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Review

Familial Hereditary Prostate Cancer: Genetic, Screening, and Treatment Strategies

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Abstract

Genetic testing for prostate cancer (PrCa) has become more common in clinical practice due to the availability of targeted therapies for specific subgroups based on genetic characteristics. This requires examining multiple genes to enable more precise treatment sequences. Identifying hereditary PrCa can guide treatment decisions and impact cancer screening for patients and their relatives. Some mutations discovered through genetic testing may be hereditary, thus requiring germline testing from normal tissue within the framework of clinical counseling. Germline testing can provide valuable information for PrCa patients in terms of treatment options and screening for other cancers in their relatives. Guidelines suggest genetic testing for all individuals with metastatic PrCa and also consider family history and tumor features for broader testing criteria. BRCA2, the gene most strongly linked to inherited PrCa, is associated with poorer survival outcomes when deficient. Targeted therapies such as poly-ADP ribose polymerase inhibitors and platinum-based chemotherapy have shown promise in treating cancer cells with BRCA1/2 deficiencies. The increasing role of genetic testing in PrCa indicates the necessity to expand its indications and consider treatment implications for metastatic PrCa patients, as well as cancer risk assessment for early-stage disease. The collaboration of experts in molecular pathology, bioinformatics, biology, and genetic counseling is vital for the evolving landscape of PrCa care.

Keywords: Familial, genetic, prostate cancer, screening, treatment

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Prostate cancer (PrCa) is the second most prevalent male malignancy worldwide and ranks as the sixth leading cause of male cancer-related mortality.[1,2] Globally, PrCa has the highest incidence in North and South America, Europe, Australia, and the Caribbean.[3] The percentage of PrCa attributed to genetic factors has been estimated to be in the range of 5-15%. In Latin America, the mean incidence rate of PrCa in males aged 55 years or older was 344 cases per 100,000, with a mean mortality rate of 210 per 100,000.[4] Familial PrCa refers to a clustering of the disease within families, while hereditary PrCa (HPrCr) is a specific subtype of familial PrCa marked by a pattern consistent with the passage of a susceptibility gene via Mendelian inheritance.[5,6] Male first-degree relatives of PrCa patients have a three-fold increased risk of developing PrCa, with a higher risk observed among relatives of younger patients.[7,8] HPrCr is defined by a family history of three generations affected, three first-degree relatives affected, or two relatives affected before age 55.[9] Approximately 43% of men diagnosed with PrCa before age 55 have HPrCr.[10] Apart from specific genetic variants like RNaseL-, ElaC2-, MSR1-, HOXB13-, and low CAG repeats in the androgen receptor gene, no other high-risk genetic variants have been identified for hereditary PrCa.[11,12] The onset of HPrCr occurs about 6 years earlier than sporadic PrCa, but the clinical course is otherwise similar. The occurrence of familial and hereditary PrCa varies across different populations. In the Asian population, the frequency of familial PrCa was found to be 8.4%, with first-degree familial PrCa accounting for 6.4% and hereditary PrCa accounting for 0.9%.[13] In a study examining HBOC families, it was determined that 30.5% harbored germline mutations in susceptibility genes, with 21.6% exhibiting pathogenic variants (PVs) and 8.9% displaying variants of uncertain significance (VUS).[14] The prevalence of hereditary/familial PrCa is estimated to range from 10-20% globally.[15] In an investigation focusing on patients under active surveillance (AS) for PrCa, it was revealed that 21% possessed a family history of PrCa, while 1% had a family history of cancer.[16] Family history of PrCa, a malignancy with a strong genetic component, is considered an established risk factor for the disease, with inherited factors predicted to account for 40%-50% of cases.[17]

Epidemiological and pedigree studies have definitively established the presence of familial aggregation in PrCa, especially among those with early-onset PrCa, emphasizing the significant role of genetic factors.[15,18] The advancement of genetic testing technology has further propelled the examination of genetic status in familial hereditary PrCa, along with its treatment, screening, and prevention, attracting growing attention from the scientific and healthcare communities.[15] Thus, providing a comprehensive overview of recent progress in familial hereditary PrCa is crucial, particularly concerning epidemiological inquiries, lineage analyses, and the link between germline mutations in DNA damage repair genes (DDRGs) and heightened PrCa susceptibility. BRCA1 and BRCA2, as representatives of DDRGs, currently stand as the most extensively understood PrCa susceptibility genes.[19] Moreover, genes like ATM, PALB2, CHEK2, and mismatch repair (MMR) genes have also been associated with an increased PrCa risk. Additionally, genes such as HOXB13 have been suggested to potentially play a role in hereditary PrCa.[20] These germline mutations not only increase the risk of PrCa but also result in specific clinical and pathological characteristics, such as early onset, familial clustering, aggressive behavior, and poor prognosis. It is important to highlight that these germline mutations in susceptibility genes provide potential targets for therapeutic interventions. Consequently, the clinical management of familial hereditary PrCa differs significantly from that of sporadic PrCa.[21] In this study, we analyzed the latest advancements in genetic screening methods for detecting hereditary risk factors linked to prostate cancer. Furthermore, we delved into innovative therapeutic strategies targeting specific genetic mutations related to this condition.

Germline Mutations

Homologous Recombination Repair (HRR) Genes

Mutations in DNA repair genes are not only linked to PrCa susceptibility but are also associated with accelerated tumor progression, unfavorable prognosis, and treatment response. The emergence of PARP inhibitors has emphasized the significance of HRR genes in treating PrCa.[22] In a study on cases of early-onset/familial PrCa, harmful mutations in HRR genes were identified in 3.9% of patients. The genes with the highest mutation rates were CHEK2 and ATM, followed by PALB2 and NBN. Additionally, mutations were found in BRCA2, RAD51C, and BRIP1, although less frequently.[23] Germline mutations in genes responsible for DDRGs have been linked to the progression of PrCa and a shorter time until the onset of biochemical recurrence in African American males.[19] A thorough analysis of whole-genome sequencing in 600 individuals diagnosed with PrCa, including 300 African American men, revealed a higher occurrence of germline mutations in DDRGs among African American men, surpassing previous findings.[21] Specifically, germline mutations in RAD family genes (RAD54L, RAD54B, RAD51), PMS2, and BRCA1 were more frequent in African American men and showed potential for targeted treatments.[24] Additionally, the HR pathway was associated with a faster disease progression leading to biochemical recurrence in African American patients.[25] In a study of Mexican men with PrCa, 2% of the 199 cases had a pathogenic germline variant, including ATM, CHEK2, BRIP1, and MUTYH, suggesting that the genetic and/or epidemiologic risk factors for PrCa are not well understood in this population.[26] Moreover, mutations in MMR genes have been linked to clinicopathological characteristics and a shorter time to castration resistance in PrCa patients. In localized PrCa, germline mutations in DNA repair genes are infrequent (4.6%). However, in metastatic PrCa, the frequency rises to 11.8% (82/692), with patients displaying germline mutations in DNA repair genes such as BRCA2 (5.3%), ATM (1.6%), CHEK2 (1.9%), BRCA1 (0.9%), RAD51D (0.4%), and

PALB2 (0.4%).[27–29] Pathogenic germline mutations in these genes are closely linked to a higher risk of PrCa in males.

