



Review

A review on the role of PCA3 lncRNA in carcinogenesis with an especial focus on prostate cancer

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ABSTRACT

The prostate cancer antigen 3 (PCA3) is a long non-coding RNA (lncRNA) with high level of specificity for prostate cancer. This lncRNA has fundamental effects in the prostate carcinogenesis through modulation of expression of miR-132-3p, miR-1261, SREBP1, PRKD3 and LAP2 α as well as regulation of p53 signaling. Expression of PCA3 in prostate cancer cells can be enhanced by Snail. Moreover, in vitro studies have documented up-regulation of PCA3 in three other types of neoplastic cells, namely those being originated from choriocarcinoma, ovarian carcinoma and thyroid carcinoma. The diagnostic value of PCA3 in differentiation of prostate cancer from benign prostate hyperplasia has been assessed in different studies. Studies aimed at identification of diagnostic power of PCA3 in prostate cancer using receiver operating characteristic curves have reported area under curve values ranging from 0.66 to 0.86. In the current review, we describe the role of PCA3 in the carcinogenesis particularly in the pathoetiology of prostate cancer. Moreover, we review the results of studies appraising diagnostic value of this lncRNA in prostate cancer.

1. Introduction

The prostate cancer antigen 3 (PCA3) is a long non-coding RNA (lncRNA) firstly recognized as an up-regulated gene in prostate cancer tissues in 1999 [8]. Since it was absent from normal tissues of different origins or neoplastic tissues originated from bladder, breast, cervix, endometrium, kidney, ovary, or testis [49], it has been regarded as marker for prostate cancer. Being located on chr9:76692287–76863019, it has at least 18 transcripts with sizes ranging from 322 bp (PCA3–217, ENST00000647409.1) to 3922 bp (PCA3–201, ENST00000412654.1). All of these transcripts have been attributed to lncRNA group of transcripts (http://asia.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000225937;r=9:76691980–76863307). PCA3 has gained much attention as a biomarker for prostate cancer that commercial kits for assessment of its expression has been designed and applied in the clinical settings since being approved by the USA Food and Drug

Administration (FDA) [74]. The diagnostic value and biomarker of PCA3 is the possibility for its detection in urine and urine exosomes in a non-invasive manner. The advent of clinically applicable measurement tools for PCA3 has been an important success in the translation of basic science into clinical use.

Several studies have verified the oncogenic effects of PCA3 in prostate cancer and identified the cellular and molecular pathways being regulated by this lncRNA. Moreover, in vitro studies have documented up-regulation of PCA3 in three other types of neoplastic cells, namely those being originated from choriocarcinoma, ovarian carcinoma and thyroid carcinoma casting doubt on the assumption of prostate specific nature of this lncRNA. In the current review, we describe the role of PCA3 in the carcinogenesis particularly in the pathoetiology of prostate cancer.

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2. Prostate cancer

In an effort to find the underlying mechanism of participation of PCA3 in prostate carcinogenesis, Lin et al. have up-regulated PCA3 expression in the PC3 cell line and compared proliferation ability, migratory potential, invasiveness and apoptosis of these cell with those of control cells. They have shown that PCA3 up-regulation increases proliferation, migration and invasiveness of PC3 cells, while inhibiting their apoptosis. Moreover, up-regulation of PCA3 has resulted in differential expression of a number of structural constituents of cytoskeleton, chaperons, isomerase as well as those with antioxidant activity. GRP78 has been among up-regulated proteins following PCA3 over-expression [45].

Expression of PCA3 has been found to be increased in LNCaP cells in response to long-term exposure to the environmental pollutant antimony. Up-regulation of PCA3 could increase antimony-associated alterations in cell proliferation and cellular contents of triglyceride and cholesterol. Moreover, expression level of PCA3 has been negatively correlated with miR-132-3p levels. PCA3 has been found to increase antimony-associated changes in lipid metabolism in prostate cancer cells through influencing miR-132-3p/SREBP1 axis [29]. Another study in LNCaP cells has shown changes in expression of several cancer-related genes such as those regulating epithelial-mesenchymal transition (EMT) as well as androgen receptor (AR) cofactors following PCA3 silencing. A short hairpin RNA sequence against PCA3 could decrease viability of LNCaP cells, suggesting PCA3 silencing as a therapeutic method for suppression of prostate cancer growth [41]. Another study in this cell line has shown the impact of the transcription factor Snail in activation of PCA3 expression. PCA3 silencing has led to up-regulation of miR-1261 levels and subsequent down-regulation of PRKD3 expression, suggesting the competing endogenous RNA (ceRNA) role for PCA3 [33]. Moreover, PCA3 has been found to regulate PRUNE2 expression through a distinctive route comprising establishment of a PRUNE2/PCA3 double-stranded RNA that is further subjected to adenosine deamination. In fact, this mechanism involves adenosine-to-inosine RNA editing system. PRUNE2 up-regulation or knock-down could decrease and increase proliferation of prostate cancer cells, respectively. Besides, PRUNE2 and PCA3 have been shown to exert opposite impacts on tumor growth in xenograft models. Cumulatively, PCA3 acts as a

dominant-negative oncogene, while PRUNE2 is a newly identified tumor suppressor gene prostate cancer [73]. Another route of participation of PCA3 in the pathogenesis of prostate cancer is mediated through interaction of PCA3 with the C-terminal region of LAP2 α . The C-terminal region of this protein binds pRb- and lamin to stabilize the lamin A in nucleoplasmic compartments. Through binding with the C-terminal region of LAP2 α , PCA3 blocks the interaction between LAP2 α and lamin A. PCA3 silencing could enhance the levels of nucleoplasmic lamin A/C and increase nuclear level of LAP2 α . Moreover, HP1 γ levels, as well as H3K9me3 and H3K36me3 amounts have been increased in PCA3-silenced cells. On the other hand, H3K4me3 has been decreased in these cells. Absence of PCA3 could also result in induction of the p53 signaling and activation of cell cycle arrest [37]. PCA3 silencing could also reduce expressions AR-associated genes, including prostate-specific antigen (PSA) and PCGEM1 lncRNA. Moreover, PCA3 knock down has enhanced effects of enzalutamide in prostate cancer cells and suppressed proliferation of prostate cancer cells, particularly the AR positive LNCaP cells [61].

Fig. 1 depicts the underlying mechanisms of oncogenic roles of PCA3 in prostate cancer.

Dihydrotestosterone (DHT) has been shown to robustly stimulates expression of PCA3, while its effects on PSA and miR-141 levels have been weaker, indicating differential regulation AR-related transcripts by androgen stimulation [26]. Meanwhile, PCA3 has been found to participate in the regulation of survival of prostate cancer cells partly via modulation of AR signaling, which indicates possibility of using PCA3 silencing as an additional treatment modality for prostate cancer [19]. Table 1 summarizes the role of PCA3 in prostate cancer cell lines.

3. Other types of cancer

PCA3 levels have been found to be increased in choriocarcinoma cells compared with normal chorionic trophoblast cells. Functionally, PCA3 enhances proliferation, migratory aptitude and invasiveness of gestational choriocarcinoma and induced EMT in these cells through acting as a ceRNA for miR-106b and release MMP2 from its inhibitory impact [89].

