memo (2024) 17:51–56
https://doi.org/10.1007/s12254-023-00921-1

memo
magazine of european medical oncology

Genetic testing and management of prostate cancer patients with pathogenic germline variants

Katharina Reiter · Melanie R. Hassler

Received: 24 July 2023 / Accepted: 2 October 2023 / Published online: 3 November 2023

Summary Prostate cancer (PCa) is an androgen-receptor signaling-dependent disease with a subset of patients harboring pathogenic germline variants (PGVs) in genes essential for DNA repair. In the last decade, several guidelines and recommendations have been developed to define which PCa patients should receive genetic testing to identify individuals at higher risk due to inherited alterations and to facilitate personalized treatment strategies. Notably, the presence of specific germline alterations in carriers undergoing PCa screening has implications for screening strategies, and PGV carriers with advanced disease are eligible to receive targeted therapies such as poly-ADP-ribose polymerase inhibitors (PARPi) or immune checkpoint inhibitors (CKI) depending on the alterations encountered. Although less information is available on carriers with localized disease, several trials are addressing this specific patient population and will help to collect data and improve clinical management of PCa patients with PGVs.

Keywords Prostate cancer · Genetic analysis · BRCA1 · BRCA2 · Lynch syndrome

Take-home message

- Approximately 5% of localized and up to 12% of metastatic prostate cancer (PCa) patients carry pathogenic germline variants, with *BRCA2* being the most prevalent alteration.
- Different guidelines recommend germline sequencing in patients with metastatic disease, a family history of PCa or specific high-risk features in order to optimize treatment, assess personal cancer risk and prognosis and further guide family counselling for cancer predisposition syndromes.
- In localized disease, underlying pathogenic germline variants should trigger shared decision-making when deciding on active surveillance and (intensified) curative treatment options.
- In metastatic PCa patients with *BRCA1/2* or *ATM* alterations, targeted treatment with poly-ADP-ribose polymerase inhibitors (PARP) inhibitors offers promising options. Additionally, a subset of metastatic PCa patients with mismatch repair (MMR) alterations could benefit from immune checkpoint inhibition.

K. Reiter · M. R. Hassler (✉)
Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria
melanie.hassler-difratta@meduniwien.ac.at

K. Reiter
Departments of Urology and Pediatric Urology, Klinik Ottakring, Vienna, Austria

Germline alterations in PCa

Prostate cancer (PCa) is the second most common cancer in men and significantly impacts global health as a leading cause of cancer-related deaths [1]. Recent studies have shown that a subset of PCa patients harbor pathogenic germline variants (PGVs) affecting DNA damage repair mechanisms, which play a distinct role in disease development and differentiation [2]. Detection and understanding the implications of these PGVs is crucial for improved clinical management with potentially beneficial outcomes for these patients.

In PCa, approximately 4–5% of patients with localized PCa and 12% of patients with metastasized PCa carry a PGV in genes essential for homologous DNA repair (DDR) or mismatch repair (MMR) [2–4]. Genes involved in DDR comprise *BRCA1, BRCA2, ATM, CHEK2*, and others. Among these, *BRCA2* is the most frequently found PGV, with a prevalence of 44% among all PCa mutation carriers [2, 4]. *BRCA1/2*

germline mutations are causing hereditary breast and ovarian cancer (HBOC) syndrome, which increases the lifetime risk of developing breast and ovarian cancer to 40–70% [5]. For male *BRCA2* carriers, the risk of developing PCa is approximately 15–30% compared to 10–15% in the general population, whereas the risk with a *BRCA1* or other PGV may only be slightly elevated [6, 7].

Table 1 Indications for genetic testing in prostate cancer (PCa). Summary of current guidelines and consensus statements

