Review Article
Prostate diseases

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Genomic Profiling of Prostate Cancer: An Updated Review

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Understanding the genomic profiling of prostate cancer is crucial, owing to the emergence of precision medicine to guide therapeutic approaches. Over the last decade, integrative genomic profiling of prostate tumors has provided insights that improve the understanding and treatment of the disease. Minimally invasive liquid biopsy procedures have emerged to investigate cancer-related molecules with the advantage of detecting heterogeneity as well as acquired resistance in cancer. The metastatic castration-resistant prostate cancer (mCRPC) tumors have a highly complex genomic landscape compared to primary prostate tumors; a number of mCRPC harbor clinically actionable molecular alterations, including DNA damage repair (*e.g.*, *BRCA1/2* and *ATM*) and PTEN/phosphoinositide 3-kinase signaling. Heterogeneity in the genomic landscape of prostate cancer has become apparent and genomic alterations of *TP53*, *RB1*, *AR*, and cell cycle pathway are associated with poor clinical outcomes in patients. Prostate cancer with mutant *SPOP* shows a distinct pattern of genomic alterations, associating with better clinical outcomes. Several genomic profiling tests, which can be used in the clinic, are approved by the U.S. Food and Drug Administration, including MSK-IMPACT, FoundationOne CDx, and FoundationOne Liquid CDx. Here, we review emerging evidence for genomic profiling of prostate cancer, especially focusing on associations between genomic alteration and clinical outcome, liquid biopsy, and actionable molecular alterations.

Keywords: Biomarkers; Decision making; Genomics; Liquid biopsy; Prostate cancer

INTRODUCTION

Prostate cancer is the second most frequent cancer among males and the cause of an estimated 385,000 deaths worldwide in 2018 [1]. Prostate carcinogenesis and progression are correlated with loss of specific chromosome regions and candidate tumor suppressor genes, such as loss of 8p21 and *NKX3.1*, loss of 10q and *PTEN*, loss of 13q and *RB1*, and loss of 17p and *TP53* [2]. Recurrent gene fusions of TMPRSS2 and ETS transcription factor genes are frequently detected in prostate cancer, suggesting that the androgen-responsive promoter elements of TMPRSS2 mediate the overexpression of ETS family members [3]. Prostate cancer development and disease progression are driven by the androgen receptor (AR) signaling pathway, which has led to the use of androgen deprivation therapy (ADT) for patients with advanced prostate cancer. Sustained AR signaling is the primary driver of castration-resistant prostate cancer (CRPC), leading researchers to develop novel treatments targeting the AR pathway, such as abiraterone and enzalutamide [4]. Molecular

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mechanisms behind AR reactivation in CRPC include *AR* gene amplification, *AR* mutations (*e.g.*, T878A, F876L, L702H, L701H, and T877A), AR splice variants (AR-Vs), changes of androgen biosynthesis, and changes in AR cofactor [5]. Recently, novel mechanisms of AR activation have been reported, such as amplification of an upstream enhancer of *AR* and *AR* gene rearrangements [6-8]. During disease progression, a subset of metastatic CRPC (mCRPC) tumors loses AR dependence and often have neuroendocrine features [9].

Recently, precision medicine has emerged to guide therapeutic approaches for patients with prostate cancer by understanding each altered gene or pathway in an individual, leading to the improvement of clinical outcomes [10]. A phase 3 clinical trial demonstrated that the alteration of *BRCA1/2* or *ATM* was associated with response to poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitor olaparib in patients with mCRPC [11]. An Akt inhibitor, ipatasertib, showed antitumor activity in patients with *PTEN*-loss tumors, in a phase 2 study [12]. Over the last decade, the integrative genomic profiling of human prostate tumors had provided the foundations for discoveries that can impact disease understanding and treatment [13-15]. Furthermore, minimally invasive liquid biopsy procedures have emerged to investigate cancer-related molecules with the advantage of detecting heterogeneity as well as acquired resistance in cancer [16,17]. Here, we review emerging evidence for genomic profiling of prostate cancer, especially focusing on association of genomic alteration and clinical outcome, liquid biopsy, and actionable molecular alterations (Fig. 1). In this review, we identified the relevant studies using electronic databases, including PubMed and Web of Science.

MAIN BODY

1. Genomic landscape of prostate cancer

Common genetic alterations in primary prostate cancer include losses of *NKX3.1* and *PTEN* [2] and fusion of ETS family transcription factor genes with androgen-responsive promoters [3]. In addition, a significant proportion of primary prostate tumors harbor large-scale genomic rearrangements [18,19]. Recurrent somatic mutations were identified in multiple genes, including *SPOP* and *FOXA1*, in patients with primary prostate cancer [20]. In 2015, The Cancer Genome Atlas (TCGA) presented a comprehensive molecular analysis of 333 primary prostate cancers, in which the tumors fell into subtypes according to specific gene fusions or mutations (*SPOP, FOXA1*, and *IDH1*) [14]. AR activity varied widely in a subtype-specific manner, with *SPOP* and *FOXA1* mutant tumors having the highest levels of AR-induced transcripts [14]. In 2015, Robinson et al [15] demonstrated that aberrations of *AR*, ETS genes, *TP53*, and *PTEN* were detected in 40% to 60% of cases in patients with mCRPC. The mCRPC tumors have a highly complex genomic landscape compared

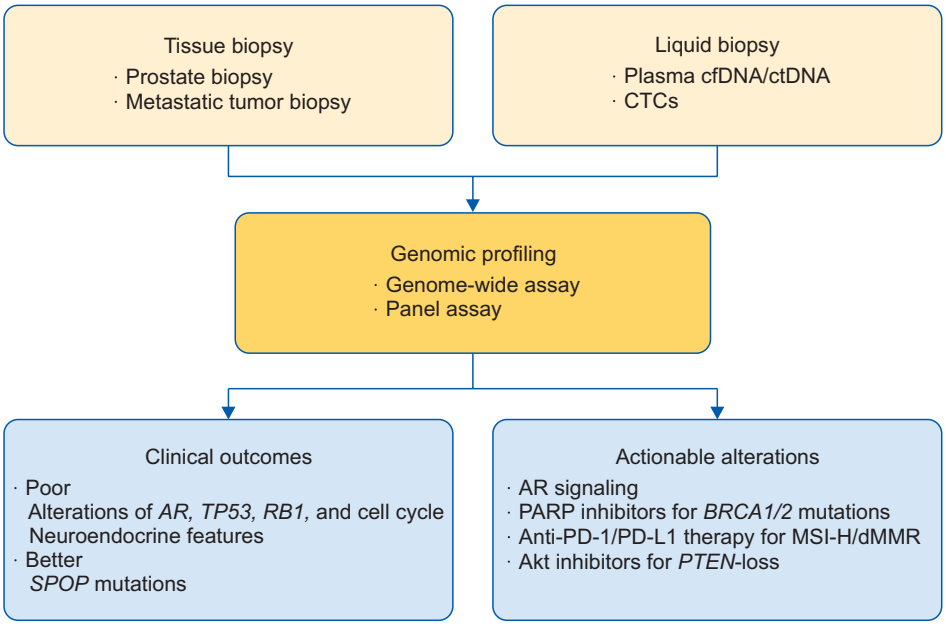

Fig. 1. Overview of genomic profiling of prostate cancer. The specific gene/pathway alterations are associated with clinical outcomes. Genomic profiling is useful to identify actionable molecular alterations. cfDNA: cell free DNA, ctDNA: circulating tumor DNA, CTC: circulating tumor cell, AR: androgen receptor, PARP: poly (adenosine diphosphate–ribose) polymerase, MSI-H: microsatellite instability-high, dMMR: deficiency in mismatch repair genes.