Another experiment in epithelial ovarian cancer cells has shown that siRNA-mediated silencing of PCA3 suppresses proliferation and

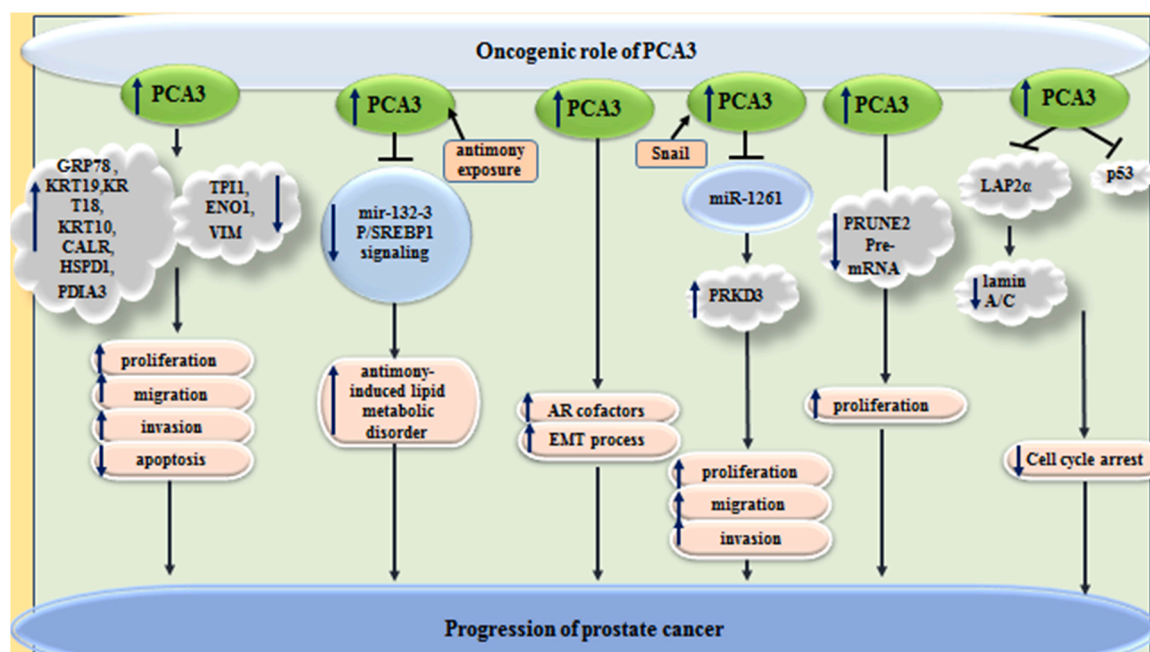


Fig. 1. Oncogenic roles of PCA3 in prostate cancer.

Table 1

The role of PCA3 in prostate cancer cell lines (Δ : knock-down or deletion, DHT: dihydrotestosterone).

Tumor type	Targets/Regulators and Signaling Pathways	Cell line	Function	Reference
Prostate cancer	GRP78, KRT19, KRT18, KRT10, CALR, HSPD1, PDIA3, TPI1, ENO1, VIM	PC3	\uparrow PCA3: \uparrow proliferation, \uparrow migration, \uparrow invasion, \downarrow apoptosis	[45]
		LNcaP	long-term antimony exposure: \uparrow PCA3: \uparrow antimony-induced lipid metabolic disorder	[29]
	-	LNcaP	\uparrow PCA3: \uparrow AR cofactors, \uparrow EMT process	[41]
	miR-1261, Snail, PRKD3	LNcaP	Δ PCA3: \downarrow proliferation, \downarrow migration, \downarrow invasion	[33]
	PRUNE2	LNcaP and PC3	Δ PRUNE2: \uparrow proliferation, (PCA3 Binds PRUNE2 Pre-mRNA and reduced its levels)	[73]
	LAP2 α , nucleoplasmic lamin A/C, HP1 γ , p53 signaling pathway	C4-2, C4-2B, LNcaP, DU145, PC3	Δ PCA3: \downarrow proliferation, \uparrow cell cycle arrest PCA3: controls chromatin organization	[37]
	-	LNcaP, LNcaP-AR+ and VCaP	Δ PCA3: \uparrow enzalutamide-mediated down-regulation of AR-related genes, \uparrow sensitivity to enzalutamide, \downarrow proliferation	[61]
	-	LNcaP	DHT treatment: \uparrow PCA3	[26]
	-	NcaP, PC3	Δ PCA3: \downarrow growth \downarrow viability, \downarrow AR target genes, \uparrow G0/G1 phase arrest, \uparrow percentage of pyknotic nuclei	[19]
	-	LNcaP	DHT treatment: \uparrow PCA3	[77]

malignant behavior of these cells, increases levels of miR-106b and decreases RhoC, Bcl/xl, P70S6K, and MMP2 levels. In fact, PCA3 has been identified as a ceRNA for miR-106b [48].

Moreover, in papillary and anaplastic thyroid carcinomas, TGF- β has been shown to increase levels of PCA3. This lncRNA has been identified as a putative oncogenes in this type of cancer [90]. Table 2 shows the results of in vitro studies in cancers other than prostate cancer.

4. Studies in human samples

In addition to PCA3, a short ncRNA has been found to be expressed from intron 1 of PCA3. This ncRNA has been named as PCA3-shRNA2 RNA. Expression of PCA3-shRNA2 has been shown to be elevated in malignant prostate tissues and exfoliated urinary cells from prostate cancer patients. Besides, its expression has been strongly correlated with expression of PCA3. Urinary levels of PCA3-shRNA2 and PCA3 have

Table 2

Role of PCA3 in other types of cancers (Δ : knock-down or deletion).

Tumor type	Targets/Regulators and Signaling Pathways	Cell line	Function	Reference
choriocarcinoma	miR-106b, MMP2	HTR-8, JAR, BeWo, JEG-3	Δ PCA3: \downarrow proliferation, \downarrow migration, \downarrow invasion, \downarrow viability, \downarrow EMT process	[89]
ovarian carcinoma	miR-106b-5p, RhoC, P70S6K, MMP2	OVCAR3, A2780, HEK293T	Δ PCA3: \downarrow proliferation, \downarrow migration, \downarrow invasion	[48]
thyroid carcinoma	-	8505 C, THJ-16 T	TGF- β treatment: \uparrow PCA3	[90]

been able to predict existence of cancer in the majority of suspected individuals. Expression of PCA3-shRNA2 has been inversely correlated with expression of COPS2, a mRNA coding gene which has been predicted to be targeted by PCA3-shRNA2 [17].

Moreover, another study has reported expression of PSA and PCA3-shRNA2 RNA in all examined clinical samples from prostate cancer patients. Moreover, PCA3 RNA has been detected in 90% of biopsied samples. Expressions of PCA3 and PCA3-shRNA2 have been correlated with each other. Most notably, authors have reported up-regulation of PCA3 in men who have been diagnosed as having prostate cancer on subsequent biopsy. In fact, PCA3 has been associated with the upcoming detection of prostate cancer. The observed correlation between PCA3 and PCA3-shRNA2 in clinical samples suggests co-expression of these ncRNAs [62]. Several other studies have demonstrated up-regulation of this lncRNA in clinical samples of prostate cancer patients compared with normal controls, patients with benign prostate hyperplasia (BPH) or patients with urolithiasis (Table 3). Notably, expression levels of PCA3 have been correlated with total tumor volume, apical and basal invasion as well as bilaterality and multifocality of tumors [87]. Although most of performed studies are consistent with this finding, an exploratory analysis of data from more than 12,000 patients has shown a bimodal distribution of PCA3 levels in biopsied and radical prostatectomy tissues, where low levels of PCA3 have been remarkably associated with high grade disease. Moreover, in radical prostatectomy tissues low levels of this lncRNA have been associated with adverse pathological characteristics, tumor recurrence and higher possibility of metastasis [2].

Urine-based assessment of PCA3 has been demonstrated to be superior to PSA in terms of diagnostic performance in men with a former negative biopsy [32,50]. Studies aimed at identification of diagnostic power of PCA3 in prostate cancer using receiver operating characteristic (ROC) curves have reported area under curve values ranging from 0.66 [84] to 0.86 [52]. A relatively recent meta-analysis has shown the pooled sensitivity, specificity, and diagnostic values of PCA3 to be 0.71, 0.68, and 5.28, respectively. Notably, this study has reported area under the summary ROC curve as 0.75. Cumulatively, this meta-analysis has shown moderate sensitivity and specificity values for PCA3 in prostate cancer diagnosis [40]. Table 4 summarizes the diagnostic value of PCA3 in prostate cancer.

