical relevance was captured using terms such as *"Epidemiology," "Incidence," "Prevalence," "Mortality," and "Risk factors."* For diagnostic strategies, keywords included *"Prostate-specific antigen (PSA)," "Digital rectal examination," "MRI," "Biomarkers," and "Liquid biopsy."* To cover therapeutic interventions, the search incorporated *"Androgen deprivation therapy," "Androgen receptor antagonists," "Enzalutamide," "Abiraterone," "Docetaxel," "Radiotherapy," "Chemotherapy," "Immunotherapy," "PARP inhibitors," "Olaparib," and "Rucaparib."* Finally, for complementary and emerging modalities, terms such as *"Phytotherapy," "Natural products," "Nutraceuticals," "Nanomedicine," "Gene therapy," and "Alternative medicine"* were included. Boolean operators (*AND*, *OR*) were systematically applied to combine terms, ensuring comprehensive coverage. Reference lists of retrieved articles were also screened to capture additional relevant publications.



PRISMA Flow Diagram

3. TUMOR HETEROGENEITY AND HERITABILITY OF PROSTATE CANCER

One of the most striking features of PCa is its biological complexity and diversity (9). Even in its localized stage, PCa rarely behaves as a single uniform disease (10). Instead, multiple tumor foci often develop within the prostate (intertumoral heterogeneity), each harboring distinct genetic alterations that drive differences in growth rate, metastatic potential, and treatment response (11). Within a single lesion, cancer cells may evolve from different ancestral cells or diverge from a single clone into multiple genetically unique subclones (12). In advanced disease, metastatic sites—though clonally related—frequently contain molecularly distinct subpopulations, further complicating therapeutic decision-making (13).

This heterogeneity challenges the traditional notion of a "dominant cancer lesion" guiding clinical outcomes (14). It also limits the predictive value of conventional prostate biopsies, since sampling a single lesion may not reflect the broader genomic landscape of the disease (15). Moreover, current therapies such as androgen deprivation therapy (ADT) and next-generation hormonal agents, while initially effective, can inadvertently fuel tumor diversity and resistance, underscoring the need for precision medicine approaches tailored to individual molecular profiles (16).

Adding another layer of complexity is the strong genetic heritability of prostate cancer (17). Large-scale population studies provide compelling evidence that inherited predisposition plays a central role in disease risk (18). The landmark Norwegian Twin Cancer Study estimated that nearly 57% of prostate cancer susceptibility is explained by heritable factors, making it one of the most heritable common cancers (19). Similarly, data from the Prostate Cancer data Base Sweden (PCBaSE) revealed that men with an affected brother face a dramatically higher lifetime risk—rising to 30% by age 75, compared to just 13% in those without a family history (20).

4. GENETIC SUSCEPTIBILITY GENES IN PROSTATE CANCER

Building upon the strong evidence for heritability, research over the last two decades has identified several high-penetrance germline mutations that significantly contribute to prostate cancer risk, aggressiveness, and treatment response (21–23). These genes are primarily involved in DNA repair pathways, transcriptional regulation, mismatch repair, and tumor suppression (4). Their characterization not only improves our understanding of prostate carcinogenesis but also provides actionable insights for risk stratification, screening, and targeted therapy (2).

DNA Repair Genes

- **BRCA2**: The most strongly implicated gene, with carriers showing a 2.5–8.6-fold increased risk of prostate cancer by age 65. BRCA2 mutations are associated with aggressive disease, higher Gleason scores, poor survival, and sensitivity to PARP inhibitors (24–26).
- **BRCA1**: Confers a moderate (≈3.7-fold) increased risk, though less pronounced than BRCA2. Still linked with early-onset and aggressive disease in some cohorts (25–28).
- **ATM**: Commonly altered in metastatic prostate cancer. ATM loss contributes to genomic instability, though its therapeutic implications differ from BRCA2 (29–31).
- **PALB2**: Partner of BRCA2 in homologous recombination repair. Recent evidence links PALB2 mutations to aggressive prostate cancer and possible resistance to PARP inhibitors (32).
- **CHEK2**: Founder mutations (e.g., 1100delC, IVS2+1G>A) confer a moderate risk, especially in Eastern European cohorts. Certain variants correlate with lethal PCa (33).
- **NBN (NBS1)**: The 657del5 founder mutation is strongly associated with familial prostate cancer and poor survival (21).

