Assessment of biochemical recurrence of prostate cancer (Review)

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Abstract. The assessment of the risk of biochemical recurrence (BCR) is critical in the management of males with prostate cancer (PC). Over the past decades, a comprehensive effort has been focusing on improving risk stratification; a variety of models have been constructed using PC-associated pathological features and molecular alterations occurring at the genome, protein and RNA level. Alterations in RNA expression (lncRNA, miRNA and mRNA) constitute the largest proportion of the biomarkers of BCR. In this article, we systemically review RNA-based BCR biomarkers reported in PubMed according to the PRISMA guidelines. Individual miRNAs, mRNAs, lncRNAs and multi-gene panels, including the commercially available signatures, Oncotype DX and Prolaris, will be discussed; details related to cohort size, hazard ratio and 95% confidence intervals will be provided. Mechanistically, these individual biomarkers affect multiple pathways critical to tumorigenesis and progression, including epithelial-mesenchymal transition (EMT), phosphatase and tensin homolog (PTEN), Wnt, growth factor receptor, cell proliferation, immune checkpoints and others. This variety in the mechanisms involved not only validates their associations with BCR, but also highlights the need for the coverage of multiple pathways in order to effectively stratify the risk of BCR. Updates of novel biomarkers and their mechanistic insights are considered, which suggests new avenues to pursue in the prediction of BCR. Additionally, the management of patients with BCR and the potential utility of the stratification of the risk of BCR in salvage treatment decision making for these patients are briefly covered. Limitations will also be discussed.

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Contents

1. Introduction
2. Stratification of BCR risk: An update
3. Searching methods for RNA-based BCR biomarkers
4. Gene expression-based biomarkers
5. Management of patients with biochemical recurrence
6. Perspectives

1. Introduction

Prostate cancer (PC) is the most commonly diagnosed cancer affecting males in developed countries and a major cause of cancer-related mortality among males (1). The disease is highly heterogeneous and progresses with a large degree of disparity. PC evolves from high-grade prostatic intra-epithelial neoplasia (HGPIN) to local carcinoma; some local tumors will develop into metastatic disease with bone as the preferential site (2). Primary tumors are managed through watchful waiting (active surveillance) and curative therapies: Radical prostatectomy (RP) or radiation therapy (RT) (3-6). The disease may relapse in the form of biochemical recurrence (BCR) with elevations in serum prostate-specific antigen (PSA) levels of >0.2 ng/ml following RP and >2 ng/ml above the nadir following RT (7). Approximately 30% (20-40%) of patients following RP (8-10) and 30-50% of males treated with RT will experience BCR (11,12) within 10 years posy-therapy. BCR represents a major progression and is associated with a significantly increased risk of PC metastasis; 24-34% of patients with BCR will develop metastasis (13,14). The standard treatment for metastatic PC remains androgen deprivation therapy (ADT); however it is largely a palliative care as metastatic castration-resistant PCs (mCRPCs) commonly develop (15). Although multiple treatment options are

currently available for mCRPCs, these therapies only marginally prolong the median overall survival (OS) and resistance develops rapidly. This is the major challenge with therapies targeting mCRPCs using docetaxel (16,17) or the second generation anti-androgens (abiraterone and enzalutamide) approved by the FDA in 2011 and 2012 (18,19). Collectively, with this knowledge of PC development and the current limitations in treating metastasis, the most beneficial management of prostate cancer is through the accurate stratification of patients with PC with a low risk of BCR progression from those with a high risk. This capacity of BCR risk stratification is of particular relevance to patients with low- and intermediate-risk PCs; low-risk and intermediate-risk PCs are defined by the European Association of Urology (EAU)-European Society for Radiotherapy and Oncology (ESTRO)-International Society of Geriatric Oncology (SIOG) as PSA <10 ng/ml, Gleason score (GS) <7, cT1-2a, and localized (low risk) and PSA levels of 10-20 ng/ml or GS 7 or cT2c and localized (intermediate risk) (3).

The current stratification of the risk of BCR in clinical practice remains poor; improvement in this capacity remains a major focus of the research community. Attributing to this massive effort and the involvement of complex networks affecting BCR progression, there are enriched data for BCR risk classification for localized tumors following primary curative treatments, particularly RP. The risk stratification is based on two general aspects of PC: Clinical characteristics and molecular properties or biomarkers. The latter includes alterations in gene expression at both the gene and protein level. Due to the overwhelming amount (search for 'prostate cancer AND biomarkers AND biochemical recurrence' in PubMed resulted in 2,500 articles) and the heterogeneity of the data, in this review, we focus on RNA-based biomarkers, which can be effective in nature. We also briefly discuss other types of BCR biomarkers to make this review comprehensive.

2. Stratification of BCR risk: An update

Assessment of BCR risk using clinical information. The clinical and tumor characteristics have long been investigated for the estimation of the risk of BCR. By using pre-treatment PSA, the GS, clinical T stage, the percentage of biopsy cores positive for cancer, and age in 1,493 patients treated with RP between 1992 and 2001, the University of California, San Francisco Cancer of the Prostate Risk Assessment (UCSF-CAPRA or CAPRA) was developed in 2005 to appraise the BCR risk; this is a score system with scale of 0-10 and higher scores represent a higher risk of BCR (20). Up to 2017, CAPRA has been validated on BCR risk stratification following RP and RT by 12 investigations carried out in the USA, Germany, Japan, Australia, Korea and Canada; these studies involved a total of 17,457 patients and demonstrated that CAPRA classifies the risk of BCR with a concordance index (c-index) ranging from 0.67 to 0.81 (20). The status of CAPRA has recently been updated by Brajtbord *et al* (21); the modified version, CAPRA-S, was subsequently developed by the same group in 2011 and independently validated (21,22). Prior to CAPRA, the D'Amico classification of the risk of BCR was generated by D'Amico *et al* in 1998 (23). The CAPRA score system seems superior to the D'Amico classification (21).

While approximately 30% of males undergoing RP will experience BCR within 10 years (8-10), two-thirds of these recurrences occur during the first 2 years (24-26). Early recurrence is associated with a higher risk of metastasis (27,28). To assess early BCR, the Walz nomogram was constructed in 2009 (29), which has recently been updated with 13,797 patients who had undergone radical prostatectomy from Hamburg (2005-2016) and validated using 5,952 males treated with RP in Vienna (30). The validation using the Vienna dataset revealed the best estimation of BCR risk by the updated nomogram in comparison to the Walz nomogram, MSKCC nomogram, and CAPRA-S (30). The nomogram estimates BCR risk at 12 and 24 months post-RP based on PSA, GS, pT stage, surgical margin status and lymph node status (30).

Stratification of BCR risk based on protein expression. Abnormalities in the regulation of cell proliferation are typical of cancer (31). Of note, alterations in the expression levels of proteins related to cell cycle regulation have been extensively examined for biomarker values in the classification of the BCR risk. These proteins include Ki-67, MYC, ETS-related gene (ERG), as well as the tumor suppressors phosphatase and tensin homolog (PTEN) and p53; their biomarker potentials have recently been reviewed (32,33). In brief, Ki-67 is an established cell proliferation marker (34) with increases in its expression being associated with adverse features of PC (33); however, its association with BCR remains uncertain (35).

MYC plays multiple roles in tumorigenesis, which includes the regulation of cancer metabolism (36,37). It is upregulated in PC (38) and contributes to PC progression in part via telomerase overexpression and the loss of PTEN (39,40). While increases in MYC protein expression are associated with higher a GS and T-stage, an association between MYC and BCR remains unclear (33).