BRCA1/2

The BRCA1/2 gene, a tumor suppressor gene, encodes a protein that repairs double-stranded DNA using the homologous recombination pathway, crucial for maintaining genomic stability.[30,31] Mutations in this gene can disrupt the DNA damage repair process, increasing susceptibility to cellular genome instability and cancer development.[32,33] Cancer cells with mutant BRCA1/2 genes have defects in DNA repair mechanisms and are vulnerable to PARP inhibitors, which exploit faulty DNA repair mechanisms.[34] Carriers of pathogenic variants in these genes have an increased risk of developing PrCa and a higher risk of experiencing worse disease and prognosis.[28] Those with BRCA1 mutations have a three-fold increased risk, while carriers of BRCA2 mutations face a seven-fold increased risk.[35] BRCA2 alterations are found in some advanced PrCa cases and are associated with a higher tumor mutation burden and frequency of ATM and BRCA1 mutations.[36] Deleterious mutations in genes linked to HRR, such as BRCA1 and BRCA2, are found in a small number of people with early-onset/familial cases of PrCa. Among 462 individuals with early-onset/familial PrCa, harmful mutations were found in 3.9% of the patients. The most frequently mutated genes were CHEK2 and ATM, followed by PALB2 and NBN, and then by BRCA2, RAD51C, and BRIP1. Additionally, two patients had exonic rearrangements, one pathogenic in BRCA2 and the other of unknown significance in BRCA1.[23] In 2021, a Chinese study of 1,836 PrCa patients from 4 tertiary cancer centers (n=1,160) and a commercial laboratory (n=676) confirmed the association between BRCA2 germline mutations and PrCa risk, demonstrating an odds ratio of 15.3.[27] BRCA1/2 gene mutations have been found in familial hereditary PrCa in Italian families.[13,27] In a study of 180 HBOC families, 8.8% had pathogenic variants in BRCA1, while 9.4% had pathogenic variants in BRCA2.[37] Another study of 300 Italian patients with metastatic PrCa found a prevalence of 3% for BRCA2 mutations.[38] In 2023, a meta-analysis aimed to estimate the frequency of BRCA mutations in patients with PrCa. The study revealed that a small percentage of patients with any stage of PrCa had specific genetic mutations. Specifically, 0.73% and 1.20% of PrCa patients at any stage had germline and somatic BRCA1 mutations, respectively. Similarly, 0.94% and 1.10% of PrCa patients with metastatic disease carried germline and somatic BRCA1 mutations, respectively. Furthermore, 1.21% and 1.10% of patients with metastatic castration-resistant prostate cancer were found to have germline and somatic BRCA1 mutations, respectively. A higher percentage of patients were found to carry BRCA2 mutations. Specifically, 3.25% and 6.29% of PrCa patients at any stage had germline and somatic BRCA2 mutations, respectively. Among PrCa patients with metastatic disease, 4.51% and 10.26% were found to carry germline and somatic BRCA2 mutations, respectively. Similarly, 3.90% and 10.52% of mCRPC patients were found to carry germline and somatic BRCA2 mutations, respectively.[28]

Patients carrying BRCA1/2 germline mutations frequently display more aggressive cancer characteristics compared to those without these mutations. These characteristics encompass higher Gleason scores, a well-established grading system for PrCa that forecasts tumor aggressiveness, along with a swifter disease progression.[39] Additionally, the existence of BRCA1/2 mutations aids in identifying lymph node metastases during diagnosis, signifying a more advanced disease stage. As a result, patients with BRCA1/2 germline mutations may face a bleaker prognosis when undergoing surgical removal of the prostate (radical prostatectomy) or radiotherapy.[40] The BRCA2 mutation is linked to poorer survival, making timely genetic screening crucial. A study showed that men with BRCA2 germline mutations have an 8.6-fold higher risk of developing PrCa by age 65 compared to those without such mutations.[22] In another study, the overall likelihood of being diagnosed with prostate cancer by age 65 varied from 7% to 33%.[41] Beyond BRCA1/2 genes, germline mutations in other DDRGs may also contribute to varying degrees of increased PrCa risk.[42] PrCa patients with BRCA2 mutations showed shorter response times and lower median survival rates specific to their tumor. These patients had worse clinical outcomes when treated with AR-targeted therapies, including hormonal or taxane therapies.[43] Tumors with BRCA2 mutations had higher genomic loss-of-heterozygosity scores and often had elevated tumor mutational burden (TMB-high). Additionally, these tumors had increased expression of cell cycle genes and were enriched in cell cycle signaling programs, which may indicate susceptibility to platinum-based chemotherapies.[44] The co-occurrence of somatic BRCA2-RB1 co-deletion and MYC amplification in BRCA2-mutated tumors also contributed to poor clinical outcomes.[45] This demonstrates the autonomous prognostic value of BRCA2 mutation status in metastatic castration-resistant PrCa, showing its influence on patient outcomes irrespective of treatment modalities. However, this survival period is significantly reduced by nearly half, and the risk of mortality is substantially increased.[43] These results emphasize the critical role of BRCA1/2 germline mutations in PrCa development and advancement, highlighting the necessity for additional research and potential targeted treatments in this patient group.