Developmental and Transcriptional Regulators

- **HOXB13**: The G84E variant is the most well-established prostate-specific risk allele, associated with early-onset and familial prostate cancer, although not strongly linked with aggressiveness (34).

Mismatch Repair (MMR) Genes – Lynch Syndrome

- **MSH2, MSH6, MLH1, PMS2**: Carriers of Lynch syndrome mutations show elevated prostate cancer risk, particularly with MSH2 variants (cumulative incidence up to 23.8% by age 75) (25,26,35).

Tumor Suppressors

- **TP53**: Classically associated with Li-Fraumeni syndrome, germline TP53 mutations confer aggressive prostate cancer phenotypes with high Gleason scores and poor survival, highlighting the need for genetic testing in affected families (36).

5. EPIDEMIOLOGY

Globally, PCa is the second most frequently diagnosed malignancy in men, with 1.4 million new cases and ~375,000 deaths reported in 2020. Incidence is highest in North America, Europe, the Caribbean, and Australia/New Zealand, largely due to widespread prostate-specific antigen (PSA) testing, while mortality remains disproportionately higher in sub-Saharan Africa, the Caribbean, and parts of South America, reflecting disparities in healthcare access and infrastructure. Projections suggest that by 2030, the global burden will rise to ~1.7 million new cases and nearly 500,000 deaths, driven by population aging (37). In the United States, recent SEER 2025 estimates indicate an incidence rate of 120.2 per 100,000 men per year and a mortality rate of 19.2 per 100,000 men per year (age-adjusted). The lifetime risk of developing PCa is approximately 12.9% (1 in 8 men), with an estimated 3.5 million men living with the disease in 2022. Stage distribution at diagnosis shows 69% localized, 14% regional, and 8% distant disease, with corresponding 5-year relative survival rates of >99%, ~99%, and ~32%, respectively. For 2025, SEER projects 313,780 new cases (15.4% of all new cancers) and 35,770 deaths (5.8% of all cancer deaths) in the U.S. These trends highlight the dual challenge of high survival in localized PCa versus poor outcomes in advanced disease, emphasizing the need for early detection, molecular risk stratification, and equitable access to care (38).

6. PATHOPHYSIOLOGY OF PROSTATE CANCER

Prostate cancer develops through a multifactorial process in which inherited susceptibility genes such as BRCA1, BRCA2, HOXB13, and ATM create a genetic background that predisposes men to malignant transformation, while acquired somatic alterations including TMPRSS2–ERG fusions, PTEN loss, MYC amplification, and defects in TP53 or RB1 progressively disrupt genomic stability and cellular signaling (39,40). These cumulative alterations initiate prostatic intraepithelial neoplasia, which represents a morphologic transition state between normal glandular epithelium and invasive carcinoma, and the shift is reinforced by aberrant activation of the androgen receptor (AR) pathway, where receptor amplification, mutations, and splice variants allow sustained growth even under androgen deprivation (41,42). In parallel, epigenetic changes such as GSTP1 promoter methylation and histone modifications remodel chromatin architecture and silence tumor suppressor networks, further tipping the balance toward malignancy (43,44). As the neoplasm expands, the tumor microenvironment comprising fibroblasts, endothelial cells, immune populations, and extracellular matrix undergoes dynamic remodeling that fosters angiogenesis, epithelial–mesenchymal transition, and immune evasion, while continuous clonal evolution generates intratumoral heterogeneity with distinct subclones that adopt lineage plasticity or undergo neuroendocrine differentiation (45,46). With disease progression, genomic instability accelerates metastatic dissemination, with a tropism for bone, lymph nodes, and visceral sites, and eventually tumors acquire the ability to thrive in the low-androgen milieu created by therapy, giving rise to castration-resistant prostate cancer (CRPC) (47). This stage is sustained by constitutive AR signaling, intratumoral steroidogenesis, and compensatory activation of bypass cascades such as PI3K/AKT/mTOR, WNT/β-catenin, and DNA repair pathway defects, which collectively produce a highly adaptable, treatment-resistant malignancy that represents the ultimate clinical challenge in prostate cancer management (48,49).

