Assessment of biochemical recurrence of prostate cancer (Review)

XIAOZENG LIN1-4, ANIL KAPOOR2,3,5, YAN GU1-4, MATHILDA JING CHOW1-4, HUI XU6, PIERRE MAJOR7 and DAMU TANG1-4

1Department of Medicine, McMaster University, Hamilton, ON L8S 4K1; 2The Research Institute of St. Joe’s Hamilton, 3Urological Cancer Center for Research and Innovation (UCCRI), St. Joseph’s Hospital; 4The Hamilton Center for Kidney Research, St. Joseph’s Hospital, Hamilton, ON L8N 4A6; 5Department of Surgery, McMaster University, Hamilton, ON L8S 4K1, Canada; 6Department of Nephrology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, P.R. China; 7Division of Medical Oncology, Department of Oncology, McMaster University, Hamilton, ON L8V 5C2, Canada

Received July 5, 2019; Accepted September 24, 2019

DOI: 10.3892/ijo.2019.4893

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 (IncRNA, miRNA and mRNA) constitute the largest proportion of the biomarkers of BCR. In this article, we systematically 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.

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 evolution 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’ and ‘DNA methyltransferase’ in PubMed; n=258. Searching for “prostate cancer” and “biomarker” and “gene expression” and “biochemical recurrence” in PubMed; n=258.

Articles based on DNA methylation, epigenetic regulation, and cohort size <100 were removed.

Articles remained n=94.

Articles mainly used immunohistochemistry or p values <0.05 were excluded.

Studies included n=60.

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 1). 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 1). Downregulations in the expression of miR-30C (62), miR-145 (63), miR-195 (64) and miR-16 (64) facilitate BCR development (Table 1).

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
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 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-301aᵇ | 585          | 180 M     | 1.42 (1.06-1.90) | 0.002 | (58)    |
| miR-21ᵇ  | 169          | 84 M      | NA          | <0.001 | (59)    |
| miR-128ᶜ | 128          | 100 M     | 3.96 (1.02-8.12) | <0.001 | (60)    |
| miR-30cᶜ | 103          | 125 M     | 0.31 (0.19-0.51) | <0.001 | (62)    |
| miR-145ᶜ | 137          | 72 M      | 3.21 (1.07-9.62) | 0.007 | (63)    |
| miR-195ᶜ | 131          | 150 M     | NA          | 0.0092 | (64)    |
| miR-16ᶜ  | 131          | 150 M     | NA          | 0.0031 | (64)    |
| miR-130bᶜ | 188         | 120 M     | NA          | 0.004  | (61)    |

ᵃHazard ratio (HR) was determined on mi-R145 downregulations;ᵇincreases andᶜdecreases in expression associated with BCR. M, months; CI, confidence interval; NA, not available; BCR, biochemical recurrence.
Table II. Associations of individual mRNAs with BCR defined by Cox analysis.

| mRNAs          | Patients (n) | Pathways          | HR (95% CI)    | P-value (Refs.) |
|----------------|--------------|-------------------|----------------|----------------|
| SFRP4<sup>a</sup> | 1,404±536    | Wnt               | 1.3±2.18<sup>b</sup> | 0.022±1.88e−7<sup>c</sup> (79.80) |
| AXIN2<sup>b</sup>  | 951          | Wnt               | 0.13±0.02 (0.67) | 0.02±(86)     |
| PDGFR-β<sup>a</sup> | 535          | Proliferation     | 1.58±1.18−2.13  | 0.002±(87)    |
| MT1E<sup>b</sup>   | 108          | Metal homeostasis | NA             | <0.001±(89)   |
| KLRK1<sup>b</sup>  | 150          | Serine protease   | 3.44±1.35−8.75  | 0.01±(100)    |
| NRPI<sup>a</sup>   | 130          | Androgen signaling| NA             | 0.0002±(102)  |
| SAMD5<sup>a</sup>  | 345          | NA                | 2.18±1.20−3.97  | 0.01±(107)    |
| SMAD4<sup>a</sup>  | 140          | TGF-β             | 4.61±2.15−9.89  | <0.001±(113)  |
| PLAGL2<sup>a</sup> | 104          | Wnt               | 3.97±1.21−13.00 | 0.023±(114)   |
| PD-L2<sup>a</sup>  | 9,393        | Immune checkpoint | 1.17±1.03−1.33  | 0.01±(119)    |
| RNase k<sup>b</sup> | 111          | RNA metabolism    | 0.85±0.77−0.91  | 0.002±(120)   |
| GLTSCR1<sup>a</sup> | 499          | Chromatin remodeling | 2.28±1.28−4.05  | 0.005±(122)   |
| BChE<sup>a</sup>   | 385          | Hydrolyzing ghrelin and bioactive esters | NA | 0.008±0.04<sup>d</sup> (125) |

<sup>a</sup> and <sup>b</sup>, increases and decreases in expression are associated with BCR, respectively; <sup>c</sup>range of HR or p-values; <sup>d</sup>odds ratio (97.5% CI).

