







Review

Prostate Cancer: Advances in Genetic Testing and Clinical Implications

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Abstract: The demand for genetic testing (GT) for prostate cancer (PCa) is expanding, but there is limited knowledge about the genetic counseling (GC) needs of men. A strong-to-moderate inherited genetic predisposition causes approximately 5–20% of prostate cancer (PCa). In men with prostate cancer, germline testing may benefit the patient by informing treatment options, and if a mutation is noticed, it may also guide screening for other cancers and have family implications for cascade genetic testing (testing of close relatives for the same germline mutation). Relatives with the same germline mutations may be eligible for early cancer detection strategies and preventive measures. Cascade family testing can be favorable for family members, but it is currently unutilized, and strategies to overcome obstacles like knowledge deficiency, family communication, lack of access to genetic services, and testing expenses are needed. In this review, we will look at the genetic factors that have been linked to prostate cancer, as well as the role of genetic counseling and testing in the early detection of advanced prostate cancer.

Keywords: metastasis; prostate cancer; prostate cancer genes; benign prostatic hyperplasia



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1. Introduction

Prostate cancer (PCa) is the most diagnosed cancer in men, with an estimated 268,490 and 34,500 newly diagnosed and died of prostate cancer in the United States in 2022, respectively [1]. Although PCa may be asymptomatic at the early stage and often has an indolent course of progression, it is the second leading cause of cancer-related death in men behind lung cancer [2].

PCa is a highly variable illness; in fact, many individuals exhibit an aggressive disease with progression and metastasis, but others exhibit a slow disease with a low tendency to advance [3].

PCa can manifest clinically as a locally indolent illness or as a fast-developing, fatal metastatic disease [4]. Even though most men are diagnosed with an organ-confined illness, the long-term oncological prognosis might vary considerably [5].

In addition, histomorphology and molecular tumor features exhibit considerable variation between patients and within a similar tumor [6].

Patients with early-onset PCa who have family members with PCa, or other heritable malignancies are appropriate candidates for genetic testing [6]

Histologically, these tumors are quantified using the Gleason score, which analyses the degree to which the biotic prostate specimen resembles the normal prostate gland [7].

It has been well-established that prostate cancer has a reliable genetic association in recent years. As a result, genetic testing has arisen as essential to prostate screening, understanding the role of genetic mutations in PCa diagnosis, and developing new treatment approaches [8].

This review aims to emphasize the essential aspects of germline genetic testing for PCa, the importance of family history, the role of genetic testing in screening, and the clinical significance of DNA repair mutation genes in treatment strategies.

2. Prostate Cancer Heritability

Recently, the heritability of prostate cancer (PCa) has been highlighted; about 20% of patients with PCa have a positive family history, which may develop not only because of genetic factors but also due to environmental factors such as shared lifestyle and exposure to the same carcinogenic elements [9]. In addition, several studies reported that about 5% of PCa risk is due to genetic heritability [10–12].

Family history of cancer remains the cornerstone of genetic risk assessment, and asking about prostate and non-prostate malignancies is essential for a thorough evaluation of potential inherited cancer risk [13].

In 2016 two important studies reported the relation between PCa and family history; the PCBaSE study demonstrated that the risk of developing cancer in men who had brothers with PCa is highly notable; at the age of 65, the risk of developing cancer for those with brothers who had PCa was three-fold more compared to those who did not have brothers with PCa. At age 75, men with brothers having PCa had more than a two-fold risk compared to those without brothers with PCa [14]. In Norway, a twin prostate cancer study was conducted on more than 200,000 twins, both monozygotic and dizygotic, and this study reported that more than 57% of PCa is attributed to genetic risk factors [15].

Additionally, in recent research of 3607 men diagnosed with PCa who underwent genetic testing between 2013 and 2018, 17.2% were found to have germline mutations, whereas 37.2% did not meet the NCCN Guidelines for Genetic/Familial High-Risk Assessment criteria for testing [16].

The argument that all men with PCa should be tested is thought-provoking, but the cost-effectiveness and actionability of widespread genetic testing in early, low-risk PCa settings without other risk factors remain unclear, which may lead to short-term unintended consequences including clinical confusion and depletion of limited genetic counselling resources with low yield [17].

