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Prostate cancer genetic background. The introduction of genetic testing in the determination of high-risk prostate cancer cases and selection of targeted chemotherapy in advanced prostate cancer patients

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Introduction Prostate cancer (PCa) is a major challenge in urology, with increasing incidence and mortality. Despite advances in diagnosis and treatment, certain patient groups remain poorly served. Genetic factors, particularly in hereditary prostate cancer (HPCa), are now recognized as significant contributors to disease progression. This review focuses on the role of genetic mutations in PCa, their impact on diagnosis, and management.

Material and methods This review summarizes current literature on genetic mutations linked to PCa, including *BRCA1, BRCA2, ATM, CHEK2*, and others. These mutations are associated with more aggressive disease, earlier onset, and may influence treatment strategies. Guidelines from the Philadelphia Prostate Cancer Consensus Conference (PPCCC), the American National Comprehensive Cancer Network (NCCN), and the European Association of Urology (EAU) on genetic testing are also discussed.

Results Genetic screening is increasingly recommended for high-risk individuals, such as those with a family history or aggressive PCa. Identifying mutations allows for early detection and tailored treatment, including more frequent screening and targeted therapies. Specific mutations, like those in *BRCA* genes, can benefit from chemotherapy in advanced stages. Genetic testing provides valuable information to guide patient management, improving early detection and patient outcomes.

Conclusions Genetic testing plays a crucial role in PCa management, enabling personalized care for high-risk patients. As genetic research advances, incorporating genetic screening into clinical practice will enhance early diagnosis and treatment outcomes, ultimately improving patient survival and quality of life.

Key Words: prostate cancer ‹› mutation ‹› hereditary prostate cancer ‹› genetic testing

INTRODUCTION

In 2020, prostate cancer (PCa) was the second most common cancer worldwide, accounting for over 1,400,000 new cases. PCa was responsible for more than 375,000 deaths, ranking fifth in cancer mortality rates that year [1]. Most PCa cases are indolent, having a minimal impact on survival rates. However, about 25–30% of PCa patients present an aggressive disease course that is prone to metastasis [2]. It is crucial to identify high-risk PCa cases that usually require a more aggressive therapeutic approach. The analysis of prostate-specific antigen (PSA) and digital rectal examination (DRE) remain the primary tools used by clinicians to detect PCa. However, this routine screening may not be effective for every patient. Diagnostics should be tailored to the individual's specific case, such as their

age at first PSA evaluation, its frequency, and referrals for genetic testing and magnetic resonance imaging (MRI). The most important PCa risk factors include genetic predispositions (such as familial cases), age, environmental factors, and ethnicity. In recent years, the genetic factors contributing to PCa development have been extensively studied. Data suggest that about 10 to 20% of PCa cases have a familial or hereditary background [3]. Such cases are usually associated with earlier onset and a familial occurrence of PCa. Patients with a family history of PCa or an aggressive form of the disease are suspected of carrying genetic mutations that determine further management and therapeutic approaches. This includes earlier PCa screening, more frequent urological consultations (including PSA, DRE, and MRI evaluations), and decisions regarding prostate biopsy. These strategies result in more efficient identification of high-risk PCa cases that may require more invasive approaches, such as radical treatment options like radical prostatectomy (RP). Such individually adapted screening reduces overtreatment and aids in deciding whether to observe more indolent PCa cases. Regarding aggressive, metastatic PCa cases, recent studies show that carriers of specific genetic mutations benefit from targeted chemotherapy (e.g. olaparib), as shown by improved survival and treatment response rates. Genetic testing has proven to be highly valuable in selected groups of patients [4, 5].

Hereditary and familial prostate cancer

Hereditary prostate cancer (HPCa) refers to PCa cases that meet specific criteria based on family history. These criteria include the following: 1) at least 3 PCa cases among first-degree relatives; 2) PCa presence in 3 consecutive generations; and 3) two or more relatives diagnosed with PCa before 55 years of age. PCa with a familial background that does not meet the criteria for HPCa is described as familial PCa. The risk of developing familial PCa increases with the number of affected relatives and is estimated to be 2 to 8 times higher than for incidental PCa [2]. HPCa is associated with a development approximately 2 years earlier compared to incidental PCa cases [5]. To date, it has not been explicitly determined whether HPCa differs from incidental PCa in terms of its aggressiveness. HPCa has the highest heritability among major malignant tumours affecting males [4]. The incidence of HPCa varies depending on ethnicity. African Americans are twice as likely to be affected as European men and 3 times as likely as Asians [4]. This tendency might be related to lifestyle differences, such as diet type or obesity rates. Genetic factors play a pivotal role in HPCa development. In Caucasian and Asian populations, specific single-nucleotide polymorphisms (SNPs) were found, unlike in African American populations [4]. Mutations contributing to HPCa development may affect various genes, including DNA damage repair (DDR) genes and DNA mismatch repair (MMR) genes. DDR genes include breast cancer type 1 and 2 (*BRCA1* and *BRCA2*), *ATM* serine/threonine kinase (*ATM*), checkpoint kinase 2 (*CHEK2*), and partner and localiser of *BRCA2* (*PALB2*). *MMR* genes include MutL protein homologue 1 (*MLH1*), MutS homologue 2 (*MSH2*), MutS homologue 6 (*MSH6*), and mismatch repair endonuclease PMS2 (*PMS2*). Other important genes impacting HPCa development include homeobox B13 (*HOXB13*), nibrin (*NBS1*), and *BRCA1* interacting helicase 1 (*BRIP1*). The inherited mutations affecting HPCa development are transmitted in an autosomal dominant pattern [2–6].
Patients with a family history of PCa have a higher probability of being diagnosed at an earlier age and usually present with a more locally advanced stage of the disease. Postsurgical biochemical recurrence rates, as assessed by PSA blood levels, are higher in such cases. However, the overall PCa survival rate is similar regardless of these risk factors [7]. PCa usually does not present any symptoms in the early stages, so early detection should be individualised. This approach would be particularly beneficial in men with a positive familial history of PCa or other hereditary cancer syndromes, such as Lynch syndrome or hereditary breast and ovarian cancer syndrome [4].

