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Review Article

Clinical implications of genomic evaluations for prostate cancer risk stratification, screening, and treatment: a narrative review

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ABSTRACT

New classification systems based on molecular features have been introduced to improve precision medicine for prostate cancer (PCa). This review covers the increasing risk of PCa and the differences in response to targeted therapy that are related to specific gene variations. We believe that genomic evaluations will be useful for guiding PCa risk stratification, screening, and treatment. We searched the PubMed and MEDLINE databases for articles related to genomic testing for PCa that were published in 2020 or earlier. There is increasing evidence that germline mutations in DNA repair genes, such as *BRCA1/2* or *ATM*, are closely related to the development and aggressiveness of PCa. Targeted prostate-specific antigen screening based on the presence of germline alterations in DNA repair genes is recommend to achieve an early diagnosis of PCa. In cases of localized PCa, even if it has a favorable risk classification, patients under active surveillance with these gene alterations are likely to develop aggressive PCa. Thus, active treatment may be preferable to active surveillance for these patients. In cases of metastatic castration–resistant PCa, *BRCA1/2* and DNA mismatch repair genes may be useful biomarkers for predicting the response to androgen receptor–targeting agents, poly (ADP-ribose) polymerase inhibitors, platinum chemotherapy, prostate-specific membrane antigen–targeted therapy, immunotherapy, and radium-223. Genomic evaluations may allow for risk stratification of patients with PCa based on their molecular features, which may help guide precision medicine for treating PCa.

1. Introduction

Prostate cancer (PCa) is common among men, and its incidences have been increasing during recent decades [1]. Similar to ovarian and breast cancers, a significant proportion of PCa cases are related to genetic factors [2,3]. Thus, there has been increasing discussion regarding genomic evaluations for PCa, as 8–12% of patients with PCa have germline mutations in tumor suppressor genes [4]. Prostate-specific antigen (PSA) has traditionally guided the diagnosis and treatment of PCa, although there is a need for new biomarkers to guide the early detection of PCa and the selection of effective treatment for advanced PCa [5].

The genomic landscapes for localized PCa and advanced PCa have recently been published. The Cancer Genome Atlas Research Network reported results for whole-exome sequencing of localized PCa (26% of the cohort had a Gleason score of 8) and noted that harmful germline or somatic mutations were relatively common in DNA damage repair genes (*BRCA1*, *BRCA2*, *CDK12*, *ATM*, *FANCD2*, and *RAD51C*) [6]. Whole-exome sequencing was also performed for the first time to provide genomic information regarding advanced PCa [7]. Robinson et al. [8] performed an integrated genomic analysis of 150 patients with metastatic castration–resistant PCa (mCRPC), which revealed frequent aberrations in *AR* (62.7%), *TP53* (53.3%), and *PTEN* (40.7%). Furthermore, they found that the rates of aberrations in *AR* and *TP53* were higher for CRPC than for primary PCa and that CRPC was associated with frequent alterations of DNA repair genes, such as *BRCA1/2* or *ATM*. Thus, genomic evaluations may be useful for the early detection of PCa, identifying high-risk PCa, and selecting appropriate treatment strategies [4,9,10].

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Information from genomic testing is provided to patients and their physicians, which makes it important to understand its clinical implications. Therefore, we performed this review to investigate the clinical implications of genomic evaluations for PCa risk stratification, screening, and treatment (Fig. 1). The PubMed and MEDLINE databases were searched for articles related to genomic testing for PCa that were published in 2020 or earlier.

2. Genomic evaluations in PCa screening

Screening strategies have been developed to identify PCa and improve survival outcomes, while avoiding overdiagnosis and overtreatment [11]. Recent studies have indicated that alterations in PCa susceptibility gene increase the risk of PCa (Table 1). In particular, high-grade malignant PCa frequently occurs at an early age in patients with alterations in DNA repair genes, such as *BRCA1*, *BRCA2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *CHEK2*, *HOXB13*, *PALB2*, and *RAD51D* [12–14].

