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Prostate cancer biomarkers detection using nanoparticles based electrochemical biosensors

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ABSTRACT:

Prostate cancer (PCa) is the most prevalent cancer with a high mortality rate. The early and accurate detection of PCa can significantly reduce mortality and saves lives. Hence, the nanomaterials based electrochemical nanobiosensors for PCa biomarkers will be the excellent alternative for diagnosis, detection and management of disease condition. In this review, we present a concise summary of the latest attainment and advancement in the use of nanoparticles for the diagnosis of PCa biomarkers. This review highlighted the importance of applying specific biomarkers along with nanomaterials like gold, magnetic, carbon nanotubes, and many other materials for developing electrochemical nanobiosensors in PCa detection. In addition to a summary on PCa detection, we further ensure future perspectives in PCa biomarkers detection, sensitivity, simplicity, rapidity, accuracy, cost-effectiveness and succeeding optimizations of novel technologies for more feasibility. Finally, closing remarks and an outlook conclude the review.

1. Introduction

Prostate cancer (PCa) is a malignant tumour which commonly begins in the outermost part of the prostate caused by several epigenetic alterations leading to uncontrolled proliferation, differentiation and invasion to nearby tissues as shown in Fig. 1 (Lawrence et al., 2010). It is further metastasize to distinct sites or organs, producing significant morbidity and mortality (DePinho, 2000; Robert et al., 2009) among men aged between 50 and 80 years (Siegel et al., 2014).

According to estimates from the World Health Organization (WHO) in 2018, that 1.3 million new cases have been diagnosed with an estimated 1.7 million incidences and 0.5 million annual mortality rate by 2030 (WHO, 2018). One of the key aspects to significantly reduce mortality risk is early and accurate detection of PCa (Carter and Pearson, 1999). With respect to prognosis and staging of prostate cancer, imaging techniques are considered to give more precise disease characterization through the scanning of anatomic (Fuchsjäger et al., 2008), functional (Lee et al., 2012), and molecular imaging information (Willmann et al., 2008). Various other clinical diagnostic techniques are, known for premature detection of disease such as ultrasonography, computed tomography (CT), digital rectal examination (DRE), magnetic resonance imaging (MRI), and cancer protein assay (Herr et al., 1993). Morphological or histopathological imaging modalities alone or in combination can be used which includes transrectal ultrasonography (TRUS) (Lee et al., 1985), CT (Heinisch et al., 2006), radionuclide imaging (RI) (Liu, 2014), MRI, positron emission tomography (PET) (Gambhir, 2002) and PET/CT (Trotman et al., 2011). Although all these techniques are robust and highly efficient in the detection of PCa, but most of these techniques still suffer from the lack of sensitivity, accuracy and specificity for clinical diagnostic applications. The limitations of these techniques are given in Table 1.

However, the sensitivities of these existing methods are constantly unacceptable, as even the most sensitive diagnostic method can only detect tumour based on size. Practically, by then a large number of malignant growth cells would have been released into the circulatory system and resulting in cancer metastasis. As the cell growth at high-speed and the biological state of the person change in response to the disease conditions. Literature suggests that detection of PCa at the first stage of development can help in maximizing the potential for therapeutic intervention and improving survival from 10% to 90% (Stewart et al., 2001). Therefore, the diagnosis of PCa in a very early stage of disease development supports initiation of much earlier treatment therapy and the most effective hope for decreasing death rate and significant improvements in survival rates (Fan et al., 2018).

The present review addresses current advancements in the early detection of PCa based on the use of various kinds of nanomaterials

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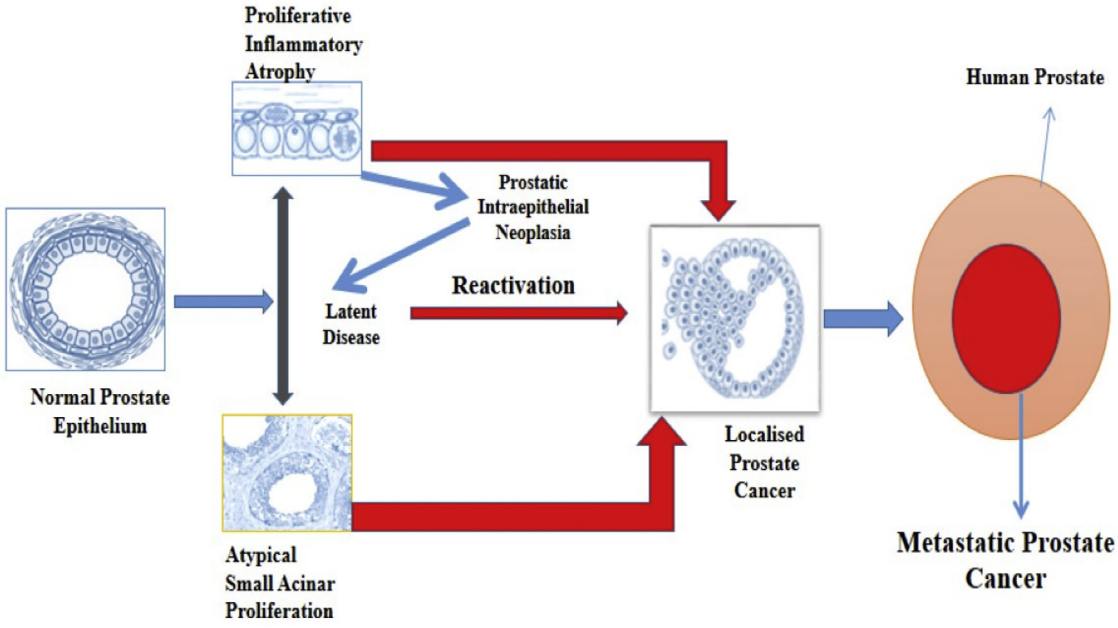