The overexpression of ERG in PC results from the fusion of the androgen target gene transmembrane serine protease 2 (*TMPRSS2*) with ERG (*TMPRSS2-ERG*) (41). The ERG protein can be detected in PC by immunohistochemistry (IHC) (42). In a systemic review, the overexpression of the ERG protein was shown to be modestly associated with BCR with P-values of 0.04, 0.006, or 0.002 (33).

In a study of 52 males with PC, an association of p53 expression with BCR was demonstrated (P=00097) (43), which was corroborated by another small cohort involving 86 patients with PC (P<0.01) (44). Collectively, IHC-detected p53 protein expression is associated with BCR (33). In a systemic review published in 2018 on the IHC-based detection of BCR (33), the loss of PTEN was found to be associated with BCR in 8 investigations.

Nonetheless, while IHC-detected protein expression can display significant associations with BCR, the associations are modest in most cases and their applications in clinical practice are limited. This is likely attributed to the limited number of proteins that can be simultaneously detected by IHC; the examination of the expression status of a panel of proteins or signatures consisting of multiple factors is critical to effectively stratify the risk of BCR.

Genomic alteration-based biomarkers. While the impact of genomic alterations on PC progression will not be covered

in this review, it is important to summarize the recent developments related to the impact of germline mutations on PC progression. A family history is a well-recognized risk factor of PC (45); nonetheless, hereditary PCs, which constitute approximately 9% of all PCs, do not differ from spontaneous PCs based on the 2016 EAU-ESTRO-SIOG guidelines (3). Thus, it was generally accepted that germline mutations do not promote PC progression and are thus without prognostic value. The exception was first observed with BRCA2 germline mutations that increase the incidence of PC along with the risk of PC progression (46,47); these mutations drive the evolvement of PC by causing genomic instability (48). In line with this concept, germline mutations in other factors regulating the DNA damage response (DDR) also increase the risk of PC progression, including ATM, CHEK2, BRCA1, RAD51D and PALB2 (49). The observation that BRCA1/2 germline mutations are associated with the risk of PC and PC progression provides additional support for the similarities between PC and breast cancer. This is consistent with a recent study demonstrating that PCs can be grouped into PAM50-based luminal A and luminal B subtypes (50), the well-known subtypes of estrogen receptor-positive breast cancer (51).

It will thus be of interest to investigate the contributions of mutations in BRCA2, ATM, CHEK2, BRCA1, RAD51D and PALB2 in a variety of combinations in the assessment of the risk of BCR. Of note, genomic alterations in 9 DDR pathways involving 17 gene sets are able to classify the risk of BCR [population size, n=545; hazard ratio (HR), 1.89; 95% confidence interval (95% CI), 1.44-2.48; P=5.01e-6] (52).

Among the PC-associated genomic abnormalities, the *TMPRSS2-ERG* fusion is the most common event; it occurs in approximately 50% of Caucasian Americans, 31% of African Americans (53) and 18.5% of Asians (54). While the fusion gene is modestly associated with T-stage [T3-T4 vs. T1-T2; odds ratio (OR), 1.4; 95% CI, 1.33-1.48] and metastasis (M1 vs. M0; OR, 1.35; 95% CI, 1.02-1.78), *TMPRSS2-ERG* is not associated with BCR (55). Collectively, the current evidence does not support genomic alterations being robust predictors in the assessment of the risk of BCR.

3. Searching methods for RNA-based BCR biomarkers

In accordance with the PRISMA guidelines (56,57), we performed a systemic literature search through the PubMed database using the terms 'prostate cancer' AND 'biomarker' AND 'gene expression' AND 'biochemical recurrence'. A total of 258 manuscripts were retrieved. We examined all abstracts and eliminated those i) with population sizes (tumor + non-tumor tissues) <100 cases; ii) that focus on DNA methylation and epigenetic regulation without a clear examination of gene expression; iii) that primarily use the immunohistochemistry approach; iv) those yielding values of P≥0.05. We thus selected and discussed 50 articles in this review (Fig. 1). These papers cover two general aspects of RNA-based biomarkers: mRNAs and microRNAs (miRNAs or miRs).

In light of the important function of long non-coding RNAs (lncRNAs) in preventing miRNA-mediated mRNA degradation via competing or sponging, we also discuss the association of lncRNAs with BCR.

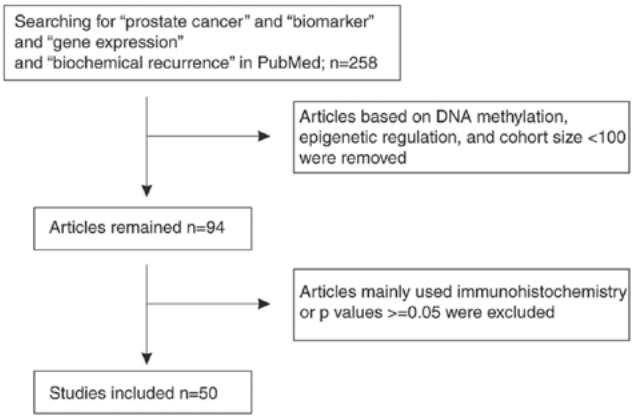

Figure 1. Systemic literature searching conditions and selection of articles for the review.

4. Gene expression-based biomarkers

miRNA-based biomarkers for the stratification of BCR risk. Alterations in individual miRNAs have been observed to be associated with BCR (Table I). In a total of 585 patients consisting of 388 non-recurrences and 197 recurrences, using the median expression level as the cut-off point, PCs with high levels of miR-301a were found to be at risk of BCR progression with an adjusted HR of 1.42 (P=0.002) (58). PCs positive for miR-21, defined by its median expression level, were also found to be associated with a rapid kinetic of BCR (59). Upregulations in the levels of miR-128 (60) and 130b (61) have also been found to be associated with a reduction in BCR-free survival (Table I). Downregulations in the expression of miR-30C (62), miR-145 (63), miR-195 (64) and miR-16 (64) facilitate BCR development (Table I).

These miRNAs affect BCR by regulating different pathways (Fig. 2), a concept that is consistent with the involvement of complex pathways in BCR occurrence. miR-301a likely promotes the recurrence of PC at least in part via the induction of epithelial-mesenchymal transition (EMT), evidence by the downregulation of E-cadherin in LNCaP cells overexpressing miR-301a (58). EMT is a major mechanism contributing to cancer stem cells (CSCs) (65). Cumulative evidence supports an essential role of CSCs in cancer progression, including PC (66). miR-21 reduces PTEN expression with the concurrent upregulation of PI3K and AKT, suggesting its role in inhibiting PTEN function in PC (67). miR-30c downregulates EMT by inhibiting the Snail-TGF-β1 connection in other settings (68) and is reduced in PC (69); miR-145 is a tumor suppressor (70) and is downregulated in PC (71,72). Both miR-195 and miR-16 inhibit programmed death-1 ligand 1 (PD-L1) expression, and thus downregulate PD-L1-mediated actions of immune checkpoints (64); reductions of either likely promote BCR.

Importantly, individual miRNAs commonly regulate multiple targets (73). This information may enhance the biomarker values of miRNAs, as BCR is certainly regulated by complex networks; however, it may also attenuate their biomarker potential if individual targets have different effects on BCR. For instance, by a functional screening of 1,129 miRNAs for their effects on the proliferation, viability and the apoptosis of 5 PC cell lines, miR-130b was among the

Table I. Associations of individual miRNAs with BCR defined by univariate Cox analysis.