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to primary prostate tumors (Fig. 2) [21,22]. Genomic alterations in *AR, TP53, RB1*, and *PTEN* are enriched during disease progression [23-25]. Approximately 90% of mCRPC harbor clinically actionable molecular alterations, including AR signaling, DNA damage repair and phosphoinositide 3-kinase (PI3K) signaling [15].

In 2018, two studies, Quigley et al [6] and Viswanathan et al [7], demonstrated the structural alterations driving mCRPC using whole-genome sequencing. Tandem duplications affect an upstream enhancer of *AR* in 70% to 87% of cases, correlating with increased AR expression [6,7]. Progression on androgen pathway inhibitors, abiraterone and enzalutamide, was associated with gains in *AR* and *AR* enhancer [7]. Tandem duplication hotspots also occur near *MYC*, associated with post-translational MYC regulation [6]. Classes of structural variations were linked to distinct DNA repair deficiencies, including associations of *CDK12* mutation with tandem duplications, *TP53* inactivation with inverted rearrangements and chromothripsis, and *BRCA2* inactivation with deletions [6,7,26].

The ethnic and racial background can influence the incidence and mortality of prostate cancer, partly due to the interplay of socioeconomic factors and environmental exposures [27]. To date, most prostate cancer genomics data have been derived from Western populations. Thus, precision oncologic studies have underrepresented patients from Asia and Africa, limiting comprehensive understanding of disparities in the diagnosis and prognosis of prostate cancer among these populations [28]. The incidence and mortality rates of prostate cancer for Asians are lower than Western populations [29]. In 2020, Li et al [30] reported on the genomic landscape of primary prostate cancer in Asian populations, in which 41% of tumors contained mutations in *FOXA1* and 18% had deletions in *CHD1*. Lower incidence of *FOXA1/CHD1* alterations in Western populations and lower incidence of TMPRSS2:ERG fusion gene and *PTEN* loss in Asian populations compared with counterparts were reported [30-33]. Thus, the genomic alteration signatures in Asian patients were markedly different from those of Western cohorts.

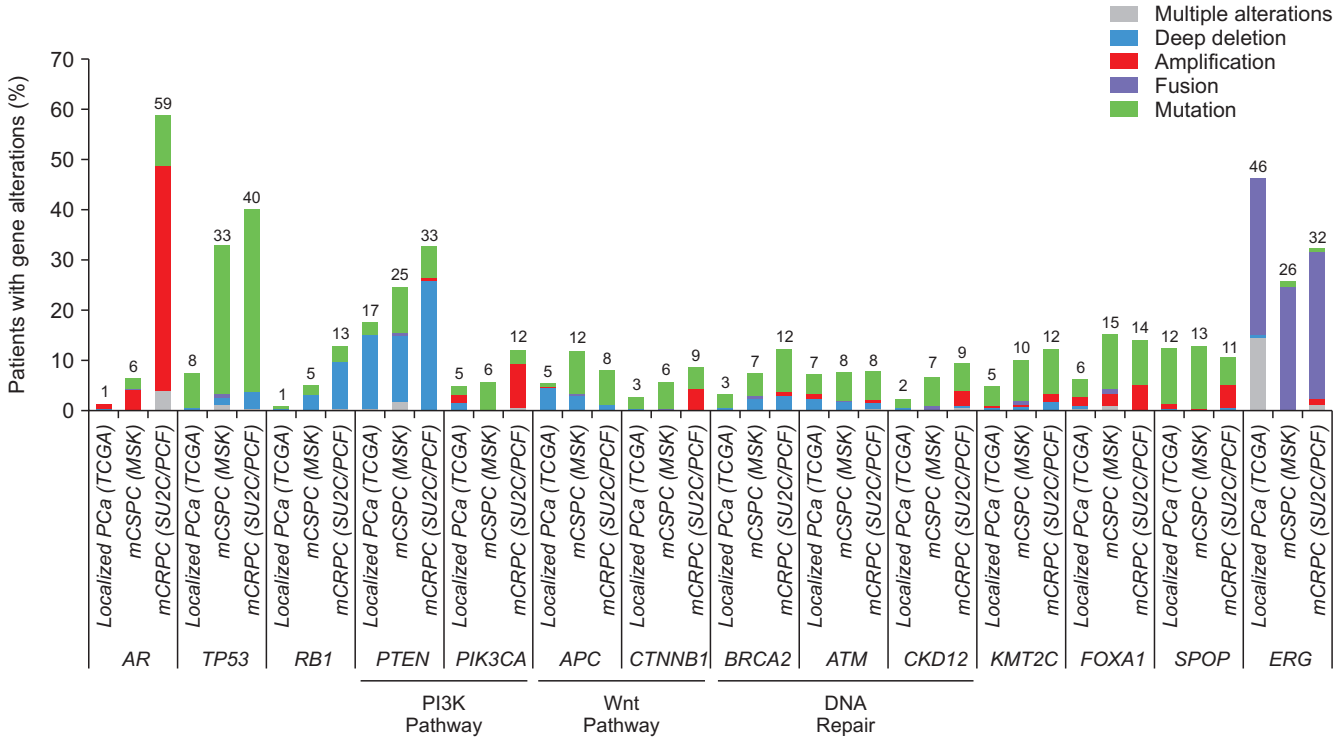

Fig. 2. Gene alterations in the different stages of prostate cancer. Localized PCa, TCGA (n=333) [14]; mCSPC, MSK (n=424) [38]; mCRPC, SU2C/PCF Dream Team (n=444) [36]. The frequency of each gene alteration was calculated based on clinical data provided by cBioPortal (https://www.cbioportal.org/) The Figures from the cBioportal are permitted to use in the publications (https://docs.cbioportal.org/1.-general/faq#can-i-use-figures-from-the-cbioportal-in-my-publications-or-presentations) [21,22]. PCa: prostate cancer, TCGA: The Cancer Genome Atlas, mCSPC: metastatic castration-sensitive prostate cancer, MSK: memorial sloan kettering, mCRPC: metastatic castration-resistant prostate cancer, SU2C/PCF: stand up to cancer/prostate cancer foundation.