ATM

The ATM gene is crucial in the development and progression of cancer, involved in cell cycle control, apoptosis, oxidative stress, and telomere maintenance.[46] Mutations in the ATM gene have been observed in patients with hereditary gastrointestinal tumors, breast cancer, and ataxia-telangiectasia, impacting the pathogenesis of these cancers and treatment efficacy.[47,48] Detecting ATM mutations can also assist in hereditary cancer prevention and screening. Identifying new compound heterozygous mutations in the ATM gene can aid in diagnosing and assessing the risk of ATM and cancer in patients.[49] Understanding the role of the ATM gene in cancer can pave the way for targeted therapies and precision medicine approaches. Men inheriting a potentially harmful ATM gene mutation were about four times more likely to develop prostate cancer.[50] Patients with advanced metastatic castration-resistant PC (CRPC) often have these mutations, which are found in up to 20% of familial prostate cancer cases in some populations and are frequently associated with a significant family history of cancer.[20] Germline ATM mutations, in particular, are associated with a strong family history of cancer and may be indicative of the progression of prostate cancer and the effectiveness of certain treatments.[51,52] Grochot et al.[52] found that PrCa patients with germline ATM mutations had a median overall survival of 7.1 years (range 2.9-14 years) from diagnosis. Additionally, the median overall survival from CRPC was 5.3 years (range 2.7-7.3 years). The median duration from diagnosis to the onset of castration resistance was 31 months (range 6-102 months).[52] The relative risk of metastatic PrCa among those carrying ATM germline mutations is 6.3, and individuals with ATM germline mutations have a less favorable prognosis compared to patients with sporadic PrCa.[32] The PRACTICAL Consortium Study revealed that carriers of a tier 1 germline ATM variant had a 4.4-fold higher risk of PrCa. It was noted that PrCa cases diagnosed at a younger age (<65 yr) exhibited higher frequencies of likely pathogenic variants. Furthermore, potentially deleterious variants were associated with a 1.4-fold increased risk of PrCa.[50]

In 2023, Paulo et al.[23] used targeted next-generation sequencing (T-NGS) to analyze eight HRR genes (ATM, BRCA1, BRCA2, BRIP1, CHEK2, NBN, PALB2, and RAD51C) and an analytical pipeline that examines both minor and major genomic variations. Their study aimed to understand the overall and relative contribution of these genes to the hereditary predisposition of PrCa in a group of 462 patients with early-onset/familial PrCa in Portugal. The results showed that harmful variants were found in 3.9% of the patients, with CHEK2 and ATM being the most commonly mutated genes (38.9% and 22.2% of carriers, respectively). This was followed by PALB2 and NBN (each accounting for 11.1% of carriers) and finally BRCA2, RAD51C, and BRIP1 (each accounting for 5.6% of carriers).[23] In 2020, Wokołorczyk et al.[20] found that 19.5% of 390 PrCa cases showed genetic alterations in BRCA1, BRCA2, NBN, ATM, CHEK2, HOXB13, MSH2, or MSH6 genes. Notably, correlations were found between CHEK2, NBN, ATM, and HOXB13 genes and increased familial PrCa risk. Mutations in BRCA2, NBN, or ATM genes were linked to a higher prevalence of high-grade tumors (Gleason 8-10), accounting for 56% of cases. These findings highlight that around 20% of familial PrCa cases in Poland may be due to genetic mutations in eight susceptibility genes. Carriers of mutations in BRCA2, NBN, and ATM genes may benefit from more intensive screening and/or chemotherapy.[20] Moreover, ATM loss occurs in a subset of prostate cancers, especially in high-grade tumors, and is associated with reduced overall survival and decreased response to therapies targeting the androgen receptor.[53] It is linked to specific genomic and clinical characteristics, requiring the use of both genomic and immunohistochemistry (IHC) investigations for identification.[54,55] ATM loss is found in about 13% of primary Gleason pattern 5 cancers and is completely sensitive in detecting biallelic ATM inactivation.[54] It is also present in a significant percentage of tumors with pathogenic germline ATM mutations. However, the connection between ATM loss and clinical outcomes in prostate cancer patients has not been firmly established.[53,54] ATM loss does not significantly affect sensitivity to PARP inhibitors but does sensitize to ATR inhibitors. Thus, prostate cancers with ATM mutations may be more inclined to benefit from ATR inhibitor therapy rather than PARP inhibitor therapy.[52] Moreover, ATM-mutated tumors have lower levels of TP53 mutations and RB1 loss, while BRCA2-mutated tumors are more frequently TMB-High and exhibit amplifications in PDCD1.[56] These findings suggest that ATM and BRCA2 mutations may have distinct clinical and molecular features in PrCa.

Other HRR Family Genes

The HRR gene family, which includes genes like CHEK2, RAD51B, RAD51C, RAD51D, BRIP, and BARD1, has been studied in relation to PrCa. However, there is limited information on other HRR genes and their connection to PrCa, especially in the Chinese population where these genes are less prevalent (<3%).[11] Therefore, larger studies are necessary to establish the link between these genes and PrCa. One noteworthy gene in the HRR family is PALB2, which produces a protein that interacts with BRCA2 and is essential for repairing homologous DNA breaks.[18] A study in Poland with 5,472 PrCa patients and 8,016 controls found

that PALB2 mutations don't increase the risk of PrCa but do make the disease more aggressive and aid tumor progression.[19] Another study of 1,836 Chinese patients suggested a strong link between PALB2 germline mutations and PrCa risk (OR=5.9).[11] These differences in results may be due to racial variations. Additionally, a Canadian cohort study of 319 patients with metastatic castration-resistant PrCa revealed that those with germline mutations in genes like BRCA2, ATM, CDK12, PALB2, and FANCA had a shorter time to progression to castration-resistant PrCa (CRPC) after castration therapy, particularly androgen-deprivation therapy (ADT), compared to patients without mutations (11.8 months vs. 19.0 months). Patients with mutations also showed a faster progression of prostate-specific antigen (PSA) after first-line novel endocrine therapy for metastatic castration-resistant PrCa (mCRPC) compared to patients without mutations (3.3 months vs. 6.2 months, p=0.01).[8] Data from a domestic study support this, indicating that patients with newly diagnosed metastatic hormone-sensitive PrCa who have mutations in germline DDRGs transition faster to the castration-resistant stage compared to patients without mutations (8.3 months vs. 13.2 months, HR=2.37, p<0.001).[9]