On the other hand, clinical predictors of germline status, such as metastatic stage iv or intraductal histology, emerging data about ductal histology, and/or history of second or multiple primary cancers at a younger age, may assist in prioritizing candidates for testing, as each has been independently associated with the presence of germline DNA repair mutations [18].

3. Genetic Markers

Several genetic mutations have been linked to the development of PCa. DNA repair (e.g., BRCA1, BRCA2, and ATM), DNA mismatch repair (e.g., MLH1, PMS2, MSH6, and MSH2), and cell cycle regulation genes (e.g., TP53) are among the mutations that have been targeted by researchers over the past years. Furthermore, other genes such as HBOX13 gene, important for prostate development, and CHEK2 gene, a tumor suppressor gene, have been linked to increased risk of PCa in men. In this section, we are discussing in detail the relationship between these genes and PCa. Table 1 represents a summary of the data discussed in this review.

Table 1. Summary of the available data demonstrating the link between gene mutations and prostate cancer.

Gene	Association
BRCA1 and BRCA2	<ul style="list-style-type: none"> BRCA2 has more impact on the development as well as the prognosis of PCa than BRCA1. Presence of these mutations is associated with a three to nine-fold increase in the risk of development of PCa. Higher risk of high-grade illness and progression to metastatic castrate-resistant prostate cancer.
ATM	<ul style="list-style-type: none"> Relative risk of metastatic prostate cancer is 6.3%
PALB2	<ul style="list-style-type: none"> Potential association between PALB2 mutation and aggressive forms of PCa.
MLH1, PMS2, MSH6, and MSH2	<ul style="list-style-type: none"> Carriers of pathogenic variants have a higher incidence of PCa compared with non-carrier. (5–24%)
HOXB13	<ul style="list-style-type: none"> Increased risk of early-onset PCa. Increased de novo lipogenesis, cell motility, and PCa metastasis.
TP53	<ul style="list-style-type: none"> Higher relative risk of PCa in individuals with TP53 mutation. TP53 variants are associated with advanced PCa.
CHEK2	<ul style="list-style-type: none"> CHEK2 1100delC mutation is associated with moderate increase in the risk of development of PCa.
FGF	<ul style="list-style-type: none"> Play a role in progression and metastasis. Associated with worse prognosis.
CCNE1	<ul style="list-style-type: none"> Higher expression level is associated with a higher tumor grade.

3.1. DNA Repair Genes

Mutations in DNA repair genes occur in up to 10% and 17% of localized and metastatic PCa, respectively [16,19–22]. Sixty-four percent of BRCA2 mutations in prostate cancer are frameshift, 31% are missense, and 5% are splice. The BRCA1 gene contains 63% missense mutations, 31% frameshift mutations, and 6% splice mutations [6]. Moreover, an aggressive phenotype was identified in a study of PCa patients with BRCA1/2 mutations [23,24]. As regards the ATM gene, 50% of mutations found in PCa are missense, 37% frameshift and 13% splice. ATM variants were associated with the aggressive and lethal phenotype of Hereditary Prostate Cancer (HPCa) disease.

In 2015, an international study explored 150 biopsies from patients with metastatic PCa, and the study reported many genetic mutations; 23% of men had DNA repair genes mutation, including BRCA1, BRCA2, and ATM [22]. DNA repair gene mutations have also been associated with metastasis of hormone-sensitive PCa [25].

3.1.1. BRCA1 and BRCA2

BRCA1 and BRCA2 are associated with ovarian and breast cancers and play an essential role in PCa predisposition. BRCA2 mutation has been associated with an increased risk of PCa, higher mortality, and a younger diagnosis of PCa than BRCA 1 mutation [19].

The relative risk of developing PCa in BRCA2 mutation carriers compared to non-carriers is between three- to nine-fold by the age of 65 [26,27]. BRCA2 mutation has been demonstrated in more aggressive subtypes of PCa [28]. Gallagher et al. showed that the risk of developing PCa in BRCA 2 mutation is three times higher than non-carriers, and the risk of recurrence and PCa-related death is also higher than non-carriers [29]. In another study, the risk of developing PCa in BRCA2 mutation carriers was estimated to be four-fold higher than the carriers of BRCA 1 [30]. All these studies demonstrated that carriers of BRCA 2 have an increased risk of developing PCa than BRCA 1 carriers [31].