Identity	Cohort size (n)	Follow-up	HR (95% CI)	P-value	(Refs.)
miR-301a[b]	585	180 M	1.42 (1.06-1.90)	0.002	(58)
miR-21[b]	169	84 M	NA	<0.001	(59)
miR-128[c]	128	100 M	3.96 (1.02-8.12)	<0.001	(60)
miR-30c[c]	103	125 M	0.31(0.19-0.51)	<0.001	(62)
miR-145[c]	137	72 M	3.21 (1.07-9.62)[a]	0.007	(63)
miR-195[c]	131	150 M	NA	0.0092	(64)
miR-16[c]	131	150 M	NA	0.0031	(64)
miR-130b[c]	188	120 M	NA	0.004	(61)

[a]Hazard ratio (HR) was determined on mi-R145 downregulations; [b]increases and [c]decreases in expression associated with BCR. M, months; CI, confidence interval; NA, not available; BCR, biochemical recurrence.

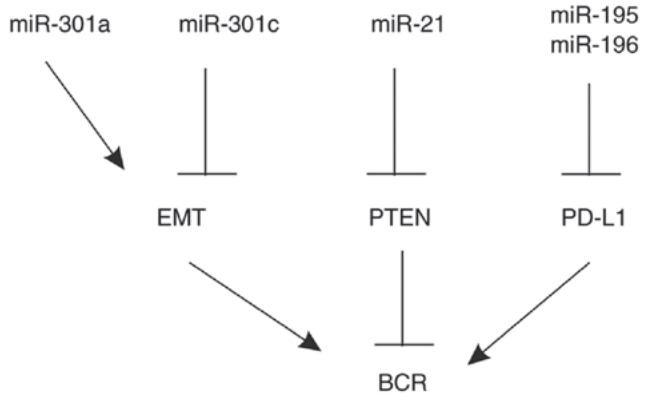

Figure 2. MicroRNAs affecting BCR through multiple pathways. BCR, biochemical recurrence; EMT, epithelial-mesenchymal transition; PTEN, phosphatase and tensin homolog; PD-L1, programmed death-1 ligand 1.

14 miRNAs selected from the screen; it affects cell proliferation and is the only miRNA exhibiting an association with a reduction in BCR-free survival (Table I) (61). The number of predicted targets for miR-130b is approaching 600 with approximately one-third being upregulated (61). Among the two most frequently affected genes, *GLYATL1* was upregulated and *PARVA* was downregulated; and only decreases in PARVA expression are associated with the occurrence of BCR, which is consistent with the effect of miR-130b on BCR (61). The numerous downstream effectors of these miRNAs may contribute to their ineffectiveness in the classification of the risk of BCR (Table I); this limitation should be considered when using miRNAs for the assessment of the risk of BCR.

Single mRNA-based biomarkers. Progression to BCR is regulated by multiple pathways, including Wnt signaling (74), cell proliferation regulations (75), the inhibition of immune checkpoints (76,77) and others. The secreted frizzled-related protein 4 (SFRP4) regulates Wnt signaling and displays oncogenic properties in PC (78). In a study of 9 cohorts, elevations in SFRP4 mRNA expression were found to be a risk factor for BCR in 7 cohorts of 1,404 patients with the HR ranging from 1.3-2.18 (Table II); however in 2 cohorts (patients, n=374), SFRP4 was not found to be significantly associated with BCR (79). In another investigation of 536 males with PC, the increase in SFRP4 expression was found to be associated with BCR (HR, 1.35; P=0.009) (80).

The AXIN2 protein plays a role in canonical Wnt signaling (81) and is expressed in tissue stem cells and CSCs (82-84). The single nucleotide polymorphism (guanine/adenine) rs2240308 is associated with a decrease in the risk of PC (OR, 0.377; 95% CI, 0.206-0.688; P=0.001) (85). Of note, the downregulation of AXIN2 mRNA expression has been found to be a risk factor of BCR (Table II) (86).

An increase in platelet-derived growth factor receptor (PDGFR)-β expression in the stroma significantly enhances BCR (Table II) (87). An elevated stromal PDGFR-β expression has been shown to be associated with a poor prognosis in both breast and prostate cancer (88).

The downregulation of metallothionein 1E (MT1E) is a risk factor for BCR in association with promoter methylation (89). MT1E belongs to the metallothionein (MT) family consisting of cysteine-rich small proteins that regulate metal homeostasis (90). In addition to PC, MT1E is also downregulated in endometrial carcinoma (91), intrahepatic cholangiocarcinoma (92), melanoma (93), non-small cell lung cancer (94), papillary thyroid carcinoma (95) and renal cell carcinoma (96); in the majority of these cancer types, the reductions are associated with hypermethylation (90). However, the upregulation of MT1E has been reported in estrogen receptor-negative breast cancer (97) and it also facilitates glioma progression (98,99).

Increases in KLK15 mRNA expression predict BCR (Table II) (100). KLK15 is a member of kallikrein-related peptidases with KLK3 being the most well-known PSA. KLK15 has been reported to exhibit biomarker value in ovarian, breast, prostate and testicular cancer (101).

An elevation in neuropilin-1 (NRP1) mRNA expression is associated with BCR following RT (Table II) (102). This transmembrane glycoprotein can activate PDGFR-β (103) and contributes to the stemness of breast CSCs via the activation of Wnt signaling (104). NRP1 has been reported to be upregulated in PC (105) and may contribute to BCR in part through the regulation of endothelial cell functions (106).

Table II. Associations of individual mRNAs with BCR defined by Cox analysis.

mRNAs	Patients (n)	Pathways	HR (95% CI)	P-value	(Refs.)
SFRP4[a]	1,404+536	Wnt	1.3-2.18[c]	0.022-1.88e-7[c]	(79,80)
AXIN2[b]	951	Wnt	0.13 (0.02-0.67)[d]	0.02	(86)
PDGFR-β[a]	535	Proliferation	1.58 (1.18-2.13)	0.002	(87)
MT1E[b]	108	Metal homeostasis	NA	<0.001	(89)
KLK15[a]	150	Serine protease	3.44 (1.35-8.75)	0.01	(100)
NRP1[a]	130	Androgen signaling	NA	0.0002	(102)
SAMD5[a]	345	NA	2.18 (1.20-3.97)	0.011	(107)
SMAD4[b]	140	TGF-β	4.61 (2.15-9.89)	<0.001	(113)
PLAGL2[a]	104	Wnt	3.97 (1.21-13.00)	0.023	(114)
PD-L2[a]	9,393	Immune checkpoint	1.17 (1.03-1.33)	0.01	(119)
RNase k[b]	111	RNA metabolism	0.85 (0.77-0.91)	0.002	(120)
GLTSCR1[a]	499	Chromatin remodeling	2.28 (1.28-4.05)	0.005	(122)
BChE[a]	385	Hydrolyzing ghrelin and bioactive esters	NA	0.008-0.04[c]	(125)

[a] and [b], increases and decreases in expression are associated with BCR, respectively; [c]range of HR or p-values; [d]odds ratio (97.5% CI). HR, hazard ratio; NA, not available; BCR, biochemical recurrence.

Increases in sterile alpha motif domain containing 5 (SAMD5) mRNA expression display biomarker values in predicting BCR (Table II) (107). SAMD5 facilitates small cell lung cancer cell proliferation (108), is upregulated in cholangiocarcinoma (109) and is associated with the response to chemotherapy in rectal cancer (110). SAMD5 facilitates the Eph receptor tyrosine kinase signaling (111), suggesting a mechanism mediating SAMD5 oncogenic potential and its association with BCR.

Consistent with SMAD4 as a tumor suppressor in the inhibition of PTEN inactivation-induced PC progression (112), a reduction in SMAD4 mRNA expression enhances the risk of BCR (113).

The downregulation of pleomorphic adenoma gene like-2 (PLAGL2) mRNA expression is a risk factor of BCR (114). PLAGL2 is a transcription factor that has been shown to activate Wnt/β-catenin signaling through unidentified mechanisms in colorectal cancer (115) and gliomas (116). PLAGL2 also contributes to hematopoietic tumorigenesis (117,118); however, its involvement in PC has not yet been fully investigated.

