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Hot Topic

Hereditary prostate cancer – Primetime for genetic testing?

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ABSTRACT

Prostate cancer (PCa) remains the most common cancer in men. The proportion of all PCa attributable to high-risk hereditary factors has been estimated to 5–15%.

Recent landmark discoveries in PCa genetics led to the identification of germline mutations/alterations (eg. BRCA1, BRCA2, ATM or HOXB13), single nucleotide polymorphisms or copy number variations associated with PCa incidence and progression. However, offering germline testing to men with an assumed hereditary component is currently controversial.

In the present review article, we provide an overview about the epidemiology and the genetic basis of PCa predisposition and critically discuss the significance and consequence in the clinical routine. In addition, we give an overview about genetic tests and report latest findings from ongoing clinical studies.

Lastly, we discuss the impact of genetic testing in personalized therapy in advanced stages of the disease.

Introduction

Prostate cancer (PCa) is the most prevalent cancer in men and one of the predominant causes of death among men in European countries [1]. While most PCa remain localized, a subset will be aggressive, leading to metastasis formation associated with significant morbidity and mortality. Thus, one major issue in PCa research is to early detect those patients who are likely to harbor an aggressive variant of PCa at young age importantly needing an active anti-cancer treatment.

Large epidemiological studies described that family history is an important risk factor for PCa incidence hence suggesting a genetic component. Genome wide association studies identified around 100 susceptibility loci that contribute to the risk of PCa development and it has been postulated that these loci account for up to 38.9% of the familial risk for PCa [2,3]. According to current guidelines, positive family history is defined as three or more relatives with PCa, or at least two relatives who have developed early-onset PCa defined as diagnosis at age of 55 or less [4,5].

Besides the hereditary PCa incidence component, genetic alterations in deoxyribonucleic acid (DNA) repair systems are found in 20% of metastatic castration resistant PCa (mCRPC) patients and emerging data suggest that they may predict therapeutic responses to developing therapies like Poly-ADP-Ribose-Polymerase (PARP) inhibition or immunotherapy leading to improved treatment strategies [6].

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In the present review article, we provide an overview about the epidemiology and the genetic basis of PCa predisposition and critically discuss the significance and consequence in the clinical routine. In addition, we give an overview about genetic tests and report latest findings from ongoing clinical studies. Lastly we discuss the impact of genetic testing in personalized medicine in mCRPC.

Epidemiology

Familial history is a well-established risk factor for the development of PCa. Approximately 10–15% of men with PCa have at least one relative who is also affected by PCa. Large epidemiologic studies have demonstrated that men who have a their first-degree relative (father and/or brother) with PCa are at increased risk of developing the disease [7-10]. Data from more than heterozygous and homozygous twins showed a PCa heritability index of varying from 42 to 58% depending on the study [11,12].

However, this *hereditary impact* varies depending on several factors such as age at diagnosis, number of affected relatives, or status of close relatives. Thus, the relative risk increased by early age at onset among relatives. For example Carter et al. showed that the cumulative proportion of PCa cases attributable to high-risk susceptibility alleles is 43% for men diagnosed <55 years, but only 9% for men >85 years [13].

Meta-analyses also suggested that the risk is greater for men with affected brothers than for men with affected fathers (relative risk (RR) 3.4 vs. 2.2, respectively) [14]. First-degree relatives also exposed to a higher risk as compared with second-degree relatives. Multiple familial cases conferred an increased risk (by 2-fold) compared with only one affected relative. Thus, Albright et al. demonstrated that a more complete family history integrating number of affected relatives, age at diagnosis, status of close relatives resulted in a better estimation of individual risk for developing PCa [15]. The RR varied from 2.5 for men with one first-degree relative to 7.7 for men with more than three affected relatives. The presence of PCa in third-degree relatives also contributed to risk, but with a significantly lower impact. The maternal or paternal family history status does not seem to influence the genetic risk.

There is also ongoing debate which clinico-pathological features affect PCa incidence in first-degree family members. Among $>21{,}000$ brothers of histologically proven PCa patients, Jansson et al. found a correlation between Gleason grade and PCa incidence. For PCa patients with Gleason scores of 2 – 6, the standardized incidence ratio was 2.53 (95% confidence interval (CI) = 1.97–3.21). In contrast, standardized incidence ratio was 4.00 (CI = 2.63–5.82) for PCa patients with Gleason scores of 8 or more [16].