Remarkably, germline changes were independent of an earlier age at diagnosis and an aggressive phenotype. As well as BRCA2 mutation carriers had a lower survival rate (61.8%) than males who did not carry the mutation (94.3%). Additionally, BRCA2

pathogenic mutations were linked with an increased risk of high-grade illness and progression to metastatic castrate-resistant prostate cancer (mCRPC). In addition, BRCA2 germline mutations contributed more to the increased PCa risk than BRCA1 mutations [32–34].

3.1.2. ATM

ATM is located on chromosome 11 and is a crucial component of the DNA damage response system. Ataxia telangiectasia syndrome is caused by homozygous loss-of-function mutations in ATM. Notably, it is also one of the known HBOC susceptibility genes; in fact, carriers of the ATM mutation have an elevated chance of developing breast, colorectal, gastric, and pancreatic cancers. Recently, the use of sequencing panels incorporating DNA-repair genes has also made it possible to identify germline ATM mutations in males with prostate cancer [35]. The relative risk of metastatic prostate cancer was 6.3% among ATM carriers [36].

Although ATM is the second most common alteration in PCa after BRCA 2, most studies demonstrate that ATM mutation is not associated with the same developments as BRCA 2 [22]. In 2015, Helgason et al. identified that the loss of function of the two variants of ATM was associated with PCa and gastric cancer [37]. However, more research is required to demonstrate the role of ATM gene mutation and PCa.

3.1.3. PALB2

PALB2 is located on chromosome 16; first discovered as a BRCA2-interacting protein, it is a crucial component in the creation of the BRCA complex. Indeed, PALB2 serves as a link between BRCA1 and BRCA2 to induce homologous recombination. It is one of the DNA repair genes; PALB2 mutations are connected with HBOC risk, especially breast and pancreatic malignancies, but few studies have revealed PALB2 variations in PCa patients [38].

However, the precise role of PALB2 in developing PCa is indistinct. Earlier studies did not demonstrate a clear association between PALB2 mutation and inherited PCa [39–41]. However, most recent studies highlighted the potential association between PALB2 mutation and the inheritance of aggressive forms of PCa [42,43]. As the PALB2 mutation is rare, more research and studies should be conducted to profoundly investigate the relationship between this gene and PCa development, the biological significance, and the potential treatment strategies of PCa [44].

3.2. DNA Mismatch Repair Genes

Lynch syndrome has been associated with endometrial cancer and colorectal carcinoma due to the mutation of mismatch repair genes. However, recently PCa has demonstrated a strong linkage to the mutation of the mismatch repair genes, including MLH1, PMS2, MSH6, and particularly MSH2. Bancroft et al. conducted a prospective international study that assessed PSA screening in patients with carriers of MSH2, MSH6, and MLH1 mutation genes; carriers of MSH2 and MSH6 pathogenic variants had a higher incidence of PCa compared with non-carrier controls which have been matched in age. However, PCa was not reported in carriers of MLH1 [45].

The Database of Lynch syndrome reported a prospective development of PCa in 28% (1808/6350) of men with Lynch syndrome. At the age of 75, the carriers of MSH2 and MSH1 mutations had an incidence of PCa up to 24% and 9%, compared to MLH1, and PMS2, who demonstrated an incidence of PCa up to 14%, and 5%, respectively [46].

3.3. HOXB13 Gene

The HOXB13 is a homeobox transcription factor, localized on chromosome 17. The HOXB13 gene produces a protein called a transcription factor, which plays a role in prostate development; however, the mechanism and pathways that lead to PCa development are unclear. HOXB13 was one of the first inherited genes related to PCa given its effect on the androgen receptors. Furthermore, it was shown to be associated with an increased risk of

early-onset and the overall incidence of PCa in white men [19,47]. In a study by Pomerantz et al., HOXB13 together with FOXA1 was shown to cause an extensive reprogramming to androgen receptor cistrome (i.e., transcription factor binding sites) which in turn plays a role in the development of PCa [48].