2.1. BRCA1 and BRCA2

Alterations in *BRCA1* and *BRCA2* are associated with the development of melanoma, pancreatic cancer, breast cancer, and ovarian cancer. Alterations in *BRCA1* (chromosome 17q21) are associated with a 1.8–4.5 times higher risk of developing PCa by the age of 65 years, while alterations in *BRCA2* (chromosome 13q12.3) are associated with a 2.5–8.6 times higher risk of developing PCa [15–20]. Moreover, PCa with *BRCA1* or *BRCA2* alterations is more likely to involve a Gleason score of ≥8 (vs. sporadic PCa) and is reportedly associated with high incidences of lymph node involvement and metastasis [21].

2.2. ATM

The *ATM* gene is involved in the DNA damage response, and germline alterations in *ATM* are associated with an increased risk of developing PCa or metastasis (vs. sporadic PCa) [22].

2.3. HOXB13

Homeobox B13 (*HOXB13*, chromosome 17q21.32) is a tumor suppressor gene that has very high penetrance characteristics. Approximately, 60% of men with *HOXB13* mutations will develop PCa by the age of 80 years [23–25].

2.4. CHEK2

The *CHEK2* gene encodes a cell cycle checkpoint protein kinase that regulates *TP53* and DNA repair. Germline alterations in *CHEK2* are associated with increased risks of breast, colon, thyroid, kidney, and prostate cancers [26].

2.5. DNA mismatch repair genes

The mismatch repair genes include *MLH1* (chromosome 3p21.3), *MSH2* (chromosome 2p21), and *MSH6* (chromosome 2p16). Mutations in these genes are associated with Lynch syndrome, which is a hereditary multicancer syndrome that is characterized by nonpolyposis colorectal cancer. Furthermore, carriers of mutations in these genes have a 3.67 times higher risk of PCa (95% confidence interval: 2.3–6.6×), relative to noncarriers [14].

Approximately, 5–10% of PCa cases involve hereditary PCa, in which genetic variations are passed on to the patient's offspring [14]. Although there is no consensus regarding PCa screening and management in this high-risk population, the National Comprehensive Cancer Network guidelines recommend genetic testing if a man has a family history of hereditary breast cancer, ovarian cancer, PCa, or Lynch syndrome [27]. Furthermore, guidelines for the early detection of PCa recommend screening from the age of 45 years if the patient has *BRCA1* alterations, *BRCA2* alterations, or a family history of hereditary breast or ovarian cancers. Prostate biopsy is also recommended if the patient has suspicious examination findings or a PSA concentration of ≥3 ng/mL [27,28].

Many studies have also indicated that carriers of *BRCA2* alterations are more likely to develop aggressive and metastatic PCa at a young age, relative to noncarriers [20,21,29]. Thus, targeted screening based on *BRCA1* or *BRCA2* status has been recognized as useful for achieving an early diagnosis of PCa. The IMPACT study has been underway since 2014 to confirm the role of *BRCA1* or *BRCA2* in PCa screening [30,31] and was the first prospective study to use germline genetic markers for identifying men with a high risk of PCa. The preliminary results revealed that targeted PSA screening based on the *BRCA* genotype can achieve early detection of aggressive PCa, as carriers of *BRCA2* alterations were diagnosed with PCa at a younger age than noncarriers (61 years vs. 64 years; $P = 0.04$) and had a higher rate of clinically significant cancer (77% vs. 4%; $P = 0.01$). Although systematic PSA screening is useful for men with *BRCA2* alterations, the significance of *BRCA1* alterations is less clear and we await the final results to help guide the development of an optimal screening strategy [30,31].

3. Genomic evaluations for localized PCa

In the era of PSA screening, most men present with localized and potentially curable PCa. However, there is a broad spectrum of localized PCa cases, ranging from entirely indolent to cancer that requires aggressive treatment. Furthermore, approximately 30% of men will experience recurrence despite receiving radiotherapy or surgery for PCa [32]. Fraser et al. have reported that no single gene was mutated at a frequency of >10% in localized PCa [33], although alterations in DNA damage repair genes are closely related to aggressive behavior of localized PCa and cancer-specific mortality [20,21,34]. Moreover, patients with PCa that involves inherited