The role of *environment* has also been suggested to overestimate the hereditary impact. Nevertheless, the risk linked to familial history remains independently significant even after adjustment for environmental factors, reinforcing the role of genetic predisposition [17].

Association of prostate cancer with hereditary cancers

Several epidemiological studies have demonstrated that an association of prostate and breast cancer can be present in certain families. The Breast Cancer Linkage Consortium evaluated 173 breast/ovarian families with a *BReast CAncer Gene (BRCA2) mutation* and showed a significantly increased risk for PCa (RR = 4.65). This risk was considered even higher before age of 65 (RR = 7.33) with an estimated cumulative incidence of 7.5%–33%, depending on the population used as reference. Statistically significant increases in risks were observed also for pancreatic cancer, gallbladder and bile duct neoplasia, gastric cancer and malignant melanoma [18]. This data was confirmed by a more recent Dutch trial that evaluated 139 BRCA2 families and demonstrated an increased risk also for pancreas, bone and pharynx [19]. Although several papers have shown that BRCA2 mutations represent an important prognostic factor for aggressive PCa, the mutation frequency is quite low and the authors considered that BRCA2 deletions accounted for a very small number of PCa (1–2%), even in cases with early onset and proven family history [20–22].

Germline *BRCA1 mutations* confer a substantial lifetime risk of breast and ovarian cancer, but also in other sites such as pancreas, colon, prostate, uterine body and cervix [23]. In contrast to BRCA2, the relative risk of PCa in BRCA1 mutation carriers is controversial. The Breast Cancer Linkage Consortium evaluated a cohort of 11 847 individuals from 699 families and reported that mutation carriers younger than 65 years old presented an elevated risk of PCa (RR = 1.82, 95% CI = 1.01–3.29, P = 0.05), but this risk was not present in patients 65 years old or older [24]. However, Leongamornlert et al, after screening 913 cases for germline BRCA1 mutation, demonstrated a relative risk of PCa of ~3.75, corresponding to a 8.6% cumulative risk by age 65 [25]. The IMPACT study has recruited to date 2481 mutation carriers and controls in order to evaluate the potential of targeted screening in men with BRCA1/2 mutations [26]. First results published in 2014 showed a predictive positive value of biopsy using a prostate specific antigen (PSA) cutoff of 3 ng/dl of 37.5% in BRCA1 carriers vs. 23.3% in controls and 48% in BRCA2 carriers vs 33.3% in BRCA2 controls, respectively. The results will be reported after 5 screening rounds and probably will establish the role of targeted screening in this population.

Lynch syndrome represents a family a hereditary multicancer disease caused by *mutations in the DNA mismatch repair (MMR) genes* MLH1 (MutL homolog 1), MSH2 (MutL homolog 2), MSH6 (mutS homolog 6) and (postmeiotic segregation 2) involved in the appearance of non-polyposis colorectal cancer. Several extra-colonic cancers such as urothelial, renal, gastric, small bowel, pancreatic, hepatobiliary, brain, endometrium, ovarian and cutaneous neoplasia's have been reported [27–29]. Barrow et al evaluated in 2013 the Manchester Regional Lynch Syndrome Database that enrolled 821 patients and demonstrated that men with a MSH2 mutation presented a 10.41-fold increase in PCa risk (CI = 2.8–26.65) [27]. Although a meta-analysis that included 23 studies estimated the relative risk of PCa in MMR gene mutation carriers was high (CI = 2.32–6.67), their role in tumorgenesis has not been fully elucidated [30]. Further studies are required before screening for PCa in Lynch syndrome patients could be recommended.

Using genomic wide scans, several other DNA mutations have been discovered to be present in different malignancies. The rs401681, an intron of the CLPTM1L gene and rs2736098 in the telomerase reverse transcriptase (TERT) protein gene locus on chromosome 5p15.33 have shown a significant association with lung, urothelial, cervical and prostate neoplasia [31]. A susceptibility locus at marker D11S1290 on chromosome 11p11 has been discovered after a genomic evaluation of 15 families with a history of PCa and primary renal cell carcinoma [32]. There may also be several other undiscovered genes and genetic pathways in patients with multiorgan cancer syndromes yet undiscovered by current testing methods. Thus, men with history of neoplasia should be considered at risk for PCa and should be screened even if genetic testing results do not clearly identify a cancer predisposition.