In an analysis of 7,826 prospectively collected RP tissues and 1,567 retrospectively obtained samples, while PD-L1 did not exhibit prognostic values, an increase in PD-L2 expression was associated with a decrease in BCR-free survival (Table II), distant-free metastasis survival (HR, 1.25; 95% CI, 1.05-1.49; P=0.01) and PC-specific survival (HR, 1.45; 95% CI, 1.13-1.86; P=0.003) (119). These observations are in line with the actions of the immune checkpoint in the downregulation of immunoresponses to cancers. Nonetheless, these associations are not particularly robust.

RNase khas been shown to be downregulated in PC (n=111) in comparison to benign prostatic hyperplasia (BPH); the downregulation was associated with BCR (Table II) (120). The contributions of RNase k to tumorigenesis in general remain unclear (121).

An upregulation of glioma tumor suppressor candidate region gene 1 (GLTSCR1) in PC vs. normal prostate tissues has been reported; the upregulation is a risk factor of BCR (122). Evidence suggests an oncogenic role of GLTSCR1 in oligodendrogliomas (123). Although the functionality of GLTSCR1 in tumorigenesis remains unclear, recent evidence indicates its role in chromatin remodeling (124), implying GLTSCR1 may contribute to BCR progression via epigenetic regulations.

Butyrylcholinesterase (BChE) was recently reported to display a biphasic alteration in PCs in both the MSKCC (n=140) and TCGA (n=245) databases; elevations in BChE mRNA expression have been shown to be associated with BCR in both cohorts (P=0.008 for MSKCC and P=0.04 for TCGA) (Table II) (125). BChE has been shown to hydrolyze butyrylcholine (126), succinylcholine (127) and ghrelin (the hunger hormone) (128-131), and thus may play a role in PC metabolism.

Collectively, the above individual mRNAs stratify BCR risk through different pathways, including the Wnt pathway, growth factor receptor-mediated cell proliferation, androgen signaling, cytokines, immune checkpoints, RNA metabolism and others (Table II). While this is in accordance with the complex nature of BCR progression, it also reveals the challenge of using individual mRNA to effectively predict BCR risk and the calls for developing multigene sets or signatures for assessing BCR development.

Multigene sets of mRNAs in assessing BCR risk. To enhance the accuracy of predicting BCR risk, there have been numerous efforts made towards the construction of multigene panels; the rapid accumulation of cancer genomic data owing to technology advances in DNA sequencing [next generation sequencing (NGS)] greatly facilitates this exploration. Among these multigene panels, only three are commercially available to assist patient management. The 22-gene Decipher is intended to predict metastasis following RP (132-134); both

the 17-gene Oncotype DX [Genomic Prostate Score (GPS)] and the 31-gene Prolaris [Cell Cycle Progression (CCP)] stratify patients at risk of PC recurrence at the time of diagnosis (135-139) and following RP (140,141). Herein, we briefly review Oncotype DX GPS and CCP and discuss other multigene panels regarding their potentials and limitations.

Oncotype DX prostate cancer assay (GPS) and prolaris (CCP). Oncotype DX Prostate Cancer Assay was developed by Genomic Health Inc. as an assay in the Oncotype DX assays for multiple cancer types. Oncotype DX GPS is a RT-PCR assay on 12 cancer-related and 5 reference genes (*ARF1*, *ATP5E*, *CLTC*, *GSP1* and *PGK1*) using biopsy tissues (135); the 12 genes function in 4 aspects of PC tumorigenesis, including a stromal process (*BGN*, *COL1A1* and *SFRP4*), cellular organization pathway (*FLNC*, *GSN*, *TPM2* and *GSTM2*), androgen signaling (*FAM13C*, *KLK2*, *AZGP1* and *SRD5A2*) and cell proliferation regulation (*TPX2*) (135). They were selected from 732 candidate genes, which were narrowed down from an initial set of 1,082 nominating candidates, through a variety of processes involving multiple data-mining models (136). PGS in the scale of 0-100 can be calculated based on the normalized expressions of 12 cancer-related genes with increased scores indicating elevations in BCR risk (136). In patients with low-risk (GS 6) or intermediate-risk (GS 3+4) PC, GPS predicts BCR (n=382; HR, 2.73; 95% CI, 1.84-3.96; P<0.001) (140). In a recent validation study, GPS classified PCs at risk of BCR (n=259; HR, 2.5; 95% CI, 1.28-3.03; P=0.002) (142). Furthermore, in a late multiple institutional investigation involving 1,200 males with very low-, low- and intermediate-risk PCs, GPS predicted adverse pathological features of PC (143). Although GPS has been independently validated for the better management of patients with low- and intermediate-risk PC, the system could be improved. For instance, GPS does not significantly predict BCR in patients who are <56 years old (n=100) (140); the cellular organization group score, 3 of 4 component genes of this group, and the proliferation group score do not individually predict BCR risk (140), which reduces the biomarker value of GPS. Although the 12 cancer-related genes were selected via a thorough and complex process from 732 candidates (136), it is of concern whether too many manipulations may not produce the best model.

Genes regulating CCP possess prognostic potential in assessing cancer progression (144). Of note, a panel of 31 CCP genes has been selected from 126 cell cycle progression genes, which together with 15 housekeeping genes form the Prolaris (CCP) multigene panel (Myriad Genetics Int.) (137). Prolaris is a RT-PCR based assay on formalin-fixed paraffin-embedded tumor tissues and provides risk assessment of BCR progression (137). The risk stratification has been validated (Table III) (141,145-147). Evidence also indicates its utilization in the risk stratification of PC fatality (n=349; HR, 2.02; 95% CI, 1.62-2.53; P<1e-9) (148). However, variations in the effectiveness of BCR risk stratification of some studies were apparent; for instance, in the study involving 236 patients (Table III), HR was modest and the lower HR in the 95% CI range was marginal (Table III). Additionally, it remains uncertain whether the Prolaris CCP test will have an impact on PC death and is unlikely to facilitate treatment decision; the cost of test is also high (149). Nonetheless, both Oncotype DX GPS and Prolaris CCP are commercially available to assess BCR risk.

Other multigene signatures with biomarker values in BCR risk assessment. Even with the construction of Oncotype DX GPS and Prolaris CCP multigene panels, there is clearly a need to improve the assessment of BCR. To fulfill this need, there are numerous additional multigene sets reported (Table IV), including a 6-differentially expressed gene (DEG) panel (150), an 8-gene panel with its risk scores predicting BCR at P=5e-7 (151), and a 10-gene panel HDDA10 (152) (Table IV).

Hypoxia is well known to promote PC progression via multiple pathways, including inflammation and notch signaling (153,154). To examine the prognostic values of hypoxia-induced events in PC progression, Yang *et al* derived a 28-gene hypoxia-related prognostic signature from 848 differentially expressed genes that were identified in human PC cell lines cultured under hypoxic and normoxic conditions (155). The signature modestly predicts BCR in RP patients receiving post-operative radiotherapy (155) (Table IV).