In 0.7% to 1.4% of prostate cancer cases and 6% of PCa patients with early onset, mutations have been reported [49]. A previous study indicated for the first time that individuals with the recurrent germline mutation G84E in HOXB13 had considerably increased risks of developing PCa compared to those without the mutation [47]. In 2015, Robson et al. reported the frequency rate of the HBOX13 G48E variant of 1.1 on 3607 patients with PCa [50]. In 2021, Loeb et al. also demonstrated that the frequency of the HBOX13 G48E variant at 1.4% in patients with PCa compared to 0.1% in patients without PCa [51]. Interestingly, in a recent study that was published in 2022, loss of HBOX13 was shown to increase cell motility in vitro and PCa metastasis in mice [52]. The authors have shown that the MEIS domain of HOXB13 interacts with HDAC3 (i.e., Histone deacetylases-3) suppressing the de novo lipogenesis through expression of lipogenic regulators such as fatty acid synthase. These regulators play an important role in producing elements necessary for sterol biosynthesis [53,54]. Loss of this interaction results in increased de novo lipogenesis and, consequently, tumorigenesis and metastasis. This was later confirmed in the same experiment in which inoculating mice with HOXB13 knockdown PCa cells was associated with higher rate of metastasis compared to controls [52]. This data could be of great value in selecting patient who would benefit from newer agents such as fatty acid synthase (FASN) inhibitor (e.g., TVB-2640) which currently being tested in a clinical trial. Such agents may have the potential to decrease lipogenesis and, eventually, tumor growth.

3.4. TP53 Gene

TP53 is a gene responsible for the production of proteins that regulate cell division and cell death [55]. Because of its function, it plays a role as a tumor suppressor gene in which its deletion or mutation has been associated with the development of several tumors [56]. An example of this association is Li Fraumeni syndrome (LFS) which is an inherited condition characterized by an increased risk for certain types of cancer early in life, most commonly breast and adrenal cancers besides sarcomas, leukemias, and lymphoma. A multi-center study was conducted to assess the relationship between TP53 gene mutation and PCa, and the study identified about 31 patients (19%) with PCa among 163 LFS males and 117 LFS patients without PCa, six of them developed PCa over a median of three years of follow-up [57]. The same study reported 38 patients out of 6850 who have TP53 which reflects a higher relative risk by 9.1-fold than the control population. Additionally, the presence of the TP53 mutation was associated with more advanced disease. The gTP53 predisposes to aggressive prostate cancer; therefore, PCa should be considered as a part of LFS screening protocols, and TP53 should be considered in germline screening of PCa [57].

3.5. CHEK2 Gene

The CHEK2 gene, localized on chromosome 22, encodes for a tumor suppressor that participates in the DNA damage signaling pathway [58]. The CHEK2 gene and its role in developing inherited PCa are still unclear because of the rarity of the studies. However, the mutation of the CHECK 2 variants, particularly 1100delC, has demonstrated a moderate increase in the risk of development of PCa [59]. Moreover, a meta-analysis of 12 studies of the CHECK2 c.1100delC variant was conducted to clarify the relationship between this variant and PCa inheritance. About half of these studies demonstrated that CHECK2 c.1100delC is associated with an increased risk of PCa [60]. However, more retrospective and prospective studies are required to emphasize this relation and the role of genetic screening of PCa patients for CHECK2 gene variants.

3.6. Fibroblast Growth Factor (FGF) Genes

FGF genes encode fibroblast growth factor receptors, a group of receptors that regulate cell proliferation and differentiation during development and tissue repair [61]. Alteration to the FGF gene was shown to be associated with several cancers. For example, elevation in FGF expression was reported in patients with breast cancers [62]. Furthermore, point mutations in R78H, S249C, F384L, A391E, and G388R of the FGF genes have been observed in patients with PCa [63–65]. Moreover, in a recent meta-analysis, G388R polymorphism was associated with worse prognosis in cancer patients including those with PCa [66]. Interestingly, FGF has been also reported to play a role in cancer progression and metastasis in mice models [67]. Consequently, this gene has become the target for researchers to utilize as a potential therapeutic option [68,69].