Genetic etiology

Germline mutation/alterations

Generally, the prevalence of inherited alterations in DNA-repair genes in healthy men and in localized PCa unselected for genetic background is relatively low with a percentage of 2.7% and 4.6% respectively. A recent milestone study by Pritchard and collaborators including 692 males with metastasized disease demonstrated that 11.8% of them harbored germline mutations in 16 genes [33,34]. Related to the whole number of mutations, those involving BRCA2 (44%), ataxia teleangiectasia mutated (ATM; 13%), checkpoint kinase 2 (CHEK2; 12%) and BRCA1 (7%) were the most common ones. It is

Table 1
Germline mutations/alterations associated with elevated risk of prostate cancer and other malignancies.

Gene	Molecular mechanism	Prostate cancer risk	Associated malignancies	Ref.
BRCA1	DNA damage repair	1.8–3.8 fold ↑ RR	Breast cancer, ovarian cancer, cervical cancer, colorectal cancer, pancreatic cancer, melanoma, gallbladder cancer, bile duct cancer	[23-26,36-38,42]
BRCA2	DNA damage repair	2.5–4.6 fold ↑ RR < 55 years 8–23 fold ↑ RR	Breast cancer, ovarian cancer, cervical cancer, melanoma, pancreatic cancer, bone cancer, pharynx cancer	[18-22,26,38-40,42,44]
CHEK2	DNA repair through phosphorylation of BRCA2	1.9–3.3 fold ↑ OR	Breast cancer, ovarian cancer, colorectal cancer, thyreoid cancer, germ cell cancer, renal cell cancer	[45-49]
ATM	DNA damage response	6.3 fold ↑ RR	Breast cancer, melanoma, gastric cancer, lymphoma, central nervous system tumors	[50-52]
MLH1	DNA mismatch repair	3.7 fold ↑ RR	HNPCC	[27-29,53,54]
MSH2	DNA mismatch repair	3.7 fold ↑ RR	HNPCC	[27-29,53,54]
MSH6	DNA mismatch repair	3.7 fold ↑ RR	HNPCC	[27-29,53,54,57]
PMS2	DNA mismatch repair	3.7 fold ↑ RR	HNPCC	[27-29,53,54,57]
HOXB13	Androgen receptor repressor	3.4–8.6 fold ↑ RR	Breast cancer, colorectal cancer, leukemia, sarcoma, testicular cancer	[58-60]

Abbreviations: DNA = Desoxyribonucleine acid; HNPCC = Hereditary Non-Polyposis Colorectal Cancer (Lynch syndrome); OR = overall risk; RR = relative risk.

likely that, given the association between the prevalence of germline alterations and disease stage, males carrying these mutations are at risk for unfavorable outcomes, thus paving the way for assessing individualized screening and treatment concepts [35].

Mutations in *BRCA1 and/or BRCA2 genes,* which products co-localize with and activate RAD51-mediated homologous recombination of DNA during double strand break repair [36], have been associated with several malignancies including breast, cervix, melanoma and pancreatic cancer [37,38]. In PCa, BRCA1 gene germline mutations confer a 1.8–3.8-fold RR of diagnosis [25,37], particularly for carriers younger than 65 years. Similarly, BRCA2 mutations are also associated with an elevated RR between 2.5 and 4.6, whereas patients aged ≤ 55 years seem to be more susceptible for PCa with a RR of 8–23 [19,21,39,40]. Notably, males with BRCA germline mutations exhibit more aggressive cancer features like higher Gleason score, locally advanced disease, nodal involvement and metastases at diagnosis as well as inferior outcomes after radical prostatectomy or radiation therapy [20,41]. Importantly, BRCA2 carriers seem to be at a higher risk for poor overall and cancer-specific survival than men with BRCA1 [42-44].

Mutations of the *CHEK2 gene* coding for a cell-cycle controlling and tumor protein 53 (p53) as well as DNA repair regulating kinase are reported to be correlated with several cancer entities like eg. breast, germ-cell and renal cell cancer [35,45-47]. A contemporary systematic review and meta-analysis of eight retrospective studies illuminated two alleles conferring an elevated risk of PCa translating in overall risk (OR) of 1.8–3.3 [48]. For European American males, a specific CHEK2 mutation, c.1100delC, was recently shown to increase the risk for lethal PCa by OR = 7.9 [49]. However, overall CHEK2 mutations were not more frequent in men with lethal compared to low-risk PCa in the entire cohort of this study comprised of European, African, and Chinese patients.