Three independent studies have reported up-regulation of PCA3 in clinical samples obtained from patients with ovarian cancer [48], thyroid cancer [90] and chronic myeloid leukemia [71]. Yet, correlations between expression levels of PCA3 and clinicopathologic data or patient's prognosis have not been studied in these malignancies.

Table 3

Results of studies that reported dysregulation of PCA3 in human prostate cancer samples (PCa: prostate cancer, TNM: tumor-node-metastasis, BPH: benign prostatic hyperplasia, EPE: Extra Prostatic Extension, BCR: biochemical recurrence, PCSM: Prostate Cancer Specific Mortality, RP: radical prostatectomy, HCs: healthy controls, CML: chronic myeloid leukemia. TBx: targeted prostate biopsy, HGPIN: high-grade prostate intraepithelial neoplasia, V1: (pre-op) Digital Rectal Examination (DRE)—voided urine collection, NIH II prostatitis: bacterial chronic prostatitis, NIH IIIa: abacterial chronic prostatitis, NIH IIIb: non-inflammatory prostatodynia, HGPIN: High-grade prostatic intraepithelial neoplasia, Bx+ : positive repeat Bx, CRPC: castration-resistant prostate cancer, LN: lymph node, phi: prostate health index, BPD: benign prostate disease, TV: tumor volume, GS: pathologic Gleason sum).

Samples	Expression (Tumor vs. Normal)	Kaplan-Meier analysis (impact of PCA3 up-regulation)	Univariate/ Multivariate cox regression	Association of PCA3 expression/ PCA3 score with clinicopathologic characteristics	Reference
116 men with and 94 men without PCa	up	-	-	PCA3-shRNA2	[62]
60 malignant and benign prostatic tissues	up in malignant than benign tissues	-	-	Urinary PCA3-shRNA2	[17]
5 sample pairs of patients and controls	up	-	-	-	[25]
5 tumor specimens and 7 para-cancerous/benign specimens	up	-	-	-	
24 patients with PCa, 40 patients with BPH, and 13 patients with urolithiasis	up in PCa	-	-	-	[43]
38 patients with PCa, 52 patients with BPH	up in PCa	-	-	-	[4]
78 patients with PCa, 37 patients with BPH	up in PCa	-	-	higher TNM stage	[61]
GRIDTM database: 1694 expression profiles from biopsy and 10,382 from RP patients with high-risk tumors	low in high grade tumors in biopsy tissues	Lower 5-year BCR free survival rates, 5-year MET free survival rates and 10-year PCSM free survival and early metastasis were associated with low PCA3.	-	Seminal Vesicle Invasion, EPE and Lymph Node Invasion were associated with low PCA3.	[2]
102 RP patients	up	-	Multifocality was found as an independent factor influencing PCA3 score.	total tumor volume, apical and basal invasion, bilaterality and multifocality	[87]
552 patients (130 Reclassifiers and 422 Non-Reclassifiers)	-	-	Cores ratio, prostate size, and PCA3 score were correlated with reclassification in the sBx1.	-	[55]
1015 patients	up in PCa	-	PCA3 score was found to be as an independent predictor of biopsy outcome.	tumor volume	[86]
195 patients with PCa and 212 patients without PCa	up	-	-	-	[52]
516 patients	up in PCa	-	-	-	[13]
72 patients with PCa	up in extracapsular extension	-	PCA3 was found to be an independent predictor of extracapsular extension and total tumor volume less than 0.5 cc.	total tumor volume	[92]
3073 patients	up in PCa	-	-	high grade prostate cancer	[10]
108 patients (24 with PCa)	up in PCa	-	-	-	[36]
1072 patients with PCa	Up (compared to what?)	-	-	positive biopsy rate and biopsy Gleason score	[5]
80 patients (40 with PCa)	up in PCa	-	-	-	[27]
282 (I guess PCa) patients	up	-	-	The PCA3 score was correlated with a 2.4% increased risk of having a positive TBx result, PI-RADS grade and a worsening Gleason score.	[15]
207 (I guess PCa) patients	up in PCa	-	-	The PCA3 score was correlated with a high Gleason score, % positive cores and an advanced clinical stage.	[91]
463 (I guess PCa) patients	up in HGPIN	-	-	-	[31]
53 patients with PCa	up	-	-	The PCA3 score was correlated with multiparametric MRI.	[60]
734 (I guess PCa) patients	up in PCa	-	-	-	[9]
34 patients with PCa and 15 HCs	up	-	-	-	[26]
98 patients whit PCa	-	-	-	Higher PCA3 scores at V1 were associated with an increased risk for perineural invasion.	[47]
360 (I guess PCa) patients	up in PCa	-	-	-	[14]
103 patients (37 with PCa)	up	-	-	-	[93]
59 patients (30 with PCa and 29 without PCa)	up	-	PCA3 was found to be the best predictor of total tumor volume in prostatectomy.	The PCA3 score was correlated with prostatectomy tumor volume and prostatectomy Gleason score.	[54]

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Table 3 (continued)

Samples	Expression (Tumor vs. Normal)	Kaplan-Meier analysis (impact of PCA3 up-regulation)	Univariate/ Multivariate cox regression	Association of PCA3 expression/ PCA3 score with clinicopathologic characteristics	Reference
215 patients with PCa	Up compared to what?	-	PCA3 was found to be a significant predictor of PCa.	-	[69]
633 patients (264 patients with PCa)	up in PCa	-	-	-	[59]
22 patients with PCa, 26 patients with PNH, and 11 controls	up in PCa	-	-	-	[11]
64 patients (49 patients with PCa)	up in PCa	-	-	-	[67]
80 patients (with and without PCa)	up in PCa	-	The PCA3 score was found to outperform all biopsy risk predictors.	-	[72]
38 patients (4 patients with urethritis, 7 with NIH II prostatitis, 11 with NIH IIIa, 16 with NIH IIIb)	PCA3 scores did not differ	-	-	-	[88]
301 patients with PCa (3 subgroups of f/tPSA, as follows: >20% (group 1), 10–20% (group 2) and < 10% (group 3))	up in group1 and group2	-	-	The PCA3 score was correlated with age, clinical T2 stage and positive biopsy.	[65]
125 patients (47 patients with PCa)	up in PCa	-	-	The PCA3 score was correlated with prostate cancer diagnosis.	[7]
48 patients (28 patients with PCa and 20 with benign tissue located distant from the tumor)	up in PCa and HGPIN	-	-	-	[66]
443 patients (196 patients with PCa)	up	-	PCA3 showed significant additional predictive value to the ERSPC risk calculator parameters.	-	[42]
463 patients	up in patients with a follow-up Bx+	-	-	-	[68]
186 patients (74 patients with PCa, 100 patients with BPH, 12 patients with prostatic intraepithelial neoplasia)	up in PCa than in benign prostatic hyperplasia	-	-	-	[38]
5 radical prostatectomy patients (270 samples from cross-sections)	up in carcinoma regions	-	-	-	[81]
20 patients with CRPC and 32 HCs	up	-	-	-	[16]
122 patients who underwent prostate biopsy	Up compared to what?	-	-	-	[23]
124 patients (59 patients with PCa)	up	-	-	-	[56]
91 patients with PCa/ disorder and HCs	PCA3 positive in 2/9 patients with metastasized cancers, no PCA3 expression in HCs	-	-	-	[82]
294 patients with PCa	PCA3 score was similar in patients with progression and without progression on biopsy	-	-	-	[79]
322 patients with PCa	lower in patients with metastasis than in those with no metastasis	-	-	-	[51]
105 patients	higher the PCA3 score: greater the probability of a positive biopsy	-	-	-	[1]
48 patients with PCa, 48 patients with BPH, 32 patients with NP	up in PCa	-	-	-	[70]
621 patients (255 with PCa)	PCA3 score of biopsy-negative vs biopsy-positive men: 20 vs 48	-	-	-	[6]
456 patients comparing which groups?	up in PCa	-	-	-	[28]
387 patients with PCa	up	-	-	The PCA3 score was significantly associated with biopsy Gleason score, tumor volume and high-grade disease.	[46]