DNA Mismatch Repair Genes

DNA MMR genes are essential for preserving the accuracy and integrity of genetic material by identifying and rectifying errors during DNA replication, recombination, and repair processes, thereby averting the accumulation of harmful mutations that could lead to genetic disorders and diseases.[57] The MMR pathways include seven genes: MSH2, MSH3, MSH6, MLH1, MLH3, PMS1, and PMS2. These genes are found on five different chromosomes. MSH2, MSH6, and PMS1 are located on chromosome 2, MLH1 is on chromosome 3, MSH3 is on chromosome 5, PMS2 is on chromosome 7, and MLH3 is on chromosome 14.[58] MMR deficiency serves as a biomarker for the response to immune checkpoint blockade (ICB) therapy. The link between these mutations and an increased risk of PrCa is well-established, but their precise role in tumor development remains incompletely understood.[23] Men carrying germline mutations in MMR genes, like MLH1, MSH2, MSH6, and PMS2, are more susceptible to PrCa compared to those without these mutations. Research has indicated that these mutations are linked to a 2 to 5-fold higher risk of PrCa.[59] It is crucial to recognize that patients with germline mutations in the MMR gene often exhibit more aggressive clinical and pathological features, leading to a higher likelihood of developing castration-resistant PrCa.[60] Moreover, individuals with MSH2/MSH6 deletion tend to have a worse prognosis. Variability in PrCa development is also noted with mutations in the MLH1 and MSH2 genes.[61] Compared to MLH1 and MSH6 mutations, individuals with MSH2 mutations have a higher likelihood of developing PrCa.[15] Individuals with mutations in MMR genes have been found to have a 3% higher susceptibility to PrCa. In 2023, Fang et al.[60] evaluated 855 Chinese prostate cancer patients; 1.52% were identified as having MMR gene mutations, including MLH1, MSH2, MSH6, and PMS2 gene mutations. In another Chinese study, it is reported that MSH2 germline mutations significantly increase the risk of developing PrCa, with the OR reaching 15.8.[62] A study on familial PrCa cases found that rare, likely harmful variants in DDRGs, including MMR genes, contribute to disease risk.[63] However, the prevalence of Lynch syndrome, caused by MMR gene mutations, in localized prostate cancer was low at 0.8%.[57] Furthermore, a study on early-onset/familial prostate cancer cases identified harmful variants in MMR genes, with CHEK2 and ATM being the most frequently mutated genes.[23] It is observed that PrCa patients with germline mutations in MMR genes tend to develop the disease at a younger age and present with a more aggressive phenotype compared to patients without such mutations.[60] It is important to note that the prevalence of germline mutations in MMR genes among PrCa cases is relatively low.[57] Data from Chinese research show that among 316 PrCa cases, the rate of pathogenic germline mutations in MSH6 and MSH2 genes was 0.63% (1/316), and no patients with germline pathogenic mutations in MLH1 and PMS2 genes were identified. In 2019, Abida et al.[64] found that 32 (3.1%) of 1,033 PrCa cases had MSI-H/dMMR, and 7 patients (0.6%) had germline mutations in the United States. Based on this data, the prevalence of a germline mutation in MMR was less than 1%, regardless of ethnic background.

HOXB13 Gene

HOXB13, a transcription factor with a homeodomain, is known for its impact on androgen response and prostate cancer development.[65] Recent research has shown that HOXB13 forms a complex with mTOR on chromatin. However, the precise functional relationship between HOXB13 and mTOR is not yet clear. Phosphorylation of HOXB13 by mTOR leads to its interaction with the E3 ligase SKP2, enhancing its oncogenic properties.[66] This phosphorylation by mTOR promotes the growth of PrCa cells both in vitro and in vivo. Analysis of gene expression patterns has revealed a gene signature dependent on phospho-HOXB13, allowing for differentiation between normal prostate tissues, primary cancer samples, and metastatic cancer samples.[67] Additionally, HOXB13 is implicated in wound healing, cellular differentiation, and angiogenesis in PrCa and other malignancies.[68] The identification of acetylation of

HOXB13 at lysine 13 (K13) serves as a biomarker for clinically significant PrCa and a potential target for therapeutic intervention.[69]

Several studies indicate that individuals with mutations in the HOXB13 gene, particularly the G84E mutation, have a significantly higher risk of developing PrCa compared to those without mutations.[70] The precise mechanism by which HOXB13 G84E mutations elevate the risk of PrCa remains unclear. However, it is well documented that the G84E mutation has been associated with a younger age at onset and high levels of prostate-specific antigen (PSA) at diagnosis.[71] Additionally, an increased risk of prostate cancer was observed in patients with a prior diagnosis of benign prostate hyperplasia (BPH).[72] Currently, there are no specific treatment options for HOXB13 mutations. Nevertheless, these mutations are important for evaluating the risk of developing tumors in close family members. As a result, the HOXB13 gene and its mutations have been extensively researched in connection with PrCa.[70] In a study of Black men with early-onset prostate cancer, researchers identified pathogenic or likely pathogenic variants in HOXB13, as well as variants in other DNA damage repair (DDR) genes, including BRCA1/2, BRIP1, ATM, CHEK2, and PALB2.[73] The HOXB13 G84E mutation is most commonly found in families from the Nordic countries of Finland and Sweden. In these countries, about 8% to 10% of early-stage familial PrCa patients have been identified as carrying the HOXB13 G84E mutation, in contrast to less than 1% of men without PrCa who have this mutation.[71,74] The International Consortium for Prostate Cancer Genetics (ICPCG) found that the HOXB13 G84E mutation is present in approximately 5% of prostate cancer families, mainly of European descent, and confirmed its association with PrCa risk after genotyping 15 SNPs in or near HOXB13 in 2,443 prostate cancer families.[75] However, different results were found when analyzing data from the Chinese Consortium for Prostate Cancer Genetics (ChinaPCa). The ChinaPCa study of 671 individuals showed that the G84E mutation was not present in their population. Instead, they identified a new mutation, G135E, in 96 patients, which was notably more prevalent in PrCa patients compared to healthy Chinese men.[76] Furthermore, a Japanese study of 7,646 PrCa cases did not find the G84E mutation but identified two G132E and F127C mutations, which were strongly associated with an elevated risk of PrCa compared to healthy Japanese men.[77] The G84E mutation has not been found in African or Asian patients, who may have other HOXB13 variants, indicating genetic diversity among different populations. Additionally, Maia et al.[78] discovered two new inherited mutations (c.383C>A and c.720C>A) among 462 Portuguese men with early-onset or familial/hereditary PrCa. The previously known G84E variant was not detected, suggesting geographic variation in the prevalence of HOXB13 mutations in early-onset or familial/hereditary PrCa.[78] This implies that targeted testing for the G84E variant in populations other than those of northern European ancestry may not be necessary. Furthermore, there is insufficient comprehensive data supporting the correlation between the G132E and G135E mutations and clinical characteristics of PrCa. Additional research is required to fully understand the impact of HOXB13 mutations on traits associated with PrCa.