ATM is a key player on DNA damage response function [35], which gene alterations confer an increased cancer predisposition, including a 20% to 30% lifetime risk of lymphoid, gastric, breast, central nervous system, skin, and other cancers [50]. For ATM carriers, the estimated RR for metastatic disease is as high as 6.3 [33]. Interestingly, mutation status of BRCA1/2 and ATM was associated with grade reclassification in men undergoing active surveillance as well as earlier age at death and shorter survival time [51,52].

As mentioned, alterations in the *DNA MMR genes* including MLH1, MSH2, MSH6 and PMS2 have demonstrated an association with hereditary non-polyposis colorectal cancer (HNPCC, syndrome) [53,54] RR for PCa was reported for MMR gene mutation carriers to be as high as 3.7 [30]. Of note, PCa of patients with MMR deficiency demonstrate aggressive clinical and pathological features [55]. Importantly, they appear to be sensitive to hormonal and anti- programmed death-ligand 1 (PD1) treatment [55]. In particular, MSH2 loss is common among very high-grade primary tumors and correlated with an enhanced tumor-infiltrating lymphocyte density [56]. Furthermore, patients with castration-resistant PCa and loss of MSH2/MSH6 are characterized by poor outcomes [57].

In 2012 it has been demonstrated for the first time that patients with a homeobox B13 *(HOXB13)* G84E mutation, which substitutes a glutamic acid for glycine at the second position of codon 84, have significantly higher odds for developing PCa than men without the mutation [58]. Basically, HOXB13 encodes a homeobox transcription factor that is involved in prostate development and regulates the transcription of androgen receptor target genes known to play a role in PCa growth [59]. In a recent study, HOXB13 mutation was associated with an augmented PCa risk in general (OR = 3.4) as well as young-onset (OR = 8.6) and hereditary (OR = 6.6; CI = 3.3–12.0) PCa [60].

Furthermore, patients carrying the G84E mutation had a significantly higher PSA at diagnosis, higher Gleason score as well as higher incidence of positive surgical margins in the radical prostatectomy specimens than non-carriers, implying that the G84E mutation maybe associated with more aggressive PCa [61].

A comprehensive overview about most important gene mutations/alterations, their molecular mechanisms as well as their association with other malignancies is illustrated in Table 1.

Several less-studied germline alterations might be of a clinical interest in the future: For example, 657del5 founder allele of the Nijmegen breakage syndrome 1 *(NBS1)* = conferred an elevated risk of familial PCa (OR = 16) and of non-familial PCa (OR = 3.9) [62]. Finally, mutations in Protein Tyrosine Phosphatase Receptor Type F Polypeptide-Interacting Protein-Binding Protein 2 *(PPFIBP2)* gene were associated with lethal PCa in an European American population (OR = 13.8) [63].

Single nucleotide polymorphisms

Generally, a single-nucleotide polymorphism (SNP) is a substitution of a single nucleotide occurring at a specific position in the genome. These SNPs are known to underlie differences in humans' susceptibility to diseases. In PCa an increasing number of SNPs had been suggested to be implicated in disease development and progression [64]. In a landmark study, Zheng et al. reported on the cumulative association of 16 SNPs from five chromosomal regions and a positive family history with PCa [65]. The investigators first examined the PCa risk ratios of 4674 Swedish men for 16 SNPs at three loci to determine which individual SNP was most strongly associated with PCa for each locus. The risk ratios for the 16 SNPs ranged from 1.07 to 1.65. When four or five high-risk genotypes were present, they were associated with a composite risk ratio for PCa of 4.47. Together, the five SNPs and family history were estimated to account for 46% of the cases of PCa.

Other investigations have focused on the diagnostic capacity of different panels of SNPs to improve prediction of biopsy results, alone or in combination with clinical parameters. A genome-wide association study showed that a panel of 23 PCa risk-associated SNPs could be used in combination with PSA to significantly improve the prediction of prostate biopsy outcomes [66]. Moreover, it was shown that a genetic prediction model including PCa risk-associated SNPs and clinical variables (age, family history, PSA/free PSA ratio) performed better than a model based solely on clinical variables [67]. Comparing the performance of 33 PCa risk-associated SNPs with clinical parameters in predicting a positive prostate biopsy in the REDUCE trial, Kader et al. found that adding SNPs to the best clinical model reclassified PCa risk in 33% of men, and the reclassified risk had a significantly better correlation to biopsy outcomes [68].