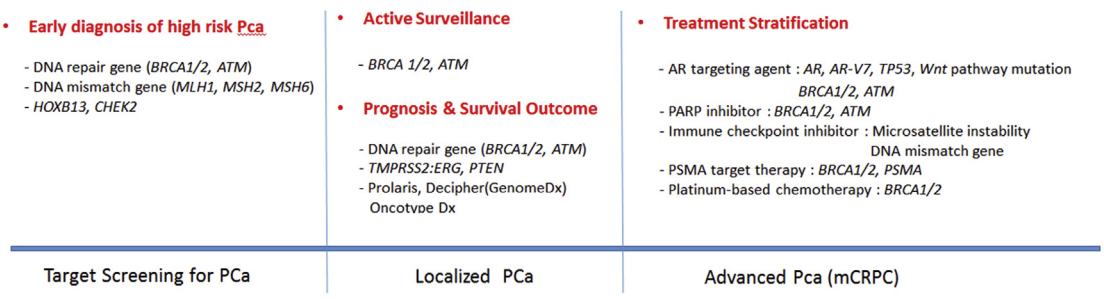

Fig. 1. Schematic diagram showing clinical application of the genomic evaluation for prostate cancer screening and treatment.

Table 1
Implications of molecular biomarkers for screening and treatment of localized prostate cancer.

Author (year)	No. of patients (n)	Surrogate marker	Outcome
PCa screening			
Leongamornlert et al. (2012) [15]	913	Germline BRCA1 mutation	Increased risk of PCa.
Edward et al. (2003) [18]	263	Germline BRCA2 mutation	Increased risk of PCa at an early age
Agalliu et al. (2007) [19]	290	Protein-truncating BRCA2 mutation	Increased risk of early-onset PCa
Kote-Jarai et al. (2011) [20]	1864	Germline BRCA2 mutation	Increased risk of PCa by age 65
Ewing et al. (2012) [23]	5083	HOXB13 G84E variant	Increased risk of hereditary PCa
Karlsson et al. (2014) [25]	9696	Germline HOXB13 G84E mutation	Increased risk of PCa.
Naslund-Koch et al. (2016) [26]	86975	CHEK2*1100delC germline mutation	Increased risk of PCa.
Page et al. (2019) [31]	3027	Germline BRCA2 mutation	Increased risk of PCa, younger age of diagnosis, clinically significant tumors.
Nyberg (2020) [29]	823	Germline BRCA1/2 mutation	Increased risk of aggressive PCa.
Active surveillance			
Carter et al. (2019) [42]	1211	Germline BRCA1/2, ATM mutation	Increased risk of grade reclassification and aggressive PCa.
Prognosis			
Castro et al. (2015) [43]	1302	Germline BRCA mutation	BRCA carriers treated with RT have significantly shorter MFS and CSS than those who underwent RP.
Castro et al. (2013) [21]	2019	Germline BRCA1/2 mutation	Increased risk of aggressive PCa with a nodal involvement and distant metastasis.
Leinonen et al. (2013) [49]	284	PTEN loss, TMPRSS2:ERG	Shorter progression-free survival
Wu et al. (2020) [41]	1694	Germline ATM, BRCA2, MSH2 mutations	Associated with grade group 5 PCa

CSS, cancer-specific survival; MFS, metastasis free survival; PCa, prostate cancer; RP, radical prostatectomy; RT, radiation therapy.

mutations in *BRCA1*/*BRCA2* or *ATM* are more likely to die because of PCa at a young age [11]. The National Comprehensive Cancer Network guidelines have also addressed genetic testing for men with PCa (Gleason score of $\geq$7) and specific family history features [27]. Therefore, better understanding of the genetic factors that drive aggressive PCa may help identify subtypes of localized PCa and guide effective treatment selection.

3.1. Active surveillance

Active surveillance (AS) is one option for patients with a favorable PCa risk profile [35,36], although it can be difficult to select AS candidates because poor outcomes are still observed among patients with a favorable PCa risk profile. Furthermore, patients may miss the opportunity to receive effective treatments in a timely manner if they are misclassified at the time of diagnosis [37]. Therefore, it is very important to accurately identify patients with a high risk of developing lethal PCa during AS. Many nomograms based on clinical data have been developed to predict the course of PCa [38–40], although the addition of genomic information may help more accurately identify indolent and lethal PCa. Wu et al. [41] reported that germline pathogenic mutations in DNA repair genes were strongly associated with PCa in grade group (GG) 5, and the risk of reclassification increased when patients with these germline mutations were undergoing AS (Table 1). Carter et al. [42] also reported that men undergoing AS with inherited mutations in *BRCA1*, *BRCA2*, and *ATM* were more likely to have aggressive PCa and that carriers of *BRCA2* mutations had a 5 times higher risk of reclassification from GG 1 to GG > 3 (vs. noncarriers). Therefore, when selecting patients for AS, urologists should consider the presence of germline alterations in *BRCA1*, *BRCA2*, and *ATM*, as these patients may be more likely to develop aggressive PCa.