Other MMR Family Genes

Multiple studies have pinpointed genes linked to familial hereditary PrCa, but these results underscore the role of other genes, including CHEK2, ATM, NBN, BRCA2, RAD51C, BRIP1, ERCC3, PARP2, and MUTYH, in familial hereditary PrCa. In a study by Foley et al.,[63] they analyzed massively parallel sequencing data from Australian and North American familial PrCa datasets to identify rare, likely deleterious variants in 35 DDR genes across 1,963 individuals. This included 700 familial and 459 sporadic PrCa cases, as well as 482 unaffected relatives and 322 screened controls. The researchers found that a variant in PARP2 (rs200603922, p=0.028) was significantly associated with risk in the Australian dataset alone, while a variant in MUTYH (rs36053993, p=0.031) was significantly associated with risk in the North American dataset.[63] In a study examining high-risk familial prostate cancer datasets, statistically significant associations were found between prostate cancer risk and rare variants in ERCC3 and BRIP1.[42] Additionally, a variant in PARP2 was significantly associated with risk in one dataset, while a variant in MUTYH was significantly associated with risk in another dataset.[23] Another study using targeted next-generation sequencing found that CHEK2 and ATM were the most frequently mutated genes in early-onset/familial prostate cancer cases, followed by PALB2, NBN, BRCA2, RAD51C, and BRIP1.[79] A rare form of EZH2, called rs78589034, has been linked to a higher risk of prostate cancer in both familial and sporadic cases.[80,81] Analysis of the transcriptome has uncovered a unique gene expression pattern in prostate tissue from carriers of this rare variant, including established downstream targets of EZH2.[82] EZH2 plays a role in disrupted function within prostate tissue, contributing to the development of prostate cancer. Furthermore, EZH2 expression is associated with a poor prognosis for prostate cancer patients.[83] Raspin et al.[80] discovered that the mutation of the EZH2 gene rs78589034 is significantly associated with an odds ratio of 3.55 for PrCa risk. Schaid et al.[84] conducted a study involving 491 patients with familial hereditary PrCa and 429 controls from ICPCG. In this study,

the researchers identified 11 genes previously associated with Prostate Cancer (ATM, BRCA2, HOXB13, FAM111A, EMSY, HNF1B, KLK3, MSMB, PCAT1, PRSS3, and TERT). Additionally, they discovered 10 novel genes (PABPC1, QK1, FAM114A1, MUC6, MYCBP2, RAPGEF4, RNASEH2B, ULK4, XPO7, and THAP3). Notably, the researchers found that, out of these 10 novel genes, all except for PABPC1 and ULK4 were primarily associated with the risk of aggressive PrCa.[84] The EGFR R831H gene was found in cases of familial PrCa. In a Chinese family with two prostate cancer patients, the PrCa phenotype co-segregated with the rare germline variant EGFR R831H.[85] Patient-derived conditionally reprogrammed cells (CRC) showed heightened EGFR and AKT phosphorylation, indicating constitutive activity of the EGFR allele. Both EGFR R831H-mutant tumors harbored biallelic CDK12 inactivation, along with prominent tandem duplication across the genome. Examination of public databases revealed a notable correlation between the mutation status of EGFR and CDK12.[86]

Single Nucleotide Polymorphisms Associated with Familial Hereditary PrCa

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation in humans, occurring approximately once in every 300 base pairs on average. SNPs are found in over 1% of the population and have various uses, including personalized medicine, human identification, and forensic screening. It is estimated that there are more than 80 million SNPs in the human genome, with the majority located in the noncoding region.[87] Over more than a decade, genome-wide association studies (GWAS) have identified nearly 300 SNPs linked to the risk of developing PrCa. It's important to note, however, that most of these studies have mainly focused on the European population, with limited representation of Asian and African populations. Despite the confirmation of these SNPs and their association with increased PrCa risk, they only account for about 25% of the risk associated with a positive family history of the disease. Additionally, no single locus has been officially recognized as a reliable tool for guiding PrCa screening.

In 2017, Lecarpentier et al.[88] conducted the first study on the associations of common genetic variants with breast and PrCa risks for male carriers of BRCA1/2 mutations. Their research involved 1,802 male carriers from the Consortium of Investigators of Modifiers of BRCA1/2 and utilized the custom Illumina OncoArray. The study revealed 103 PrCa susceptibility variants linked to PrCa risk (OR 1.56; 95% CI, 1.35-1.81).[88] In 2021, Ren et al.[89] identified 32 SNPs with distinct regulatory activities from a total of 213 PrCa risk-related loci in 22Rv1 cells. Their research revealed that a variation in one specific regulatory SNP, rs684232, has the potential to alter the binding of the transcription factor FOXA1 to the chromatin in the DNA region. As a result, the expression of VPS53, FAM57A, and GEMIN4 genes becomes abnormally dysregulated, and these genes are known to play crucial roles in the development of malignant tumors, particularly in PrCa.[89] In 2016, Teerlink et al.[90] conducted a GWAS and identified multiple statistically significant SNPs at six distinct genomic regions: 3q26.31, 6q24.3, 8q24.21, 10q11.23, 11q13.3, and 17q12, with a total of 135 significant SNPs detected. The study's findings showed that the majority (92%) of individuals carrying the risk allele at rs138042437 had a consistently estimated haplotype spanning approximately 100 Kbp of the genomic region 8q24.21. This specific haplotype contained the minor alleles of three rare polymorphisms: PRNCR1 rs183373024, CASC19 rs188140481, and rs138042437. Additionally, scientists extensively explored any correlation signals between SNPs situated within established predisposition genes for PrCa, specifically BRCA1, BRCA2, and HOXB13. The connections noted between the SNPs and the BRCA1/2 genes were relatively moderate. Regarding HOXB13, rs138213197 exhibited an estimated effect size similar to that documented in a recent meta-analysis of PrCa involving a group of 120,617 men. Their results showed that most individuals with the risk allele at rs138042437 had a consistently estimated haplotype spanning about 100 kb of 8q24.21. This haplotype comprised the minor alleles of three rare SNPs, including rs183373024, rs188140481, and rs138042437.[90] In a computational study on the functional impact of SNPs and their involvement in hereditary PrCa, Chandrasekaran et al.[91] found that among the 21 non-synonymous single nucleotide polymorphisms (nsSNPs) located on the HOXB13 protein, seven (rs761914407, rs8556, rs138213197, rs772962401, rs778843798, rs770620686, and rs587780165) had a significant impact on the protein. The substitutions G84E, G135E, and A128V led to increased protein stability, whereas the substitutions R215C, C66R, Y80C, and S122R resulted in decreased stability. These alterations in stability are expected to modify the binding patterns of the HOXB13 protein.[91] Gusev et al.[92] utilized genotype data from 59,089 men of European and African American ancestries, along with cell-type-specific epigenetic data, to construct a genomic atlas of single nucleotide polymorphism heritability in PrCa. Their findings revealed significant differences in heritability between variants in prostate-relevant epigenetic marks in normal versus tumor tissue, as well as between tissue and cell lines. The majority of SNP heritability was identified in regions marked by H3K27 acetylation in prostate adenocarcinoma cell lines or by DNaseI hypersensitive sites in cancer cell lines. The study also indicated a high degree of similar-