SNPs have also been investigated for association with PCa aggressiveness. SNPs on chromosomes 17p12 and 15q13 had been reported to be present at significantly greater frequencies in men with aggressive disease [69,70]. Similarly, the risk allele on rs11672691 was significantly associated with an increased risk for PCa-specific mortality [71].

Copy number variations

Genomic instability resulting in copy number variation (CNV) is a hallmark of malignant transformation that may be identified by genetic sequencing techniques. In 2009, Liu et al. reported for the first time on a novel germ-line CNV that was significantly, but moderately, associated with PCa risk [72]. In another study, CNVs of the genomes in PCa tumor, in benign prostate tissues adjacent to the tumor (AT), and in the blood of patients with PCa were shown to predict biochemical (PSA) recurrence and short PSA doubling time [73]. Interestingly, an investigation of ten high-risk African American families found that the duplication at 14q32.33 encompasses the IGHG3 gene which has been shown to have both significant gains in copy number as well as overexpression in prostate tumors in African Americans [74]. The authors concluded that these CNVs may represent a component of genetic predisposition which contributes to the high prevalence and mortality of PCa in African American men.

A germline CNV analysis in Finnish families with hereditary PCa observed a higher frequency of deletion in in the EPHA3 gene in PCa patients as compared to controls [75]. Moreover, PCa-specific mortality was higher among EPHA3 deletion carriers (24.3%) than among patients with a normal EPHA3 copy number (3.4%).

A recent pilot genome-wide CNV analysis found that a total of 314 CNV regions were to be unique to PCa subjects [76]. In addition, CNV analysis revealed five putative rare or novel CNV loci associated with susceptibility to PCa. CNV gain regions were harbored genes that are crucial in the p53 and cancer pathways. The most recent genome-wide association study for CNV was performed in 1417 PCa cases and 1008 controls in Chinese population [77]. The authors found 7 risk-associated CNV regions that involved actionable genes envisioning a potential for targeted therapy.

Genetic screening for hereditary prostate cancer

In general, screening for hereditary PCa can have major clinical implications considering the fact that PCa has a certain degree of heritability even mimicking autosomal dominant pathways [13]. Nevertheless, most PCa occur in a sporadic manner, thus screening for hereditary PCa should be focused on specific clinical scenarios leading to the fact that compared to other tumor entities like breast or colorectal cancer genetic counseling in PCa is still in its infancy [5]. However, is it well recognized that if an inherited cancer is suspected in a family, genetic counseling and testing represents a critical element of risk stratification.

Current *EAU (European Association of Urology) guidelines* (2019 edition) do not exert clear recommendations for genetic testing stating that genetic factors are associated with risk of (aggressive) PCa but ongoing trials will need to define the clinical applicability of screening for genetic susceptibility to PCa. Yet, the guidelines of the *American Society of Urology (AUA)* (2017 edition) recommend genetic counseling in patients who either have (i) first-degree relatives diagnosed with PCa < 55 years, or have a personal diagnosis of PCa < 55 years with a first-degree relative diagnosed with PCa at any age or death due to PCa in a first-degree relative at < 60 years; (ii) two close blood relatives with PCa on the same side of the family, with at least one diagnosed < 55 years; (iii) any first-degree relative with a hereditary cancer diagnosed with PCa < 50 years or (iv) tumor sequencing that shows mutations in hereditary cancer genes. Similarly, according to the *American College of Medical Genetics (ACMG) guidelines* genetic testing should be performed if ≥ 3 first- degree relatives or ≥ 2 first- degree relatives < 55 years are diagnosed with PCa or patients with a high risk PCa (GS ≥ 8) and a family history of two members with breast, ovarian or pancreatic cancers. The *NCCN (National Comprehensive Cancer Network) guidelines* clearly recommend men with a pathogenic or likely pathogenic BRCA 1 or 2 mutation to start PCa screening at age 45 years. Testing should also be strongly considered by men with a broader family history, including a family history of hereditary breast and ovarian cancer, hereditary PCa or Lynch syndrome.

Summarizing the present literature and guidelines one can recommend that patients with (1) multiple affected first-degree PCa (2) PCa occurrence < 55 years and those with (3) a family history of the BRCA1/2 mutation or breast-, ovarian- or pancreatic cancer should be referred to a genetic counselor for genetic testing. In addition, men with a personal history of Gleason ≥ 7 PCa with a family history of a BRCA1/2 mutation, or one close relative with ovarian or breast cancer at age < 50 years, or two relatives with breast, pancreas, or Gleason ≥ 7 PCa at any age should undergo genetic counseling.