Genes associated with prostate cancer

Almost all human chromosomes (except for chromosomes 15, 16, 21, and 23) contain loci that are prone to HPCa development [3]. The most commonly found defective genes are *HOXB13, BRCA2, CHEK2, ATM, MMR* group, *BRCA1, PALB2, BRIP1*, and *NBS1*. The remaining HPCa cases are caused by gene mutations that remain unknown. Other important genes associated with PCa include the prostate cancer antigen 3 (*PCA3*) gene, distal-less homeobox 1 (*DLX1*) gene, the fusion gene of transmembrane protease serine 2, the erythroblast transformation-specific related gene (*TMPRSS2-ERG*), ras association domain family member 1 (*RASSF1*) gene, and adenomatous polyposis coli (*APC*) gene [3] (Table 1).

HOXB13 gene

The *HOXB13* gene is considered the most common gene associated with PCa development. HOXB13

belongs to a group of transcription factors that impact androgen receptors (ARs). Due to this interaction, HOXB13 stimulates physiological prostatic cell development and differentiation through lipogenesis, cell migration, and proliferation. One of the most widely observed *HOXB13* alterations is a recurrent germline mutation, *G84E* [3].

Ewing et al. reported that the prevalence rate of the *HOXB13 G84E* variant is 20 times higher in men with PCa than in a control group. It was more frequently found in patients with a familial PCa history and earlier disease onset. The authors concluded that the *HOXB13 G84E* germline mutation is linked with an increased risk of HPCa [8].

Nyberg et al. determined the risk of PCa development for *G84E* variant carriers. It was observed that the risk of PCa for *G84E* mutation carriers by age 85 years ranged from 60% (for men without a familial PCa history) to 98% (for men with a familial history of at least 2 relatives diagnosed with PCa at an early age). The average risk for the control group was 15% [9].

The *HOXB13 G84E* mutation is associated with the so-called founder effect, as this variation primarily involves patients of European origin. Other variants affecting specific populations have been reported. In Portugal, 2 variants were observed: F240L and A128D. The G135E variant was present in the Chinese population [8–11].

BRCA1 and BRCA2 genes

BRCA1 and *BRCA2* gene malfunctions are primarily associated with hereditary breast-ovarian cancer syndromes (HBOC). Defective variants of *BRCA1* and *BRCA2* are also involved in the development of several other malignant tumours, including PCa, melanoma, and pancreatic cancer. Both genes belong to the tumour suppressor category, and their physiological function involves maintaining genome integrity through homologous recombination (HR). The population prevalence of *BRCA* mutations is estimated at 0.2% to 0.3% [5]. Specific variations associated with the so-called founder effect are characteristic of specific populations. For example, *BRCA1* alterations, such as 185delA and 5382insC, and the *BRCA2* 6174delT variant are more common in the Ashkenazi Jewish population [4], in whom the likelihood of possessing at least one of these mutations was estimated at 2% to 2.5% [12].

Both *BRCA1* and *BRCA2* mutations significantly increase the risk of PCa development. Male carriers