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Table 3 (continued)

Samples	Expression (Tumor vs. Normal)	Kaplan-Meier analysis (impact of PCA3 up-regulation)	Univariate/ Multivariate cox regression	Association of PCA3 expression/ PCA3 score with clinicopathologic characteristics	Reference
226 Patients with high risk PCa for LN metastasis	up in metastatic LNs	-	-	The PCA3 score was significantly associated with tumor cell density in patients with tumor-invaded LNs.	[80]
245 patients (126 with PCa and 11 without PCa)	up in PCa	-	-	-	[85]
534 patients (174 with PCa)	up in PCa	-	-	-	[84]
62 patients with PCa	up in significant PCa	-	-	-	[83]
52 patients (34 with PCa and 18 with BPH)	up in PCa	-	-	-	[95]
124 patients (70 with PCa)	up in PCa (intermediate- and high-risk PCa)	-	-	-	[57]
160 patients with PCa	Up comparing which groups?	-	The PCA3 score was found to be an independent predictor of a tumor volume and positive surgical margins.	The PCA3 score was significantly associated with tumor volume.	[18]
154 patients with PCa	Up comparing which groups?	-	The PCA3 score was found to be an independent predictor of a tumor volume ≥ 0.5 mL. Only PHI predicted Gleason score ≥ 7 and multifocality.	-	[76]
291 patients (173 with PCa)	up	-	The PCA3 score and PSA density were remarkably correlated with presence of Grade 4.	The PCA3 score was associated with presence of PCa and the percentage of positive cores at biopsy.	[12]
34 patients with PCa and 15 HCs	up in some plasma samples	-	-	-	[77]
160 patients comparing which groups?	up in PCa	-	Both the phi index and PCA3 score was found to reach an overall diagnostic accuracy of 0.77.	-	[64]
19 patients (13 with PCa and 6 with BPD)	up in PCa	-	-	-	[3]
50 patients (6 with PCa)	5 PCa patients had a positive PCA3 test	-	-	-	[34]
100 patients (28 with PCa)	PCA3 score of biopsy-negative vs biopsy-positive men: 35 vs 57	-	-	-	[63]
251 patients comparing which groups?	up in PCa	-	-	-	[20]
29 patients comparing which groups?	up in PCa	-	-	-	[35]
57 patients comparing which groups?	up in only 3.8% of PCa	-	-	-	[24]
40 patients with PCa and 40 patients with BPH	up in PCa	-	-	-	[22]
78 patients comparing which groups?	up	-	-	Levels of PCA3 were significantly correlated with TV ≥ 0.5 mL, GS ≥ 7 and pT3 disease.	[21]
105 patients (38 with PCa)	up in PCa	-	PCA3 score and PSA density were found to be the independent predictors for PCa.	-	[58]
53 patients (with PCa, BPH and PIN)	up in PCa	-	-	-	[53]
38 patients (with PCa and without PCa)	up in PCa	-	-	-	[75]
139 patients with PCa and 226 patients without PCa plus 79 patients with PCa and 121 patients without PCa	up in PCa	-	PCA3 distinguished patients with PCa from patients without PCa better than other clinical features included PSA, f/t PSA, age, prostate volume and DRE status.	Aggressiveness of PCa	[44]
271 patients (142 with PCa)	up in PCa	-	-	high grade	[39]
314 healthy men	-	-	PCA3 score was significantly correlated with age.	-	[78]

5. Discussion

PCA3 is a tissue, blood and urinary marker for diagnosis of prostate cancer. Assessment of its expression levels is regarded as a strategy to decrease unnecessary prostate biopsies. This lncRNA can also be used as part of multivariable risk-assessment tools for cancer diagnosis [49].

In spite of extensive efforts for identification of clinical applicability of PCA3, functional studies to unravel the mechanistical points of PCA3

participation in cancer are extremely few. However, it has been found that PCA3 regulates chromatin structure through modulation of the nucleoplasmic pool of lamins, indicating that nuclear lamins have a role in the progression of neoplasms [37]. Moreover, establishment of double-stranded RNA and further adenosine deamination as a step in adenosine-to-inosine RNA editing is another route of participation of PCA3 in the carcinogenesis [73].

Similarly, the therapeutic application of PCA3 silencing in prostate

Table 4

Diagnostic value of PCA3 in prostate cancer (PCa: prostate cancer, BPH: benign prostatic hyperplasia).

Numbers of clinical samples	Distinguish between	Area Under Curve	Sensitivity (%)	Specificity (%)	Accuracy (%)	References
78 patients with PCa, 37 patients with BPH	patients with PCa vs. patients with BPH	0.790	-	-	-	[61]
1015 patients	-	0.76	68	71	69	[86]
195 patients with PCa and 212 patients without PCa	patients with PCa vs. patients without PCa	0.865	97.9	33.3	-	[52]
80 patients (40 with PCa)	Patients with PCa vs. Patients without PCa	0.668	47.5	15	-	[27]
633 patients (264 patients with PCa)	Patients with PCa vs. Patients without PCa	0.742	66.5	71.6	-	[59]
64 patients (15 patients without PCa)	Patients with PCa vs. Patients without PCa	0.77	52	87	-	[67]
534 patients (174 with PCa)	Patients with PCa vs. Patients without PCa	0.66	65	66	-	[84]
52 patients (34 with PCa and 18 with BPH)	Patients with PCa vs. Patients with BPH	-	82.4	77.8	-	[95]
54 studies (17,575 patients, 4034 with PCa)	Patients with PCa vs. Patients without PCa	0.75	71	68	-	[40]
139 patients with PCa and 226 patients without PCa	Patients with PCa vs Patients without PCa	0.751	-	-	-	[44]
142 patients with PCa (34 with high grade tumors)	Low grade tumor vs high grade tumor	0.88	0.972	0.373	-	[39]

cancer has not been adequately addressed in animal models. The high specific pattern of PCA3 expression in prostate cancer suggests that therapies against this lncRNA can be specifically used for treatment of prostate cancer with no/limited side effects.

Taken together, although the biomarker role of PCA3 has been vastly investigated in prostate cancer, less effort has been directed toward understanding the mechanism of involvement of PCA3 in this cancer or other types of cancers. Future investigations in this field can facilitate introduction of this lncRNA as a therapeutic target for cancers. Since PCA3 knock down has been shown to enhance effects of enzalutamide in prostate cancer [61], therapeutic targeting of PCA3 is a putative strategy for improvement of the efficacy of currently used therapeutic options. Moreover, the impact of PCA3 on regulation of survival of prostate cancer cells via modulation of AR signaling proposes PCA3 silencing as an additional treatment modality for prostate cancer [19].

Another unexplored field about PCA3 is the importance of this lncRNA in regulation of target genes through acting as a ceRNA. Although this route is an acknowledged route of participation of lncRNAs in regulation of genes expressions [30,94], few miRNA partners have been experimentally validated for PCA3. Identification of these partners facilitates design of diagnostic/prognostic multigene panels for prostate cancer.