Importantly, apart from the guidelines, specific attention on patientś individual risks like age, co-morbidities, race or other risk factors known for PCa have to be concerned. Thus, preferably genetic counseling consists of both a genetic counselor as well as a physician respecting clinical features like co-morbidities, PSA values, digito-rectal examinations or conducted imaging eg. multiparametric magnetic resonance imaging. Moreover, it must be also taken into account that genetic testing is associated with significant costs mostly not covered by the health insurance, variable depending on the laboratory and the panel size of genetic testing. Several different companies are offering genetic testing on a person's blood or saliva sample to search for a genetic mutation that causes hereditary PCa. However, it is important to understand for patients that a negative genetic test result does not eliminate the possibility of a hereditary PCa syndrome as each test only includes a limited number of tested genes. An overview about current available PCa specific screening panels are illustrated in Table 2.

Surveillance strategies for high risk patients after local therapy

A special focus should be set on patients with a confirmed hereditary component in the surveillance after primary local therapy. More than 20 years ago, Kupelian and colleagues reported 3-year rates of freedom from biochemical PSA recurrence (BCR) of 52% and 72% in men with and without a family history of PCa, respectively. The 5-year BCR was 52% for men without a family history of PCa and 29% for men with such a history [78]. Also a recent German study evaluated the difference in clinical outcomes for men with familiar versus sporadic PCa in 11,645 men undergoing radical prostatectomy. Data also revealed that men with a familiar PCa history are at higher risk of BCR [79]. However, there exist also opposing data that sporadic, familial and hereditary PCa have the same recurrence free survival rates following radical prostatectomy or radiation therapy [80,81]. Admittedly, these findings may be caused by the fact that patients with a positive family history are diagnosed earlier than sporadic patients.

Table 2
Overview about commercially available prostate cancer screening panels (29.05.2019).

Test name	Company	Tested gene(s)	Patient material	Genotyping assay
HOXB13 genotyping	Neogenomics	HOXB13	5 ml EDTA blood	Bi-directional sequencing of exons 1 and 2 of the HOXB13 gene for detection of G84E mutation
Uroseq	Strand Diagnostics	BRCA1, BRCA2, ATM, CHEK2, HOXB13, PALB2, RAD51D, MLH1, MSH2, MSH6, PMS2, EPCAM	Buccal swab	Germline DNA testing
Hereditary Prostate Cancer Panel	GeneDx	ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PSM2, TP53	2–5 ml whole blood alternatively buccal swab, fibroblasts or oral rinse	Deletion/Duplication analysis NGS
Prostate Cancer comprehensive Panel	Fulgent	ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53	8 ml EDTA blood or extracted DNA or buccal swab or saliva	Deletion/Duplication analysis NGS
Prostate Next	Ambry Genetics	ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51 D, TP53	6–10 ml blood (preferably EDTA)	NGS or Sanger sequencing of all coding domains Confirmation by PCR and agarose gel electrophoresis (excluding EPCAM)
Invitae Prostate Cancer Panel	Invitae	ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PSM2, TP53 (BRIP1, FANCA, PALB2, RAD51C, RAD51D)	3 ml whole blood alternatively DNA or saliva/assisted saliva	Full-gene sequencing Deletion/Duplication analysis NGS
Prostate Gene	GeneHealth	BRCA1, BRCA2, HBOC, HOXB13, MLH1, MSH2, MSH6, PMS2, EPCAM, ATM, CHEK2	Blood or saliva	NGS Copy number variant analysis

Abbreviations: NGS = next generation sequencing; EDTA = ethylene diamine tetraacetic acid; PCR = polymerase chain reaction.

Current *EAU, AUA and NCCN guidelines* recommend offering germline genetic testing for BRCA1, BRCA2, ATM, PALB2, and FANCA to all patients with high risk or metastatic disease regardless of family history. For those patients with lower-risk disease, germline genetic testing should be considered when there is a strong family history (brother or father or multiple family members diagnosed with PCa < 60 years), known germline abnormalities and/or more than 1 family member with breast, ovarian, or pancreatic cancer (suggestive of BRCA2 mutations); or more than 1 family member with Lynch syndrome. In March 2019, an updated version of the *NCCN guidelines* were published stating that if next generation sequencing (NGS) is used, the panel must include BRCA1, BRCA2, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, and PMS2 based on recent study of 3607 PCa patients who underwent germline genetic unselected for family history, stage of disease, or age at diagnosis [82]. A recent expert opinion position paper summarizing the guidelines states that PCa screening is proposed for men with a known germline mutation in a known moderate-to-high penetrance cancer predisposition gene such as BRCA1/2 as well as for men with a first-degree or second-degree family member metastatic PCa [83].