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 (ARFI, 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 GMT2), 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). GPS 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, 1.95-2.73; 95% CI, 1.84-3.96; P<0.001) (140). In a recent validation study, 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, 1.28-3.03; 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.

**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 it 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 GI phase (165,166). In accordance with this knowledge, OIP5 is an independent risk factor for 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). 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)
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.

| Table III. Prolaris predicts BCR risk. |
|--------------------------------------|
| **Cohort (n)** | **HR (95% CI), P-value**<sup>a</sup> | **HR (95% CI), P-value**<sup>b</sup> | **(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)       |

<sup>a</sup>Univariate analysis; <sup>b</sup>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**<sup>a</sup> | **(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, CNPANAT1, NAGLU, LPIN3, ASRG1L1, HMGCS2 | 308            | NA, P=5e-7                         | (151)       |
| HDDA10        | FRZB, LEF1, SDCBP, WNT2, ING3, ANK3, MEIS2, ANXA4, PL2G7, CHD5 | 758            | 2.08 (1.2-3.6), P=0.008            | (152)       |
| 28-Gene hypoxia-related prognostic signature | ADAMTS4, ATF3, BHLHE40, BG2, 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     | SLC2A2A1, CGNL1, SUPV3L1, TATDN2, MGA4B, 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.

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.
tumor invasion and metastasis (195). In a multicentre (SChLAP1; LINC00913) is upregulated in PC and promotes activation (190).

and miR-5059 in cholangiocarcinoma, leading to MYCN tumorigenesis in part by sponging miR122‑5P in HCC (194) lung cancer (192), and others (193). LINC01296 facilitates cholangiocarcinoma (190), breast cancer (191), non-small cell observed in bladder cancer (187,188), gastric cancer (189), reported as a biomarker of CRC (186); its oncogenic activities association of lncRNA-ATB with BCR warrants further inves
carcinoma, breast cancer and others (184). Collectively, 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 BC 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 expression 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 IncRNA 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 IncRNA 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 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 invasa
tion (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 V) (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 anal
lysis (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
used to stratify the risk of BCR; the scores were calculated based on the following formula: Risk scores=$\sum (\text{coef}_i \times \text{DE-DE_i}),$ where $\text{DE-DE_i}$ is the $i^{th}$ DE-lncRNA expression ($i=1, … n$) and coef$_i$ is the Cox coefficient of DE-DE$_i$ (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-ASI’). 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 IncRNAs have been identified; the discovery rate has been significantly accelerated since 2013 (174). Although the field of IncRNA is new, it is clear that IncRNA affects tumorigenesis via complex mechanisms at the genome, RNA and protein levels (172,174). With respect to gene expression, the actions of IncRNAs 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 IncRNAs predict the risk of BCR; this will facilitate the formulation of IncRNA signatures with enhanced accuracy to stratify the risk of BCR. As an emerging and rapidly developing field, the biology of IncRNAs 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 negatives. 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 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 18F-PSMA-1007 PET/CT, the PET-positive rate was 86, 89, 100 and 100% for patients with PSA levels ≤0.5, 0.5-1.0, 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 a 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 [spT3a, 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 investigated 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: Phospho-AKT^{high}/MYC^{low} or phospho-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 regu- lated 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.

Acknowledgements

Not applicable.

Funding

DT was supported by grants from the Cancer Research Society, Canadian Cancer Society (grant no. 319412), CIHR and by funds from the Urological Cancer Center for Research and Innovation (UCCRI). PM was supported by CIHR. YG was supported by Studentship provided by Ontario Graduate Scholarships and Research Institute of St. Joe’s Hamilton.

Availability of data and materials

Not applicable.

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.

References

1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69: 7-34, 2019.
2. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, et al: EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 68: 467-470, 2014.
3. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, et al: EAU-ESTRO-SIOG Guidelines on prostate cancer. Part I: Screening, diagnosis, and local treatment with curative intent. Eur Urol 71: 618-629, 2017.
4. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, Nordling S, Häggman M, Andersson SS, Spängberg A, et al: Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 370: 932-942, 2014.
5. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Lee PA and McMahon PM: Observation versus initial treatment for men with localized, low-risk prostate cancer: A cost-effectiveness analysis. Ann Intern Med 158: 853-860, 2013.
6. Godtman RA, Holmberg E, Khatami A, Stranne J and Hugosson J: Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Göteborg randomised population-based prostate cancer screening trial. Eur Urol 63: 101-107, 2013.
7. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, Henry AM, Joniau S, Lam TB, Mason MD, et al: EAU-ESTRO-SIOG Guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 71: 630-642, 2017.
8. Zaorsky NG, Raj GV, Trabulsi EJ, Lin J and Den RB: The dilemma of a rising prostate-specific antigen level after local therapy: What are our options? Semin Oncol 40: 322-336, 2013.
9. Roehl KA, Han M, Ramos CG, Antenor JA and Catalona WJ: Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: Long-term results. J Urol 172: 910-914, 2004.
10. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC and Partin AW: Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 294: 433-439, 2005.
1. Kupelian PA, Mahadevan A, Reddy CA, Reuther AM and Klein EA: Use of different definitions of biochemical failure after external beam radiotherapy changes conclusions about relative treatment efficacy for localized prostate cancer. Urolgy 68: 593-598, 2006.