2. Association of genomic alteration and clinical outcome

Heterogeneity in the genomic landscape of prostate cancer has become apparent through several comprehensive profiling studies. Growing evidence suggests that the genomic alterations correlate with clinical outcomes (Table 1). In 2014, Hieronymus et al [34] reported an association between biochemical recurrence and the pattern of DNA copy number alteration (CNA) in primary prostate cancer, raising the possibility of CNA as a prognostic biomarker. Since 2018, several studies have demonstrated the association of specific gene/pathway alterations and clinical outcomes based on the genome-wide study of prostate cancer [25,35-39]. Wang et al [35] reported that the gene-based pathway of cell cycle progression was associated with shorter time to treatment change (TTTC) in patients with mCRPC who were treated with abiraterone (hazard ratio [HR], 2.11; 95% confidence interval [CI], 1.17–3.80; p=0.01). Abida et al [36] demonstrated that *RB1* alteration was associated with poor overall survival (OS), whereas alterations in *RB1, AR,* and *TP53* were associated with shorter TTTC in patients with mCRPC treated with abiraterone or enzalutamide. Chen et al [37] reported that two DNA alterations in *RB1* were predictive of poor OS (median 14.1 mo *vs.* 42.0 mo; p=0.007), and *CTNNB1* mutations were exclusive to enzalutamide-resistant patients (p=0.01), associating with poor OS (median 13.6 mo *vs.* 41.7 mo; p=0.025) in patients with mCRPC treated with enzalutamide. Stopsack et al [38] reported that rates of castration resistance (HR, 1.84; 95% CI, 1.40–2.41) and death (HR, 3.71; 95% CI, 2.28–6.02) were higher in high-volume metastatic castration-sensitive prostate cancer (mCSPC), associating with genomic alterations. Rates of castration resistance differed 1.5-fold to 5-fold according to alterations in *AR*, cell cycle pathway, MYC pathway, *TP53*, WNT pathway (inverse), and *SPOP* (inverse), whereas OS rates differed 2-fold to 4-fold according to *AR*, cell cycle pathway, WNT pathway (inverse), and *SPOP* (inverse) [38]. Mateo et al [25] reported that patients with *RB1* loss in the primary prostate cancer had a worse prognosis. Among men with matched hormone-naive and mCRPC biopsies, *RB1*/*TP53*/*AR* aberrations were enriched in later stages [25]. Deek et al [39] reported that the frequency of driver mutations in *TP53* (p=0.01), *WNT* (p=0.08), and cell cycle (p=0.04) genes increased across the mCSPC spectrum. Mutations in *TP53* were independently associated with shorter radiographic progression free survival (PFS) (HR, 1.59; p=0.03) and the development of CRPC (HR, 1.71; p=0.01) [39]. Hamid et al [40] reported that deleterious tumor suppressor genes, *TP53*, *PTEN*, and *RB1*, were associated with an increased risk of relapse and death in patients with CSPC.

Prostate cancer with mutant *SPOP* shows a distinct pattern of genomic alterations, defining a new molecular subtype [20]. Boysen et al [41] reported that *SPOP* mutations were associated with a higher response rate to abiraterone (odds ratio, 14.50; 95% CI, 2.92–71.94; p=0.001) and a longer time on abiraterone (HR, 0.37; 95% CI, 0.20–0.69; p=0.002) in patients with mCRPC. Swami et al [42] reported that SPOP mutations were significantly associated with better PFS (median 35 mo *vs.* 13 mo; HR, 0.47; 95% CI, 0.25–0.87; p=0.016) and OS (97 mo *vs.* 69 mo; HR, 0.32; 95% CI, 0.12–0.88; p=0.027) in patients with mCSPC treated with ADT. Although AR is a ubiquitination degradation substrate of SPOP E3 ligase, prostate-cancer-associated SPOP mutants cannot bind to and promote AR degradation [43]. The *SPOP* mutant tumors have the highest AR transcriptional activity among prostate cancer subtypes [14]. Thus, the *SPOP* mutant tumors may primarily be driven by AR signaling and in turn will be responsive to AR targeted therapies [42].

Taken together, genomic alterations of *TP53, RB1, AR*, and cell cycle pathway are associated with poor clinical outcomes in patients with prostate cancer, whereas *SPOP* mutations are associated with better clinical outcomes (Table 1).

3. Liquid biopsy

A liquid biopsy is a minimally invasive procedure to investigate the cancer-related molecules in circulating tumor cells (CTCs) and cell-free tumor nucleic acids. There is a high consistency between metastatic tumor tissue and matched circulating tumor DNA (ctDNA) or CTCs [44-47]. Liquid biopsies have the advantage of detecting acquired resistance in prostate cancer [17,48]. In 2016, Ulz et al [16] performed whole-genome sequencing on plasma samples derived from patients with metastatic prostate cancer, and identified driver aberrations in cancer-related genes, including gene fusions (TMPRSS2:ERG), focal deletions (*PTEN, RYBP*, and *SHQ1*), and amplifications (*AR* and *MYC*). In serial plasma analyses, the focal amplifications were detected

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Table 1. Genomic alterations in prostate cancer tissue samples associated with clinical outcome