Overall, precision diagnosis requires specific markers for differential patient populations. Interestingly, there is evidence that biomarkers behave different in men with and without a hereditary component: For example, the IMPACT study evaluated PSA screening in men with a known genetic PCa predisposition due to BRCA1/2 mutations and found that PSA is more strongly predictive in BRCA carriers than non-carriers. In addition, no evidence was observed in this trial that PSA velocity aids decision-making for BRCA carriers over absolute PSA value alone [84].

Genetic testing for precision oncology in mCRPC patients

In the past years the treatment landscape of mCRPC expanded leading to the fact that several different drugs like chemotherapeutic agents, or hormonal therapies are approved in the same therapy line claiming for appropriate biomarkers for therapy response [85,86]. In this context, genetic testing can harbor a major impact on therapy decisions. Some years ago, a multi-institutional integrated sequencing analysis of 150 PCa patients demonstrated that 23% of mCRPC harbor DNA repair pathway aberrations, and 8% harbor germline findings highlighting the need for genetic counseling to inform precision medicine in affected individuals with advanced PCa [6].

Interestingly it has been demonstrated that mCRPC patients with germline defects in a DNA damage repair have a decreased response to androgen receptor (AR) targeted therapy [87]. By contrast, Antonorakis et al found an improved response to second generation androgen deprivation therapy (ADT) abiraterone or enzalutamide therapy in men with BRCA or ATM mutations compared to those without deleterious germline mutations [88]. A recent retrospective study reviewed clinical outcome of 390 mCRPC patients who underwent standard therapies including second generation ADT (abiraterone, enzalutamide), docetaxel chemotherapy or PARP inhibitors or platinum therapy according to their germline DNA damage repair gene mutation status. Overall no significant differences in median progression free survival (PFS) and responses rates from docetaxel and including second generation ADT based on gDDRm status was observed. These data are of major interest to the clinical community as in *NCCN guidelines* in 2018 recommend germline testing for all men suffering from mPCa.

Apart from ADT there is also evidence of efficacy of PARP inhibitors and platinum based chemo- therapy in patients with germline and/or somatic biallelic defects in DNA repair genes. In 2015, Mateo et al showed for the first time in a Phase II study that treatment with the PARP inhibitor olaparib has durable antitumor activity in men with mCRPC harboring germline BRCA2 or ATM mutations [89]. Consecutive clinical trials with PARP inhibitors also showed significant response rates up to 88% for PCa patients having BRCA1/2 or ATM mutations [90] leading to the consequence that currently various PARP

inhibitors (eg. olaparib, rucaparib, niraparib) are under clinical evaluation for patients whose cancers harbor DNA-repair defects and BRCA1/2 mutations even as monotherapy or in combination with approved mCRPC treatment options. Platinum-based chemotherapy is generally not used for the treatment of mCRPC since phase III studies have failed to show a survival benefit in unselected patients. Nevertheless, responses to single-agent chemotherapy with a platinum analogue have been reported [91]. However, considering the mechanisms of action of platinum DNA-repair defects they may be associated with platinum sensitivity. Indeed, there is clinical evidence that patients with bi-allelic inactivation of BRCA2 achieved exceptional response to platinum chemotherapy [92].

Finally, there is also evidence that mCRPC patients with high tumor mutational burden (TMB), such as tumors which are DNA mismatch repair deficient, are particularly sensitive to checkpoint inhibition. For instance, it has been recently demonstrated that in a small patient cohort harboring MMR deficiency are particular sensitive to hormonal therapies (LHRH, abiraterone/enzalutamide) [55]. Furthermore, it has been demonstrated in this study that 2/4 patients receiving a PD-1 inhibitor achieved a $\geq$50% PSA after 12 weeks of therapy with a median progression free survival duration of 9 months. These findings are in line with an interim analysis from the Keynote-199 study presented at the *ASCO (American Society of Clinical Oncology) meeting 2018*, where the clinical benefit of the PD-1 inhibitor pembrolizumab was evaluated in mCRPC patients. Results of this study revealed that only a small proportion of men benefit from immunotherapy being those with microsatellite instability-high/MMR tumors exerting excellent treatment responses *(De Bono et al, ASCO 2018, oral presentation)*. Although final results of the study have not been published yet, the PD-1 inhibitor pembrolizumab has recently FDA (food and drug administration) approved for microsatellite instability-high/MMR PCa.