2. Artibani W, Porcaro AB, De Marco V, Cerruto MA and Siracusano S: Management of biochemical recurrence after primary curative treatment for prostate cancer: A review. Urol 100: 251-262, 2016.

3. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD and Walsh PC: Natural history of progression after PSA elevation following radical prostatectomy. JAMA 281: 1591-1597, 1999.

4. Boorjian SA, Thompson RH, Tellefson MK, Rangel LJ, Bergstralh EJ, Blake ML, and Karnes RJ: Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: The impact of time from surgery to recurrence. Eur Urol 59: 893-899, 2011.

5. Heinlein CA and Chang C: Androgen receptor in prostate cancer. Endocr Rev 25: 276-308, 2004.

6. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska E, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the TAX 327 study. J Clin Oncol 26: 242-245, 2008.

7. Du Chane J and Carroll PR, Cooperberg MR, Pasta DJ, Elkin EP, with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 364: 1995-2005, 2011.

8. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M and Tannock IF: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351: 1502-1512, 2004.

9. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chen KN, Jones RJ, Goodman OB Jr, Saad F, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364: 1995-2005, 2011.

10. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367: 1187-1197, 2012.

11. Cooperberg MR, Pasta DJ, Elkin EP, Litwin MS, Latini DM, Du Chane J and Carroll PR: The University of California, San Francisco Cancer of the Prostate Risk Assessment score: A straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 173: 1938-1942, 2005.

12. Braitbard JS, Leapman MS and Cooperberg MR: The CAPRA-S Score at 10 Years: Contemporary perspectives and analysis of supporting studies. Eur Urol 71: 705-709, 2017.

13. Cooperberg MR, Hilton JF and Carroll PR: The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer 117: 5039-5046, 2011.

14. D’Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Bean BJ, et al: Biochemical recurrence, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280: 969-974, 1998.

15. Dillioglugil O, Leibman BD, Kattan MW, Scale-Hawkins C, Wheeler TM and Scardino PT: Hazard ratios for progression after radical prostatectomy for clinically localized prostate cancer. Urology 50: 93-99, 1997.

16. Han M, Partin AW, Zahurak M, Pietrantonio S, Epstein JI and Walsh PC: Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. Urol 169: 517-525, 2008.

17. Simmons MN, Stephenson AJ and Klein EA: Natural history of biochemical recurrence after radical prostatectomy: Risk assessment for secondary therapy. Eur Urol 51: 1175-1184, 2007.

18. Lange PH, Ercole CJ, Lightner DJ, Fraley EE and Vessella R: The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urol 141: 873-879, 1989.

19. Kim DK, Koo KC, Lee KS, Hah YS, Rha KH, Hong SJ and Chung BH: Time to disease recurrence is a predictor of metastasis and mortality in patients with High-risk prostate cancer who achieved undetectable prostate-specific antigen following Robot-assisted radical prostatectomy. J Korean Med Sci 33: e285, 2018.

20. Walz J, Chan FK, Klein EA, Reuther A, Saad F, Graefen M, Huber H and Karakiewicz PI: Nomogram predicting the probability of early recurrence after radical prostatectomy for prostate cancer. J Urol 181: 601-608, 2009.

21. Popeo RS, Bandini M, Preissier F, Marchioni M, Zaffuto E, Tian Z, Salomon G, Schlimm T, Huland H, Graefen M, et al: Contemporary approach to predict early biochemical recurrence after radical prostatectomy: Upgrading the Walz nomogram. Prostate Cancer Prostatic Dis 21: 386-393, 2018.

22. Scher HI: Cancer cell cycles. Science 274: 1672-1677, 1996.

23. Ross AE, D’Amico AV and Freedland SJ: Which, when and why? Rational use of tissue-based molecular testing in localized prostate cancer. Prostate Cancer Prostatic Dis 19: 1-6, 2016.

24. Carneiro A, Barbosa ARG, Takemura LS, Kayapo PP, Moran NKS, Chen CK, Wroclawski ML, Lemos GC, da Cunha IW, Obara MT, et al: The role of immunohistochemical analysis as a tool for the diagnosis, prognostic evaluation and treatment of prostate cancer. Urology 87: 146-152, 2015.

25. Iatropoulos MJ and Williams GM: Proliferation markers. Exp Toxicol Pathol 48: 175-181, 1996.

26. Fantony JJ, Howard LE, Csizmadi I, Armstrong AJ, Lark AL, Galet C, Aeronon WJ and Freedland SJ: Is Ki67 prognostic for aggressive prostate cancer? A multicenter real-world study. Biomark Med 12: 727-736, 2018.

27. Wong N, Ojo D, Yan J and Tang D: PKM2 contributes to cancer metabolism. Cancer Lett 356: 184-191, 2015.

28. Carabat LA, Rennie PS and Cherkasov A: Therapeutic inhibition of msi in cancer. Structural and functional bases and future computer-aided drug discovery approaches. Int J Mol Sci 20: pii: E120, 2018.