References

- [1] A. Adam, M.J. Engelbrecht, M.S.R. Bornman, S. Manda, E.M. Moshokoa, R. A. Feilat, The role of the PCA3 assay in predicting prostate biopsy outcome in a South African setting, *BJU Int.* (2011).
- [2] M. Alshahala, G.W. Verhaegh, E.A. Gibb, M. Santiago-Jiménez, N. Erho, J. Jordan, K. Yousefi, L.L. Lam, T. Kolisnik, J. Chelissery, Low PCA3 expression is a marker of poor differentiation in localized prostate tumors: exploratory analysis from 12,076 patients, *Oncotarget* 8 (2017) 50804.
- [3] E. Arámbula-Meraz, F. Bergez-Hernández, E. Leal-León, E. Romo-Martínez, V. Picos-Cárdenas, F. Luque-Ortega, J. Romero-Quintana, M. Alvarez-Arrazola, N. García-Magallanes, Expression of miR-148b-3p is correlated with overexpression of biomarkers in prostate cancer, *Genet. Mol. Biol.* 43 (2020).
- [4] M. Askari, A. Yazdani, M. Yazdani, M.H. Izadpanahi, Serum levels of total and urine level of PCA3 in patients with benign prostatic hyperplasia and prostate cancer, *Am. J. Clin. Exp. Urol.* 8 (2020) 43.
- [5] S.M. Aubin, J. Reid, M.J. Sarno, A. Blase, J. Aussie, H. Rittenhouse, R. Rittmaster, G.L. Andriole, J. Groskopf, PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial, *J. Urol.* 184 (2010) 1947–1952.
- [6] M. Auprich, A. Haese, J. Walz, K. Pummer, A. de la Taille, M. Graefen, T. de Reijke, M. Fisch, P. Kil, P. Gontero, External validation of urinary PCA3-based nomograms to individually predict prostate biopsy outcome, *Eur. Urol.* 58 (2010) 727–732.
- [7] S. Bernardeau, T. Charles, G. Fromont-Hankard, J. Irani, The role of a single PCA3 test before a first negative prostate biopsy: 5-year follow-up, *Prog. En. Urol. J. De. L'Assoc. Fr. D. Urol. Et. De. la Soc. Fr. D. Urol.* 27 (2017) 325–330.
- [8] M.J. Bussemakers, A. Van Bokhoven, G.W. Verhaegh, F.P. Smit, H.F. Karthaus, J. A. Schalken, F.M. Debruyne, N. Ru, W.B. Isaacs, DD3: a new prostate-specific gene, highly overexpressed in prostate cancer, *Cancer Res.* 59 (1999) 5975–5979.
- [9] E. Capoluongo, C.F. Zambon, D. Basso, S. Boccia, S. Rocchetti, E. Leoncini, S. Palumbo, A. Padoan, G. Albino, A. Todaro, PCA3 score of 20 could improve prostate cancer detection: results obtained on 734 Italian individuals, *Clin. Chim. Acta* 429 (2014) 46–50.
- [10] K.K. Chevli, M. Duff, P. Walter, C. Yu, B. Capuder, A. Elshafei, S. Malczewski, M. W. Kattan, J.S. Jones, Urinary PCA3 as a predictor of prostate cancer in a cohort of 3,073 men undergoing initial prostate biopsy, *J. Urol.* 191 (2014) 1743–1748.
- [11] F.F. Coelho, F.L. Guimarães, W. Cabral, P. Salles, E.C. Mateo, L. Nogueira e Nogueira, C. Fonseca, K.B. Gomes, Expression of PCA3 and PSA genes as a biomarker for differential diagnosis of nodular hyperplasia and prostate cancer, *Genet. Mol. Res.* 14 (2015) 13519–13531.
- [12] J.N. Cornu, G. Cancel-Tassin, C. Egrot, C. Gaffroy, F. Haab, O. Cussenot, Urine TMPRSS2: ERG fusion transcript integrated with PCA3 score, genotyping, and biological features are correlated to the results of prostatic biopsies in men at risk of prostate cancer, *Prostate* 73 (2013) 242–249.
- [13] A. de la Taille, J. Irani, M. Graefen, F. Chun, T. de Reijke, P. Kil, P. Gontero, A. Mottaz, A. Haese, Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions, *J. Urol.* 185 (2011) 2119–2125.
- [14] S. De Luca, R. Passera, S. Cappia, E. Bollito, D.F. Randone, A. Milillo, M. Papotti, F. Porpiglia, Fluctuation in prostate cancer gene 3 (PCA3) score in men undergoing first or repeat prostate biopsies, *BJU Int.* 114 (2014) E56–E61.
- [15] S. De Luca, R. Passera, G. Cattaneo, M. Manfredi, F. Mele, C. Fiori, E. Bollito, S. Cirillo, F. Porpiglia, High prostate cancer gene 3 (PCA 3) scores are associated with elevated Prostate Imaging Reporting and Data System (PI-RADS) grade and biopsy Gleason score, at magnetic resonance imaging/ultrasonography fusion software-based targeted prostate biopsy after a previous negative standard biopsy, *BJU Int.* 118 (2016) 723–730.
- [16] S. Dijkstra, G.H. Leyten, S.A. Jannink, H. de Jong, P.F. Mulders, I.M. van Oort, J. A. Schalken, KLK3, PCA3, and TMPRSS2-ERG expression in the peripheral blood mononuclear cell fraction from castration-resistant prostate cancer patients and response to docetaxel treatment, *Prostate* 74 (2014) 1222–1230.
- [17] R.M. Drayton, I. Rehman, R. Clarke, Z. Zhao, K. Pang, S. Miah, R. Stoehr, A. Hartmann, S. Blizard, M. Lavin, Identification and diagnostic performance of a small RNA within the PCA3 and BMCC1 gene locus that potentially targets mRNA, *Cancer Epidemiol. Prev. Biomark.* 24 (2015) 268–275.
- [18] X. Durand, E. Xylinas, C. Radulescu, R. Haus-Cheymol, S. Moutereau, G. Ploussard, A. Forgues, G. Robert, F. Vacherot, S. Loric, The value of urinary prostate cancer gene 3 (PCA3) scores in predicting pathological features at radical prostatectomy, *BJU Int.* 110 (2012) 43–49.
- [19] L.B. Ferreira, A. Palumbo, K.D. de Mello, C. Sternberg, M.S. Caetano, F.L. de Oliveira, A.F. Neves, L.E. Nasciutti, L.R. Goulart, E.R.P. Gimba, PCA3 noncoding RNA is involved in the control of prostate-cancer cell survival and modulates androgen receptor signaling, *BMC Cancer* 12 (2012) 1–15.
- [20] M. Ferro, D. Bruzzese, S. Perdonà, C. Mazzarella, A. Marino, A. Sorrentino, A. Di Carlo, R. Autorino, G. Di Lorenzo, C. Buonerba, Predicting prostate biopsy outcome: prostate health index (phi) and prostate cancer antigen 3 (PCA3) are useful biomarkers, *Clin. Chim. Acta* 413 (2012) 1274–1278.
- [21] M. Ferro, G. Lucarelli, D. Bruzzese, S. Perdonà, C. Mazzarella, G. Perruolo, A. Marino, V. Cosimato, E. Giorgio, V. Tagliamonte, Improving the prediction of pathologic outcomes in patients undergoing radical prostatectomy: the value of prostate cancer antigen 3 (PCA3), prostate health index (phi) and sarcosine, *Anticancer Res.* 35 (2015) 1017–1023.
- [22] E. Floriano-Sánchez, N. Cárdenas-Rodríguez, M. Castro-Marin, P. Alvarez-Grave, E. Lara-Padilla, DD3PCA3 gene expression in cancer and prostatic hyperplasia, *Clin. Invest. Med.* (2009) E258–E264.