Philadelphia prostate cancer consensus conference 2019 [15]
Recommended: Metastatic PCa *Men with first-degree relatives or two or more male relatives with either:* PCa diagnosis at age < 60 years PCa-related death Metastatic PCa *Consider:* Advanced stage of disease (≥ T3a) Intraductal/ductal pathology PCa with Gleason pattern ≥ 8 ≥ 2 cancers in HBOC or Lynch syndrome in any relatives within one family trait Ashkenazi Jewish ancestry
NCCN prostate cancer guidelines [12]
Recommended: Metastatic PCa Regional, node-positive PCa High-risk or very high-risk localized PCa Personal history of breast cancer ≥ 1 first-, second-, or third-degree relative with breast, endometrial or colorectal at age ≤ 50 years or male breast, ovarian, exocrine pancreatic cancer or advanced PCa at any age ≥ 1 first-degree relative with PCA diagnosis at age ≤ 60 years ≥ 2 first-, second- or third-degree relatives with breast or PCa at any age ≥ 3 first- or second-degree relatives with Lynch syndrome-related cancer Known FH or familial PGVs Ashkenazi Jewish ancestry *Consider:* Intermediate-risk PCa with intraductal/cribriform pathology Personal history of exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract or small intestinal cancer
EAU guidelines on prostate cancer [14]
Weak strength rating: Metastatic PCa High-risk PCa with FH of PCa at age < 60 Any PCa with multiple family members < 60 years or FH with PCa-related death FH of high-risk PGVs FH of multiple cancers within one family trait
AUA guidelines on localized and advanced prostate cancer [16]
Recommended: Metastatic PCa *Consider:* Adverse tumor characteristics Strong personal history of associated cancers Strong FH of PCa Strong FH of associated cancers Known PGVs Ashkenazi Jewish ancestry
AUA American Urological Association, *EAU* European Association of Urology, *FH* family history, *HBOC* hereditary breast and ovarian cancer, *NCCN* National Comprehensive Cancer Network®, *PGV* pathogenic variant

Genes involved in MMR comprise *MSH2*, *MSH6*, *MLH1* and *PMS2* or *EPCAM*—an epigenetic silencer of *MSH2*. These genes predispose affected individuals to a high lifetime risk of developing colon, endometrial, and other cancers (Lynch syndrome [LS]) [8, 9]. Although only a subset of PCa patients harbor germline alterations in these genes (3–4% of all PGV carriers), their presence has a significant impact on the molecular alterations present in PCa tumors, as deficiencies in the DNA mismatch repair system can lead to a phenomenon called microsatellite instability (MSI) [2, 8]. Tumors with high MSI are characterized by high mutation rates and may have increased responses to immune checkpoint inhibitor (CKI) therapy, which otherwise has limited effects in unselected PCa patients [10, 11].

Indications for genetic testing

Currently, there are several guidelines regarding which PCa patients should receive genetic testing for hereditary cancer syndromes (Table 1). The testing criteria encompass personal cancer history, cancer features and pathology, family history, and precision therapy indications [12–15]. All guidelines recommend germline testing of men with metastatic PCa, as the prevalence of PGVs in this population is over 10% [2]. In addition, guidelines state that a family history of PCa or the presence of two or more cancers within the HBOC or LS spectrum in relatives on the same family side should trigger genetic testing. Furthermore, some guidelines state that patients with high-risk (T3a or ISUP 4 or PSA >20 ng/ml) or very-high risk (T3b-T4 or primary Gleason pattern 5 or >4 cores with ISUP 4 or 5) localized PCa, presence of intraductal, ductal or cribriform histology, an Ashkenazi Jewish ancestry, or a diagnosis of PCa <60 years can be offered genetic testing [12, 15, 16]. There is no consensus set of genes that must be included in PCa germline testing assays, but in general, multiple genes that may be relevant to optimize targeted therapy approaches or account for the patient's cancer and family history are analyzed. Typical panels always include *BRCA1/2* but vary in coverage regarding other homologous DNA repair or DNA mismatch genes, which should be considered when ordering these tests [12, 13, 15]. It is important to note that patients undergoing germline testing need pretest and posttest genetic counseling on potential test results and their impact on further management, and conducting genetic tests and counseling is often regulated by national laws [17].

Clinical management of PCa patients with germline mutations

PCa screening

PCa screening for the early detection of PCa in the population of PGV carriers is an intense subject of de-

bate due to potentially increased rates of unnecessary biopsies and their association with overdiagnosis and overtreatment [18]. Several prospective studies have been evaluating PCa screening among PGV carriers [6, 19–21]. The IMPACT trial is evaluating targeted PCa screening in men with and without germline *BRCA1/2* and MMR alterations [19]. In the study, men aged 40–69 underwent prostate-specific antigen (PSA) screening for 3 years, and if their PSA was higher than 3.0 ng/ml, they were offered prostate biopsy. The study reported interim results in 2019, and after 3 years of screening, *BRCA2* mutation carriers had a higher incidence of PCa, were younger at diagnosis, and had more clinically significant tumors [19]. Based on this, PSA screening for men with *BRCA2* mutations should start at the age of 40 or 10 years before the youngest relative was diagnosed with PCa [12, 13]. For *BRCA1* carriers, no significant differences were detected compared to *BRCA1* noncarriers. However, guidelines recommend that men with *BRCA1* alterations should consider a screening approach similar to *BRCA2* carriers [12, 13]. For carriers of *MSH2* and *MSH6* PGVs, a higher incidence of PCa compared with age-matched noncarriers has been reported after the first PSA screening round, indicating that PSA screening in *MSH2*/*MSH6* carriers should start at a similar age as for *BRCA2* carriers [20].