Author	Year	Patients	Number of patients	Therapy	Endpoint	Genomic alterations	Outcome
Hieronymus et al [34]	2014	Localized PCa	168	Px	Risk of BCR	CNA burden	HR, 1.99; 95% CI, 1.11–3.55; p=0.021
Wang et al [35]	2018	mCRPC	77	ABI	TTTC	Cell cycle progression scores (≥50)	HR, 2.11; 95% CI, 1.17–3.80; p=0.01
Boysen et al [41]	2018	mCRPC	89	ABI	TTTC	*SPOP*	HR, 0.37; 95% CI, 0.20–0.69; p=0.002
Abida et al [36]	2019	mCRPC	128	ABI or ENZ	TTTC	*RB1*	CPE=0.818; p<0.001
						AR	CPE=0.651; p=0.005
						TP53	CPE=0.609; p=0.046
					OS	*RB1*	CPE=0.768; p=0.002
Chen et al [37]	2019	mCRPC	101	ENZ	OS	*RB1*	Median 14.1 mo *vs.* 42.0 mo; p=0.007
						CTNNB1	Median 13.6 mo *vs.* 41.7 mo; p=0.025
Hamid et al [40]	2019	Localized PCa	205	Local therapy	PFS	*TP53, PTEN*, and *RB1*	HR, 1.95; 95% CI, 1.22–3.13; p=0.005
					Time to CRPC	*TP53, PTEN*, and *RB1*	HR, 3.36; 95% CI, 1.01–11.16; p=0.04
Stopsack et al [38]	2020	mCSPC	424	N/A	Time to CRPC	*AR*	HR, 5.30; 95% CI, 2.97–9.46
						Cell cycle pathway	HR, 2.12; 95% CI, 1.50–3.00
						MYC pathway	HR, 2.04; 95% CI, 1.35–3.10
						TP53	HR, 1.57; 95% CI, 1.17–2.12
						WNT pathway	HR, 0.66; 95% CI, 0.47–0.95
						SPOP	HR, 0.63; 95% CI, 0.39–1.00
					OS	*AR*	HR, 4.06; 95% CI, 1.71–9.68
						Cell cycle pathway	HR, 2.03; 95% CI, 1.18–3.50
						WNT pathway	HR, 0.45; 95% CI, 0.22–0.90
						SPOP	HR, 0.33; 95% CI, 0.13–0.84
Mateo et al [25]	2020	Primary PCa	203	N/A	OS	*RB1*	Median 2.32 y *vs.* 4.28 y; p=0.006
Swami et al [42]	2020	mCSPC	121	ADT	PFS	*SPOP*	Median 35 mo *vs.* 13 mo; HR, 0.47; 95% CI, 0.25–0.87; p=0.016
					OS	*SPOP*	Median 97 mo *vs.* 69 mo; HR, 0.32; 95% CI, 0.12–0.88; p=0.027
Deek et al [39]	2021	mCSPC	294	N/A	rPFS	*TP53*	HR, 1.59; 95% CI, 1.04–2.41; p=0.03
					Time to CRPC	*TP53*	HR, 1.71; 95% CI, 1.16–2.52; p=0.01

PCa: prostate cance, BCR: biochemical recurrence, CNA: copy number alteration, HR: hazard ratio, CI: confidence interval, mCRPC: metastatic castration-resistant prostate cancer, ABI: abiraterone, TTTC: time to treatment change, ENZ: enzalutamide, CPE: concordance probability estimate, OS: overall survival, mCSPC: metastatic castration-sensitive prostate cancer, PFS: progression free survival, N/A: not applicable, ADT: androgen deprivation therapy, rPFS: radiographic PFS.

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in 40% of cases, suggesting a high plasticity of prostate cancer genomes with newly occurring focal amplifications as a driving force in progression [16]. Although ADT rapidly reduces ctDNA availability [49], the emergence of *AR* amplification in ctDNA is detected during treatment with abiraterone and enzalutamide [50]. Tumor fraction in cell free DNA (cfDNA) correlates with metastatic burden, and the decline of ctDNA can be a promising biomarker for therapeutic response in patients with CRPC [51]. Decreases in cfDNA concentration independently associated with outcome in patients with metastatic prostate cancer who were treated with PARP inhibitor olaparib (HR for OS at week 8, 0.19; 95% CI, 0.06–0.56; p=0.003) [52].

Recently, a number of studies demonstrated the association between genomic alterations in liquid biopsy and clinical outcome in prostate cancer (Table 2). As sustained AR signaling pathway remains a key driver for CRPC progression [5], considerable efforts have been made to profile *AR* aberrations using circulating nucleic acids [53]. Resistance to AR pathway inhibitors, abiraterone and enzalutamide, has been observed in patients with CRPC harboring AR copy number gain/amplification [54-59], somatic AR mutations [54-56], and constitutively active AR-Vs, such as AR-V3, AR-V7, and AR-V9 [58,60]. AR copy number gain has also been associated with poor outcomes in patients receiving chemotherapy [58,61], likely reflecting aggressive intrinsic disease biology. Furthermore, genomic alterations of *RB1*, *TP53*, *MYC*, cell cycle pathway, and DNA repair pathway are detected in liquid biopsy, and are reported to be associated with poor clinical outcomes in patients with prostate cancer [55,62-66].

4. Actionable molecular alterations

DNA repair alterations are observed in about one fourth of prostate cancer, in which most commonly mutated genes include *BRCA2*, *BRCA1*, and *ATM* [23]. These gene alterations can occur at either a somatic or a germline level [23]. Although the mutations in DNA-repair genes occurred more often in Black men than in White men [28], the germline alterations in DNA-repair genes were identified in 31% of the patients in Asian populations, including mutations in *BRCA2* (5.3%) [67]. The germline mutations in *BRCA1/2* and *ATM* are associated with prostate cancer risk [68], as well as aggressive prostate cancer phenotype [69-74]. Family history of cancer remains a foundation of genetic risk assessment, especially inquiring about prostate cancer as well as non-prostate cancers, including breast, ovary, pancreas, and melanoma, with their known association with mutations in *BRCA1/2*. [75]. *BRCA1/2* and *ATM* are involved in homologous recombination repair. Tumors that lose the homologous recombination pathway are preferentially sensitive to PARP inhibition *via* the mechanism of synthetic lethality [76]. A randomized, phase 3 trial evaluated the PARP inhibitor olaparib in men with mCRPC who had disease progression while receiving a new hormonal agent (*e.g.*, enzalutamide or abiraterone) [11]. Among patients who had at least one alteration in *BRCA1, BRCA2*, or *ATM*, radiological PFS was significantly longer in the olaparib group than in the control group (median 7.4 mo *vs.* 3.6 mo; HR, 0.34; 95% CI, 0.25–0.47; p<0.001) [11].

The solid tumors which harbor deficiency in mismatch repair genes (dMMR), such as *MSH2*, *MSH6*, *PMS2*, and *MLH1*, can be effectively treated by the anti–programmed cell death protein 1 (PD-1) antibody pembrolizumab, regardless of tissue of origin [77]. In 2019, Abida et al [78] reported that 32 of 1,033 patients with prostate cancer (3.1%) had microsatellite instability (MSI)–high or dMMR, of whom 7 (21.9%) carried a germline mutation in a Lynch syndrome–associated gene. The dMMR prostate cancers are associated with higher MSI scores, and enriched for higher T cell infiltration and PDL1 protein expression [79]. Screening for MSI-H/dMMR in advanced prostate cancer is beneficial for identifying patients who have potential for durable responses to anti–PD-1/PD-L1 therapy.

Approximately 40% to 60% of mCRPC tumors have a functional loss of PTEN, a tumor suppressor phosphatase, which causes hyperactivation of the PI3K–Akt–mTOR pathway [13,15]. Ipatasertib (GDC-0068) is a novel selective ATP-competitive small-molecule inhibitor of all three isoforms of Akt. Sensitivity to ipatasertib is associated with high tumoral levels of phosphorylated Akt, PTEN protein loss or genetic mutations, and PIK-3CA kinase domain mutations [80]. In a phase 2 study, combined treatment with abiraterone and ipatasertib showed superior antitumor activity to abiraterone alone in patients with mCRPC, especially in patients with PTEN-loss tumors [12]. A phase 3 trial is ongoing to test the efficiency of ipatasertib plus abiraterone in patients with mCRPC (IPATential150, NCT03072238).