Instead of focusing on a particular pathway, a 15-gene signature has recently been formulated from the MUC1 network (SigMuc1NW) (156); the signature was validated in the MSKCC dataset. SigMuc1NW stratifies the BCR risk in the MSKCC dataset at P-value 3.11e-15 (156). MUC1 is the most intensively investigated tumor-associated antigen (157-159) and is an attractive target for developing immunotherapies for multiple tumor types (160). MUC1 upregulation is weakly associated with BCR occurrence and PC mortality (161,162). The biomarker potential of MUC1 alterations in the classification of BCR risk was significantly enhanced in a 9-gene genomic signature (163). The 15-gene SigMuc1NW was derived using the 9-gene signature-associated DEGs (156). SigMuc1NW is an independent risk factor of BCR (HR, 2.44; 95% CI, 1.53-3.87; P=1.62e-4) after adjusting for age at diagnosis, GS, surgical margin and tumor stage (156). Among its 15 component genes, 8 (SLCO2A1, SUPV3L1, TATDN2, MGAT4B, VAV2, SLC25A33, ASNS and OIP5) individually predict BCR after adjusting the clinical features (156). Another attractive feature of SigMuc1NW lies in its novelty; among the 15 component genes, 11 have not been reported in PC particularly and/or tumorigenesis in general (156).

The inclusion of Opa interacting protein 5 (OIP5) in SigMuc1NW is intriguing; it is a cancer-testis antigen and thus a tumor-associated antigen (TAA) detected in other cancer types (164). OIP5 is likely a novel PC-associated TAA. More appealingly, recent developments revealed an essential role of OIP5 in chromosome segregation during cell cycle progression. OIP5 is also known as Miss18β, that plays a critical role in centromere formation during the G1 phase (165,166). In accordance with this knowledge, OIP5 is an independent risk factor for BCR (HR, 1.94; 95% CI, 1.20-3.12; P=0.00638) after adjusting for age at diagnosis, GS, surgical margin and tumor stage (156); OIP5 promotes bladder cancer metastasis and chemoresistance (167), glioblastoma metastasis (168), it displays a biomarker potential in clear cell renal cell carcinoma (169), and it is upregulated in colorectal and breast cancer (170,171).

In line with the concept of the involvement of multiple pathways in BCR progression and the robustness of SigMuc1NW in the classification of BCR risk (Table IV) (156), our recent analysis revealed the signature's 15 component genes (Table IV)

Table III. Prolaris predicts BCR risk.

Cohort (n)	HR (95% CI), P-value[a]	HR (95% CI), P-value[b]	(Refs.)
366	1.89 (1.54-2.31), 5.6e-9	1.77 (1.4-2.22), 4.3e-6	(137)
413	2.1 (1.6-2.9), <0.001	2.0 (1.4-2.8), <0.001	(141)
141	2.55 (1.43-4.55), 0.0017	2.11 (1.05-4.25), 0.034	(145)
582	1.6 (1.35-1.90), 2.4e-7	1.47 (1.23-1.76), 4.7e-5	(146)
236	1.46 (1.06-2.10), 0.002	1.41 (1.02-1.96), 0.039	(147)

[a]Univariate analysis; [b]multivariate analysis. HR, hazard ratio; BCR, biochemical recurrence.

Table IV. Multigene sets with the potential to assess BCR risk.

Gene set	Components	Cohort (n)	HR (95% CI), P-value	(Refs.)
6 DEG	SMIM22, NINL, NRG2, TOP2A, REPS2, TPCN2	358	3.815 (2.1-6.932), P<0.001	(150)
8 genes	CHST1, ACOX1, CTBS, CNPNAT1, NAGLU, LPIN3, ASRGL1, HMGCS2	308	NA, P=5e-7	(151)
HDDA10	FRZB, LEF1, SDCBP, WNT2, ING3, ANK3, MEIS2, ANXA4, PLA2G7, CHD5	758	2.08 (1.2-3.6), P=0.008	(152)
28-Gene hypoxia-related prognostic signature	ADAMTS4, ATF3, BHLHE40, BTG2, CSRNP1, CYR61, EGR1, EGR2, EGR3, FOSB, FOSL2, GEM, JUNB, KLF10, KLF6, LIF, MCL1, NR4A3, PPP1R15A, RHOB, SELE, SIK1, SLC2A14, SLC2A3, SOCS3, THBS1, TIPARP, ZFP36	130	2.81 (1.33-6.0), P=0.007	(155)
SigMuc1NW	SLCO2A1, CGNL1, SUPV3L1, TATDN2, MGAT4B, VAV2, SLC25A33, MCCC1, ASNS, CASKIN1, DNMT3B, AURKA, OIP5, CTHRC1, GOLGA7B	490	4.16 (2.74-6.36), P=5.54e-11	(156)

HR, hazard ratio; BCR, biochemical recurrence.

being grouped into 5 clusters using Kendall, Spearman's and Pearson correlation (Fig. 3). Collectively, evidence supports SigMuc1NW as a novel and robust multigene signature. Nonetheless, its biomarker value has not been independently tested.

Evaluation of BCR risk using lncRNAs. While the mechanisms underlying the lncRNA-mediated regulation of gene expression remain incompletely understood, they are likely regulated through complex actions at the genome (chromatin remodeling), mRNA and protein levels (172). Of these, its function as miRNA sponges is emerging as a prevalent mechanism (172,173). In this regard, this section reviews the current evidence for lncRNAs as classifiers of BCR risk. For a comprehensive review, we first searched PubMed for 'lncRNA' AND 'prostate cancer' AND 'biochemical recurrence', and retrieved 15 articles. With exclusion of one non-accessible publication and three articles in which the association of lncRNAs with BCR was not clear, 11 manuscripts are included (179) and Tables V and VI.

A set of PC-associated lncRNAs (n=54) have been recently reviewed (174); they are involved in PC initiation and progression. A well-known lncRNA in PC is PCA3. It is robustly upregulated in PC compared to prostate tissues (175) and is the second biomarker used in the clinic for PC detection, particularly in decision making for repeat biopsies (176-178). Several lncRNAs have been demonstrated to predict the risk of BCR either individually or in a panel; this has been reviewed in 2017 by Ma *et al* (179) and Wu *et al* (180). In this section, we provide an update of the topic with current research.

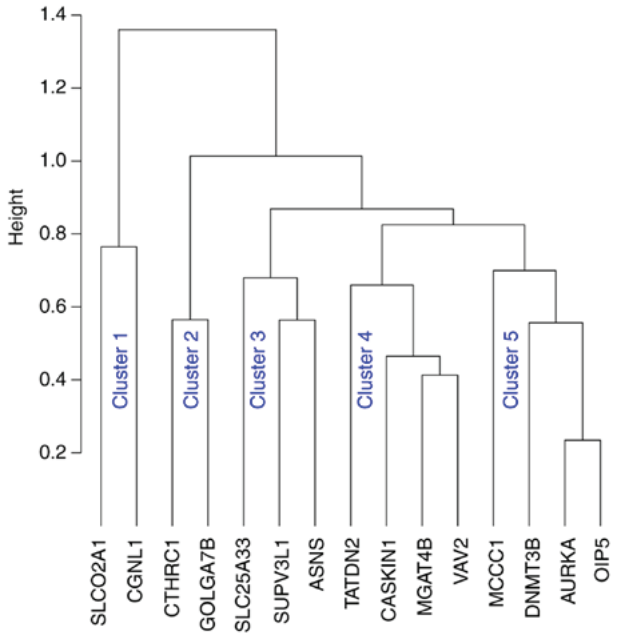

Figure 3. Hierarchical clustering of SigMuc1NW. The RNA sequencing data of the 15 component genes of SigMuc1NW (Table IV) were retrieved (156) and clustered using Kendall, Spearman's and Pearson's correlation with similar results being obtained. The results based on the Spearman's correlation are shown.

Prediction of BCR risk with individual lncRNAs. Elevations in the levels of lncRNA LOC400891 have been observed in tumors vs. prostate tissue (181). The upregulation increases BCR risk in patients (Table V); its overexpression and knockdown accordingly enhance and inhibit PC cell proliferation *in vitro*. There is evidence to indicate a role of LOC400891 in the activation of the PI3K pathway (181). Nonetheless, the involvement of LOC400891 in PC and other cancer types has yet to be further investigated.