3.2. The response of BRCA mutant carriers to conventional treatments for localized PCa

A recent study of localized PCa revealed a difference in the survival rate after radical prostatectomy or external beam radiation therapy according to the presence or absence of *BRCA1* or *BRCA2* alterations [21,43]. For example, relative to noncarriers, carriers of germline *BRCA2* mutations had significantly lower metastasis-free survival rates at 5 years (94% vs. 72%) and at 10 years (84% vs. 50%, $p < 0.001$). Moreover, carriers had significantly lower cancer-specific survival (CSS) rates at 5 years (94% vs. 76%) and at 10 years (84% vs. 61%, $p < 0.001$). However, it is interesting that there was no significant difference in the CSS rates after radical prostatectomy between *BRCA2* mutation carriers and noncarriers, although a significant difference in CSS after radiotherapy was observed between *BRCA2* mutation carriers and noncarriers [43]. Thus, the poorer survival outcomes for carriers of germline *BRCA2* mutations may be more relevant among patients who receive radiotherapy [44]. Nevertheless, that study only evaluated a small sample of patients and that their characteristics were not balanced.

3.3. Molecular biomarkers not related to DNA repair genes

Treatment decisions for localized PCa can also be guided by evaluation of the TMPRSS2:ERG fusion gene, *PTEN* status, the Prolaris test for cell cycle progression genes, the Decipher test (GenomeDx), and the Oncotype DX Genomic Prostate Score [5,45]. A meta-analysis of 5,074 patients who underwent radical prostatectomy revealed that the TMPRSS2:ERG fusion gene was not associated with biochemical recurrence (BCR) or mortality [46]. However, fusion status is considered a key genomic event that should be taken into consideration when the prognostic value of genomic biomarkers is being investigated [45,47,48]. For example, loss of *PTEN* is associated with a high risk of BCR but is only associated with shorter progression-free survival in ERG-positive cases [49,50]. Genomic panels include the Prolaris test (46 genes), the Decipher genetic test (GenomeDX, 22 genes), and the Oncotype DX Genomic Prostate Score (17 genes), which can be used to predict the risk of BCR and metastatic progression after radical prostatectomy [51–58]. A recent study evaluated whether results from the Prolaris test influenced the treatment selection for patients diagnosed with localized PCa, which revealed that the treatment was

Table 2
Implications of molecular biomarkers for treatment of mCRPC.

Author (year)	No. of patients (n)	Surrogate marker	Outcome
AR-targeting agent			
Antonarakis et al. (2014) [63]	62	CTC-based *AR-V7*	Increased risk of resistance to enzalutamide and abiraterone
De Laere et al. (2019) [68]	168	CTC-based *TP53* alteration	TP53 alteration is superior to any AR-derived marker in predicting AR-targeting agent responsiveness
Isaacsson et al. (2020) [70]	137	Somatic Wnt-activating mutations	Decrease the effectiveness of abiraterone and enzalutamide
Chung et al. (2019) [69]	37	CTC-based AR, AR-V7, PSCA, NKX3.1, Wnt5b, PSA	Decrease the effectiveness of abiraterone and enzalutamide
Annala et al. (2017) [71]	319	Germline ctDNA-based DNA repair defects	Attenuated responses to abiraterone and enzalutamide
Antonarakis et al. (2018) [72]	172	Germline BRCA1/2, ATM	Increase the effectiveness of abiraterone and enzalutamide
PARP inhibitor			
Mateo et al. (2015) [76]	50	BRCA1/2, ATM, CHEK2, PALB2, FANCA and HDAC2 alteration	Increased responses to PARP inhibitors olaparib
Abida et al. (2020) [77]	78	ATM, CDK12, CHEK2	Limited responses to PARP inhibitor rucaparib
Marshall et al. (2019) [78]	23	Germline or somatic ATM mutation	Do not respond as well as men with BRCA1/2 mutation
Immune checkpoint inhibitor			
Le et al. (2017) [79]	86	Germline mismatch repair deficiency (MSH2, MSH6, PMS2, and MLH1)	Sensitive to immune checkpoint blockade
Antonarakis et al. (2019) [80]	127	MSH2, MSH6, MLH1, and PMS2	Anecdotal sensitivity to PD-1 inhibitors, pembrolizumab
PSMA target therapy			
Paschalis et al. (2019) [85]	60	DNA repair defects	High mPSMA expression and may respond better to PSMA targeting treatments
Crumbaker et al. (In press) [86]	Case report	Biallelic BRCA2 inactivation	Exceptional response to PSMA target therapy
Platinum-based chemotherapy			
Cheng et al. (2016) [89]	Case series	Biallelic BRCA2 inactivation	Increased response to platinum-based chemotherapy
Pomerantz et al. (2017) [90]	141	Germline BRCA2	Increased response to platinum-based chemotherapy
Zafeiriou et al. (2019) [91]	Case series	DNA repair defects (BRCA2, ATM)	Increased response to platinum-based chemotherapy
Radium-223			
Isaacsson et al. (2019) [95]	190	BRCA2, ATM, CHEK2, ATR, FANCI, FANCL and PALB2)	Increased response to radium-223
Van et al. (2020) [96]	93	DNA repair defects (BRCA2, ATM, CDK12)	Increased response to radium-223