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Table 2. Genomic alterations in liquid biopsy associated with clinical outcome

Author	Year	Sample	Patients	Number of patients	Therapy	Endpoint	Genomic alterations	Outcome
Azad et al [54]	2015	Plasma cfDNA	mCRPC	39	ENZ	c/rPFS	*AR gain/mut*	Median 2.3 mo *vs.* 7.0 mo; p<0.001
Wyatt et al [55]	2016	Plasma cfDNA	mCRPC	65	ENZ	PFS	*AR* gain/amp	HR, 2.92; 95% CI, 1.59-5.37; p=0.001
							Multiple *AR* mut	HR, 3.94; 95% CI, 1.46-10.64; p=0.007
							RB1 loss	HR, 4.46; 95% CI, 2.28-8.74; p<0.001
							MET gain	HR, 4.53; 95% CI, 1.97-10.45; p<0.001
							MYC gain	HR, 2.58; 95% CI, 1.39-4.77; p=0.003
Conteduca et al [56]	2017	Plasma cfDNA and CTC	CRPC	171	ABI or ENZ	PFS	*AR* gain	HR, 2.22; 95% CI, 1.48–3.34; p<0.001
							AR mut	HR, 2.59; 95% CI, 1.24–5.44; p=0.012
						OS	*AR* gain	HR, 4.26; 95% CI, 2.76–6.55; p<0.001
							AR mut	HR, 3.80; 95% CI, 1.77–8.15; p=0.001
				94	ENZ	rPFS	*AR* gain	HR, 8.06; 95% CI, 3.26–19.93; p<0.001
						OS	*AR* gain	HR, 11.08; 95% CI, 2.16–56.95; p=0.004
De Laere et al [60]	2017	Plasma cfDNA and CTC	CRPC	17	ABI or ENZ	PFS	ARVs	HR, 4.53; 95% CI, 1.424–14.41; p=0.0105
Kohli et al [57]	2018	Plasma cfDNA	mCRPC	70	ABI	OS	*AR amp*	HR, 5.25; 95% CI, 2.21-12.46; p=0.0002
Annala et al [62]	2018	Plasma cfDNA	mCRPC	202	ABI or ENZ	PFS	*BRCA2/ATM*	HR, 6.14; 95% CI, 3.35–11.26; p<0.001
							TP53	HR, 2.70; 95% CI, 1.86–3.91; p<0.001
Conteduca et al [61]	2019	Plasma cfDNA	mCRPC	163	DTX	OS	*AR* gain	HR, 1.61; 95% CI, 1.08–2.39; p=0.018
De Laere et al [63]	2019	Plasma cfDNA and CTC	mCRPC	168	ABI or ENZ	PFS	*TP53*	HR, 1.88; 95% CI, 1.18–3.00; p=0.008
Sonpavde et al [64]	2019	Plasma cfDNA	mCRPC	163	N/A	OS	*MYC* amp	HR, 5.85; 95% CI, 2.17-15.77; p<0.001
Fettke et al [58]	2020	Plasma cfDNA/cfRNA	mCRPC	67	ABI, ENZ, DTX, CBT	c/rPFS	*AR* gain	HR, 3.2; 95% CI, 1.3–8.0; p=0.01
						OS	*AR* gain	HR, 2.8; 95% CI, 1.1–7.2; p=0.04
Du et al [59]	2020	Plasma cfDNA	mCRPC	88	ABI	TTTC	*AR* amp	HR, 3.27; 95% CI, 1.78–6.84; p=0.0003
							OPHN1 amp	HR, 3.70; 95% CI, 1.08–7.00; p=0.0002
Ritch et al [65]	2020	Plasma cfDNA	mCSPC	210	ADT	Time to CRPC	dMMR	Median 9.1 mo *vs.* 18.2 mo; p=0.00025
Kohli et al [66]	2020	Plasma cfDNA	mCRPC	69	N/A	OS	*RB1*	HR, 4.2; 95% CI, 2.0-8.7; p=0.00015
			mCSPC	73	N/A	OS	*ATM*, *BRCA1*, *BRCA2*, and *CHEK2*	HR, 4.0; 95% CI, 1.4-11.8; p=0.0000475

cfDNA: cell free DNA, mCRPC: metastatic castration-resistant prostate cancer, ENZ: enzalutamide, c/rPFS: clinical/radiographic progression free survival, HR: hazard ratio, CI: confidence interval, CTC: circulating tumor cell, CRPC: castration-resistant prostate cancer, ABI: abiraterone, OS: overall survival, ARVs: androgen receptor splice variants, DTX: docetaxel, N/A: not applicable, cfRNA: cell free RNA, CBT: cabazitaxel, ADT: androgen deprivation therapy, dMMR: deficiency in mismatch repair genes.

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5. Neuroendocrine prostate cancer

Neuroendocrine prostate cancer is an aggressive variant of prostate cancer, which may arise de novo or in patients who were previously treated with hormonal therapies [81]. A subset of mCRPC tumors show small-cell neuroendocrine features during disease progression on metastatic biopsy [82]. This phenomenon may reflect an epithelial plasticity that enables tumor adaptation in response to AR-targeted therapies [9]. Neuroendocrine prostate cancer is associated with worse OS, even when platinum-based chemotherapy is used [81,83]. In 2016, Beltran et al [9] demonstrated that CRPC with neuroendocrine features (CRPC-NE) is associated with low AR signaling and a paucity of somatic *AR* gene alterations, concurrent loss of *RB1* and *TP53* (in 53.3% of CRPC-NE *vs* 13.7% of CRPC-Adenocarcinoma; $p<0.0004$), changes in DNA methylation profile, and upregulation of mRNA encoding the histone methyltransferase EZH2. There was high concordance between ctDNA and biopsy tissue genomic alterations in patients with CRPC-NE, supporting the use of ctDNA profile to recognize transformation to CRPC-NE during the course of CRPC treatment [84].