Fig. 1. Schematic workflow of PCa.

Table 1
Limitations of the available techniques for the detection of PCa.

S. No.	Techniques	Limitations	Ref.
1.	TRUS	1. It has a low-resolution imaging modality with low sensitivity and specificity. 2. The inherent speckle in the pattern of ultrasonography. 3. Small cancer foci are often not visible at all.	Siddiqui et al. (2013)
2.	CT	1. It shows limited specificity in differentiating cancer from benign prostate condition. 2. It showed poor soft-tissue contrast resolution.	Hövels et al. (2008)
3.	MRI	1. The technique has low scanning velocity, expensive and insensitive to calcifications.	(Dickinson et al., 2011; Picchio et al., 2011)
4.	RI	1. Resolution is lower than TRUS, CT and MRI.	(Lecouvet et al., 2007; Turkbey et al., 2009)
5.	PET	1. PET has limited spatial resolution (~4–6 mm).	(DeGrado et al., 2001; Liu et al., 2001)

Table 2
A comparative compilations of challenges in conventional diagnosis for prostate cancer and recent alternative.

Limitations of conventional diagnosis	Recent diagnosis and their benefits
Lack of specificity	High specificity
Lack of sensitivity	High sensitivity
Time consuming	Simple and cost effective
Chances of error in detection	Lack of error
Hectic and manual	Simple in handling the kits
Lack of US-FDA approval	US-FDA approved biomarkers
Unable to differentiate close symptoms related with prostate	Differentiate the disease
Low access to patients	Easy access to patients

along with the restricted practical applicability of conventional techniques as given in Table 2. We aim to give a thorough review covering the limitations in achieving high selectivity, sensitivity and reliability for the detection of PCa biomarkers. Despite the variety of nanomaterials used in electrochemical detection, we have highlighted the use of carbon materials and metals nanoparticles in electrochemical nanobiosensors. In this review, we compiled recent progress regarding the new emerging biomarkers and advantages of those biological and clinical biomarkers. The content could be a broad reference for the scientists and researchers working in related domains to provide benefits of human beings.

2. Role of biomarkers in prostate cancer diagnostics and prognosis

The National Cancer Institute (NCI) defines 'biomarkers' as a biological molecule found in blood, fluids, or tissues that can be objectively measured and evaluated as a sign of a normal/abnormal biological process and a pathogenic condition/disease (Sawyers, 2008). These biomarkers refer to the quantity that can be measured in a particular biological state or disease conditions. In the case of PCa detection, biomarkers play an important role in screening, detection and prognosis and clinical management. PCa biomarkers are biomolecules, which act as an indication of the disease condition and can be of diverse origins like ribose nucleic acid transcripts (RNA) (Bussemakers et al., 1999), proteins (Renehan et al., 2004), deoxyribose nucleic acid (DNA) or epigenetic modifications of DNA, metabolites or other alterations. They can be detected in tissue samples (biopsy or surgical resection) or non-invasively (by isolation of cells or molecules from body fluids) using human blood or urine sample (Hessels et al., 2003). Early detection of PCa biomarkers can allow the medical professionals to start sooner treatment which further enhances the patient compliance in terms of increased drug treatment efficacy and minimized risk of health deterioration and mortality rate.

2.1. Prostate cancer-biomarkers

PCa biomarkers cover a wide range of biochemical entities, such as proteins, nucleic acids and urinary. These biomarkers can be utilised for risk assessments, investigation, medical diagnosis, and further for the

prediction of treatment therapy, potency and toxicity of the drug. As the growth of tumours is rapid, uncontrollable and it releases numerous DNA, proteins and metabolites. The levels of these are associated with the stages of tumours development and biomarkers can be used for screening and clinical diagnosis of PCa (Landers et al., 2005). Detection of PCa by biomarkers helps to distinguish the healthy normal cells from the malignant (Adam et al., 2002). A significant difference can be observed in secretion, production and accumulation of various biomarkers in cancer cells as compared to normal cells or tissues (Gabrilovich, 2004). Biomarkers are being focused and developed in the recent few decades by monitoring the progression of disease at regular interval of time. It is progression during "watchful waiting" to become aware of micrometastatic disease (which is below the limit of detection for imaging) (Engers, 2007). It is also supportive in evaluating better therapeutic responses to in progress or given therapies. Early and accurate detection of PCa with the help of biomarkers can increase patient compliance.