Table 1. *Genes associated with prostate cancer (PCa)*

Gene	Location	Mutation incidence	Reference
ATM	Chromosome 11	1.6% to 2.03%	Pritchard et al. 2016 [58], Nicolosi et al. 2019 [59]
BRCA1	Chromosome 17	0.9% to 1.25%	Pritchard et al. 2016 [58], Nicolosi et al. 2019 [59]
BRCA2	Chromosome 13	1.2% to 5.3%	Pritchard et al. 2016 [58], Nicolosi et al. 2019 [59]
BRIP1	Chromosome 17	0.1% to 0.28%	Nicolosi et al. 2019 [59], Pritzlaff et al. 2020 [60]
CHEK2	Chromosome 22	1.9% to 2.88%	Pritchard et al. 2016 [58], Nicolosi et al. 2019 [59]
HOXB13	Chromosome 17	0.6% to 4.5%	Nicolosi et al. 2019 [59], Pritzlaff et al. 2020 [60]
MMR group *(MLH1, MSH2, MSH6, PMS2)*	Chromosome 2 (*MSH2*, *MSH6*), chromosome 3 (*MLH1*), chromosome 7 (*PMS2*)	1.74% to 2.8%	Nicolosi et al. 2019 [59], Pritzlaff et al. 2020 [60]
NBS1	Chromosome 8	0.2% to 0.32%	Nicolosi et al. 2019 [59], Pritzlaff et al. 2020 [60]
PALB2	Chromosome 16	0.4% to 0.56%	Pritchard et al. 2016 [58], Nicolosi et al. 2019 [59]
PCA3	Chromosome 9	Currently unknown	Muñoz Rodríguez et al. 2019 [32]
DLX1	Chromosome 2	Currently unknown	Liang et al. 2018 [33]
TMPRSS2-ERG	Both genes located on chromosome 21	TMPRSS2 and ERG alterations observed in over 47% of PCa cases	Wang et al. 2017 [57]
RASSF1	Chromosome 3	Currently unknown	Friedemann et al. 2021 [35]
APC	Chromosome 5	0.8% to 1.28%	Nicolosi et al. 2019 [59], Pritzlaff et al. 2020 [60]
Other genes not yet determined	Currently unknown	79% to 92%	Vietri et al. 2021 [4]

ATM '– ATM serine/threonine kinase; BRCA1 – breast cancer type 1; BRCA2 – breast cancer type 2; BRIP1 – BRCA1 interacting helicase 1; CHEK2 – checkpoint kinase 2; HOXB13 – homeobox B13, MMR group – DNA mismatch repair; MLH1 – protein homologue 1; MSH2 – mutS homologue 2; MSH6 – mutS homologue 6; PMS2 – mismatch repair endonuclease PMS2; NBS1 – nibrin; PALB2 – partner and localizer of BRCA2; PCA3 – prostate cancer antigen 3; DLX1– distal less homeobox 1; TMPRSS2-ERG – gene fusion of transmembrane protease serine 2 and erythroblast transformation-specific related gene; RASSF1 – ras association domain family member 1; APC – adenomatous polyposis coli

of *BRCA1* germline variations have approximately a 3.75-fold increased risk of PCa development before age 65 years [13], while male carriers of *BRCA2* germline variations have an 8.6-fold increased risk [14]. The presence of *BRCA1* and/or *BRCA2* germline alterations is associated with a more aggressive course of PCa. *BRCA2* mutations lead to a more aggressive disease course and worse clinical outcomes, measured by earlier PCa onset and overall survival (OS) rates [3–5]. PCa patients carrying a *BRCA2* mutation had an OS rate of 4.8 years, whereas non-carriers had an OS rate of 8.5 years [15]. Studies on the Polish population of familial PCa show a prevalence of *BRCA2* gene alterations of 1%. Seventy-five per cent of PCa cases in *BRCA2* mutation carriers had a Gleason score ranging from 8 to 10, compared to 22% in the control group. However, there were no statistically significant differences in OS [14].
Interestingly, recent studies show that male patients with a *BRCA1*/*BRCA2* germline mutation, as opposed to sporadic PCa cases, are more sensitive to specific types of chemotherapeutics such as olaparib. Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor and a type of targeted therapy that exploits the weakness in the homologous recombination repair process characteristic of *BRCA*-mutated cells, making them susceptible to synthetic lethality. Synthetic lethality refers to the situation where a defect in 2 genes leads to cell death, but a defect in only one gene does not. This finding has significant implications for the personalised treatment of advanced PCa [16].

CHEK2 gene

Mutations in the *CHEK2* gene are associated with several malignant tumours and syndromes, including Li-Fraumeni and HBOC syndromes, as well as thyroid, kidney, and colon cancers. *CHEK2* encodes a tumour suppressor protein involved in the DNA damage response signalling pathway [3–5, 17]. According to Heidegger, the presence of *CHEK2* mutations increases the risk of hereditary prostate cancer (HPCa) by 1.8% to 3.3% [18]. Wokołorczyk found that *CHEK2* alterations were the most common mutations, present in 10% of the studied cases. Carriers of the *I157T CHEK2* variant have a 1.5- to 2-fold increased risk of familial PCa development, while carriers of truncating *CHEK2* variants have a 3- to 5-fold increased risk. No significant differences in disease aggressiveness were observed compared to non-familial PCa cases [16].