Similar observations have also been reported in lncRNA-ATB (Table V) (182). lncRNA-ATB is upregulated in TGF-β-induced EMT (183). The upregulation of lncRNA-ATB and its oncogenic activities have been reported in multiple cancer types, including hepatocellular carcinoma (HCC), gastric cancer, colorectal cancer (CRC), renal cellular carcinoma, breast cancer and others (184). Collectively, the association of lncRNA-ATB with BCR warrants further investigation, which should be conducted in context of the pathways (such as TGF-β) affected by lncRNA-ATB in the course of BCR development.

Increases in the levels of lncRNA LINC01296 are associated with BCR (Table V) (185). LINC01296 was first reported as a biomarker of CRC (186); its oncogenic activities and association with cancer progression were subsequently observed in bladder cancer (187,188), gastric cancer (189), cholangiocarcinoma (190), breast cancer (191), non-small cell lung cancer (192), and others (193). LINC01296 facilitates tumorigenesis in part by sponging miR122-5P in HCC (194) and miR-5059 in cholangiocarcinoma, leading to MYCN activation (190).

Second chromosome locus associated with prostate-1 (SChLAP1; LINC00913) is upregulated in PC and promotes tumor invasion and metastasis (195). In a multicentre study involving 937 patients, SChLAP1 overexpression was associated with lethal PC (196). Of note, elevations in SChLAP1 expressoin have been shown to predict PSA relapse (Table V) (197), an event which has also been observed by others (179), and PC metastasis (198). While SChLAP1 has been reported to prevent the association of the SWI/SNF complex with chromatin and thereby inhibiting the complex-associated tumor suppression in PC (195), late development revealed a SWI/SNF-independent action of SChLAP1 in PC tumorigenesis (199); the mechanisms through which SChLAP1 affects PC require further investigation.

The lncRNA urothelial carcinoma-associated 1 (UCA1) marginally predicts the risk of BCR (200). The prediction is consistent with the associations of UCA1 with reductions in the 5-year disease-free survival in PC (n=130; HR, 2.88; 95% CI, 1.36-6.21; P=0.007) (200) and in overall survival (n=40, P<0.001) (201). Additionally, the upregulation of UCA1 has also been shown to be a risk factor for the progression of ovarian cancer (202), gastric cancer (203), melanoma (204), pancreatic cancer (205), glioma (206) and others (207). Mechanistically, UCA1 facilitates PC at least in part through upregulations of ATF2 and CXCR4 by sponging miR-204 (208,209). Intriguingly, UCA1 sequesters miR-204, leading to EMT in glioma, TGF-β signaling in oral cancer and Sox4 actions in esophageal cancer (207); UCA1 also sponges other miRNAs in promoting tumorigenesis in other cancer types (207). In this regard, the association of UCA1 with BCR could be strengthened by consideration of UCA1-regulated oncogenic factors.

The downregulation of the lncRNA prostate cancer-associated transcript 7 (PCAT7) is an independent factor predicting BCR (Table V) (210), consistent with its reductions following advance in GS and its downregulations independently predicting metastasis (210). Similar clinical associations were also confirmed by a multicenter study, in which PCAT14 was found to be an independent risk factor of metastasis (n=910; HR, 0.56, 95% CI, 0.41-0.71; P=1.09e-6), prostate cancer-specific survival (HR, 0.53; 95% CI. 0.39-0.72; P=6.54e-5) and overall survival (HR, 0.67; 95% CI, 0.54-0.83; P=0.00019) (211). Apart from these two investigations, the involvement of PCAT14 in PC and other cancer types has not yet been thoroughly examined; the potential mechanisms of PCAT14 downregulation and its impact on PC progression have yet to be reported. Nonetheless, it appears that PCAT14 affects tumorigenesis in a complex manner; in HCC, PCAT14 is upregulated and promotes HCC cell proliferation and invasion (212).

Stratification of BCR risk with multi-lncRNAs (lncRNA panels). Multi-lncRNA panels have been constructed to stratify the risk of BCR, including a 4-lncRNA (213), 5-lncRNA (214), 7-lncRNA (215) and 8-lncRNA panels (Table VI) (216). All these studies were bioinformatics analyses of the TCGA dataset using different modules and sub-datasets. Differentially expressed lncRNAs (DE-lncRNAs) in the setting of PCs vs. prostate tissues were derived, followed by selection for their associations with BCR using either univariate Cox analysis (213,215,216) or the LASSO (least absolute shrinkage and selection operator) Cox regression (214); DE-lncRNAs with significant associations with BCR constituted the individual lncRNA panels (Table VI). Risk scores of these panels were

Table V. Associations of lncRNAs with BCR.

lncRNAs	Cohort (n)	HR (95% CI)	P-value	(Refs.)
LOC400891	81	2.12 (1.23-3.64)[a]	0.007	(181)
lncRNA-ATB	57	1.75 (2.31-14.25)[a]	<0.001	(182)
LINC01296	70	6.58 (1.95-22.22)[b]	0.002	(185)
SChLAP1	157	2.34 (1.29-4.27)[b]	0.005	(197)
UCA1	209	2.73 (0.97-7.63)[b]	0.056	(200)
PCAT14	585	0.64 (0.49-0.84)[a]	0.00126	(210)

[a]Multivariate Cox analysis; [b]univariate Cox analysis. HR, hazard ratio; BCR, biochemical recurrence.

Table VI. lncRNA panels predict BCR risk.

lncRNA panels	Components	Cohort (n)	HR (95% CI), P-value	(Refs.)
4-lncRNA	RP11-108P20.4	291	3.33 (1.59-6.97)[a], P=0.01	(213)
	RP11-757G1.6			
	RP11-347I19.8		3.13 (1.45-6.78)[b], P=0.004	
	LINC01123			
5-lncRNA	RP11-783K16.13	457	0.44 (0.27-0.72)[a,c], P<0.05	(214)
	RP11-727F15.11			
	PRKAG2-AS1	343[c]	0.22 (0.09-0.56)[a,d], P<0.05	
	AC013460.1	141[d]		
	CRNDE			
7-lncRNA	SNHG1	457	0.32 (0.2-0.52), P<0.001	(215)
	CRNDE			
	CTC-296K1.4			
	UBNX10-AS1			
	PART1			
	CTC-296K1.3			
	PGM5-AS1			
8-lncRNA	PCAT7	307	2.19 (1.67-2.88)[a,c], P<0.0001	(216)
	SLC12A9-AS1			
	RGMB-AS1	184[d]	2.19 (1.49-3.22)[b,c], P<0.0001	
	PCAT1	123[d]		
	AP002992.1			
	AC025265.1		1.37 (1.09-1.71)[a,d], P=0.006	
	LINC00593		1.67 (1.06-2.63)[b,d], P=0.027	
	AC005632.2			

[a]Univariate Cox analysis; [b]multivariate Cox analysis; [c]discovery set; [d]validation set. HR, hazard ratio; BCR, biochemical recurrence.

used to stratify the risk of BCR; the scores were calculated based on the following formula: Risk scores=sum ($coef_i$ x $DE\text{-}lncRNA_i$), where $DE\text{-}lncRNA_i$ is the i^{th} DE-lncRNA expression (i=1, … n) and $coef_i$ is the Cox coefficient of DE-lncRNAi (213-216).