- [23] L. Foj, M. Milà, L. Mengual, P. Luque, A. Alcaraz, W. Jiménez, X. Filella, Real-time PCR PCA3 assay is a useful test measured in urine to improve prostate cancer detection, *Clin. Chim. Acta* 435 (2014) 53–58.
- [24] S. Fontenete, J. Silva, A. Teixeira, R. Ribeiro, E. Bastos, F. Pina, R. Medeiros, Controversies in using urine samples for prostate cancer detection: PSA and PCA3 expression analysis, *Int. Braz. J. Urol.* 37 (2011) 719–726.
- [25] S. Ge, Y. Mi, X. Zhao, Q. Hu, Y. Guo, F. Zhong, Y. Zhang, G. Xia, C. Sun, Characterization and validation of long noncoding RNAs as new candidates in prostate cancer, *Cancer Cell Int.* 20 (2020) 1–15.
- [26] U. Gezer, D. Tiryakioglu, E. Bilgin, N. Dalay, S. Holdenrieder, Androgen stimulation of PCA3 and miR-141 and their release from prostate cancer cells, *Cell J.* 16 (2015) 488.
- [27] S. Gilani, M. Shakery, P. Shoureshi, H. Salimi, H. Maleki, A. Alavi, F. Khodadadi, How is the association between urinary prostate cancer antigen 3 (PCA3) levels and Gleason scores in patients suspicious of prostate cancer, *Int. J. Physiol. Pathophysiol. Pharmacol.* 11 (2019) 283.
- [28] R.R. Goode, S.J. Marshall, M. Duff, E. Chevli, K.K. Chevli, Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients, *Prostate* 73 (2013) 48–53.
- [29] S. Guo, Y. Zhang, S. Wang, T. Yang, B. Ma, X. Li, Y. Zhang, X. Jiang, lncRNA PCA3 promotes antimony-induced lipid metabolic disorder in prostate cancer by targeting MIR-132-3P/SREBP1 signaling, *Toxicol. Lett.* (2021).
- [30] Z. Guo, L. Han, Y. Fu, Z. Wu, Y. Ma, Y. Li, H. Wang, L. Jiang, S. Liang, Z. Wang, Systematic evaluation of the diagnostic and prognostic significance of competitive endogenous RNA networks in prostate cancer, *Front. Genet.* 11 (2020) 785.
- [31] A. Haese, A. de la Taille, H. Van Poppel, M. Marberger, A. Stenzl, P.F. Mulders, H. Huland, C.-C. Abbou, M. Remzi, M. Tinzl, Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy, *Eur. Urol.* 54 (2008) 1081–1088.
- [32] A. Haese, A. de la Taille, H. van Poppel, M. Marberger, A. Stenzl, P.F. Mulders, H. Huland, C.C. Abbou, M. Remzi, M. Tinzl, S. Feyerabend, A.B. Stillebroer, M. P. van Gils, J.A. Schalken, Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy, *Eur. Urol.* 54 (2008) 1081–1088.
- [33] J.-H. He, B.-X. Li, Z.-P. Han, M.-X. Zou, L. Wang, Y.-B. Lv, J.-B. Zhou, M.-R. Cao, Y.-G. Li, J.-z. Zhang, Snail-activated long non-coding RNA PCA3 up-regulates PRKD3 expression by miR-1261 sponging, thereby promotes invasion and migration of prostate cancer cells, *Tumor Biol.* 37 (2016) 16163–16176.
- [34] J. Henderson, K.R. Ghani, J. Cook, M. Fahey, J. Schalken, R. Thilagarajah, The role of PCA3 testing in patients with a raised prostate-specific antigen level after Greenlight photoselective vaporization of the prostate, *J. Endourol.* 24 (2010) 1821–1824.
- [35] R.J. Hendriks, S. Dijkstra, S.A. Jannink, M.G. Steffens, I.M. van Oort, P.F. Mulders, J.A. Schalken, Comparative analysis of prostate cancer specific biomarkers PCA3 and ERG in whole urine, urinary sediments and exosomes, *Clin. Chem. Lab. Med. (CCLM)* 54 (2016) 483–492.
- [36] D. Hessels, J.M.K. Gunnewiek, I. van Oort, H.F. Karthaus, G.J. van Leenders, B. van Balken, L.A. Kiemeny, J.A. Witjes, J.A. Schalken, DD3PCA3-based molecular urine analysis for the diagnosis of prostate cancer, *Eur. Urol.* 44 (2003) 8–16.
- [37] S. Ito, T. Ueda, A. Yokoyama, A. Fujihara, F. Hongo, O. Ukimura, PCA3 controls chromatin organization and p53 signal activation by regulating LAP2 α -lamin A complexes, *Cancer Gene Ther.* (2021) 1–11.
- [38] J. Klecka, L. Holubec, M. Pesta, O. Topolcan, M. Hora, V. Eret, J. Finek, M. Chottova-Dvorakova, M. Babjuk, K. Novak, Differential display code 3 (DD3/PCA3) in prostate cancer diagnosis, *Anticancer Res.* 30 (2010) 665–670.
- [39] I. Kohaar, Y. Chen, S. Banerjee, T. Borbiev, H.-C. Kuo, A. Ali, L. Ravindranath, J. Kagan, S. Srivastava, A. Dobi, A. Urine, Exosome gene expression panel distinguishes between indolent and aggressive prostate cancers at biopsy, *J. Urol.* 205 (2021) 420–425.
- [40] D. Lee, S.R. Shim, S.T. Ahn, M.M. Oh, D.G. Moon, H.S. Park, J. Cheon, J.W. Kim, Diagnostic performance of the prostate cancer antigen 3 test in prostate cancer: systematic review and meta-analysis, *Clin. Genitourin. Cancer* 18 (2020) 402–408, e405.
- [41] A.E.G. Lemos, L.B. Ferreira, N.M. Batoreu, P.P. de Freitas, M.H. Bonamino, E.R. P. Gimba, PCA3 long noncoding RNA modulates the expression of key cancer-related genes in LNCaP prostate cancer cells, *Tumor Biol.* 37 (2016) 11339–11348.
- [42] G.H. Leyten, D. Hessels, S.A. Jannink, F.P. Smit, H. de Jong, E.B. Cornel, T.M. de Reijke, H. Vergunst, P. Kil, B.C. Knipscheer, Prospective multicentre evaluation of PCA3 and TMPRSS2-ERG gene fusions as diagnostic and prognostic urinary biomarkers for prostate cancer, *Eur. Urol.* 65 (2014) 534–542.
- [43] M. Li, D. Zhou, W. Zhang, S. Gao, X. Zhou, Urine PCA3 mRNA level in diagnostic of prostate cancer, *J. Cancer Res. Ther.* 14 (2018) 864.
- [44] Y. Li, J. Ji, J. Lyu, X. Jin, X. He, S. Mo, H. Xu, J. He, Z. Cao, X. Chen, A novel urine exosomal lncRNA assay to improve the detection of prostate cancer at initial biopsy: a retrospective multicenter diagnostic feasibility study, *Cancers* 13 (2021) 4075.
- [45] C. Lin, J. Wang, Y. Wang, P. Zhu, X. Liu, N. Li, J. Liu, L. Yu, W. Wang, GRP78 Participates in PCA3-regulated prostate cancer progression, *Anticancer Res.* 37 (2017) 4303–4310.
- [46] D.W. Lin, L.F. Newcomb, E.C. Brown, J.D. Brooks, P.R. Carroll, Z. Feng, M. E. Gleave, R.S. Lance, M.G. Sanda, I.M. Thompson, Urinary TMPRSS2: ERG and PCA3 in an active surveillance cohort: results from a baseline analysis in the canary prostate active surveillance study, *Clin. Cancer Res.* 19 (2013) 2442–2450.