ity in genetic architecture between European and African-American ancestries, implying a comparable genetic basis for PrCa risk.[92] Cremers and colleagues performed genotyping on a cohort of 620 patients with SPC, 312 patients with HPrCr from the national Dutch registry, and 1,819 population-based referents, investigating the presence of 74 susceptibility SNPs that had been previously reported in the literature up until June 2014. Notably, the SNPs with the highest ORs were found to be shared between SPC and HPrCr, specifically rs16901979 and rs1447295. These findings suggest a significant overlap in the low-penetrance susceptibility SNPs between SPC and HPrCr, indicating a potential similarity in their genetic etiology.[93] In a study, the SNP rs4919743 at the KRT8 locus on chromosome 12q13.13 was consistently linked to PrCa risk in various populations.[94] Stegeman et al.[95] conducted a comprehensive study on SNP associations related to 169 miRSNPs target genes in a large-scale analysis of 22,301 cases and 22,320 controls of European ancestry from 23 participating studies. Their results revealed that 22 miRSNPs were linked to the risk of PrCa, with 10 of them located within 7 genes not previously identified by GWAS studies. Additionally, through the use of miRNA mimics and reporter gene assays, they demonstrated that miR-3162-5p exhibits specific affinity for the KLK3 rs1058205 miRSNP T-allele, while miR-370 has a stronger affinity for the VAMP8 rs1010 miRSNP A-allele, confirming their functional role. Furthermore, their findings unveiled two significant PDK1 miRNA-SNPs, namely rs1530865 and rs2357637, in the 3'UTR that are strongly associated with PrCa risk. The research findings expanded our understanding of PDK1's role in PrCa cells and further clarified the critical association between miRNA-SNP interactions and the progression of PrCa.[95]

Copy Number Variations

Copy number variation (CNV) refers to changes in the number of copies of a specific DNA segment within the genome. CNVs have important implications in human genetics, oncogene discovery, clinical decision-making, and drug development.[96] Accurate detection of CNVs is crucial due to their association with cancer, mental illness, and genetic diseases.[97] Various methods, including scatterplot-based analysis, meta-barcoding, qPCR, metagenomics, and next-generation sequencing (NGS) data analysis, have been developed to identify CNVs.[96] Several studies have investigated the factors influencing the impact of CNV on PrCa development. By analyzing multi-omics data, researchers have found a significant correlation between increased CNV and the appearance of a stem-like phenotype in PrCa cells. The study suggests that heightened stemness caused by high CNV could accelerate the progression of the disease. Therefore, understanding the complex relationship between CNV and cancer cell biology could provide valuable insights and lead to the development of new treatment approaches for PrCa metastasis.[98] Laitinen et al.[99] conducted a thorough study on CNVs at a genome-wide level. Their research focused on polymorphisms in a group of 105 HPrCa patients and 37 unaffected individuals from 31 Finnish families. They identified a 14.7 kilobase deletion in the intronic region of the EPHA3 gene, which encodes the class A ephrin receptor. This deletion was present in 11.6% of PrCa patients and 6.1% of the control group. Discovering genes in these CNV regions offers promising opportunities for targeted therapies, marking a significant advancement in PrCa treatment. Analysis of familial segregation patterns revealed that the majority of PrCa patients (56.1%) carried this deletion, compared to only 36.1% of unaffected family members. Additionally, the percentage of unaffected males with the deletion was even lower, at 31.2%.[99] In a different study of the Finnish population, Siltanen et al.[100] examined the significance of ARLTS1 Cys148Arg (T442C) in relation to the risk of PrCa. The researchers employed array comparative genomic hybridization (aCGH) to assess alterations in the copy number of ARLTS1 at 13q14.3 in xenografts and cell lines associated with PrCa. The results strongly support the important role of the ARLTS1 Cys148Arg mutation in PrCa susceptibility and its potential as an indicator of prognosis for a serious illness.[100,101] In 2018, a study by Wu et al.[102] found that several new germline CNVs were significantly associated with susceptibility to PrCa. The study involved 1,417 PrCa patients and 1,008 control individuals in China, resulting in the discovery of 41 CNVs. Out of these, 27 were considered risk variations and 14 were identified to have a protective effect against PrCa. Importantly, 25 of these CNVs (19 duplications and 6 deletions) were located within gene regions, while the remaining 16 CNVs (9 duplications and 7 deletions) were situated within intergenic regions.[102] In 2013, Ledet et al.[103] conducted a study on ten high-risk African-American families with three or more affected individuals and an early onset of PrCa. They used array comparative genomic hybridization to analyze the genetic makeup and discovered previously unidentified CNVs at chromosomes 1p36.13 and 16q23.3. Additionally, they found a 9.4 kb duplication on chromosome 14q32.33, present in PrCa patients within these high-risk families. This duplication includes the IGHG3 gene, which has been observed to exhibit significant gains in CNVs and overexpression in PrCa among African-Americans.[103] Raspin et al.[104] identified recurring CNVs, such as EEF2 amplification, in familial prostate tumors. Williams et al.[105] found germline CNVs in HPrCr cases through targeted resequencing, with deletions in genes like NBPF1, NBL1, SRSF10, and RHD.

Brezina et al.[106] compared genome-wide screening data and observed a higher CNV frequency, especially copy number losses on chromosomes 8, 9, and 10, in aggressive prostate cancer patients.