ATM gene

The *ATM* gene is involved in DNA repair through the homologous recombination (HR) repair pathway, and it activates the double-strand break (DSB) repair mechanism. Mutations in *ATM* are associated with ataxia-telangiectasia, HBOC syndromes, and various cancers, including prostate, breast, pancreatic, gastric, and colorectal cancers [3–5]. In a study of 121 PCa patients with a familial history or early onset of the disease, *ATM* alterations were the most prevalent defect, appearing in about 5.8% of the studied men, followed by *CHEK2* variants at 3.3% prevalence [19]. Heidegger et al. estimated the average risk of metastatic PCa for defective *ATM* carriers at 6.3% [18]. In 2020, Rantapero et al. suggested that *ATM* defects might predispose individuals to a more aggressive course of PCa, finding *DNA repair gene* mutations in 12.3% of lethal PCa cases, with *CHEK2* and *ATM* variants being the most common [20]. These reports suggest that *ATM* mutations may be linked not only with increased PCa risk but also with a more aggressive disease course [3].

MMR genes

The mismatch repair (*MMR*) gene group, which includes *MLH1, MSH2, MSH6*, and *PMS2*, is associated with HPCa risk. Lynch syndrome is linked to *MMR* gene dysfunctions, increasing the risk of endometrial and colorectal cancer. *MMR* germline mutation carriers also have a higher risk of developing prostate, urothelial, pancreatic, gastric, small intestine, and brain cancers [4]. Raymond et al. estimated that Lynch syndrome patients have a 2-fold higher lifetime risk of PCa compared to the general population [21]. Haraldsdottir et al., studying 188 male patients with Lynch syndrome, found an approximately 5-fold increased risk of PCa, with no impact on the clinical course of the disease [22]. *MSH2* variations are associated with a significantly higher risk of PCa development compared to *MSH6* and *MLH1* carriers [23, 24].

PALB2 gene

The *PALB2* gene encodes a *BRCA2* binding protein that enables *BRCA1* and *BRCA2* to form a complex necessary for initiating the HR repair process. *PALB2* alterations are associated with HBOC syndrome, increasing the risk of developing breast and pancreatic cancer, as well as PCa [3, 4]. Pritchard et al. found *PALB2* germline variations in 0.4% of metastatic HPCa patients [25], while Nicolosi et al. reported *PALB2* germline mutations in 0.56% of an unselected PCa cohort [26]. Horak et al. presented a case in which a *PALB2* mutation carrier received chemotherapy with a PARP inhibitor (olaparib) combined with platinum-based chemotherapy,

resulting in clinical remission and disease stabilisation. This suggests that *PALB2* status might influence therapy selection based on genetic status [27].

BRIP1 gene

The *BRIP1* gene encodes a helicase involved in the DSB repair mechanism. Studies suggest that *BRIP1* mutations are associated with an increased risk of PCa [3, 4]. Kote-Jarai et al. reported that carriers of the c.2392C>T *BRIP1* truncating variant have an increased risk of early-onset and familial PCa [28]. Leongamornlert et al. confirmed this association and identified 2 families with PCa history carrying the c.2392C>T *BRIP1* mutation [29].

NBS1 gene

The *NBS1* gene is involved in the DSB repair mechanism, and mutations in this gene are thought to play a crucial role in PCa cases of hereditary and familial backgrounds [3, 4]. In 2004, Cybulski et al. demonstrated that carriers of the founder mutation c.657del5 under 60 years old have a 3-fold increased risk of PCa development, which rises to 4-fold with a familial PCa history [30]. A 2013 study found that the *NBS1 c.657del5* mutation leads to a more aggressive disease course and higher mortality rate [31].

Prostate cancer antigen 3

PCA3 is a non-coding RNA specific to PCa. A meta-analysis involving 9 studies from 2007 to 2014 with 3028 participants assessed the effectiveness of the *PCA3* test. It reported a specificity of 0.65, sensitivity of 0.69, and a diagnostic odds ratio of 4.244, indicating that the *PCA3* test has acceptable value in identifying PCa and could be useful in deciding whether to perform a prostate biopsy [32].

Distal less homeobox 1

The dysregulation of homeobox family genes, such as *DLX1*, can lead to carcinogenesis. *DLX1* is associated with PCa. Liang et al. [33] studied 492 PCa patients and 152 controls and found significantly elevated levels of *DLX1* in PCa tissues, suggesting it could serve as a valuable diagnostic marker for PCa.

Gene fusion of transmembrane protease serine 2 and erythroblast transformation-specific related gene

The gene fusion of transmembrane protease serine 2 and erythroblast transformation-specific related gene (*TMPRSS2-ERG*) fusion gene involves *TMPRSS2* (an androgen-related gene) and *ERG* (a transcription factor), both of which are overexpressed in PCa. The fusion affects about 50% of Caucasian Americans, 31% of African Americans, and 18.5% of Asians. It is associated with PCa stage, metastasis, and Gleason score, but not with lymph node involvement or tumour size. *TMPRSS2-ERG* might become a predictive biomarker for PCa, but more data are required [34].

Ras association domain family member 1

Studies on DNA methylation in PCa show that certain genes tend to be hypermethylated. Ras association domain family member 1 (*RASSF1*), particularly its RASSF1A isoform, is significantly hypermethylated in PCa patients. Friedemann et al. found that *RASSF1* methylation levels were significantly increased across all PCa groups, suggesting its potential as a biomarker in men with ambiguous PSA levels (2–10 ng/ml) [35].