In contrast to the IMPACT study, the current practice uses imaging-based PCa examinations before definitive biopsy. This approach is tested for *BRCA1/2* carriers using a combination of multiparametric magnetic resonance imaging (mpMRI)-based and PSA-based screening [21]. So far, interim results have shown that initial mpMRI-based screening may be beneficial, especially for *BRCA* carriers younger than 55 years, compared to PSA screening alone [21]. No data have demonstrated a benefit from prophylactic prostatectomy in PGV carriers, but clinical trials are in discussion [22]. Thus, for optimized screening approaches in this population, new biomarkers and risk calculators are urgently needed to prevent unnecessary biopsies and improve the detection of clinically significant PCa.

Active surveillance

Active surveillance (AS) intends to spare PCa patients from aggressive interventions such as surgery or radiation therapy and is indicated when the disease is low-risk after biopsy and clinical staging. However, patients with PGVs and low-risk PCa might carry a higher risk of upstaging than noncarrier patients. Indeed, a study evaluating *BRCA1/2* and *ATM* germline mutation carriers with PCa under AS reported higher tumor grade reclassification rates than in noncarriers (hazard ratio [HR] 2.74, 95% confidence interval [CI] 1.26–5.96; $p = 0.01$) [23]. However, reclassification rates are similar to rates described in other AS cohorts [24]. Another study in 15 patients with low-risk PCa and DDR mutations under AS for a median of 28 months reported a PCa reclassification rate of 20%, similar to that in the general AS population [25]. Based on this limited evidence, AS is, in principle, feasible among PGV carriers and could reduce overtreatment, but given the significant reclassification rates, shared decision-making with the option of local treatment for patients with *BRCA2* mutations is recommended [18].

Localized prostate cancer

After local therapy (radical prostatectomy or external-beam radiotherapy), *BRCA1/2* PGV carriers have been reported to have a higher risk of metastasis and mortality with a cancer-specific survival of 61% versus 85% in noncarriers ($p < 0.001$) at 10 years [26]. The difference in this retrospective cohort was especially noted for patients after radiation therapy, as surgery reduced PCa-specific mortality by 48%. Patients in the radiotherapy cohort had more aggressive disease than those in the surgery cohort, which limits the direct comparison of the two groups. Among the 2019 patients enrolled in PCa screening trials, the rates of high-risk PCa, lymph node involvement (15% vs. 5%), and metastasis (18% vs. 9%) were higher in *BRCA1/2* carriers than in noncarriers [4]. In addition, lower cancer-specific survival was observed in carriers than in noncarriers after standard-of-care therapy (8.6 years versus 15.7 years), and median overall survival was also decreased in carriers compared to noncarriers (8.1 years vs. 12.9 years). In a study on neoadjuvant androgen deprivation therapy followed by radical prostatectomy, a similar pathological response and no difference in the 3-year biochemical recurrence-free survival rate was reported between DDR germline mutation carriers and noncarriers [27]. Of note, *BRCA2* carriers represented only one-third of the DDR cohort. Whether a specific therapeutic approach, therapy intensification, or adjuvant therapy offers therapeutic advantages for high-risk localized PCa patients with PGVs is currently unclear, but ongoing clinical trials are addressing this pending question (NCT03432897, NCT04030559, NCT04037254).

Metastatic prostate cancer

For patients with metastatic castration-resistant (mCRPC) disease and *BRCA1/2*, other DDR alterations or PGVs in DNA mismatch genes, targeted therapies are available in the context of precision medicine approaches.

Several trials have shown a benefit in survival when treating DDR carriers with PARP inhibitors (PARPi), either as monotherapy or in combination with androgen receptor inhibitors (ARIs) [28–32]. The PARPi olaparib significantly prolonged survival compared to ARIs in mCRPC patients with somatic *BRCA1/2* or *ATM* mutations after previous treatment with a different ARI [28]. Another PARPi, rucaparib, has been

tested as monotherapy in a phase III study in patients with somatic *BRCA1/2* or *ATM* mutations evaluating rucaparib or physician's choice of abiraterone, enzalutamide or docetaxel after progression on ARIs. Recent results show that rucaparib significantly prolongs progression-free survival (PFS) compared to ARIs or docetaxel in this setting [30]. The PROpel trial reported that concurrent olaparib plus abiraterone versus abiraterone alone in first-line mCRPC treatment leads to improved PFS regardless of mutation status. However, subgroup analysis showed that the effect was more pronounced in patients with somatic DDR mutations [29]. Improvement of PFS was also observed in mCRPC patients receiving talazoparib plus enzalutamide versus enzalutamide in patients with and without alterations, with a noteworthy benefit especially among patients with somatic *BRCA2* alterations [31]. In contrast to these unselected populations, a trial comparing niraparib and abiraterone versus abiraterone alone in first-line mCRPC observed a significant improvement in PFS solely in patients with somatic DDR alterations [32]. These trials demonstrate a significant benefit from PARPi therapy in mCRPC patients with PGVs or somatic alterations in *BRCA1/2*. Several other trials with PARPi in earlier-stage PCa are ongoing, i.e., the NADIR trial in high-risk localized PCa, the AMPLITUDE trial in metastatic castration-sensitive PCa, and a trial evaluating olaparib monotherapy in biochemical recurrence after radical prostatectomy in patients with and without *BRCA1/2* alterations, which may lead to further indications for PARPi in PCa [33–35].