29. Gurel B, Iwata T, Koh CM, Jenkins RB, Lan F, Van Dang C, Hicks JL, Morgan J, Cornish TC, Sultcliffe S, et al: Nuclear MYC protein overexpression is an early alteration in human prostate cancer. Neoplasia 12: 590-598, 2010.

30. Baena-De Valle JA, Zheng Q, Espanó DM, Rubenstein MB, Hubbard GK, Moncaliano MC, Hruszkewycz A, Vaghasia A, Yegnasubramanian S, Wheelan SJ, et al: MYC drives overexpression of telomerase RNA (hTR/TEIRC) in prostate cancer. J Pathol 244: 11-24, 2018.

31. Hubbard GK, Motton LN, Khalili M, McMullin RP, Hicks JL, Bianchi-Frias D, Horn LA, Kulac I, Moubarek MS, Nelson PS, et al: Combined MYC activation and pten loss are sufficient to create genomic instability and lethal metastatic prostate cancer. Cancer Res 76: 283-292, 2016.

32. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun W, Varambally S, Cao X, Rubin MA, Shah RB, et al: Recurrence of TP53 in prostate cancer. Science 300: 644-648, 2003.

33. Park K, Tomlins SA, Mudalil KM, Chun YL, Esghially S, Mehra R, Saleman K, Varambally S, Peonen JC, MacDonald T, et al: Antibody-based detection of ERG rearrangement-positive prostate cancer. Neoplasia 12: 590-598, 2010.

34. Inoue T, Segawa T, Shiraishi T, Yoshida T, Toda Y, Yamada T, Kimukawa N, Kinoshita H, Kanno T and Ogawa O: Androgen receptor, Ki67, and p53 expression in radical prostatectomy specimens predict treatment failure in Japanese population. Urology 66: 332-337, 2005.

35. Osman I, Drobnjak M, Fazzari M, Ferrara J, Scher HI and Cordon-Cardo C: Inactivation of the p53 pathway in prostate cancer: Impact on tumor progression. Clin Cancer 5: 2082-2088, 1999.

36. Hemminki K: Familial risk and familial survival in prostate cancer. World J Urol 30: 143-148, 2012.

37. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, Mahmud M, Dadaev T, Govindasami K, Gupta R, et al: Germline BRCA2 mutations drive prostate cancer. Nat Commun 10: 1-11, 2019.

38. Fantoni CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Barbero H, Garotelo A, Gulati R, Carrasco S, Eccles R, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375: 443-453, 2016.
High expression of... DNA damage and repair pathway profiles and prognosis after prostatectomy for high-risk prostate cancer. JAMA Oncol 2: 471-480, 2016.

Maggi-Galluzzi C, Tsuiki T, Elson P, Zimmerman K, Lafargue C, Esposito R, Klein E, Rubin MA and Zhou M: TMRPR52-E2G gene fusion prevalence and class are significantly different in prostate cancer of Caucasian, African-American and Japanese patients. Prostate 71: 489-497, 2011.

Ren S, Peng Z, Mao JH, Yu Y, Yin C, Gao X, Cui Z, Zhang J, Yi K, Xu W, et al: RNA-seq analysis of prostate cancer in the Chinese population identifies recurrent gene fusions, cancer-associated long noncoding RNAs and aberrant alternative splicings. Cell Res 22: 806-821, 2012.

Song C and Chen H: Predictive significance of TMRPR52-E2G fusion in prostate cancer: A meta-analysis. Cancer Cell Int 18: 173, 2018.

Shamseer L, Moher D, Clarke L, Gheris D, Liberati A, Petticrew M, Shkekelle P and Stewart LA; PRISMA-P Group: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 350: g7647, 2015.

Shamseer L, Moher D, Clarke M, Petticrew M, Shkekelle P and Stewart LA; PRISMA-P Group: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: statement. Syst Rev 4: 1, 2015.

Nam RK, Benatar T, Wallis CJ, Fan J, Yang S, Chen C and Wang DW: MicroRNA-30c serves as an independent prognostic marker for biochemical recurrence and predicts advanced tumor stage in prostate cancer. PLoS One 6: e20293, 2011.

Mo RJ, Han ZD, Liang YK, Ye JH, Wu SL, Lin SX, Zhang YQ, Song SD, Jiang FN, Zhong WD and Wu CL: Expression of PD-L1 in tumor-associated lymphocytes correlates with reduced CD8+ tumor-associated lymphocytes and poor prognosis in prostate cancer. Int J Cancer 144: 3099-3110, 2019.

Gevensleben H, Dietrich D, Golletz C, Steiner S, Jung M, Thiesler T, Majores M, Stein J, Uhl B, Müller S, et al: The immune checkpoint regulator PD-L1 is highly expressed in aggressive primary prostate cancer. Clin Cancer Res 22: 1969-1977, 2016.

Luo JH, Yu YP, Cieply K, Lin F, Deflavia P, Dhir R, Finkelstein S, Michelopoulos G and Becich M: Gene expression analysis of prostate cancers. Mol Carcinog 33: 25-35, 2002.