These lncRNA panels (Table VI) are novel. In the 4-lncRNA panel, only LINC01123 was reported in a prognostic lncRNA panel of head and neck squamous cell carcinoma (217). The lncRNA colorectal neoplasial differentially expressed (CRNDE) of the 5-lncRNA panel (Table VI) has been relatively well studied (n=72 in PubMed under 'CRNDE' AND 'Cancer'). CRNDE is upregulated in CRC, glioma, HCC, lung cancer, ovarian cancer, breast cancer and others; it may play a role in cell proliferation, migration, invasion and apoptosis (218). Apart from CRNDE, other lncRNAs of the 5-lncRNA panel have not yet been reported, at least to the best of our knowledge.

In the 7-lncRNA panel (Table VI), small nucleolar RNA host gene 1 (SNHG1) was reported to upregulate CDK7 by sponging miR-199-3p, thereby enhancing PC cell proliferation (219); its involvement in cancer has been widely investigated (n=64 in PubMed under 'SNHG1' AND 'Cancer'). In addition to PC, SNHG1 is upregulated in CRC, liver cancer, lung cancer, gastric cancer and others; the

upregulation correlated with adverse features of cancer (220). For PART1, PubMed has listed 16 articles related to 'PART1' AND 'Cancer'. The lncRNA prostate androgen-regulated transcript 1 (PART1) facilitates the progression of prostate cancer through the Toll-like receptor pathway (221) and non-small cell lung cancer via the JAK-STAT pathway (222); it displays oncogenic activities in bladder cancer (223). The lncRNA PGM5-AS1 has been limitedly studied (n=4 in PubMed under 'PGM5-AS1'). Evidence suggests PGM5-AS1 suppresses esophageal squamous cell carcinoma by facilitating PTEN actions though sponging miR-466 (224). Apart from SNHG1, CRNDE, PART1 and PGM5-AS1, the others in the 7-lncRNA panel (Table VI) have not yet been reported, at least to the best of our knowledge

In the 8-lncRNA panel (Table VI), the lncRNA PCAT7 has been investigated in 3 articles based on PubMed; evidence suggests that it enhances non-small cell lung cancer progression by inhibiting miR-134-5p (225). For the lncRNA PCAT1, there are 31 publications listed under PubMed that are related with 'PCAT1' and 'Cancer', in which 20 articles are PC-related. In PC, PCAT1 is a disease risk factor (226) and enhances CRPC by activating the AKT and NF-κB signaling (227). PCAT1 was mapped to 8q24, a well-studied cancer (including PC) risk region (228). In line with this notion, PCAT1 promotes esophageal squamous cell carcinoma through sponging miR-326 (229), is a risk factor of CRC (230), and is associated with a poor prognosis in endometrial carcinoma (231). Apart from PCAT7, PGM5-AS1 and PCAT1, the others in the 8-lncRNA panel have not yet been reported, at least to the best of our knowledge.

Evaluation of BCR risk using lncRNAs: Perspectives and limitations. Since the discovery of the lncRNA H19 in 1991 (232) and Xist in 1992 (233), a large number and complex sets of lncRNAs have been identified; the discovery rate has been significantly accelerated since 2013 (174). Although the field of lncRNA is new, it is clear that lncRNA affects tumorigenesis via complex mechanisms at the genome, RNA and protein levels (172,174). With respect to gene expression, the actions of lncRNA are likely complex. For instance, a prevalent mechanism is to associate with miRNAs, which prevent miRNAs from inhibiting mRNAs (172,173). miRNAs are known to affect the expression of a large number of genes. Of note, miR-130b target genes are approaching 600 (61). It will thus be important to illustrate the major mechanisms, pathways and factors through which lncRNAs predict the risk of BCR; this will facilitate the formulation of lncRNA signatures with enhanced accuracy to stratify the risk of BCR. As an emerging and rapidly developing field, the biology of lncRNAs and the mechanisms mediating their biological actions have not been thoroughly investigated. In this regard, their potential as classifiers of BCR risk has yet to be fully recognized.

5. Management of patients with biochemical recurrence

PSA relapse offers the early identification of patients with failure following initial curative therapies with RP and RT. While BCR precedes clinical disease recurrence, the management of males with PSA relapse needs to consider multiple factors including tumor recurrence (234,235). The nature of BCR is heterogeneous with local and distant recurrence (236). Additionally, not all patients with BCR will progress to lethal disease (13). In addition to these variations are the improvements in risk stratification of BCR and metastasis as well as advances in salvage treatment. The heterogeneity of BCR along with the aforementioned advances complicates the management of patients with BCR. This topic has been recently discussed by several recent reviews (236-238). We also highlight the recent advances and suggest improvement on management of these patients in the context of BCR risk stratification using RNA-based biomarkers.

Detection of clinical recurrence following BCR. Recent developments have improved the diagnosis of clinical recurrence following BCR using the prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET) imaging in comparison to conventional imaging modalities: Computed tomography (CT), magnetic resonance imaging (MRI) and bone scan (239,240). PMSA (glutamate carboxypeptidase II) is an enzyme encoded by the folate hydrolase 1 (*FOLH1*) gene (https://en.wikipedia.org/wiki/Glutamate_carboxypeptidase_II) (241). It is mainly expressed in the prostate with weaker expressions detected in the brain, salivary gland and small intestine (242). PSMA expression is markedly upregulated in PC and the level of overexpression is associated with PC progression, including castration-resistant prostate adenocarcinoma (242-245). Nonetheless, its expression is suppressed in neuroendocrine prostate cancer (NEPC) (246), which will produce false negativities. False positivity is also a concern (246). Nonetheless, PSMA-PET has higher sensitivities in detecting recurrent sites at BCR in comparison to other imaging modalities (247). In a recent single-arm clinical trial on patients with BCR (n=635) to assess the accuracy of ^{68}Ga-PSMA-11 PET in detecting recurrent PCs, the overall detection rate was 75% (475/635) and the PET-positive rates in different PSA groups were 38% for <0.5 ng/ml, 57% for 0.5-<1.0 ng/ml, 84% for 1.0-<2.0 ng/ml, 86% for 2.0-<5.0 ng/ml, and 97% for ≥5.0 ng/ml respectively (248). In a recent diagnostic study of 100 patients with BCR using ^{18}F-PSMA-1007 PET/CT, the PET-positive rate was 86, 89, 100 and 100% for patients with PSA levels ≤0.5, 0.51-1.0, 1.0-2.0, and ≥2.0 ng/ml, respectively (249).

Clinical recurrence in the setting of BCR can also be at distant sites or metastasis. The diagnosis of metastasis can be facilitated using the Decipher test (GenomeDx Bioscience), a 22-gene genomic classifier (GC). This is an RNA-based gene panel consisting of coding and non-coding transcripts that function in multiple pathways including cell proliferation, adhesion, immune response, cell cycle progression and others (132). The Decipher GC predicts metastasis in patients following RP (132-134). In a recent multicenter study on 561 males with adverse pathological features, GC independently stratified the risk of prostate cancer-specific mortality (PCSM) following RP (250). The prediction was improved by combining GS with CAPRA-S (251) a classifier of BCR risk following PR (21,22). In this regard, it would be expected that combination of GS with those RNA-based biomarkers discussed herein may strengthen the accuracy in predicting PCSM in the setting of RP; this will facilitate management of patients with BCR with respect to decision making on salvage treatment selection.

Other biomarkers could also be considered. RP produces excellent outcomes in patients with localized low- and intermediate-risk PCs. However, the biochemical relapse rates for high-risk localized disease [PSA>20 ng/ml, GS>7, or cT2c (3)] can increase to 50-80% (252). Males with high-risk tumors can be managed with adjuvant therapy following RP; in a small group of patients (n=127) treated with adjuvant hormone therapy, high level of PDL1 expression is an independent risk factor of BCR (253). The PDL1 expression status could facilitate the diagnosis of BCR following RP.