Other genes

Other genes associated with PCa include *TP53, APC, RAD51C*, and *RAD51D*. Germline *TP53* (gTP53) mutations are linked with an increased risk and a more aggressive course of PCa, particularly among men with Li-Fraumeni syndrome (LFS) [3, 4]. The *APC* gene encodes a protein responsible for regulating β-catenin levels and is often hypermethylated in PCa patients. Its downregulation correlates with more advanced and metastatic PCa cases [37]. More data are needed to clarify the relationship between these genes and PCa development risk [3, 4].

Guidelines referring to genetic testing in prostate cancer

A familial history of PCa is associated with a higher risk of early onset PCa. Moreover, specific germline mutations affecting genes involved in DNA repair lead to an increased risk of a more aggressive course of PCa. Therefore, men with such genetic predispositions who are exposed to high-risk PCa cases require more precise screening methods involving genetic testing tools [38].

Philadelphia Prostate Cancer Consensus Conference guidelines

The importance of genetic testing in hereditary PCa (HPCa) was highlighted in 2017 during the Philadelphia Prostate Cancer Consensus Conference (PPCCC).

In 2019, the subsequent PPCCC provided clinicians with specific recommendations regarding PCa genetic screening. It was recommended that genetic testing be performed on men with metastatic PCa and those with a familial history of PCa who meet certain criteria. These criteria include at least one first-degree relative or 2 relatives diagnosed with PCa under the age of 60 years, who died from PCa, or who had metastatic PCa. Patients with non-metastatic PCa should be considered for genetic testing if they have advanced PCa (at least T3a), confirmed intraductal or ductal pathology, a Gleason grade of 8 or higher, or Ashkenazi Jewish ancestry. For metastatic PCa, testing for BRCA and MMR gene mutations is recommended, with an optional test for *ATM* mutations. In non-metastatic PCa, testing for *BRCA2* mutations is recommended, with consideration for *ATM* mutations. Men meeting the aforementioned familial PCa history criteria should be tested for *BRCA2* and *HOXB13* mutations, with consideration given to *BRCA1, ATM,* and *MMR* gene mutations. Based on familial and personal history, the authors recommend including additional genes for testing. The guidelines reflect the need for a personalised management approach. In metastatic PCa, genetic status may guide the selection of targeted chemotherapy (e.g. PARP inhibitors/platinum-based chemotherapy in *BRCA*-positive patients). For non-metastatic PCa, genetic status may impact PCa management protocols, such as active surveillance (AS) based on *BRCA* status. In men not yet diagnosed with PCa, genetic status impacts the initiation and frequency of PCa screening. For instance, *BRCA2* carriers are recommended for early PCa screening starting at age 40, or 10 years before the youngest PCa diagnosis in the family. Carriers of *BRCA1, ATM, HOXB13*, and *MMR* gene mutations should also be considered for this management approach [38].

European Society for Medical Oncology guidelines

In 2020, the European Society for Medical Oncology (ESMO) recommended genetic testing of DNA repair genes, including *BRCA2*, in all cases of metastatic PCa. The tests were also recommended for localised PCa patients with a family history of hereditary cancer syndromes (such as PCa, breast, ovarian, or pancreatic cancer) affecting at least 2 close blood relatives. In men with metastatic castration-resistant PCa (mCRPCa), tumour testing for HR and *MMR* gene mutations should be considered. ESMO concluded that identifying PCa mutation carriers may have beneficial value for prevention and early diagnosis in relatives. The guidelines highlighted the potential benefits of determining specific genetic statuses to select targeted therapies (e.g. PARP inhibitors) [39].

National Comprehensive Cancer Network guidelines

In 2021, the National Comprehensive Cancer Network (NCCN) recommended an adjusted early PCa screening strategy based on personal risk factors and familial PCa history. PCa screening (DRE, PSA evaluation) should be initiated in high-risk men who fulfil one of the following criteria: Black/African American men, men with high-risk germline mutations (e.g. *BRCA* mutations), or men with a familial PCa history [40].

American Urological Association guidelines

In its 2023 guidelines, the American Urological Association (AUA) did not include recommendations for PCa genetic testing. However, it strongly recommended initiating early PCa screening at ages 40–45 years for men at increased risk of PCa. The risk factors include Black ancestry, a strong familial PCa history, and germline mutations such as *BRCA1/2*. The guidelines also mentioned *ATM, CHEK2, HOXB13, MLH1, MSH2, MSH6, NBS1,* and *PMS2* mutations, noting that their impact on PCa development requires further research. The AUA concluded that genetically predisposed patients might benefit from earlier initiation of PSA evaluation and more frequent PSA screening [41].

European Association of Urology guidelines

The 2024 guidelines from the European Association of Urology (EAU) highlight evidence indicating the beneficial value of genetic testing in early PCa detection and management. A weak recommendation was given for genetic germline testing in men with a familial history of PCa diagnosed before age 60 years and in those whose family member died from PCa. A strong recommendation was given to offer germline testing to men with a family history of high-risk germline mutations or multiple cancers affecting the same family members. Another strong recommendation was to offer germline testing to men with *BRCA* mutations identified in somatic testing. The EAU concluded that more data are required to develop specific guidelines regarding PCa early detection, screening, and treatment in mutation carriers and their family members [42] (Table 2).