Sandmark E, Andersen MK, Bofin AM, Bertilsson H, Drabløs F, Bathen TF, Rye MB and Tøssem MB: SFRP4 gene expression is increased in aggressive prostate cancer. Sci Rep 7: 14276, 2017.

Mortensen MM, Hayer S, Lyumpern AS, Ørntoft TF, Sørensen KD, Borre M and Dysrødt L: Expression profiling of prostate cancer tissue delineates genes associated with recurrence after prostatectomy. Scie Rep 5: 16018, 2015.

Mazzoni SM and Fearon ER: AXIN1 and AXIN2 variants in gastrointestinal cancers. Cancer Lett 355: 1-8, 2014.

Li J, Hu SB, Wang LY, Zhang X, Zhou X, Yang B, Li JH, Xiong J, Liu N, Li Y, et al: Autophagy-dependent generation of AXIN2+ cancer stem-like cells promotes hepatocarcinogenesis in liver cirrhosis. Oncogene 36: 6725-6737, 2017.

Martins-Neves SR, Corver WE, Paiva-Oliveira DI, van den Akker BE, Briare-de Bruijn IH, Bovée JV, Gomes CM and Clleton-Jansen AM: Osteosarcoma stem cells have active Wnt/β-catenin signaling and express SOX2 and KLF4. J Cell Physiol 231: 876-886, 2016.

Lim X, Tan SH, Yu KL, Lim SB and Nusse R: AXIN2 marks quiescent hair follicle bulge stem cells that are maintained by autocrine Wnt/β-catenin signaling. Proc Natl Acad Sci USA 113: E1498-E1505, 2016.

Ma C, Liu C, Huang P, Kaku H, Chen J, Guo K, Ueki H, Sakai A, Nasu Y, Kumon H, et al: Significant association between the AXIN2 rs2240308 single nucleotide polymorphism and the incidence of prostate cancer. Oncol Lett 8: 789-794, 2014.

Hu BR, Fairey AS, Madhav A, Yang D, Li M, Grossen S, Stephens C, Kim PH, Virk N, Wang L, Ling XH, Han ZD, Xia D, Yu Y, Yin C, Gao X, Cui Z, Zhang J, Yi K, Xu W, et al: RNA-seq analysis of prostate cancer in the Chinese population identifies recurrent gene fusions, cancer-associated long noncoding RNAs and aberrant alternative splicings. Cell Res 22: 806-821, 2012.

Shibue T and Weinberg RA: EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. Nat Rev Clin Oncol 14: 611-629, 2017.

Mei W, Lin X, Kapoor A, Gu Y, Zhao K and Tang D: The contributions of prostate cancer stem cells in prostate cancer initiation and metastasis. Cancers (Basel) 11: pii: E434-199, 2019.

Yan Y, Guo Y, Zhao ZQ: miR-21 affects the differentiation and migration of human osteosarcoma cells. Mol Carcinog 231: 876-886, 2016.

Zhou C, Hou X, Zhu J, Jiang C and Wei W: Expression of miR-30c and miR-29b in prostate cancer and its diagnostic significance. Oncol Lett 16: 3140-3144, 2018.

Sachdeva M, Liu Q, Cao J, Lu Z and Mo Y: Negative regulation of miR-145 by C/EBPβ dampens the Akt pathway in cancer cells. Nucleic Acids Res 40: 6683-6692, 2012.

Ozen M, Creighton CJ, Ozdemir M and Ittmann M: Widespread deregulation of microRNA expression in human prostate cancer. Oncogene 27: 1789-1793, 2008.

Wach N, Nolte E, Puczyczka J, Stöhr R, Hartmann A, Örtftot T, Dryskt J, Eltze E, Wieland W and Keck B: MicroRNA profiles of prostate carcinoma detected by multiplatform microRNA screening. Int J Cancer 130: 611-621, 2012.

Liu B, Li J and Cairns MJ: Identifying miRNAs, targets and mechanisms that enhance chemoresistance. Brief Funct Genomics 15: 1-19, 2016.

Chen CS, Huang CY, Huang SP, Lin VC, Yu CC, Chang TY and Bao BY: Genetic interaction analysis of TCFT7L2 for biochemical recurrence after radical prostatectomy in localized prostate cancer. Int J Med Sci 12: 243-247, 2015.

Malhotra S, Lapointe J, Salari K, Higgins JP, Ferrari M, Montgomery K, van de Rijn M, Brooks JD and Pollack JR: A tri-marker proliferation index predicts biochemical recurrence after surgery for prostate cancer. PLoS One 6: e20293, 2011.

Mo RJ, Han ZD, Liang YK, Ye JH, Wu SL, Lin SX, Zhang YQ, Song SD, Jiang FN, Zhong WD and Wu CL: Expression of PD-L1 in tumor-associated lymphocytes correlates with reduced CD8+ tumor-associated lymphocytes and poor prognosis in prostate cancer. Int J Cancer 144: 3099-3110, 2019.