Salvage therapies following BCR. Treatment selection for patients with BCR depends on the site of recurrence and the extent of progression; this information will be derived using imaging and other assessment including biomarker-based (such as GS) risk evaluation and PSA changes (236). Life expectancy, quality of life (QOL) and the time span of approximately 8 years for metastatic progression from BCR (7,13) are among the factors that affect treatment decision making (237,254).

Salvage radiotherapy (SRT) to the prostate bed is commonly used in patients with BCR following RP; it controls biochemical failure in approximately 50% cases, reduces distant metastasis and improves PCSM (236,255,256). The PSA status can guide local salvage treatment. EAU-ESTRO-SIOG recommends surveillance and delayed SRT in males exhibiting an increase in PSA with a favorable prognostic setting [≤pT3a; time to BCR, >3 years; PSA doubling time (DT), >12 months; and GS ≤7], and beginning SRT at PSA <0.5 ng/ml (7). On the other hand, the National Comprehensive Cancer Network (NCCN) recommends the initiation of SRT with confirmed increasing PSA levels, and many favor SRT at PSA 0.2 ng/ml (238). For patients with BCR following RT, salvage RP is an option with confirmed local recurrence according to EAU-ESTRO-SIOG guidelines (7). Similarly, the prostate cancer guidelines from the European Association of Nuclear Medicine (EAU-EANM)-European Society of Urogenital Radiology (ESTRO-ESUR)-SIOG classify males with BCR into a low-risk [PSA-DT >1 year and pathological GS (pGS) <8 or International Society of Urological Pathology (ISUP) grade <4] and high-risk group (PSA-DT ≤1 year, pGS 8-10 or ISUP grade 4-5) for biological recurrence following RP or a low-risk [IBF (interval from primary therapy to biochemical failure) >18 months and biopsy GC (bGS) <8 or ISUP grade <4] and high-risk (IBF ≤18 months and) groups (pGS 8-10 or ISUP grade 4-5) (254). The stratification was recently validated based on the 5-year risk of developing metastasis and PCSM in a large cohort of patients with BCR (n=1,040) (257). The guidelines call for the surveillance for males with BCR in the low-risk group and salvage ADT should not be given to these patients (254). It appears that SRT plus hormone therapy (bicalutamide) improved the outcome (258,259). The risk of metastasis following SRT in patients with BCR can be stratified using Decipher GC (260). It is thus possible to assign patients with BCR following RP with combination therapy of SRT and ADT based on GC scores. Following this logic, whether incorporating BCR risk stratification with GS will enhance the decision making warrants further investigations in the future.

6. Perspectives

BCR precedes clinical disease recurrence and is significantly associated with increases in metastasis development and CRPC (13,14,261), conditions to which our knowledge and ability to intervene remain poor. While more than half of patients with high-risk PCs will experience BCR following RP (252), the curative therapy yields good results in males with low- and intermediate-risk tumors. Accurately predicting the risk of BCR is thus highly relevant in the management of these patients. In view of the metastasis progression following BCR, the stratification of the risk of BCR also contributes to the management of males with PSA relapse (please see section above entitled 'Salvage therapies following BCR'). Collectively, the effective evaluation of the risk of BCR is an essential aspect of patient management. With this recognition, a major research focus has been searching for biomarkers to robustly assess BCR risk, which is evident by 2,502 articles listed under 'prostate cancer' AND 'biomarker' AND 'biochemical recurrence' by PubMed. However, none of these had succeeded in progressing to routine clinical application (262); this clearly outlines the challenges in the identification of effective biomarkers.

While individual biomarkers, regardless of whether they are clinical feature-, DNA-, RNA-, and protein-based, may display a significant association with BCR, it is unlikely that they can effectively stratify BCR risk individually. BCR is regulated by complex mechanisms, which is likely an attribute to the lack of overlapping genes between two commercially available multigene panels, Oncotype DX GPS and Prolaris, despite both assessing the risk of BCR (135,137). It is thus conceivable that multigene panels will certainly enhance the effectiveness of BCR biomarkers. In this regard, it will be intriguing to systemically analyze Oncotype DX, Prolaris and other RNA-based biomarkers along with clinical feature-based (PSA, GS, stage, surgical margin status, lymph node status and others) BCR risk classifiers (CAPRA-S, Walz nomogram, and others) for the stratification of the risk of BCR. This may produce a much more robust system, covering essential pathways leading to BCR, in predicting the risk of BCR, which will greatly improve patient management with prostate cancer.

Another avenue worthy of exploration for the improvement of the stratification of the risk of BCR is the process of DNA damage response (DDR). Genomic instability is a hallmark of cancer and the driving force of cancer progression (263); genomic stability is maintained through DDR by coordinating checkpoint activation and DNA lesion repairs (264-266). It is surprising that factors in DDR regulation have not been intensively investigated for their biomarker potential.

The same situation applies to stromal factors. While a variety of tumor properties have been examined for prognostic purposes, the stromal contributions and the communications between he stroma and tumor have not been actively determined for biomarker purposes. A potential mechanism causing stromal alterations is through PC-associated metabolic reprogramming, which results in the accumulation of metabolic intermediates (267); these materials affect gene expression via epigenetic alterations (268). Metabolic reprogramming is a well-established mechanism supporting not

only tumorigenesis, but also cancer progression (36,267,268). In this regard, PC-associated metabolic alterations will have a prognostic potential which has been recently reviewed by Lucarelli *et al* (267). It is of interest that PCs can be grouped into two metabolic profiles: Phopho-AKT^{high}/MYC^{low} or phopho-AKT^{low}/MYC^{high} with the former and latter affecting the glucose-related processes and lipid metabolism, respectively (269). Nonetheless, the prognostic potential of PC-associated metabolic alterations remains complex. For instance, the AKT- and MYC-related metabolic signatures are not associated with GS and pathological stage (269); of note, neither MYC overexpression nor AKT phosphorylation displays a strong prognostic potential in PC (267,270,271). While increases in body mass index (BMI) and obesity are associated with PC-related mortality (272), there is also evidence to support the reverse association (273). A similar situation also applies to the association between cholesterol and PC progression. A meta-analysis of 27 clinical studies up to 2012 with a pooled population of 1.8 million males revealed a 7% reduction in PC cases and a 20% decrease in PC progression in statin users (274). Statins were reported to reduce BCR following RT (275) and RP (276). However, other studies observed no clinical benefits in males with PC who were statin users (277,278) and reported statins having no impact on BCR following RP (279). Clearly, the prognostic values of metabolic alterations in PC warrant further investigations.

The plasticity of cancer, including PC, presents a major challenge not only in cancer therapy, but also in assessing the risk of cancer progression. Cancer plasticity is regulated by complex mechanisms, including those functioning in CSCs and DDR (280,281). It is noteworthy that BMI1, a well-established factor in maintaining CSC (282), also compromises genomic instability via attenuating ATM and ATR functions (264,283-285). In this regard, DDR regulations and stroma-cancer cell communications, both of which contribute to cancer plasticity, should be actively brought into the picture of BCR risk assessment; with these components incorporated, the ability to accurately classify BCR risk will likely be significantly improved.

PC is associated with high levels of intratumoral and intertumoral heterogeneity (286). This aspect has not been given sufficient consideration and should be pursued in PC biomarker development. Collaborative efforts involving multiple institutes in sharing materials and expertise will certainly be helpful to achieve this goal.

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Availability of data and materials

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Authors' contributions

XL, AK, HX, PM and DT were involved in the conception of the study. XL, YG and MJC were involved in the literature search. XL, PM and DT were involved in the writing and preparation of the original draft of the manuscript. All authors were involved in the writing and reviewing of the article. YG, PM and DT were involved in the writing and editing of the article. DT supervised the study. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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