7. RISK FACTORS

PCa arises from a multifactorial interplay between nonmodifiable and modifiable determinants (50). Nonmodifiable risk factors such as age, family history (51), and germline mutations (BRCA1/2, HOXB13, ATM) remain the strongest contributors (3), while polygenic risk scores (PRS) integrating >260 SNPs further refine individual susceptibility (52). Lifestyle and dietary factors also exert a significant impact: high dairy intake, red/processed meat consumption, and obesity have been linked to increased risk, whereas physical activity, vegetarian/soy-based diets, legumes, coffee, and lycopene-rich foods appear protective. In addition, metabolic syndrome, prostatitis, infertility, and exposure to pesticides, heavy metals, or night-shift work represent emerging contributors. Infectious agents such as HPV-16 and sexually transmitted infections may promote carcinogenesis, while higher ejaculation frequency seems protective. Socio-demographic factors, including marital status and social deprivation, influence stage at diagnosis and treatment outcomes rather than disease initiation. These determinants are summarized in **Table 1**.

Table 1. Established and emerging risk factors for prostate cancer

Category	Risk Factors	Effect on Risk	Evidence Strength
Nonmodifiable	Age, family history, BRCA1/2, HOXB13, ATM, tall stature, baldness	↑ Risk	Strong–Moderate
Genetic Susceptibility	>260 SNPs, Polygenic Risk Scores (PRS)	↑ Risk (esp. early-onset)	Strong
Lifestyle/Diet	High dairy, red/processed meat, trans fats, obesity	↑ Risk	Moderate

	(aggressive PCa), smoking		
	Physical activity, vegetarian/soy diet, legumes, coffee, lycopene	↓ Risk	Moderate
Medical Conditions	Obesity, metabolic syndrome, prostatitis, infertility, vasectomy	↑ Risk	Weak–Moderate
	Type 2 diabetes mellitus	↓ Risk (possibly protective)	Weak–Moderate
Environmental /Occupational	Firefighting, police service, pesticides, chromium/cobalt, night-shift work	Slight ↑ Risk	Moderate
Infectious/Sexual	HPV-16, other STIs	↑ Risk	Emerging
	High ejaculation frequency	↓ Risk	Moderate
Socio-demographic	Unmarried/widowed status, lower socioeconomic background	Delayed diagnosis, poorer outcome	Moderate

SNP – single nucleotide polymorphism; PRS – polygenic risk score; STIs – sexually transmitted infections; PCa – prostate cancer. Note: "↑ Risk" indicates association with increased prostate cancer risk; "↓ Risk" indicates protective effect. Evidence strength is based on ***Bergengren et al. 2023*** (53)

8. DIAGNOSIS OF PROSTATE CANCER

The diagnosis of PCa remains a multidimensional process that integrates clinical screening, histopathology, imaging, biomarkers, and genetic testing. Early detection remains challenging, as most men with localized disease are asymptomatic (54).

Screening Approaches: The cornerstone of PCa screening continues to be PSA testing combined with digital rectal examination (DRE). PSA, a kallikrein-related serine protease secreted by prostatic epithelium, is not cancer-specific, and levels can also rise in benign prostatic hyperplasia (BPH) and prostatitis. PSA thresholds of 4–10 ng/mL carry ~25% likelihood of PCa, whereas levels >10 ng/mL confer >50% likelihood. While widespread PSA screening has reduced advanced-stage presentations, it is limited by overdiagnosis and overtreatment of indolent tumors, with high false-positive rates. Consequently, informed decision-making and age-adjusted baseline PSA determination are emphasized in current guidelines (55,56).

Histopathological Diagnosis: Confirmation requires prostate biopsy, obtained either transrectally or transperineally, typically under transrectal ultrasound (TRUS) or MRI guidance. Histological assessment using the Gleason grading system, revised by the International Society of Urological Pathology (ISUP) into grade groups 1–5, remains the gold standard for determining aggressiveness and guiding treatment decisions (57).