CTC, circulating tumor cell; mCRPC, metastatic castration–resistant PCa; PCa, prostate cancer; PSA, prostate-specific antigen; PSCA, prostate stem cell antigen.

changed in 65% of the cases based on the genomic evaluation, with a lower treatment burden in 40% of the cases [59]. These results indicate that genomic evaluations can significantly influence treatment selection.

4. Genomic evaluation for mCRPC

Treatment for mCRPC has improved significantly over the last decade, although there remains controversy regarding the optimal treatment selection algorithms, based on the substantial heterogeneity in treatment responses [60]. Therefore, it would be useful to identify biomarkers for predicting treatment responses, and substantial effort has been dedicated to achieving treatment stratification through genomic evaluations (Table 2). Given the implications for treatment selection, some experts have suggested routine genomic evaluations for all men with mCRPC [4,9,22]. Furthermore, approximately 90% of patients with mCRPC harbor clinically actionable molecular alterations, which frequently involve *AR* (62%), the *ETS* family (56.7%), *TP53* (53.3%), and *PTEN* (40.7%). In addition, aberrations have been observed in the PI3K pathway (49%), the DNA repair pathway (19%), CDK inhibitors (7%), and the Wnt pathway (5%). Finally, aberrations in *BRCA1*, *BRCA2*, and *ATM* have been observed in approximately 20% of patients with mCRPC [8].

4.1. Androgen axis agents

Androgen receptor signaling inhibitors (ARSIs), such as abiraterone or enzalutamide, are options for treating patients with mCRPC. However, approximately 30–40% of these patients do not respond to ARSI treatment or develop resistance within a brief period of time [61–63]. The AR variant 7 (AR-V7) has been suggested as a biomarker for predicting response to ARSI treatment, although AR-V7–positive patients account for only a small percentage of ARSI nonresponders and subsets of AR-V7–positive patients do respond to ARSI treatment [64,65]. Given the lack of clear data, a recent consensus statement indicated that there is insufficient evidence to support the implementation of AR-V7 testing in clinical practice [66,67]. Nevertheless, inactivation of *TP53* is superior to any *AR*-derived biomarker for predicting ARSI responsiveness, and it has been reported that the *TP53* status can be used to predict a good or poor prognosis for 50–55% of patients with mCRPC undergoing ARSI treatment [68].

In addition to *AR* signaling–based markers, genes related to the Wnt pathway, epithelial–mesenchymal transition, and stemness have potential clinical relevance in PCa [69,70]. Furthermore, the response to ARSI treatment may vary according to the presence of germline alterations in DNA repair genes [71,72], which occur in 8–12% of patients with mCRPC [3,8,22]. Patients with *BRCA2* germline mutations are also generally known to have a poor prognosis, and Annala et al. [71] have suggested that carriers of these mutations with mCRPC also experience a poor response to therapies targeting the AR signaling axis. However, conflicting evidence has also been published, as carriers of germline *BRCA*/*ATM* alterations had a better response to ARSI treatment, relative to noncarriers [72]. Thus, further studies are needed to address these conflicting results.