6. Clinical utility of genomic profiling

Tumor genomic profiling is a fundamental component of precision medicine, enabling the identification of genomic alterations in genes and pathways that can be targeted therapeutically. In 2017, the U.S. Food and Drug Administration (FDA) approved two comprehensive next generation sequencing panel assays, MSK-IMPACT and FoundationOne CDx [85]. At Memorial Sloan Kettering Cancer Center, MSK-IMPACT was developed and implemented to detect protein-coding mutations, CNAs, and selected promoter mutations and structural rearrangements in 341 (and, more recently, 468) cancer-associated genes [85,86]. FoundationOne CDx, a similar 324 gene assay, was developed to identify actionable genomic aberrations in cancer [85]. For the effective analysis of genomic tests, the quality of tumor tissue samples is crucial. Although formalin-fixed paraffin-embedded blocks obtained from prostate tumor biopsies are widely used to identify clinically actionable molecular alterations, DNA degradation can occur during mid- to long-term storage of samples [87]. Genomic heterogeneity is commonly detected in primary prostate cancer [88-90]. Furthermore, genomic alterations can occur during CRPC progression [16,91]. Thus, a metastatic biopsy provides a reasonable assessment for genomic profiling in patients with mCRPC [92]. In 2020, FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay, was approved by the FDA [93]. This laboratory test can be used as a companion diagnostic tool that can identify if patients with mCRPC harbor *BRCA1/2* alterations which may benefit from treatment with PARP inhibitors [93]. After eliminating clonal hematopoiesis variants, ctDNA was detected in 87.9% of patients with prostate cancer showing its high detectability [94]. Thus, cfDNA-based genomic tests provide a noninvasive approach to elucidate a patient's genomic landscape and actionable information.

CONCLUSIONS

The integrative genomic profiling of prostate tumors has provided comprehensive information and novel discoveries which improve our understanding of the disease. A number of mCRPC harbor clinically actionable molecular alterations, including changes to DNA damage repair pathway and PTEN/PI3K signaling. The genomic alterations of *TP53*, *RB1*, *AR*, and cell cycle pathway are associated with poor clinical outcomes, whereas *SPOP* mutation is associated with better clinical outcomes. Several genomic profiling tests are emerging to identify patients who could benefit from targeted therapy. Thus, the genomic profiling of prostate cancer provides useful information for diagnosis and treatment in this new era of precision medicine.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: KH, NN. Data curation: KH. Formal analysis: KH. Funding acquisition: KH, NN. Investigation: KH. Methodology: KH. Project administration: KH, NN. Resources: KH. Software: KH. Supervision: NN. Validation: KH, NN. Visu-

alization: KH. Writing – original draft: KH. Writing – review & editing: KH, NN.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Abate-Shen C, Shen MM. Molecular genetics of prostate cancer. Genes Dev 2000;14:2410-34.
3. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 2005;310:644-8.
4. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer 2015;15:701-11.
5. Fujita K, Nonomura N. Role of androgen receptor in prostate cancer: a review. World J Mens Health 2019;37:288-95.
6. Quigley DA, Dang HX, Zhao SG, Lloyd P, Aggarwal R, Alumkal JJ, et al. Genomic hallmarks and structural variation in metastatic prostate cancer. Cell 2018;174:758-69.e9.
7. Viswanathan SR, Ha G, Hoff AM, Wala JA, Carrot-Zhang J, Whelan CW, et al. Structural alterations driving castration-resistant prostate cancer revealed by linked-read genome sequencing. Cell 2018;174:433-47.e19.
8. Li Y, Yang R, Henzler CM, Ho Y, Passow C, Auch B, et al. Diverse *AR* gene rearrangements mediate resistance to androgen receptor inhibitors in metastatic prostate cancer. Clin Cancer Res 2020;26:1965-76.
9. Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyrta J, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nat Med 2016;22:298-305.
10. Ku SY, Gleave ME, Beltran H. Towards precision oncology in advanced prostate cancer. Nat Rev Urol 2019;16:645-54.
11. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091-102.
12. de Bono JS, De Giorgi U, Rodrigues DN, Massard C, Bracarda S, Font A, et al. Randomized phase II study evaluating Akt blockade with ipatasertib, in combination with abiraterone, in patients with metastatic prostate cancer with and without PTEN loss. Clin Cancer Res 2019;25:928-36.
13. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, et al. Integrative genomic profiling of human prostate cancer. Cancer Cell 2010;18:11-22.
14. Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011-25.
15. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215-28.
16. Ulz P, Belic J, Graf R, Auer M, Lafer I, Fischereder K, et al. Whole-genome plasma sequencing reveals focal amplifications as a driving force in metastatic prostate cancer. Nat Commun 2016;7:12008.
17. Mayrhofer M, De Laere B, Whitington T, Van Oyen P, Ghysel C, Ampe J, et al. Cell-free DNA profiling of metastatic prostate cancer reveals microsatellite instability, structural rearrangements and clonal hematopoiesis. Genome Med 2018;10:85.
18. Baca SC, Prandi D, Lawrence MS, Mosquera JM, Romanel A, Drier Y, et al. Punctuated evolution of prostate cancer genomes. Cell 2013;153:666-77.
19. Fraser M, Sabelnykova VY, Yamaguchi TN, Heisler LE, Livingstone J, Huang V, et al. Genomic hallmarks of localized, non-indolent prostate cancer. Nature 2017;541:359-64.
20. Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat JP, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet 2012;44:685-9.
21. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2:401-4.
22. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:pl1.
23. Abida W, Armenia J, Gopalan A, Brennan R, Walsh M, Barron D, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017;2017:PO.17.00029.
24. Armenia J, Wankowicz SAM, Liu D, Gao J, Kundra R, Reznik E, et al. The long tail of oncogenic drivers in prostate cancer. Nat Genet 2018;50:645-51.
25. Mateo J, Seed G, Bertan C, Rescigno P, Dolling D, Figueiredo I, et al. Genomics of lethal prostate cancer at diagnosis and castration resistance. J Clin Invest 2020;130:1743-51.
26. van Dessel LF, van Riet J, Smits M, Zhu Y, Hamberg P, van der Heijden MS, et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. Nat Commun 2019;10:5251.
27. Dess RT, Hartman HE, Mahal BA, Soni PD, Jackson WC, Cooperberg MR, et al. Association of black race with pros-