Gevensleben H, Dietrich D, Golletz C, Steiner S, Jung M, Thiesler T, Majores M, Stein J, Uhl B, Müller S, et al: The immune checkpoint regulator PD-L1 is highly expressed in aggressive primary prostate cancer. Clin Cancer Res 22: 1969-1977, 2016.

Luo JH, Yu YP, Cieply K, Lin F, Deflavia P, Dhir R, Finkelstein S, Michelopoulos G and Becich M: Gene expression analysis of prostate cancers. Mol Carcinog 33: 25-35, 2002.
Neuropilin-1 is upregulated in the adaptive response.

Neuropilin 1 binds PDGF-D and VEGFR1 and NRP1 endothelial expressions predict distant metastases.

PLag1 and PLagl2 are oncogenes that induce cell proliferation of small cell lung cancer through beta-catenin signaling.

Expression profiling of intrahepatic cholangiocarcinoma.

Early growth response 4 promoters in prostate cancer. Tumour Biol 35: 3333-3337, 2014.

Zheng H, Ying H, Wiedemeyer R, Yan H, Quayle SN, Ivanova EV, Park JH, Zhang H, Xiao Y, Perry SR, et al.: PLAGL2 regulates Wnt signaling and predicts prostate cancer.

J. Biol. Chem. 293: 3892-3903, 2018.

PLoS One 11: e0158667, 2016.

PLoS One 12: e0175355, 2017.

Watanabe T, Kobunai T, Akiyoshi T, Matsuda K, Ishihara S and Nozawa K: Prediction of response to preoperative chemoradiotherapy in rectal cancer by using reverse transcriptase-polymerase chain reaction analysis of four genes. Dis Colon Rectum 57: 23-31, 2014.

PLoS One 11: e0158667, 2016.

PLoS One 12: e0175355, 2017.

Wang Y, Shang Y, Li J, Chen W, Li G, Wan J, Liu W and Zhang M: Specific Eph receptor-cytosolic effector signaling mediated by SAM-SAM domain interactions. Elle 7: pii: e35677, 2018.

Ding Z, Wu CJ, Chu GC, Xiao Y, Ho D, Zhang J, Perry SR, Ladrin ES, Xu X, Liu H, Liu W, et al.: SMAD4-dependent barrier constrains prostate cancer growth and metastatic progression. Nature 470: 269-273, 2011.

Zheng DT, Shi JG, Liu Y and Jiang HM: The prognostic value of Smaa4 mRNA in patients with prostate cancer. Tumour Biol 35: 3333-3337, 2014.

Guo J, Wang M, Wang Z and Liu X: Overexpression of pleomorphic adeno gene-like 2 is a novel poor prognostic marker of prostate cancer. PLoS One 11: e0158667, 2016.

PLoS One 12: e0175355, 2017.
Prolaris cell cycle progression test for prostate cancer: A healthcare technology assessment. Ont Health Technol Assess Ser 17: 1-75, 2017.

Cui H, Jiang Y, Major P and Tang D: Construction of a set of novel robust gene expression signatures predicting prostate cancer recurrence. Mol Oncol 12: 1559-1578, 2018.

Klein EA, Cooperberg MR, Magi-Galluzzi C, Simko JP, Falzaroni SM, Maddala T, Chan JM, Li J, Cowan JE, Tsatis AC, et al: A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 66: 559-566, 2014.

Cuzick J, Swanson GP, Fisher G, Brothman AR, Berney DM, Reid JE, Mesher D, Speights VO, Stankiewicz E, Foster CS, et al: Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: A discovery and validation study. Lancet Oncol 12: 245-255, 2011.

Oderda M, Cozzi G, Daniele L, Sapino A, Munegato S, Renne G, De Cobelli O and Gontero P: Cell-cycle Progression-Score might improve the current risk assessment in newly diagnosed prostate cancer patients. Urology 102: 73-78, 2017.

Albala D, Kemerer MJ, Feltig PB, Lu R, John V, Stoy D, Denes B, McCall M, Shindel AW and Dubek F: Health economic impact and prospective clinical utility of the Oncotype DX genomic prostate score. Rev Urol 18: 123-132, 2016.

Cullen J, Rosner IL, Brand TC, Zhang N, Tsatis AC, Moncur J, Ali A, Chen Y, Knezevic D, Maddala T, et al: A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. Eur Urol 68: 123-131, 2015.

Cooperberg MR, Simko JP, Cowan JE, Reid JE, Djuliblavad A, Bhatnagar S, Guttin A, Lanchbury JS, Swanson GP, Stone S and Carroll PR: Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol 31: 1428-1432, 2013.

Van Den Eeden SK, Lu R, Zhang N, Quesenberry CP Jr, Shan J, Hsu SS, Tsuchida H, Leimpter G, Lu R, John V, HF, Feltig PB and Presti JC: A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. Eur Urol 73: 129-138, 2018.

Eggenger S, Karsh LI, Richardson T, Shindel AW, Lu R, Rosenberg S, Goldischer E, Korman H, Bennett J, Newmark J, Quesenberry CP Jr, Shan J, Hsu SS, Tsuchida H, Leimpter G, Lu R, John V, HF, Feltig PB and Presti JC: A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. Eur Urol 73: 129-138, 2018.