3.7. Cyclin E1 Gene

Cyclin E1 (CCNE1) is one of the genes that regulate the transition from the G1 to the S phase of the cell cycle [70]. This gene has been implicated in different types of cancer such as breast and liver cancer [70–73]. Furthermore, several studies have suggested a potential role for CCNE1 as a prognostic and therapeutic tool [71,74,75]. In a recent study that was published in 2022 which investigated the role of CCNE1 in PCa, polymorphism CCNE1 rs997669 was not associated with a significant impact on prostate cancer risk [76]. However, a higher expression level of CCNE1 was significantly associated with a higher tumor grade [76]. In *in vitro* and *in vivo* studies, CCNE1 was shown to be regulated through speckle-type POZ protein (SPOP) in a way that over-expression of SPOP suppresses the tumor cell's progression [77]. Interestingly, this observation was limited to certain cell lines including prostate and bladder cancer. Furthermore, the wild-type SPOP was shown to have the opposite effect on these cell lines [77]. Although the exact underlying mechanism that would explain this mode of selectivity and variability in the effect is still unknown, this area of research should receive more attention as it could unveil a potential novel therapeutic option for PCa patients [78].

4. Clinical and Therapeutic Implications of Genetic Testing

Recommendations by different societies concerning genetic testing are variable, however, generally, testing is advised in patients who have a strong family history of PCa. This includes PCa in first and second-degree family members or multiple family members who were diagnosed before the age of 60 or died from PCa, hereditary Lynch syndrome, and hereditary breast, and ovarian cancer. This approach aims to enhance the ability for early detection and management of the condition [19,79–82].

Based on the recommendations of experienced societies, the genetic testing of PCa has been guided by some panels. If genetic testing is being performed in the context of advanced PCa, BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, and PMS2 should be included due to potential treatment implications, although this list is expected to be refined over time [44].

Among the potential consequences of germline testing is the detection of a mutation (pathogenic or potentially pathogenic variation), which may indicate further PCa treatment options and clinical trials and provide information regarding the risk of other malignancies [19].

This result would also indicate a 50/50 chance that first-degree relatives inherited the same risk gene and thus would prompt a recommendation for the patient to share this information (including a copy of test results) with relatives and for referral of family members to genetic counseling for cascade genetic testing. Insurance often covers single-site testing for a particular mutation at low cost. Another possible outcome is a variation of unknown significance (VUS), which implies that existing data in the field were inadequate at the time of test interpretation to define the finding as either benign or pathogenic. A VUS result should not be used to direct clinical management [83].

Other studies are available to help reclassify VUS, and these can be discussed with a genetic counselor. In one study, 7.7% of VUS results were reclassified: 91% as benign/likely benign and 9% as pathogenic/likely pathogenic. It is also possible that no alterations were found therefore (a benign result). The absence of a single mutation linked with hereditary cancer risk does not eliminate the higher risk of prostate cancer among family members with a strong family history. If testing is negative (benign, without mutations) or a VUS is identified, the clinical family history should be utilized to guide cancer screening for family members [84].

In 2017, the AUA/ASTRO/SUO guidelines recommended that patients with localized PCa and a strong family history of specific cancers (breast, ovarian and pancreatic) should be suspected of high-risk PCa and referred to genetic counseling and testing [80].

In 2019, the Philadelphia Prostate Cancer Consensus Conference provided recommendations for genetic testing criteria for PCa [19]. In addition, this consensus conference remarked that genetic testing should be strongly recommended for men with metastatic castration-resistant prostate cancer (mCRPC) and metastatic hormone-sensitive prostate cancer (mHSPC) and men with a strong PCa family history of first, second-degree, or multiple male relatives diagnosed with PCa at age <60 year or who died from metastatic PCa. Additional criteria were considered for testing. These criteria are pathologic criteria (intraductal pathology), stage (advanced disease), and family history criteria (Ashkenazi Jewish ancestry, or Lynch syndrome, especially if diagnosed at age <50 year or with ≥ 2 cancers in the HBOC). DNA repair genes (particularly BRCA2 and BRCA1) were recommended for genetic counseling and testing based on personal and family history regardless of the stage [19]. Moreover, in 2019 consensus recommendations recommended that the majority of men with newly diagnosed metastatic PCa should undergo genetic counseling and testing for BRCA1 and BRCA2 [82].

In 2020, EAU guidelines summarized the increase of germline mutations and their impact on clinical management, particularly for PARP inhibitor response, and the 2020 AUA/ASTRO/SUO advanced prostate cancer guideline recommended that patients with metastatic hormone-sensitive PCa should be offered genetic counseling and testing regardless of age and family history [81].