tate cancer-specific and other-cause mortality. JAMA Oncol 2019;5:975-83.
28. Mahal BA, Alshalalfa M, Kensler KH, Chowdhury-Paulino I, Kantoff P, Mucci LA, et al. Racial differences in genomic profiling of prostate cancer. N Engl J Med 2020;383:1083-5.
29. Kimura T. East meets West: ethnic differences in prostate cancer epidemiology between East Asians and Caucasians. Chin J Cancer 2012;31:421-9.
30. Li J, Xu C, Lee HJ, Ren S, Zi X, Zhang Z, et al. A genomic and epigenomic atlas of prostate cancer in Asian populations. Nature 2020;580:93-9.
31. Orikasa K, Fukushige S, Hoshi S, Orikasa S, Kondo K, Miyoshi Y, et al. Infrequent genetic alterations of the PTEN gene in Japanese patients with sporadic prostate cancer. J Hum Genet 1998;43:228-30.
32. Mao X, Yu Y, Boyd LK, Ren G, Lin D, Chaplin T, et al. Distinct genomic alterations in prostate cancers in Chinese and Western populations suggest alternative pathways of prostate carcinogenesis. Cancer Res 2010;70:5207-12.
33. Miyagi Y, Sasaki T, Fujinami K, Sano J, Senga Y, Miura T, et al. ETS family-associated gene fusions in Japanese prostate cancer: analysis of 194 radical prostatectomy samples. Mod Pathol 2010;23:1492-8.
34. Hieronymus H, Schultz N, Gopalan A, Carver BS, Chang MT, Xiao Y, et al. Copy number alteration burden predicts prostate cancer relapse. Proc Natl Acad Sci U S A 2014;111:11139-44.
35. Wang L, Dehm SM, Hillman DW, Sicotte H, Tan W, Gormley M, et al. A prospective genome-wide study of prostate cancer metastases reveals association of wnt pathway activation and increased cell cycle proliferation with primary resistance to abiraterone acetate-prednisone. Ann Oncol 2018;29:352-60.
36. Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A 2019;116:11428-36.
37. Chen WS, Aggarwal R, Zhang L, Zhao SG, Thomas GV, Beer TM, et al.; West Coast Prostate Cancer Dream Team. Genomic drivers of poor prognosis and enzalutamide resistance in metastatic castration-resistant prostate cancer. Eur Urol 2019;76:562-71.
38. Stopsack KH, Nandakumar S, Wibmer AG, Haywood S, Weg ES, Barnett ES, et al. Oncogenic genomic alterations, clinical phenotypes, and outcomes in metastatic castration-sensitive prostate cancer. Clin Cancer Res 2020;26:3230-8.
39. Deek MP, Van der Eecken K, Phillips R, Parikh NR, Isaacsson Velho P, Lotan TL, et al. The mutational landscape of metastatic castration-sensitive prostate cancer: the spectrum theory revisited. Eur Urol 2021. doi: 10.1016/j.eururo.2020.12.040 [Epub ahead of print].
40. Hamid AA, Gray KP, Shaw G, MacConaill LE, Evan C, Bernard B, et al. Compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors in localized and metastatic prostate cancer. Eur Urol 2019;76:89-97.
41. Boysen G, Rodrigues DN, Rescigno P, Seed G, Dolling D, Riisnaes R, et al. SPOP-mutated/CHD1-deleted lethal prostate cancer and abiraterone sensitivity. Clin Cancer Res 2018;24:5585-93.
42. Swami U, Isaacsson Velho P, Nussenzveig R, Chipman J, Sacristan Santos V, Erickson S, et al. Association of SPOP mutations with outcomes in men with de novo metastatic castration-sensitive prostate cancer. Eur Urol 2020;78:652-6.
43. An J, Wang C, Deng Y, Yu L, Huang H. Destruction of full-length androgen receptor by wild-type SPOP, but not prostate-cancer-associated mutants. Cell Rep 2014;6:657-69.
44. Wyatt AW, Annala M, Aggarwal R, Beja K, Feng F, Youngren J, et al. Concordance of circulating tumor DNA and matched metastatic tissue biopsy in prostate cancer. J Natl Cancer Inst 2017;109:djx118.
45. Ramesh N, Sei E, Tsai PC, Bai S, Zhao Y, Troncoso P, et al. Decoding the evolutionary response to prostate cancer therapy by plasma genome sequencing. Genome Biol 2020;21:162.
46. Faugeroux V, Lefebvre C, Pailler E, Pierron V, Marcaillou C, Tourlet S, et al. An accessible and unique insight into metastasis mutational content through whole-exome sequencing of circulating tumor cells in metastatic prostate cancer. Eur Urol Oncol 2020;3:498-508.
47. Fan L, Fei X, Zhu Y, Pan J, Sha J, Chi C, et al. Comparative analysis of genomic alterations across castration sensitive and castration resistant prostate cancer via circulating tumor DNA sequencing. J Urol 2021;205:461-9.
48. Heitzer E, Ulz P, Belic J, Gutschi S, Quehenberger F, Fischereder K, et al. Tumor-associated copy number changes in the circulation of patients with prostate cancer identified through whole-genome sequencing. Genome Med 2013;5:30.
49. Vandekerkhove G, Struss WJ, Annala M, Kallio HML, Khalaf D, Warner EW, et al. Circulating tumor DNA abundance and potential utility in de novo metastatic prostate cancer. Eur Urol 2019;75:667-75.
50. Belic J, Graf R, Bauernhofer T, Cherkas Y, Ulz P, Waldispuehl-Geigl J, et al. Genomic alterations in plasma DNA from patients with metastasized prostate cancer receiving abiraterone or enzalutamide. Int J Cancer 2018;143:1236-48.
51. Choudhury AD, Werner L, Francini E, Wei XX, Ha G, Freeman SS, et al. Tumor fraction in cell-free DNA as a biomarker in prostate cancer. JCI Insight 2018;3:e122109.
52. Goodall J, Mateo J, Yuan W, Mossop H, Porta N, Miranda S,