Advanced Imaging Tools: Imaging plays a pivotal role in staging and targeted diagnosis. Multiparametric MRI (mpMRI), integrating T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences, enhances localization, allows targeted biopsies, and reduces unnecessary sampling (58). Standardized interpretation via PI-RADS v2 has improved reproducibility. Prostate-specific membrane antigen positron emission tomography (PSMA-PET) outperforms choline or acetate PET for nodal and distant staging and has revolutionized detection of recurrent/metastatic disease, with ^68Ga-PSMA PET widely adopted (59).

Emerging Biomarkers: Several blood- and urine-based assays improve risk stratification before biopsy. The 4Kscore and Prostate Health Index (PHI) outperform PSA in predicting clinically significant PCa (csPCa) (60). IsoPSA differentiates PSA isoforms, while Proclarix combines multiple plasma proteins (PSA, free PSA, THBS1, CTSD) (61). Multivariable models like the Stockholm-3 test integrate PSA, SNPs, clinical variables, and novel biomarkers, outperforming PSA alone (62). Urine-based markers such as ExoDx Prostate (EPI), MyProstateScore, and SelectMDx demonstrate potential in identifying high-grade disease (63).

Genetic Testing and Precision Diagnostics: In recognition of the heritable component of PCa, the **NCCN guidelines (v1.2022; reaffirmed 2025)** recommend **germline genetic testing** for:

- Patients with high-risk, very high-risk, node-positive, or metastatic PCa.
- Men meeting family history criteria (BRCA1/2, Lynch syndrome, strong family history, Ashkenazi Jewish ancestry).
- Individuals with intraductal/cribriform histology or personal history of related cancers (breast, pancreas,

colorectal, melanoma, biliary tract, glioblastoma).

Genes to be prioritized include BRCA1, BRCA2, ATM, CHEK2, PALB2, and Lynch syndrome mismatch repair genes (MSH2, MSH6, MLH1, PMS2). Broader next-generation sequencing (NGS) panels are increasingly used, especially in advanced disease and clinical trial enrollment. Optimal delivery of germline testing remains debated, but genetic counseling and cascade testing are essential components of implementation (64).

9. PHARMACOLOGICAL INTERVENTIONS IN PROSTATE CANCER

Pharmacological management of prostate cancer has evolved substantially over the past several decades, transitioning from traditional androgen deprivation approaches to highly sophisticated molecularly targeted agents and immunotherapies (65). The therapeutic landscape reflects a deepening understanding of tumor biology, AR signaling, genetic vulnerabilities, and immune evasion mechanisms.

1. Androgen Deprivation Therapy – The Cornerstone

The earliest pharmacological approach, introduced in the 1940s following Huggins and Hodges' seminal work, was **ADT**, based on the androgen dependency of prostate cancer (66). ADT was initially achieved through surgical castration (orchiectomy), later replaced by pharmacological agents including (16):

- **Luteinizing hormone-releasing hormone (LHRH) agonists** (leuprolide, goserelin, triptorelin) that initially cause a testosterone surge followed by receptor downregulation (67).
- **LHRH antagonists** (degarelix, relugolix) that directly block gonadotropin release without the flare phenomenon (68).
- **Anti-androgens** (flutamide, nilutamide, bicalutamide) used to block androgen receptor binding, often in combination with ADT (combined androgen blockade) (69).

Despite efficacy, long-term ADT commonly leads to **castration-resistant prostate cancer (CRPC)**, driving the need for advanced pharmacological strategies (70).

2. Next-Generation Androgen Receptor Pathway Inhibitors

The understanding that CRPC remains AR-driven prompted the development of potent AR-targeting agents:

- **Abiraterone acetate**: A CYP17A1 inhibitor that blocks androgen biosynthesis in adrenal glands, testes, and tumor tissues, combined with prednisone to mitigate mineralocorticoid excess (71).
- **Enzalutamide**: A second-generation AR antagonist that inhibits nuclear translocation, DNA binding, and coactivator recruitment (72).
- **Apalutamide and Darolutamide**: Similar AR antagonists, approved for non-metastatic CRPC and metastatic castration-sensitive PCa, showing improved tolerability and survival benefit (73).