A subset of mCRPC patients with MMR alterations may benefit from CKI therapies. In a basket trial by Le et al., CKI therapy with pembrolizumab was tested in MMR-deficient cancers across 12 advanced cancer types, including PCa [36]. In this heavily pretreated and heterogenous cohort, CKI treatment showed an overall response rate of 53% and a complete response rate of 21%, which led to US Food and Drug Administration (FDA) approval for pembrolizumab for all solid tumors with MMR deficiency or MSI high without satisfactory alternative treatment options [37]. A case series of PCa patients with tumor and germline sequencing has shown that approximately 3% of PCa patients have MMR deficient tumors and that 25% carry a germline mutation in MMR genes. The retrospective study further showed that although these alterations were found in a small subset of PCa patients, approximately 45% of PCa MSI-high tumors clinically benefited from pembrolizumab treatment [38].

Conclusion

Management of prostate cancer (PCa) patients with germline mutations is essential in PCa screening,

Table 2 Selected studies with impact on clinical management of prostate cancer patients with germline mutations

Study	Patients included	Genes tested	Type of testing	Study design	Impact on clinical management
Screening					
IMPACT [19, 20]	3027	*BRCA1/2* + additional 3 MMR genes	Germline	Prospective	PSA screening is indicated for *BRCA2, MSH2* and *MSH6* PGV carriers
Active surveillance					
Carter et al. [23]	1211	*BRCA 1/2, ATM* + additional 51 DNA repair genes ($n = 54$)	Germline	Prospective	PGVs in *BRCA1/2* and *ATM* are associated with aggressive PCa
Localized prostate cancer					
Castro et al. [26]	1302	*BRCA1/2* ($n = 2$)	Germline	Retrospective	Outcomes for conventional treatment of localized PCa was worse in *BRCA 1/2* carriers compared to noncarriers
Metastatic castration-resistant prostate cancer					
De Bono et al. PROfound: olaparib [28]	4425	*BRCA 1/2, ATM* + additional 12 other genes	Somatic	Randomized phase III	PFS was superior in patients with HRR alterations treated with olaparib compared to enzalutamide or abiraterone
Fizazi et al. TRITON3: rucaparib [30]	4855	*BRCA 1/2, ATM*	Germline + somatic	Randomized phase III	PFS was longer in PCa patients with underlying *BRCA* alterations treated with rucaparib compared to control medication
Clarke et al. PROPel: olaparib + abiraterone [29]	796	*BRCA 1/2, ATM* + additional 11 genes	Somatic	Randomized phase III	Combination of abiraterone and olaparib prolonged PFS irrespective of HRR alteration status
Chi et al. MAGNITUDE: niraparib + abiraterone [32]	742	*BRCA 1/2, ATM* + additional 6 genes	Somatic	Randomized phase III	Niraparib + abiraterone prolonged PFS in patients with underlying HRR alterations
Agarwal et al. TALAPRO-2: talazoparib + enzalutamide (ongoing) [31]	805	*BRCA 1/2, ATM* + additional 9 genes	Somatic	Randomized phase III	PFS improved in patients treated with talazoparib + enzalutamide irrespective of HRR gene alterations
Le et al. [36]	86	*MLH1, MSH2, MSH6, PMS2*	Germline + somatic	Nonrandomized phase II	MMR-deficient cancers responded to PD-1 blockage irrespective of tumor type

HRR homologous recombination repair, *MMR* mismatch repair, *PCa* prostate cancer, *PFS* progression-free survival

active surveillance, and localized or metastatic PCa treatment (Table 2). Given the recent recommendations for genetic testing and subsequent identification of mutation carriers, data on the best management of PCa patients with pathogenic germline variants (PGVs) at different stages during disease development is still scarce. In particular, experience how to manage patients with less well-studied but still rather frequently encountered alterations such as *CHEK2* or *ATM* is limited, and further studies are needed to offer optimal clinical management for these patients.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest K. Reiter and M.R. Hassler declare that they have no competing interests.

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