Impact of genetic markers on patient management

Given the increased risk of more aggressive PCa and its earlier onset in genetically predisposed individuals, recent studies have aimed to determine a more individualised screening approach and its effectiveness. Some men carry specific mutations and may benefit more from targeted chemotherapy [38].

The approach to screening

Walker et al. evaluated the usefulness of adjusted PCa screening in genetically high-risk patients who carry *BRCA* mutations. The study compared 53 carriers of *BRCA1/2* mutations to 53 men with a positive familial PCa history. The review included screening characteristics (PSA level, DRE, and biopsy), treatment outcomes, and pathological features. The use of a PSA cut-off above 4 ng/ml would lead to PCa being overlooked in both groups. In the men with a positive PCa familial history, the cancer detection rate was higher (21%, 11 men) compared to the mutation carrier group (15%, 8 men). Among the carriers, 6 men had *BRCA2* mutations and 2 had *BRCA1* mutations. The carriers were significantly more likely to present with intermediate- or high-risk PCa (88% vs 36% for men with a positive familial history). AS was applied to 3 men with a positive familial history and 2 carriers. In total, 8 men with a positive family history and 6 carriers underwent radical prostatectomy (RP). Mutation carriers were more likely to require additional treatments such as ADT, chemotherapy, and/or salvage radiotherapy, whereas none of the patients with a positive familial history required such therapies. Five *BRCA2* mutation carriers required ADT, one *BRCA2* carrier required salvage radiotherapy, and 2 *BRCA2* carriers required chemotherapy. The men with *BRCA2* mutations displayed a more aggressive disease course and were more likely to have distant metastases (4 cases), compared

Table 2. *The recent guidelines on prostate cancer (PCa), recommendations on genetic testing*

Guidelines (year)	Recommendations on genetic testing	Impact on the management	Reference
PPCCC (2019)	Yes; metastatic PCa men (recommended), men with familial (≥1 first-degree relative or ≥2 relatives diagnosed with PCa before 60 years old or PCa death or metastatic PCa) PCa history (recommended), non-metastatic PCa cases with ≥1 of: localized stage (≥T3a), intraductal/ductal involvement, Gleason grade ≥8, Ashkenazi Jewish ancestry (genetic testing should be considered)	Possible selection of targeted PARP-inhibitor or platinum-based chemotherapy in particular group of patients (metastatic PCa), active surveillance management in the particular patient group (non-metastatic PCa), the age of PCa screening initiation and its frequency (depending on patient genetic status)	Giri et al. 2019 [38]
ESMO (2020)	Yes; metastatic PCa, localised PCa with familial history of ≥2 close blood relatives diagnosed with cancers associated with hereditary cancer syndromes (PCa, breast, ovarian, pancreatic cancer), mCRPCa men should be considered for tumour testing in search of HR and MMR gene mutations	Not specified, genetic testing may have a beneficial value for the prevention and early diagnosis of PCa cases in patients' family members	Parker et al. 2020 [39]
NCCN (2021)	No	Adjusted early PCa screening based on personal risk factors and familial PCa history, earlier initiation of PCa screening (DRE, PSA assessment) in high-risk men (≥1 of: Black/African American ancestry, high-risk germline mutations e.g. BRCA, familial PCa history)	Prostate Cancer Early Detection, version 2.2021 NCCN Clinical Practice Guidelines in Oncology (2021) [40]
AUA (2023)	No	Initiation of early PCa screening starting at age 40-45 years for men with increased PCa risk (≥1 of: black ancestry, strong familial PCa history, germline mutations e.g. BRCA)	Early detection of prostate cancer: AUA/SUO guideline (2023) [41]
EAU (2024)	Yes; weak recommendation to offer germline testing in the group of men with ≥1 of: familial PCa death or familial PCa diagnosis before 60 years of age, strong recommendation to offer germline testing in the group of men with ≥1 of: familial history of high-risk germline mutations or familial history of multiple cancers affecting the same side of the family, strong recommendation to offer germline testing in the group of men with BRCA mutations identified during somatic testing	Not specified; more data is required to offer specific PCa management protocol regarding genetic status	European Association of Urology (2024) [42]

AUA – American Urological Association; EAU – European Association of Urology; ESMO – European Society for Medical Oncology; mCRPCa – metastatic castration resistant PCa; NCCN – National Comprehensive Cancer Network; PARP – poly(ADP-ribose) polymerase; PCa – prostate cancer; PPCCC – Philadelphia Prostate Cancer Consensus Conference

to men carrying BRCA1 mutations (no cases) or men with a positive familial history (no cases). It could be beneficial for *BRCA1/2* mutation carriers to have a more standardised screening approach that includes not only DRE and PSA assessment but also monitoring PSA increase velocity and lowering the PSA cut-off [43].