- [47] M.A. Liss, R. Santos, K. Osann, A. Lau, T.E. Ahlering, D.K. Ornstein, PCA3 molecular urine assay for prostate cancer: association with pathologic features and impact of collection protocols, *World J. Urol.* 29 (2011) 683–688.
- [48] Y. Liu, Z.-H. Zong, X. Guan, L.-l Wang, Y. Zhao, The role of long non-coding RNA PCA3 in epithelial ovarian carcinoma tumorigenesis and progression, *Gene* 633 (2017) 42–47.
- [49] S. Loeb, A.W. Partin, Review of the literature: PCA3 for prostate cancer risk assessment and prognostication, *Rev. Urol.* 13 (2011) e191–e195.
- [50] L.S. Marks, Y. Fradet, I.L. Deras, A. Blase, J. Mathis, S.M. Aubin, A.T. Cancio, M. Desaulniers, W.J. Ellis, H. Rittenhouse, J. Groskopf, PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy, *Urology* 69 (2007) 532–535.
- [51] L. Martínez-Piñero, J.A. Schalken, P. Cabri, P. Maisonnobe, A. de la Taille, P.J. S. Osther, T.S. Group, Evaluation of urinary prostate cancer antigen-3 (PCA3) and TMPRSS2-ERG score changes when starting androgen-deprivation therapy with triptorelin 6-month formulation in patients with locally advanced and metastatic prostate cancer, *BJU Int.* 114 (2014) 608–616.
- [52] R. Merola, L. Tomao, A. Antenucci, I. Sperduti, S. Sentinelli, S. Masi, C. Mandoj, G. Orlandi, R. Papalia, S. Guaglianone, PCA3 in prostate cancer and tumor aggressiveness detection on 407 high-risk patients: a national cancer institute experience, *J. Exp. Clin. Cancer Res.* 34 (2015) 1–6.
- [53] D. Mikhaylenko, D. Perepechin, M. Grigoryeva, T. Zhinzhiro, N.Y. Safronova, G. Eremov, A. Sivkov, PCA3 and TMPRSS2: ERG genes expression in biopsies of benign prostate hyperplasia, intraepithelial neoplasia, and prostate cancer. *Urologiia (Moscow, Russia: 1999)* (2015) 46–50.
- [54] H. Nakanishi, J. Groskopf, H.A. Fritsche, V. Bhadkamkar, A. Blase, S.V. Kumar, J. W. Davis, P. Troncoso, H. Rittenhouse, R.J. Babaian, PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance, *J. Urol.* 179 (2008) 1804–1810.
- [55] L.F. Newcomb, Y. Zheng, A.V. Faino, D. Bianchi-Frias, M.R. Cooperberg, M. D. Brown, J.D. Brooks, A. Dash, M.D. Fabrizio, M.E. Gleave, Performance of PCA3 and TMPRSS2: ERG urinary biomarkers in prediction of biopsy outcome in the canary prostate active surveillance study (PASS), *Prostate Cancer Prostatic Dis.* 22 (2019) 438–445.
- [56] Y. Nygård, S.A. Haukaas, G.E. Eide, O.J. Halvorsen, K. Gravdal, J. Frugård, L. A. Akslen, C. Beisland, Prostate cancer antigen-3 (PCA3) and PCA3-based nomograms in the diagnosis of prostate cancer: an external validation of Hansen's nomogram on a Norwegian cohort, *Scand. J. Urol.* 49 (2015) 8–15.
- [57] Y. Nygård, S.A. Haukaas, O.J. Halvorsen, K. Gravdal, J. Frugård, L.A. Akslen, C. Beisland, A Positive Real-Time Elastography (RTE) combined with a Prostate Cancer Gene 3 (PCA3) score above 35 convey a high probability of intermediate-or high-risk prostate cancer in patient admitted for primary prostate biopsy, *BMC Urol.* 16 (2016) 1–8.
- [58] A. Ochiai, K. Okihara, K. Kamoi, T. Iwata, A. Kawauchi, T. Miki, Z. Fors, Prostate cancer gene 3 urine assay for prostate cancer in Japanese men undergoing prostate biopsy, *Int. J. Urol.* 18 (2011) 200–205.
- [59] A. Ochiai, K. Okihara, K. Kamoi, T. Oikawa, T. Shimazui, S.I. Murayama, K. Tomita, T. Umekawa, H. Uemura, T. Miki, Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy, *BJU Int.* 111 (2013) 928–933.
- [60] S. Okcelik, H. Soydan, F. Ates, U. Berber, H. Saygin, G. Sönmez, K. Karademir, Evaluation of PCA3 and multiparametric MRI's: collective benefits before deciding initial prostate biopsy for patients with PSA level between 3–10ng/mL, *Int. Braz. J. Urol.* 42 (2016) 449–455.
- [61] E. Özgür, A.I. Celik, E. Darendeliler, U. Gezer, PCA3 silencing sensitizes prostate cancer cells to enzalutamide-mediated androgen receptor blockade, *Anticancer Res.* 37 (2017) 3631–3637.
- [62] K.H. Pang, D.J. Rosario, S.L. Morgan, J.W. Catto, Evaluation of a short RNA within prostate cancer gene 3 in the predictive role for future cancer using non-malignant prostate biopsies, *PLoS One* 12 (2017), e0175070.
- [63] P. Pepe, F. Aragona, Prostate cancer detection rate at repeat saturation biopsy: PCPT risk calculator versus PCA3 score versus case-finding protocol, *Can. J. Urol.* 20 (2013) 6620–6624.
- [64] S. Perdoma, D. Bruzzese, M. Ferro, R. Autorino, A. Marino, C. Mazzarella, G. Perruolo, M. Longo, R. Spinelli, G. Di Lorenzo, Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy, *Prostate* 73 (2013) 227–235.
- [65] G. Ploussard, A. Haese, H. Van Poppel, M. Marberger, A. Stenzl, P.F. Mulders, H. Huland, L. Bastien, C.C. Abbou, M. Remzi, The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies? *BJU Int.* 106 (2010) 1143–1147.
- [66] I. Popa, Y. Fradet, G. Beaudry, H. Hovington, G. Beaudry, B. Tétu, Identification of PCA3 (DD3) in prostatic carcinoma by in situ hybridization, *Mod. Pathol.* 20 (2007) 1121–1127.
- [67] C.G. Ramos, R. Valdevenito, I. Vergara, P. Anabalón, C. Sanchez, J. Fulla, PCA3 sensitivity and specificity for prostate cancer detection in patients with abnormal PSA and/or suspicious digital rectal examination. First Latin American experience. *Urologic Oncology: Seminars and Original Investigations*, Elsevier, 2013, pp. 1522–1526.
- [68] M. Remzi, A. Haese, H. Van Poppel, A. De La Taille, A. Stenzl, J. Hennenlotter, M. Marberger, Follow-up of men with an elevated PCA3 score and a negative biopsy: does an elevated PCA3 score indeed predict the presence of prostate cancer? *BJU Int.* 106 (2010) 1138–1142.
- [69] M. Rigau, J. Morote, M.C. Mir, C. Ballesteros, I. Ortega, A. Sanchez, E. Colás, M. Garcia, A. Ruiz, M. Abal, PSGR and PCA3 as biomarkers for the detection of prostate cancer in urine, *Prostate* 70 (2010) 1760–1767.
- [70] G. Robert, S. Jannink, F. Smit, T. Aalders, D. Hessels, R. Cremers, P.F. Mulders, J. A. Schalken, Rational basis for the combination of PCA3 and TMPRSS2: ERG gene fusion for prostate cancer diagnosis, *Prostate* 73 (2013) 113–120.