Summarizing, given the potential for durable responses of new treatment options for mCRPC patients findings support the use of prospective tumor sequencing to test patients with advanced PCa for genetic variants.

Genetic alterations across ethnicities

Generally, most genetic studies have been performed in European and Asian populations, while studies of genetic susceptibility in African descent populations are limited. However, there are strong hints that genetic etiology differs among population diversity. For example, it has been shown that SNPs that had been previously reported in white or Asian populations were not replicated in Afro-American men [93]. In line with this trial also other GWAS studies did not replicate most of the previously reported loci identified in European or Asian descent populations [94,95].

On the other hand, a novel locus on chromosome 10p14 (SNP, rs7918885) exclusively detected in African men has been described [95]. In addition, somatic alterations seem to be different as e.g. TMPRSS2-ERG or PTEN deletion occur less frequently in Afro-American men while SPINK1, a marker for aggressive prostate cancer, is more commonly expressed [96].

Ongoing clinical trials

To identify relevant ongoing trials related to this topic, we searched recruiting and not yet recruiting trials in ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home). The terms “germline”, “hereditary”, or “genetic mutations” were used in association with “prostate cancer”. The following information was abstracted from ClinicalTrials.gov and analyzed: title, sponsor, status, objective, primary and secondary outcomes, and eligibility criteria.

A trial (*NCT00959023*) led by Institute of Cancer Research in United Kingdom, is collecting blood and tumor samples from men with PCa and their relatives to identify genes that predispose to PCa. In this trial, the investigators will propose the analysis of PCa predisposition genes and their correlation with disease and treatment parameters, and environmental factors as well. Another exploratory trial (*NCT00579514*) is currently recruiting thousands of patients to determine association of germline polymorphisms and different cancers including PCa. In this trial, the following polymorphisms are addressed: PTEN, APC, TGF βR-I, BLM, CHK2, a p85 phosphoprotein, ATM, ER, PR, MCP-1, MPIF, CCR2/5, CCR3, SULT1A1. Genes with SNPs associated with the development or treatment of lymphoid malignancies will also be targeted. In the Impact study (*NCT00261456*), the role of germline mutation regarding PCa screening is specifically addressed. In this trial, 850 men with known pathogenic BRCA1 and BRCA2 mutations and their controls (age-matched men without BRCA1/2 mutations) will perform annual PSA to determine differences in the incidence of PCa between both groups. Another trial (*NCT02543905*) is also investigating the impact on targeted screening of several genetic changes thought to increase the risk of PCa. In this trial, men with family history of PCa are recruiting to perform targeted prostate screening including PSA and prostate biopsies, and genetic profiling as well.

The prognostic significance of hereditary PCa is also of importance. The GENPROS trial (*NCT02705846*) is recruiting men treated for PCa with BRCA1, BRCA2, HOXB13 mutations, or Lynch Syndrome to assess specific outcomes after PCa diagnosis and treatment in these patients. In this study, gene mutation carriers will be matched with men with PCa but without mutation. Finally, several trials analyze tolerance and response to medical treatment according mutations observed in hereditary PCa. These trials are currently recruiting patients treated with docetaxel and carboplatin (*NCT02985021*) or olaparib (*NCT03570476, NCT03810105*).

Conclusion

It is well recognized that genetic predisposition represents an important risk factor for PCa development and progression. Various recent studies suggest a hereditary component in 8 to 12% of PCa cases mostly associated with germline mutations or alterations in genes like BRCA1, BRCA2, HOXB13 or DNA MMR genes. Moreover, SNPs and copy number variations are discussed as drivers for PCa development and progression. Early onset of aggressive PCa combined with family members also suffering from PCa or other heritable cancers are strong predictors for a hereditary component claiming that those patients are candidates to undergo a genetic testing.

In the past years, ongoing advances in molecular and genetic knowledge combined with the development of new technologies like NGS led to the evolvement of different commercially available tests, which have to proof their clinical impact in the next years. Until then guidelines give no consistent recommendations which patients at what stage of the disease should undergo genetic testing.

Furthermore, genetic profiling will help us in the next years to treat PCa patients in a personalized manner as there is evidence that patients with certain germline mutations like outstanding from specific mCRPC medical treatment options.

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Declaration of Competing Interest

None regarding the topic of this article.

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