Treatment Strategies

Treatment approaches for HPrCa involve genetic testing to identify specific genetic alterations in the tumor that can guide targeted therapies. The field of genetic testing for PrCa is rapidly expanding and can reveal options for precision therapy and hereditary cancer-predisposition syndromes with unique clinical features.[15] BRCA2 is the most commonly implicated gene associated with inherited PrCa, and targeted therapeutic agents have been identified for BRCA1/2 deficient cancer cells. Inherited PrCa has been linked to genetic mutations associated with other hereditary cancer syndromes, emphasizing the importance of genetic counseling and testing.[107] Advances in DNA sequencing technologies have revealed several genes associated with hereditary PrCa, which can inform screening strategies and treatment options. Treatment options for PrCa primarily include surgical intervention, such as radical prostatectomy, as well as radiotherapy, endocrine therapy, chemotherapy, targeted therapy, and immunotherapy.[15] In the case of hereditary PrCa, the approaches to surgery, radiotherapy, and endocrine therapy are not significantly different from those used in sporadic PrCa cases. However, due to the presence of germline mutations in DNA damage repair genes (DDRGs), hereditary PrCa exhibits a highly unstable genome and shows resistance to platinum chemotherapy drugs and PARP inhibitors, while demonstrating sensitivity to inhibitors and immunotherapy.[15,108] Consequently, this consensus will focus on specialized treatment strategies tailored specifically for hereditary PrCa. PrCa is distinct due to its reliance on androgens for growth and progression, making androgen deprivation therapy a standard and effective treatment. Nevertheless, individuals with DNA damage repair (DDR) germline mutations that have PrCa experience a reduced response to androgen receptor-targeted therapy, and the effectiveness of new endocrine therapy drugs remains a topic of debate. Research has indicated that the use of newer endocrine therapies, such as abiraterone or enzalutamide, yields better outcomes in men with BRCA or ATM mutations compared to those without deleterious germline mutations. Meanwhile, a study by Antonarakis et al.[109] suggested that the median time for patients with germline DDR mutations to progress to metastatic castration-resistant PrCa is notably shorter than that of patients without mutations (8.3 months vs. 13.2 months, HR=2.37). Additionally, Wei et al.[110] reported that the median time to progression in individuals with BRCA2 germline mutations is nearly halved compared to those without mutations (6.3 months vs. 13.2 months, HR=3.73). Therefore, the mutational status of genes associated with familial hereditary PrCa may influence treatment strategies.

Platinum-Based Chemotherapy

Platinum-based chemotherapy has demonstrated potential in treating familial hereditary PrCa. A phase II trial found that platinum-based chemotherapies had a high response rate in patients with anaplastic PrCa, a subgroup with clinical features similar to small cell carcinoma of the prostate (SCCP).[111] Despite the lack of positive results from the phase II clinical trial of platinum-based chemotherapy for all patients with metastatic castration-resistant PrCa (mCRPC), ongoing research continues to investigate its effectiveness in those with BRCA2 mutations.[112] Pomerantz et al.[113] discovered that metastatic PrCa patients with germline BRCA2 mutations and a family history of malignancy had significant and enduring responses to carboplatin treatment. The research demonstrated significant and long-lasting responses to carboplatin treatment in these individuals. Furthermore, it emphasized that those with BRCA2 mutations witnessed a substantial decrease in PSA levels over a 12-week period while undergoing carboplatin-based chemotherapy. It is noteworthy that 75% of carriers experienced this reduction, in contrast to only 10% of non-carriers. Moreover, approximately 17% of participants observed a reduction in PSA levels by over 50% within the same 12-week period.[113] Furthermore, Conteduca et al.[114] found that higher expression of the DNA/RNA helicase SLFN11 was linked to a better response to platinum chemotherapy in metastatic castration-resistant PrCa (CRPC) patients.[115] These results indicate that platinum-based chemotherapy could be beneficial in treating familial hereditary PrCa, particularly in patients with specific genetic mutations or clinical characteristics. Nonetheless, it is crucial to acknowledge that further comprehensive clinical research is necessary to comprehend the efficacy and safety of platinum-based chemotherapy in PrCa patients with various mutations, given the limited sample size and the inclusion of only patients with BRCA2 mutations.

Immunotherapy

Immunotherapy could have significant implications for treating familial and hereditary PrCa. Germline testing can pinpoint specific genetic alterations, such as mutations in MMR genes, indicating potential benefits from immunotherapy.[108] Detecting germline mutations in DNA repair genes, like BRCA2, can assist in treatment decisions and determining eligibility for PARP inhibitors, known for their effectiveness in PrCa.[44] Men with DNA MMR deficiency may

have the option of immunotherapy with pembrolizumab. In a phase II clinical trial with 86 patients having advanced solid tumors, the PD-1 antibody Pabo Livizumab exhibited high sensitivity in treating advanced solid tumors with MMR defects.[116] In 2017, the US FDA approved pembrolizumab for the treatment of individuals with unresectable or metastatic MMR deficiency (dMMR) or microsatellite instability-high (MSI-H) solid tumors.[117] Velho et al.[118] showed that 21% of patients achieved complete responses (CR) and 53% achieved an objective radiographic response (ORR). It is noteworthy that the response rate was consistent across various tumor types.[118] In a study by Graham et al.,[119] 27 individuals with metastatic prostate cancer having MSI-high/MMRd were examined. Results showed that 48% had M1 disease at diagnosis. Among 24 participants who had a prostate biopsy, a significant 79% had a Gleason score of 8 or higher. The overall survival rate post-metastasis onset was indeterminable in the 33.6-month follow-up, with a 95% confidence interval ranging from 23.8 to 50.5 months. In a subgroup of 17 individuals treated with pembrolizumab, 15 had data on PSA response, with 53% showing PSA50 responses.[119,120] Antonarakis et al.[121] studied thirteen patients, with most (46%) having MSH6 mutations; 73% exhibited microsatellite instability. Among the four patients who were given PD-1 inhibitors, two achieved a prostate-specific antigen response of ≥50% at 12 weeks, with a median PFS of 9 months in this subgroup. Despite the aggressive nature of the disease, individuals with MMR-mutated advanced prostate cancer appear to display a unique sensitivity to hormonal therapies and occasional responses to PD-1 inhibitors.[121] These results indicate that immunotherapy may hold promise for managing familial and hereditary PrCa, particularly in individuals with specific genetic mutations. Nevertheless, further research is crucial to fully grasp the role of immunotherapy in this particular context.