The IMPACT study assessed the effectiveness of PCa screening in *BRCA1* or *BRCA2* mutation carriers. The study included 89 *BRCA1* and 116 *BRCA2* mutation carriers, with a control group of 95 men. Men with a family history of *BRCA1* or *BRCA2* mutations underwent annual PSA evaluations. Prostate biopsy was recommended for men with PSA levels exceeding 3 ng/ml. In the baseline year 1, a total of 22 patients had PSA levels above 3 ng/ml. Biopsies were performed in 21 individuals (17 mutation carriers and 4 controls), with positive results in 10 cases. Among these, 8 were mutation carriers and 2 were controls. In year 2 of the study, one PCa case was diagnosed. Overall, 11 PCa cases were diagnosed, of whom 9 were mutation carriers. Among *BRCA1*/*BRCA2* mutation carriers, 2 low-risk and 7 high-risk (6 intermediate-risk and one high-risk PCa patient) cases were identified. In the control group, there was one case of low-risk and one case of high-risk PCa. Three low-risk patients were managed with AS, while all 9 men with clinically significant PCa received treatment (8 underwent RP and one received brachytherapy). Although it is difficult to explicitly determine the PSA level that should lead to a referral for prostate biopsy, the IMPACT study data indicate that *BRCA1* and/or *BRCA2* mutation carriers benefit from biopsy referral when PSA levels exceed 3 ng/ml. This approach improves the likelihood of identifying clinically significant PCa cases that require further invasive management. Most of the PCa cases in BRCA mutation carriers were clinically significant, suggesting a more aggressive nature. The results support the value of PSA screening followed by prostate biopsy in detecting clinically significant PCa in *BRCA* mutation carriers [44].

The BARCODE1 pilot study assessed the effectiveness of PCa screening in genetically predisposed men. Out of 1,434 participants, 297 underwent DNA genotyping. The top 10% of the group (25 patients) with the highest polygenic risk scores (PRS) were offered MRI and prostate biopsy. Of these, 7 out of 18 men (38.9%) were diagnosed with PCa. These cases were classified as low-risk and managed with AS. The remaining 11 patients had negative biopsies and were followed up with annual PSA evaluations, with decisions on repeating MRI and biopsy based on PSA levels. It is estimated that men with a PRS above the 90th percentile have a 2.7-fold higher risk of PCa. The genotyping included 130 single nucleotide polymorphisms (SNPs) that contribute to both non-aggressive and aggressive PCa cases. This approach helped identify men who are likely to benefit most from an adjusted screening strategy. The pilot study highlighted the potential benefits of MRI-based screening for this group of men. The results suggest that adjustments to standard PCa screening are necessary to better identify high-risk cases among genetically predisposed men, who are more susceptible to aggressive PCa. This strategy reduces overtreatment and allows for initial management with AS, followed by more invasive treatments if necessary. This led to the initiation of the main BARCODE1 study, which aims to recruit 5,000 men in the UK [45].

Currently, the PROFILE study in the UK aims to recruit 1,050 men for genetic analysis and targeted PCa screening, including PSA evaluation, MRI, and prostate biopsy. The study proposes modifications to standard PCa screening based on recent findings that men with early-onset PCa are often genetically predisposed and may have a more aggressive disease course. All eligible participants must be aged 40 to 69 years. The study will consist of 3 cohorts of 350 individuals each: men with a familial PCa history, men of African or Caribbean descent, and men carrying PCa susceptibility mutations. The study aims to determine whether genetic analysis combined with the proposed screening methods can effectively identify patients at high risk for PCa. The authors anticipate that the guidelines for PCa screening may need to be adjusted to offer a more effective strategy for evaluating PCa risk in the highest-risk patients, ultimately improving PCa survival rates [46].

The research conducted and ongoing should provide clinicians with valuable insights into screening approaches for genetically predisposed patients. It is essential to identify high-risk patients who may require more invasive and accurate diagnostic tools.

The reports on targeted therapies

Recent reports indicate that advanced or metastatic prostate cancer (PCa) patients often carry somatic and/or germline mutations affecting DNA repair genes (e.g. *BRCA1, BRCA2, PALB2, CHEK2, ATM*). These mutations are present in approximately 5% to 10% of localised PCa cases and 12% to 17% of metastatic cases, confirming a higher susceptibility to a more aggressive course of PCa in genetically burdened individuals. Patients treated with PARP

inhibitors and platinum-based chemotherapy generally exhibit better prognoses, including higher survival and progression-free survival rates, compared to those receiving standard treatments such as enzalutamide or abiraterone. The U.S. Food and Drug Administration (FDA) has approved olaparib and rucaparib, with additional PARP inhibitors like talazoparib and niraparib currently under investigation. Genetic testing could further enhance survival rates by guiding treatment decisions [47].