4.2. Poly ADP ribose polymerase (PARP) inhibitors (olaparib and rucaparib)

In 2005, a novel inhibitor of poly[adenosine diphosphate-ribose] polymerase (KU-0059436) was reported to specifically kill cell lines with silenced or lost *BRCA1/2* expression [73,74]. The US Food and Drug Administration subsequently approved the use of olaparib (a poly ADP ribose polymerase (PARP) inhibitor) for treating patients with mCRPC who harbored *BRCA1*, *BRCA2*, or *ATM* alterations and had previously received taxane-based chemotherapy or ARSI treatment. Several landmark studies demonstrated that PARP inhibitors were associated with an increased response rate in men with mCRPC harboring *BRCA1/2* alterations [75,76]. The TOPARP-A trial (ClinicalTrials.gov NCT01682772) also revealed that 88% of patients with *BRCA1/2* alterations responded to PARP inhibitors, although only 6% of patients without these alterations responded to PARP inhibitors. Nevertheless, preliminary results from the TRITON2 study revealed that men with mCRPC harboring *ATM* mutations did not respond as well to rucaparib as men harboring *BRCA1/2* alterations [77]. Similarly, patients with mCRPC and *ATM* mutations had a lower rate of response to olaparib treatment than patients with *BRCA1/2* mutations [78]. Therefore, alternative treatments are needed for patients with *ATM* mutations.

4.3. Immune checkpoint inhibitors

Patients with several cancers, including Lynch syndrome, are known to be sensitive to immune checkpoint inhibitors if they have microsatellite instability or DNA mismatch repair gene alterations [79]. The US Food and Drug Administration has recently approved the use of immune checkpoint inhibitors, such as pembrolizumab, for treating solid tumors with mismatch repair deficiency, which suggests that genomic evaluations have become an essential step in guiding cancer treatment [9,79]. Antonarakis et al. [80] have also anecdotally reported that patients with mismatch repair gene–mutated advanced PCa appear to respond to PD-1 inhibitors, such as pembrolizumab. However, the role of PD-1/PDL-1 in mCRPC remains unclear, and there is limited evidence regarding an exceptional response in the presence of microsatellite instability [14].

4.4. PSMA-targeted treatment

Radiolabeled anti-PSMA therapies, such as 177 Lu-PSMA-617, are well tolerated and lead to a 50% reduction in PSA concentrations in 30–60% of patients with mCRPC, although 30% of patients do not respond to anti-PSMA treatment at all [81–84]. Interestingly, patients with mCRPC and DNA repair gene alterations have much higher membranous PSMA expression than those without alterations, which may help identify patients who are more likely to respond to anti-PSMA treatment [85,86].

4.5. Platinum-based chemotherapy

Platinum chemotherapy is rarely used to treat PCa, except in cases involving neuroendocrine differentiation [87]. However, previous studies have shown that *BRCA1/2* alterations may predict the response to platinum-based chemotherapy in cases of breast and ovarian cancer [87,88]. Even in patients with mCRPC, germline alterations in DNA repair genes are associated with the response to platinum-based chemotherapy, especially in patients with mCRPC and *BRCA2* alterations [89–91].

4.6. Radium-223

Radium-223 is an alpha particle emitter that is a therapeutic option for patients with mCRPC and symptomatic bone metastases and no visceral metastases [92]. It selectively targets the bone microenvironment and emits high-energy alpha particles that cause double-strand DNA breaks [91,93], which exert potent localized cytotoxic effects [94]. Patients harboring aberrations in

DNA repair genes experience a greater benefit from radium-223, relative to patients without these mutations [95,96].

5. Conclusion

There is accumulating evidence that germline alterations in DNA repair genes, including *BRCA1/2* and *ATM*, are associated with increased risks of developing early onset and/or high-risk PCa. These molecular markers may have a profound influence on the diagnosis and treatment of PCa, especially in terms of selecting and sequencing targeted therapy for patients with mCRPC. While these markers have not been incorporated into clinical decision-making processes at this time, genomic evaluations may help guide these processes in borderline cases where additional information would be useful.

Conflicts of interest

All the authors declare no potential conflict of interest to disclose.

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