Targeted Therapy with Poly (ADP-ribose) Polymerase Inhibitors

PARP inhibitors are cutting-edge cancer treatments targeting DNA repair issues. Recent research has linked DNA repair to advanced PrCa.[23] The use of PARP inhibitors prevents the repair of single-stranded DNA, leading to issues in homologous recombination repair for those with genetic mutations related to DNA restoration. This disruption causes the accumulation of DNA double-strand damage, resulting in the death of cancerous cells, known as the synthetic lethal effect.[122] In a 2015 study, the Trial of PARP Inhibition in Prostate Cancer (TOPARP-A) showcased the potent anti-tumor impact of PARP inhibitors in metastatic PrCa patients with DNA repair deficiencies.[123] The TRITON3 and TALAPRO-2 studies have shown that PARP inhibitors are effective in mCRPC patients with DNA repair gene mutations, particularly in genes associated with homologous recombination repair.[124,125] Research indicates that PARP inhibitors such as rucaparib and talazoparib have extended radiographic progression-free survival in these patients with manageable side effects. These findings suggest that PARP inhibitors could be a beneficial treatment option for mCRPC patients with DNA repair gene mutations, including those with BRCA1/2 alterations. The phase III PROfound study assessed the effectiveness of olaparib versus endocrine therapy in patients with BRCA1/2 or ATM mutations. The study revealed that olaparib treatment led to longer progression-free survival (PFS) compared to the control group. In Cohort A of the study, which involved patients with BRCA/ATM alterations, olaparib treatment resulted in a median PFS of 7.4 months, compared to 3.5 months in the control group.[126] Moreover, in a real-world scenario, exposure to olaparib at any treatment stage was linked to extended overall survival (OS) from the initiation of I-line treatment for metastatic gBRCA pancreatic cancer patients.[127,128] Olaparib shows a prolonged period of imaging progression-free survival in patients with HRR gene mutations, lasting 5.8 months compared to 3.5 months (HR=0.49, 95% CI:0.38-0.63, p<0.0001). An analysis of overall survival indicates that olaparib reduces the risk of all-cause mortality by 31% in patients with BRCA1/2 or ATM mutations (HR=0.69, 95% CI:0.50-0.97, p=0.0175) and by 21% in patients with HRR mutations (HR=0.79; 95% CI:0.61-1.03). Taking into account the crossover effect, the risk of all-cause mortality can be decreased by 58% and 45%, respectively.[129] In 2020, the FDA approved two PARP inhibitors for treating PrCa. Lynparza is approved for mCRPC patients with disease progression after new endocrine therapies and mutations in HHR genes such as BRCA1, BRCA2, ATM, BARD1, CDK12, CHK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L. In contrast, rucaparib is approved for mCRPC patients with disease progression after new endocrine therapies and paclitaxel chemotherapy, specifically with BRCA1 or BRCA2 mutations.[130]

Screening of Hereditary PrCa

The current international guidelines present inconsistent recommendations on patient and disease stage for genetic testing. There is a lack of consensus on precise criteria for optimal testing timing. However, leading medical bodies offer varied suggestions. The American College of Medical Genetics (ACMG) recommends testing for individuals with hereditary PrCa and a Gleason score over 7, as well as patients with at least two relatives impacted by certain cancer types.[108] The American Urological As-

sociation (AUA) and the European Association of Urology (EAU) advise germline genetic testing for high-risk or metastatic PrCa, as well as low or intermediate-risk cases.[131] It is crucial to identify scenarios where genetic testing is strongly recommended, such as when multiple family members have PrCa before age 60. Additionally, testing should be considered with known germline mutations or if multiple family members have specific cancers. Testing is also recommended if multiple family members have Lynch syndrome.[108,131] The 2019 Philadelphia PrCa Consensus suggests genetic testing for all metastatic PrCa patients, as well as those with a first-degree relative with PrCa or multiple relatives diagnosed before 60, or those with family experiences of PrCa death or metastasis.[59] The National Comprehensive Cancer Network (NCCN) PrCa Clinical Practice Guidelines recommend testing for genes like BRCA1, BRCA2, ATM, PALB2, and CHEK2 for high or very high-risk localized, locally advanced, and metastatic PrCa. For metastatic PrCa, NCCN suggests germline gene testing including MLH1, MSH2, MSH6, and PMS2. NCCN proposes a genetic testing approach covering germline and somatic gene testing, including BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12, specifically advised for all metastatic PrCa patients. Therefore, targeted PARP inhibitor therapy shows potential for familial hereditary PrCa. The guidelines also cover managing negative biopsy results and optimizing the detection of clinically significant prostate cancer while minimizing the detection of indolent disease. They further discuss using radiation therapy (RT) in treating prostate cancer, with recommendations based on the quality of evidence supporting RT's role in specific tumor types. The NCCN Guidelines for Prostate Cancer also offer recommendations for managing localized, regional, recurrent, and metastatic disease, including systemic therapy for metastatic prostate cancer.[15,132]

Prostate-Specific Antigen Screening

Prostate-specific antigen (PSA) screening is under evaluation for its efficacy in HPrCr. Research focusing on genetic factors that influence PSA levels aims to improve screening accuracy. A multi-ancestry genome-wide analysis identified 128 genetic variants associated with PSA levels, explaining a significant portion of PSA variability.[133] The use of a polygenic risk score to adjust PSA values has been shown to improve diagnostic precision and predict aggressive prostate cancer.[134] However, there is a lack of compliance with genetic testing and counseling recommendations for high-risk prostate cancer patients.[135] Enhanced awareness and adherence to guidelines are crucial for promptly identifying individuals at risk and facilitating early screening. Men with a family history of PrCa have higher PSA screening rates compared to the general male population. Conversely, Black men with a family history of PrCa did not exhibit a significant change in PSA screening rates.[136] PSA testing is a widely used method for PrCa screening, well-recognized within the medical community. Nevertheless, it is important to recognize the presence of false positives, which could lead to unnecessary prostate biopsy procedures. Current research on familial hereditary PrCa screening primarily focuses on BRCA mutations. The NCCN and the EAU recommend that individuals with BRCA1/2 mutations start yearly PSA screening and digital rectal exams at age 40.[44,137] Moreover, the Philadelphia PrCa Consensus recommends that people carrying BRCA2 mutations, and potentially those with BRCA1, HOXB13, ATM, and other DNA MMR gene mutations, commence PrCa screening at 40 years old.[59]

Conclusion

In recent years, advancements in genomics and genetic testing technology have significantly deepened. Consequently, numerous genetic foundations linked to familial hereditary PrCa have been uncovered, profoundly impacting precise treatment. International guidelines have also outlined corresponding testing and screening recommendations. However, it is crucial to recognize that current discoveries merely skim the surface of this complex issue, with many genetic risks associated with PrCa still unknown. The identification of additional genes and genetic variations tied to PrCa risk, and their integration into clinical practice, presents a substantial challenge for researchers globally. Nonetheless, with ongoing research progress and advancements in science and technology, we are optimistic that the comprehension of familial hereditary PrCa will become more comprehensive. This progress will lead to new breakthroughs in treatment, screening, and detection techniques. Going forward, collaborative efforts among researchers, healthcare providers, and genetic specialists will be vital in unraveling the intricacies of hereditary PrCa. By exploring the genetic landscape further and harnessing advanced technologies like CRISPR-Cas9 and next-generation sequencing, the medical community aims to enhance personalized patient care approaches. As the field advances, a more nuanced understanding of the interplay between genetic predispositions and environmental factors is likely to emerge, paving the way for customized interventions and preventive strategies. With a shared dedication to pushing the boundaries of genomic research, the future shows promise for transforming the management of familial hereditary PrCa.

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