- [71] E. Sajjadi, A. Atashi, M.A.M.H. Tajrishi, Z. Saei, Gene expression analysis of noncoding PCA3 gene in patients with chronic myeloid leukemia, *J. Cancer Res. Ther.* 14 (2018) 1079.
- [72] M. Salagierski, P. Mulders, J.A. Schalken, Predicting prostate biopsy outcome using a PCA3-based nomogram in a Polish cohort, *Anticancer Res.* 33 (2013) 553–557.
- [73] A. Salameh, A.K. Lee, M. Cardó-Vila, D.N. Nunes, E. Efstathiou, F.I. Staquicini, A.S. Dobroff, S. Marchiò, N.M. Navone, H. Hosoya, PRUNE2 is a human prostate cancer suppressor regulated by the intronic long noncoding RNA PCA3. *Proceedings of the National Academy of Sciences* 112, 2015, pp. 8403–8408.
- [74] D.A. Sartori, D.W. Chan, Biomarkers in prostate cancer: what's new? *Curr. Opin. Oncol.* 26 (2014) 259–264.
- [75] C. Stephan, M. Jung, S. Rabenhorst, E. Kilic, K. Jung, Urinary miR-183 and miR-205 do not surpass PCA3 in urine as predictive markers for prostate biopsy outcome despite their highly dysregulated expression in prostate cancer tissue, *Clin. Chem. Lab. Med. (CCLM)* 53 (2015) 1109–1118.
- [76] L. Tallon, D. Luangphakdy, A. Ruffion, M. Colombel, M. Devonec, D. Champetier, P. Paparel, M. Decaussin-Petrucci, P. Perrin, V. Vlaeminck-Guillem, Comparative evaluation of urinary PCA3 and TMPRSS2: ERG scores and serum PHI in predicting prostate cancer aggressiveness, *Int. J. Mol. Sci.* 15 (2014) 13299–13316.
- [77] D. Tiryakioglu, E. Bilgin, S. Holdenrieder, N. Dalay, U. Gezer, miR-141 and miR-375 induction and release are different from PSA mRNA and PCA3 upon androgen stimulation of LNCaP cells, *Biomed. Rep.* 1 (2013) 802–806.
- [78] J.J. Tosoian, R.L. Dunn, Y.S. Niknafs, A. Saha, R.A. Vince Jr, J.L.S. Sauver, D. J. Jacobson, M.E. McGree, J. Siddiqui, J. Groskopf, Association of urinary myprostatescore, age, and prostate volume in a longitudinal cohort of healthy men: long-term findings from the Olmsted County Study, *Eur. Urol. Open Sci.* 29 (2021) 30–35.
- [79] J.J. Tosoian, S. Loeb, A. Kettermann, P. Landis, D.J. Elliot, J.I. Epstein, A.W. Partin, H.B. Carter, L.J. Sokoll, Accuracy of PCA3 measurement in predicting short-term biopsy progression in an active surveillance program, *J. Urol.* 183 (2010) 534–538.
- [80] I. Tsaour, J. Hennenlotter, E. Oppermann, M. Munz, U. Kuehs, A. Stenzl, D. Schilling, PCA3 and PSA gene activity correlates with the true tumor cell burden in prostate cancer lymph node metastases, *Cancer Biomark.* 15 (2015) 311–316.
- [81] R.-M. Väänänen, N.T. Ochoa, P.J. Boström, P. Taimen, K. Pettersson, Altered PCA3 and TMPRSS2-ERG expression in histologically benign regions of cancerous prostates: a systematic, quantitative mRNA analysis in five prostates, *BMC Urol.* 15 (2015) 1–8.
- [82] R.-M. Väänänen, M. Rissanen, O. Kauko, S. Junnila, V. Väisänen, J. Nurmi, K. Alanen, M. Nurmi, K. Pettersson, Quantitative real-time RT-PCR assay for PCA3, *Clin. Biochem.* 41 (2008) 103–108.
- [83] M.P. van Gils, D. Hessels, C.A. Hulsbergen-van de Kaa, J.A. Witjes, C.F. Jansen, P. F. Mulders, H.G. Rittenhouse, J.A. Schalken, Detailed analysis of histopathological parameters in radical prostatectomy specimens and PCA3 urine test results, *Prostate* 68 (2008) 1215–1222.
- [84] M.P. van Gils, D. Hessels, O. van Hooij, S.A. Jannink, W.P. Peelen, S.L. Hanssen, J. A. Witjes, E.B. Cornel, H.F. Karthaus, G.A. Smits, The time-resolved fluorescence-based PCA3 test on urinary sediments after digital rectal examination; a Dutch multicenter validation of the diagnostic performance, *Clin. Cancer Res.* 13 (2007) 939–943.
- [85] V. Vlaeminck-Guillem, J.-L. Campos-Fernandes, D. Champetier, K. Chikh, M. Decaussin-Petrucci, M. Devonec, N. Gobeaux, P. Paparel, P. Perrin, C. Rodriguez-Lafresse, Value of PCA3 urinary test for prostate biopsy decision: the Lyon-Sud University Hospital experience, *Ann. De. Biol. Clin.* (2011) 31–39.
- [86] V. Vlaeminck-Guillem, M. Devonec, D. Champetier, M. Decaussin-Petrucci, P. Paparel, P. Perrin, A. Ruffion, Urinary PCA3 to predict prostate cancer in a cohort of 1015 patients, *Prog. En. Urol.* 25 (2015) e1–e8.
- [87] V. Vlaeminck-Guillem, M. Devonec, M. Colombel, C. Rodriguez-Lafresse, M. Decaussin-Petrucci, A. Ruffion, Urinary PCA3 score predicts prostate cancer multifocality, *J. Urol.* 185 (2011) 1234–1239.
- [88] V. Vlaeminck-Guillem, M. Bandel, M. Cottancin, C. Rodriguez-Lafresse, J. M. Bohbot, P. Sednaoui, Chronic prostatitis does not influence urinary PCA3 score, *Prostate* 72 (2012) 549–554.
- [89] Y.-N. Wang, S.-Y. Liu, L. Wang, L.-Y. Han, Long noncoding RNA PCA3 contributes to the progression of choriocarcinoma by acting as a ceRNA against miR-106b, *Int. J. Clin. Exp. Pathol.* 12 (2019) 1609.
- [90] Y. Wang, H. Hardin, Y.-H. Chu, K. Esbona, R. Zhang, R.V. Lloyd, Long non-coding RNA expression in anaplastic thyroid carcinomas, *Endocr. Pathol.* 30 (2019) 262–269.
- [91] W. Wei, J. Leng, H. Shao, W. Wang, High PCA3 scores in urine correlate with poor-prognosis factors in prostate cancer patients, *Int. J. Clin. Exp. Med.* 8 (2015) 16606.
- [92] E.J. Whitman, J. Groskopf, A. Ali, Y. Chen, A. Blase, B. Furusato, G. Petrovics, M. Ibrahim, S. Elsamanoudi, J. Cullen, PCA3 score before radical prostatectomy predicts extracapsular extension and tumor volume, *J. Urol.* 180 (2008) 1975–1979.
- [93] A. Wu, A. Reese, M. Cooperberg, N. Sadetsky, K. Shinohara, Utility of PCA3 in patients undergoing repeat biopsy for prostate cancer, *Prostate Cancer Prostatic Dis.* 15 (2012) 100–105.
- [94] N. Xu, Y.-P. Wu, H.-B. Yin, X.-Y. Xue, X. Gou, Molecular network-based identification of competing endogenous RNAs and mRNA signatures that predict survival in prostate cancer, *J. Transl. Med.* 16 (2018) 1–15.
- [95] K. Zheng, Y. Dou, L. He, H. Li, Z. Zhang, Y. Chen, A. Ye, W. Liu, L. Kong, Improved sensitivity and specificity for prostate cancer diagnosis based on the urine PCA3/PSA ratio acquired by sequence-specific RNA capture, *Oncol. Rep.* 34 (2015) 2439–2444.