Lin X, Gu Y, Kapoor A, Wei F, Yan J, Aziz T, Zheng M, Jayasekera D, Cutz JC, Chow MJ and Tang D: Amplification of MUC1 in prostate cancer metastasis and CRPC development. Oncotarget 7: 83115-83133, 2016.

Lin X, Gu Y, Kapoor A, Wei F, Aziz T, Ojo D, Jiang Y, Bonert M, Shayegan B, Yang H, et al: Overexpression of MUC1 and genomic alterations in its network associate with prostate cancer progression. Neoplasia 19: 3383-3393, 2014.

Eminaga O, Wei W, Hawley SJ, Auman H, Newcomb LF, Simko J, Hurtado-Coll A, Troyer DA, Carroll PR, Carroll PR, et al: MUC1 expression by immunohistochemistry is associated with adverse pathologic features in prostate cancer: A Multi-institutional Study. PLoS One 11: e0165236, 2016.

Wong N, Major P, Kapoor A, Wei F, Yan J, Aziz T, Zheng M, Jayasekera D, Cutz JC, Chow MJ and Tang D: Amplification of MUC1 in prostate cancer metastasis and CRPC development. Oncotarget 7: 83115-83133, 2016.

Lin X, Gu Y, Kapoor A, Wei F, Aziz T, Ojo D, Jiang Y, Bonert M, Shayegan B, Yang H, et al: Overexpression of MUC1 and genomic alterations in its network associate with prostate cancer progression. Neoplasia 19: 3383-3393, 2014.

Eminaga O, Wei W, Hawley SJ, Auman H, Newcomb LF, Simko J, Hurtado-Coll A, Troyer DA, Carroll PR, Carroll PR, et al: MUC1 expression by immunohistochemistry is associated with adverse pathologic features in prostate cancer: A Multi-institutional Study. PLoS One 11: e0165236, 2016.

Wong N, Major P, Kapoor A, Wei F, Yan J, Aziz T, Zheng M, Jayasekera D, Cutz JC, Chow MJ and Tang D: Amplification of MUC1 in prostate cancer metastasis and CRPC development. Oncotarget 7: 83115-83133, 2016.

Lin X, Gu Y, Kapoor A, Wei F, Aziz T, Ojo D, Jiang Y, Bonert M, Shayegan B, Yang H, et al: Overexpression of MUC1 and genomic alterations in its network associate with prostate cancer progression. Neoplasia 19: 3383-3393, 2014.

Eminaga O, Wei W, Hawley SJ, Auman H, Newcomb LF, Simko J, Hurtado-Coll A, Troyer DA, Carroll PR, Carroll PR, et al: MUC1 expression by immunohistochemistry is associated with adverse pathologic features in prostate cancer: A Multi-institutional Study. PLoS One 11: e0165236, 2016.

Wong N, Major P, Kapoor A, Wei F, Yan J, Aziz T, Zheng M, Jayasekera D, Cutz JC, Chow MJ and Tang D: Amplification of MUC1 in prostate cancer metastasis and CRPC development. Oncotarget 7: 83115-83133, 2016.
169. Gong M, Xu Y, Dong W, Guo G, Ni W, Wang Y, Wang Y and An R: Expression of Opa interacting protein 5 (OIP5) is associated with tumor stage and prognosis of clear cell renal cell carcinoma. Acta Histochem 115: 810-815, 2013.

170. Chen HH, Hsiao KS, Kim HC, Kang JE, Kang MA, Kim JT, Choi EH, Jung KE, Kim HM, Song EY, et al: OIP5 is a highly expressed potential therapeutic target for colorectal and gastric cancers. BMC Rep 43: 349-354, 2010.

171. Mobasher MI, Shirkooi R and Modarressi MH: Cancer/Tests OIP5 and OIP7: Genes are Upregulated in breast cancer. Asian Pac J Cancer Prev 16: 4623-4628, 2015.

172. Lópeza-Urrutía E, Bustamante Montes LP, Ladrón de Guevara Cervantes D, Pérez-Plasencia C and Campos-Parra AD: Crosstalk between long Non-coding RNAs, Micro-RNAs and mRNAs: Deciphering molecular mechanisms of master regulators in cancer. Front Oncol 9: 669, 2019.

173. Salmena L, Poliseno L, Tay Y, Kats L and Pandolfo PP: A cRNA hypothesis: The Rosetta stone of a hidden RNA language? Cell 146: 353-358, 2011.

174. Ramiz-Marina VR, Kobelev M, Gibb EA, Nouri M, Lin D, Wang Y, Buttyn R, Davicieni E, Zoubeidi A and Collins CC: The evolution of long noncoding RNA acceptance in prostate cancer initiation and progression, and its clinical utility in disease management. Eur Urol: Aug 22, 2019 (Epub ahead of print).

175. Bussemakers MJ, van Bokhoven A, Verheagh GW, Smit FP, Karthaus HF, Schalken JA, Debruyne FM, Ru N and Isaacs WB: DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Res 59: 5975-5979, 1999.