Olaparib's approval was based on the results of the phase 3 PROfound trial, which tested olaparib in patients with progressive metastatic castration-resistant prostate cancer (mCRPCa) harbouring mutations in homologous recombination (HR) repair genes (e.g. *BRCA1, BRCA2, ATM*). The study involved 387 men divided into 2 cohorts: Cohort A with ≥1 aberration in *BRCA1/2* or *ATM* (245 men) and Cohort B with aberrations in at least one of 12 other genes (e.g. *BRIP1, BARD1, CDK12, CHEK1/2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*) (142 men). Patients were randomly assigned to receive either olaparib (256 men) or enzalutamide/abiraterone (131 men). The olaparib group showed better responses compared to the control group. Imaging-based assessments indicated a median progression-free survival (PFS) of 7.4 months for the olaparib group compared to 3.6 months for the control group. The PSA50 response rate (a 50% decrease in PSA level from baseline) was 43% in the olaparib group and only 8% in the control group. Identifying specific mutations may help select more effective targeted therapies for these patients [48, 49].

The phase 2 TRITON2 study led to the FDA approval of rucaparib for use in mCRPCa patients with BRCA mutations. This study included 115 patients with BRCA alterations who had progressed after 1 or 2 cycles of next-generation androgen receptor-directed therapy (ARDT) and 1 cycle of taxane-based chemotherapy (e.g. docetaxel, paclitaxel). The study demonstrated rucaparib's antitumour activity, with an objective response rate (ORR) of 50.8% based on investigator assessment and 43.5% based on independent, blinded radiology review. A total of 63 out of 115 patients achieved a PSA50 response (54.8%). These results suggest that genetic screening is valuable for identifying patients who may benefit from PARP inhibitor-based chemotherapy [50].

In 2021, Wu et al. conducted a meta-analysis of phase II and III clinical trials to assess the utility of PARP inhibitors in treating genetically burdened mCRPCa patients. The analysis included 926 men with homologous recombination deficiency (HRD) and 139 without HRD, across 9 trials involving a total of 1219 patients. The HRD group was further divided into subgroups with BRCA mutations (418 cases) and those without BRCA mutations (508 cases). The primary endpoints were ORR, defined as at least a 50% decrease in PSA levels, and progression-free survival (PFS). The analysis found that PARP inhibitors provided significantly better ORR (OR = 5.50) and PFS at 6 months (PFS6 = 3.96) and 12 months (PFS12 = 3.34) for HRD patients compared to non-HRD patients. Specifically, *BRCA* mutation carriers had notably better results (ORORR 9.97, ORPFS6 4.34, ORPFS12 3.23) compared to non-HRD patients. These data underline the value of PARP inhibitors in treating mCRPCa patients with HRD [51].

The phase III MAGNITUDE trial was a double-blind, randomised study involving 423 patients with HR repair gene aberrations (e.g. *BRCA1/2, ATM, BRIP1, CHEK2, PALB2*) and 247 patients without HRR aberrations. The *BRCA1/2* subgroup was included. All patients had mCRPCa and were divided into 2 groups: one group received a combination of niraparib, abiraterone, and prednisone, while the second group received a placebo, abiraterone, and prednisone. The main endpoint was radiographic progression-free survival (rPFS), defined as the time from patient assignment to radiographic progression or death. The results showed that *BRCA1/2* patients receiving niraparib, abiraterone, and prednisone had a significantly improved rPFS of 16.6 months compared to 10.9 months for those receiving placebo, abiraterone, and prednisone. In the HRR-positive group, niraparib, abiraterone, and prednisone resulted in a rPFS of 16.5 months vs 13.7 months for the placebo group. These results demonstrate improved rPFS for HRR-positive mCRPCa patients receiving niraparib in addition to abiraterone and prednisone [52].

The ongoing phase III TALAPRO-3 study is a double-blind, randomised trial evaluating the effectiveness of talazoparib in mCRPCa patients with HR gene aberrations. This study involves 599 men divided into 2 groups: one receiving talazoparib and enzalutamide, and the other receiving placebo and enzalutamide. The primary endpoint is rPFS, with overall survival (OS) as a secondary endpoint [53].

Several other ongoing trials, such as PROpel III (olaparib), KEYLYNK-007 (olaparib), and TRITON3 (rucaparib), are investigating the use of PARP inhibitors in metastatic and advanced PCa cases. These studies may provide further evidence supporting the benefits of PARP inhibitors in selected patient groups [54–56].

CONCLUSIONS

The genetic background significantly impacts the progression of prostate cancer (PCa). Tailoring screening recommendations based on individual genetic profiles and familial PCa history is essential. Even though diagnostic methods include advanced tools such as MRI, some patients still have their PCa overlooked. For example, according to Zattoni et al., even 11% of men with clinically significant PCa had negative MRI results [61]. Identifying high-risk PCa cases is crucial from a clinical perspective because it helps address concerns related to overtreatment and ensures that low-risk patients are not subjected to unnecessary early invasive diagnostics. Recent research highlights the value of genetic testing in advanced metastatic PCa cases, showing that patients with specific genetic mutations often respond well to PARP inhibitor-based chemotherapy. Ongoing research is expected to provide further insights into these issues and refine our approach to managing PCa [61].

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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