These agents have redefined standards of care, significantly extending survival in advanced disease (74,75).

3. Chemotherapy in Advanced Prostate Cancer

Chemotherapy became an important adjunct for CRPC, particularly for patients with visceral metastases or rapid progression:

- **Docetaxel**, a microtubule-stabilizing taxane, was the first chemotherapy to demonstrate survival benefit in metastatic CRPC (mCRPC), establishing it as frontline therapy (76).
- **Cabazitaxel**, a next-generation taxane effective in docetaxel-resistant cases, further improved outcomes (77).
- Combination regimens of docetaxel with ADT have also shown survival advantages in metastatic hormone-sensitive prostate cancer (78).

4. Radiopharmaceuticals

Advances in nuclear medicine introduced targeted radiotherapies:

- **Radium-223 dichloride**, an alpha-emitter targeting bone metastases, improved survival and reduced skeletal-related events in mCRPC (79).
- More recently, lutetium-177–labeled prostate-specific membrane antigen (^177Lu-PSMA-617) has demonstrated significant efficacy in patients with PSMA-positive metastatic disease, marking a breakthrough in theranostics (80).

5. Targeted Molecular Therapies

Genomic profiling has identified actionable mutations in subsets of prostate cancer:

- **PARP inhibitors** (olaparib, rucaparib, talazoparib, niraparib) exploit synthetic lethality in tumors with homologous recombination repair (HRR) deficiencies such as BRCA1/2 and ATM mutations (81).
- Combination strategies, including PARP inhibitors with AR antagonists (e.g., olaparib + abiraterone), are under clinical evaluation to overcome resistance (82).
- Targeting PI3K/AKT/mTOR pathway alterations (e.g., ipatasertib) is also being actively explored (83).

6. Immunotherapy Approaches

While prostate cancer has been historically immunologically "cold," immunotherapy has gradually gained traction:

- **Sipuleucel-T**, an autologous dendritic cell vaccine, was the first FDA-approved immunotherapy for asymptomatic or minimally symptomatic mCRPC, offering modest survival benefit (84).
- **Immune checkpoint inhibitors**: Pembrolizumab (anti–PD-1) has shown benefit in subsets with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors (85).
- Ongoing trials are evaluating combinatorial regimens of checkpoint inhibitors with AR antagonists, PARP inhibitors, or radioligand therapies to enhance response (86).

7. Emerging and Investigational Therapies

Several promising pharmacological strategies are in late-stage development:

- **Bispecific T-cell engagers (BiTEs)** and **CAR-T cell therapies** targeting PSMA or other prostate-specific antigens (87).
- **Epigenetic modulators** and **metabolic pathway inhibitors**, aiming to tackle tumor heterogeneity and drug resistance (88).

10. CONCLUSION

Prostate cancer remains a major global health challenge, driven by complex interactions between genetic predisposition, molecular alterations, and environmental factors. Advances in our understanding of tumor biology have transformed the diagnostic and therapeutic landscape, moving from conventional digital rectal examinations and PSA testing to the integration of multiparametric imaging, molecular biomarkers, and genetic screening. Similarly, treatment strategies have evolved from traditional androgen deprivation therapy to next-generation androgen receptor inhibitors, taxane-based chemotherapy, targeted radioligand therapies, PARP inhibitors, and immunotherapeutic approaches. Despite these advances, challenges persist, including tumor heterogeneity, resistance mechanisms, and the risk of overdiagnosis and overtreatment. The future of prostate cancer management lies in precision medicine, guided by genomic profiling, biomarker-driven risk stratification, and the rational combination of systemic therapies. Continued research into molecular pathways, tumor microenvironment, and immune modulation is essential to develop more durable and patient-specific interventions. Ultimately, a multidisciplinary approach that integrates genetics, diagnostics, novel therapeutics, and patient-centered care offers the most promising path toward reducing mortality and improving quality of life for men affected by prostate cancer.

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