176. Crawford ED, Rove KO, Trabulsi EJ, Qian J, Drewnowska KP, Kato N, Koyama T, Kim H, Tkachuk T, Bilowus ML, Predmore SJ, Glover WL Jr and Bostwick DG: Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: A prospective study of 1962 cases. J Urol 188: 1726-1731, 2012.

177. Duras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H and Groskopf J: PCA3: A molecular urinary assay for predicting prostate biopsy outcome. J Urol 179: 1587-1592, 2008.

178. Gittelman MC, Hertzman B, Bailen J, Rybicki LA, Davis KM, Magnuson T: SWI/SNF remains localized to chromatin in the absence of ATP hydrolysis. Cancer Res 73: 5692-5700, 2013.

179. Hondros GM, Mahaffey J, McCombs B, Vogel CL, Pfaltz RN, Breznay RE, Koo S, Partin AW, Day JR, Koo S, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H and Groskopf J: PCA3: A molecular urinary assay for predicting prostate biopsy outcome in men with previous negative biopsies: A prospective multicenter clinical study. J Urol 190: 64-69, 2013.

180. Mu A, Chen X, Ding L, Ma J, Jing W, Lan T, Sattar H, Wei Y, Zhou F and Yuan Y: The prognostic value of long noncoding RNAs in prostate cancer: A systematic review and meta-analysis. Oncotarget 8: 5775-57765, 2017.

181. Xu S, Yi XM, Tang CP, Ge JP, Zhang ZY and Zhou WQ: Long non-coding RNA-ATB in cancers: A meta-analysis. Int J Mol Sci 18: 1469-1480, 2017.

182. Ma W, Chen X, Ding L, Ma J, Jing W, Lan T, Sattar H, Wei Y, Zhou F and Yuan Y: The prognostic value of long noncoding RNAs in prostate cancer: A systematic review and meta-analysis. Oncotarget 8: 5775-57765, 2017.

183. Wang J, Cheng G, Li X, Pan Y, Qin C, Yang H, Hua L and Wang Z: Overexpression of long non-coding RNA LOC400891 promotes tumor progression and poor prognosis in prostate cancer. Tumour Biol 37: 9603-9613, 2016.

184. Hu J, Chen L, Hu Q, Guo H and Yu C: Involvement of SRPK1 in cisplatin resistance related to long non-coding RNA UCA1 in human ovarian cancer cells. Neoplasma 62: 432-438, 2015.

185. Zhang Q, Wu F, Dai WY, Zheng DC, Zheng C, Ye H, Zhou B, Chen JJ and Chen P: Aberrant expression of UCA1 in gastric cancer and its clinical significance. Clin Transl Oncol 17: 640-646, 2015.

186. Tian Y, Zhang X, Hao Y, Fang Z and He Y: Potential roles of abnormally expressed long non-coding RNA UCA1 and Malat-1 in metastasis of melanoma. Melanoma Res 24: 335-341, 2014.

187. Chen P, Wan D, Zheng D, Zheng Q, Wu F and Zhi Q: Long non-coding RNA UCA1 promotes the tumorogenesis in pancreatic cancer. Biomed Pharmacother 83: 1220-1226, 2016.

188. Wang K, Zhang M, Wang C and Ning X: Long Noncoding RNA LINCOLN1296 Harbors miR-21a to regulate colon carcinoma proliferation and invasion. Oncol Rep 27: 541-549, 2019.

189. Qin QH, Yin ZQ, Li Y, Wang BG and Zhang MF: Long intergenic noncoding RNA 01296 aggravates gastric cancer cell invasion and migration. FEBS Lett 593: 1901-1914, 2019.
Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases.
Diagnostic performance of statin use after radical prostatectomy: A phospho–Akt immunoreactivity in AKT1 of PI3 kinase related kinases (PIKKs) in DNA damage response. Biomolecules 5: 3396-3415, 2015.

Lin X, Ojo D, Wei F, Wong N, Gu Y and Tang D: A novel aspect of genome instability in cancer. Cancer Metastasis Rev 32: 37-51, 2013.

Persson JL: Overcoming drug resistance and treating advanced prostate cancer with salvage treatment after radical prostatectomy. Eur J Urol 70: 588-596, 2016.

Spratt DE, Dess RT, Zumsteg ZS, Lotan Y, Briganti A, Loidl W, Faison T et al: Contemporary update of a Multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. J Clin Oncol 34: 3648-3654, 2016.

Lin DW, Montorsi F, Lin X, Gu Y and Tang D: BMI1, ATM and DDR. Oncoscience 2: 375-384, 2009.

Hematol Oncol Stem Cell Ther 2: 375-384, 2009.

Lin X, Ojo D, Wei F, Wong N, Gu Y and Tang D: A novel aspect of tumorigenesis-BMI1 functions in regulating DNA damage response. Biomolecules 5: 3396-3415, 2015.

Lin X, Lan J and Tang D: ERK, kinases modulate the activation of PI3 kinase related kinases (PIKKs) in DNA damage response. Histol Histopathol 28: 1547-1554, 2013.