In addition to the benefit of using genetic testing as a screening and diagnostic tool, it can also be used as a guide for treatment selection. Poly (ADP-ribose) polymerase (PARP) inhibitors are a new anticancer group that was specifically designed to target the DNA damage response in BRCA1/2 mutated breast and ovarian cancers [85]. Currently, several members of this group are being studied for the treatment of PCa. Of these agents, olaparib and rucaparib have recently received FDA approval for the treatment of men with metastatic, castration-resistant PCa harboring a BRCA1 or BRCA2 gene mutation [86,87]. Olaparib, which was tested in patients with a mutation in genes related to homologous recombination repair, has been shown to enhance progression-free survival compared to enzalutamide or abiraterone [87]. Additionally, in a study that included 115 patients, who have BRCA alteration, rucaparib (at ≥ 1 dose) resulted in an objective response rate of 43.5% (95% CI, 31.0% to 56.7%; 27 of 62 patients) and 50.8% (95% CI, 38.1% to 63.4%; 33 of 65 patients) per independent radiology review and investigator assessment, respectively [86]. Furthermore, the confirmed PSA response rate ($\geq 50\%$ decrease from baseline) was 54.8% (95% CI, 45.2% to 64.1%; 63 of 115 patients) [86]. Talazoparib and niraparib have also shown good efficacy in the management of PCa patients with niraparib receiving the FDA breakthrough therapy designation for the treatment of patients with BRCA1/2-mutated metastatic castration-resistant PCa therapy in October 2019 [88–90].

While several trials are still ongoing investigating the efficacy of this anticancer group alone and in combination with other anticancer agents such as programmed cell death protein-1 inhibitors for the management of PCa (NCT05501548, NCT04824937, NCT04030559, NCT04703920, NCT05327621, NCT04550494, NCT02854436, NCT04179396, NCT02975934, NCT04821622, NCT01078662), this highlights the importance of genetic

testing in formulating the treatment plan for these patients, especially those who failed to respond to the conventional treatments [91–102].

Another interesting treatment option that is being studied as a potential therapeutic target for several cancers is FASN inhibitors [103–105]. Lipogenesis is a critical process that solid tumors rely on to secure an energy source sufficient for their growth, which is achieved via de novo lipid synthesis [106]. PCa is among the tumors that exhibit this behavior which makes it a suitable candidate for this drug group [107]. Over the past years, several molecules that possess an inhibitory effect on FASN have been reported in the literature such as GSK2194069, JNJ-54302833, IPI-9119, and TVB-2640 [108]. Only TVB-2640 has moved into clinical testing and, currently, five ongoing trials targeting subjects with solid tumors such as breast cancer and PCa (NCT03179904, NCT05743621, NCT02980029, NCT03808558, and NCT03032484) [109–114]. Keeping in mind the role of HOXB13 in regulating lipogenesis, patients with deletion or mutation to this gene could be a good candidates for FASN inhibitors.

Given the role the FGFR plays in PCa, inhibitors for these receptors represent a promising therapeutic option. Data from preclinical and clinical studies support a potential role for these agents as a novel therapeutic option [69,115]. For example, pemigatinib, a tyrosine kinase inhibitor that acts on FGFR and is approved by the FDA for the management of cholangiocarcinoma and myeloid/lymphoid neoplasms, actively inhibited the growth of PCa cells in in vitro and in vivo models [116]. Interestingly, the activity of the androgen receptors seems to affect the response to these agents as reported by Bluemn et al. Based on the results from their study they suggested that FGFR inhibitors are specifically active in castration-resistant prostate cancer patients with absent or limited AR function [117]. Thus, genetic analysis for androgen receptors to determine any mutation, such as amplification, could be of value before starting such agents.

5. Conclusions

According to the clinically significant prevalence of germline genetic mutation, genetic testing has increased as an indication of screening in PCa patients, especially the advanced and metastatic cases. Furthermore, with the comprehensive support of recent studies, genetic testing is expected to be widely integrated into all PCa patients, which will help in clinical assessment and critical decisions in treatment strategies for patients with inherited PCa.

Therefore, a clear policy regarding genetic testing could point to more accurate active surveillance as a management strategy for patients with low-risk PCa. More retrospective and prospective studies are required to achieve, advance, and support the theory of genetic testing in the upcoming years.

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Abbreviations

PCa: Prostate Cancer, BPH: Benign Prostatic Hyperplasia.

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