et al.; TOPARP-A investigators. Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition. Cancer Discov 2017;7:1006-17.
53. Sumiyoshi T, Mizuno K, Yamasaki T, Miyazaki Y, Makino Y, Okasho K, et al. Clinical utility of androgen receptor gene aberrations in circulating cell-free DNA as a biomarker for treatment of castration-resistant prostate cancer. Sci Rep 2019;9:4030.
54. Azad AA, Volik SV, Wyatt AW, Haegert A, Le Bihan S, Bell RH, et al. Androgen receptor gene aberrations in circulating cell-free DNA: biomarkers of therapeutic resistance in castration-resistant prostate cancer. Clin Cancer Res 2015;21:2315-24.
55. Wyatt AW, Azad AA, Volik SV, Annala M, Beja K, McConeghy B, et al. Genomic alterations in cell-free DNA and enzalutamide resistance in castration-resistant prostate cancer. JAMA Oncol 2016;2:1598-606.
56. Conteduca V, Wetterskog D, Sharabiani MTA, Grande E, Fernandez-Perez MP, Jayaram A, et al. Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study. Ann Oncol 2017;28:1508-16.
57. Kohli M, Li J, Du M, Hillman DW, Dehm SM, Tan W, et al. Prognostic association of plasma cell-free DNA-based androgen receptor amplification and circulating tumor cells in pre-chemotherapy metastatic castration-resistant prostate cancer patients. Prostate Cancer Prostatic Dis 2018;21:411-8.
58. Fettke H, Kwan EM, Docanto MM, Bukczynska P, Ng N, Graham LK, et al. Combined cell-free DNA and RNA profiling of the androgen receptor: clinical utility of a novel multianalyte liquid biopsy assay for metastatic prostate cancer. Eur Urol 2020;78:173-80.
59. Du M, Tian Y, Tan W, Wang L, Wang L, Kilari D, et al. Plasma cell-free DNA-based predictors of response to abiraterone acetate/prednisone and prognostic factors in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 2020;23:705-13.
60. De Laere B, van Dam PJ, Whitington T, Mayrhofer M, Diaz EH, Van den Eynden G, et al. Comprehensive profiling of the androgen receptor in liquid biopsies from castration-resistant prostate cancer reveals novel intra-AR structural variation and splice variant expression patterns. Eur Urol 2017;72:192-200.
61. Conteduca V, Jayaram A, Romero-Laorden N, Wetterskog D, Salvi S, Gurioli G, et al. Plasma androgen receptor and docetaxel for metastatic castration-resistant prostate cancer. Eur Urol 2019;75:368-73.
62. Annala M, Vandekerkhove G, Khalaf D, Taavitsainen S, Beja K, Warner EW, et al. Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Discov 2018;8:444-57.
63. De Laere B, Oeyen S, Mayrhofer M, Whitington T, van Dam PJ, Van Oyen P, et al. TP53 outperforms other androgen receptor biomarkers to predict abiraterone or enzalutamide outcome in metastatic castration-resistant prostate cancer. Clin Cancer Res 2019;25:1766-73.
64. Sonpavde G, Agarwal N, Pond GR, Nagy RJ, Nussenzveig RH, Hahn AW, et al. Circulating tumor DNA alterations in patients with metastatic castration-resistant prostate cancer. Cancer 2019;125:1459-69.
65. Ritch E, Fu SYF, Herberts C, Wang G, Warner EW, Schönlau E, et al. Identification of hypermutation and defective mismatch repair in ctDNA from metastatic prostate cancer. Clin Cancer Res 2020;26:1114-25.
66. Kohli M, Tan W, Zheng T, Wang A, Montesinos C, Wong C, et al. Clinical and genomic insights into circulating tumor DNA-based alterations across the spectrum of metastatic hormone-sensitive and castrate-resistant prostate cancer. EBioMedicine 2020;54:102728.
67. Wu J, Wei Y, Pan J, Jin S, Gu W, Gan H, et al. Prevalence of comprehensive DNA damage repair gene germline mutations in Chinese prostate cancer patients. Int J Cancer 2021;148:673-81.
68. Momozawa Y, Iwasaki Y, Hirata M, Liu X, Kamatani Y, Takahashi A, et al. Germline pathogenic variants in 7636 Japanese patients with prostate cancer and 12 366 controls. J Natl Cancer Inst 2020;112:369-76.
69. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-57.
70. Decker B, Karyadi DM, Davis BW, Karlins E, Tillmans LS, Stanford JL, et al. Biallelic BRCA2 mutations shape the somatic mutational landscape of aggressive prostate tumors. Am J Hum Genet 2016;98:818-29.
71. Na R, Zheng SL, Han M, Yu H, Jiang D, Shah S, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2017;71:740-7.
72. Mijuskovic M, Saunders EJ, Leongamornlert DA, Wakerell S, Whitmore I, Dadaev T, et al. Rare germline variants in DNA repair genes and the angiogenesis pathway predispose prostate cancer patients to develop metastatic disease. Br J Cancer 2018;119:96-104.

73. Castro E, Romero-Laorden N, Del Pozo A, Lozano R, Medina A, Puente J, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2019;37:490-503.
74. Wei Y, Wu J, Gu W, Wang J, Lin G, Qin X, et al. Prognostic value of germline DNA repair gene mutations in de novo metastatic and castration-sensitive prostate cancer. Oncologist 2020;25:e1042-50.
75. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. J Natl Compr Canc Netw 2019;17:515-21.
76. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science 2017;355:1152-8.
77. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
78. Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Vargas HA, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol 2019;5:471-8.
79. Nava Rodrigues D, Rescigno P, Liu D, Yuan W, Carreira S, Lambros MB, et al. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. J Clin Invest 2018;128:4441-53.
80. Lin J, Sampath D, Nannini MA, Lee BB, Degtyarev M, Oeh J, et al. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res 2013;19:1760-72.
81. Conteduca V, Oromendia C, Eng KW, Bareja R, Sigouros M, Molina A, et al. Clinical features of neuroendocrine prostate cancer. Eur J Cancer 2019;121:7-18.
82. Aggarwal R, Huang J, Alumkal JJ, Zhang L, Feng FY, Thomas GV, et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. J Clin Oncol 2018;36:2492-503.
83. Wang HT, Yao YH, Li BG, Tang Y, Chang JW, Zhang J. Neuroendocrine Prostate Cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from NEPC diagnosis-a systematic review and pooled analysis. J Clin Oncol 2014;32:3383-90.
84. Beltran H, Romanel A, Conteduca V, Casiraghi N, Sigouros M, Franceschini GM, et al. Circulating tumor DNA profile recognizes transformation to castration-resistant neuroendocrine prostate cancer. J Clin Invest 2020;130:1653-68.
85. Allegretti M, Fabi A, Buglioni S, Martayan A, Conti L, Pescarmona E, et al. Tearing down the walls: FDA approves next generation sequencing (NGS) assays for actionable cancer genomic aberrations. J Exp Clin Cancer Res 2018;37:47.
86. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23:703-13.
87. Guyard A, Boyez A, Pujals A, Robe C, Tran Van Nhieu J, Allory Y, et al. DNA degrades during storage in formalin-fixed and paraffin-embedded tissue blocks. Virchows Arch 2017;471:491-500.
88. Boutros PC, Fraser M, Harding NJ, de Borja R, Trudel D, Lalonde E, et al. Spatial genomic heterogeneity within localized, multifocal prostate cancer. Nat Genet 2015;47:736-45.
89. Espiritu SMG, Liu LY, Rubanova Y, Bhandari V, Holgersen EM, Szyca LM, et al. The evolutionary landscape of localized prostate cancers drives clinical aggression. Cell 2018;173:1003-13.e15.
90. Løvf M, Zhao S, Axcrona U, Johannessen B, Bakken AC, Carm KT, et al. Multifocal primary prostate cancer exhibits high degree of genomic heterogeneity. Eur Urol 2019;75:498-505.
91. Carreira S, Romanel A, Goodall J, Grist E, Ferraldeschi R, Miranda S, et al. Tumor clone dynamics in lethal prostate cancer. Sci Transl Med 2014;6:254ra125.
92. Kumar A, Coleman I, Morrissey C, Zhang X, True LD, Gulati R, et al. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. Nat Med 2016;22:369-78.
93. Foundation Medicine. FoundationOne® Liquid CDx: technical information [Internet]. Cambridge (MA): Foundation Medicine; c2020 [cited 2021 Apr 30]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032C.pdf.
94. Zhang Y, Yao Y, Xu Y, Li L, Gong Y, Zhang K, et al. Pan-cancer circulating tumor DNA detection in over 10,000 Chinese patients. Nat Commun 2021;12:11.