2.1.1. Blood or serum biomarkers

Blood or serum samples are anticipated rich source of PCa biomarkers. Prostate-specific antigen (PSA)/human kallikrein-3 remained the first-line and the most preferred diagnosis and detection method as a standard. In 1994, the United States Food and Drug Administration (USFDA) approved PSA followed with a DRE for the diagnosis and detection of PCa. It has been established that PSA value in prostate cancer positive patients may have below 4 ng/mL as a cut-off level in the blood. Some cases have been diagnosed as positive even with the value 4–10 ng/mL. It is noteworthy that the PSA value above 4.0 ng/mL can be associated with benign prostate hyperplasia (BPH) or prostate inflammation (Damborska et al., 2017; Varambally et al., 2002). In last two decades, the main limitation of PSA based detection was lack of specificity wherein the report of biopsy corroborated negative result in $^{>}$ 75% men even with PSA level in the range of 4.0–10.0 ng/mL (Barry, 2001). It has been reported that PCa with high PSA level ($^{>}$ 2.0 ng/mL in male) in the year before diagnosis, had been found to have a higher risk of death after radical prostatectomy (Roddam et al., 2005). Analysis of commonly used PSA biomarkers helps to overcome limitations of prostate biopsy and improve accurate assessment (Armstrong et al., 2012). Thus, PSA based diagnosis is unable to differentiate PCa from other prostatic symptoms (DeMarzo et al., 2007). However, owing to inherent limitations of PSA as a biomarker, the field of prostate cancer biomarkers is evolving rapidly. In some incidences, prostate cancer had been observed even in complete absence of an elevated PSA level. Nonetheless, increased levels of PSA may suggest the presence of prostate cancer. Thus, a clinician can suggest better treatment by monitoring and assessing routinely the serum level of PSA from the patients. The list of blood or serum-based biomarkers has been listed in Table 3. Employing new technologies in both genomics and proteomics may play a significant part in the area of biomarkers discovery to contribute in diagnosis, prognosis, prediction of the disease and future therapy.

2.1.2. Urine biomarkers

Urine is a human waste available in the form of a liquid produced from the kidneys. It contains both organic and inorganic compounds in the form of hormones, proteins and metabolites (Mousavi et al., 2010). It has gain attention from the researchers due to its advantages and eases to assess as diagnostic and prognostic biomarkers. The method is simplest and non-invasive without any interference while analysis as compared to blood, tissue and serum wherein innate interferences in isolation may result in inaccurate measurements of biomarkers (Ploussard et al., 2010). On the other hand, detection of PCa biomarker using a urine sample can be carried out employing various urinary substrates, complete urine sample, urine sediments, exosomes and cell-free fractions (Leyten et al., 2014). For diagnosis, urine samples are collected just after a DRE, since it increases the total content of PCa related biomarker. Conclusively, the future of urine-based PCa biomarkers could be a potential diagnostic tool to authenticate several newly discovered biomarkers to find out new biomarkers to identify men with indolent PCa and to decrease the need of biopsy (Dijkstra et al., 2014). Thus, this may be helpful to (1) categorize male patients with aggressive diseased conditions, (2) distinguish between patients receiving benefits from local therapy and likely avail local therapy and require adjuvant intervention (Roach et al., 2008) and (3) find out surrogate markers for clinical progression or survival (DeBono et al. 2008a,b). Currently, available urine-based biomarkers have been enlisted in Table 4.

2.1.3. Tissue biomarkers

Tissue specimens are another biomarker alternative to serum, blood or urine biomarkers. However, these tissue-based biomarkers are unable to specify an exact target for the treatment of localized PCa patients with poor-risk disease. These tissue biomarkers serve as factors at the clinical level to correlate with a physiological pathway while pathologic analysis in response to a specific therapy and bridged these inadequacies of traditional clinical factors (Jensen et al., 2009). From last few years, PCa tissue specimens have been focused due to apparent understanding of the pathophysiology of PCa. The main reason behind the gained interest is due to improvement in the Weld of laser capture microdissection (LMC) which allowed sampling of homogenous cell populations for new biomarker finding (Cho et al., 2007; Diamandis et al., 2003). The harmony amongst various biomarkers is at the minimum and serves as a surrogate to determine pathophysiological endpoint (Kulasingam et al., 2008). Molecular biomarkers could be considered as critical causative effectors for targeting the desired process under scrutiny. The tissue-based biomarkers are listed in Table 5.

3. Nanomaterial biosensors for early stage screening of prostate cancer

Despite the fact that some downsides are present in relation to the attained level of sensitivity, the use of nanoparticle-based detectors in PCa biomarker detection offers some positive aspects in comparison to traditional techniques. Premature and truthful detection of PCa probed with nanomaterial-based biosensor could be an accurate solution for the unbeaten treatment of the disease (Sharifi et al., 2019). Presently, the assessment of the PSA biomarker is the only diagnosis tools for the patients with PCa. In general, urine and blood samples contain sarcosine content ranged as 1–20 mM. However, poor sensitivity and specificity of PCa based detection method led to false–negative and false–-positive result where patients are subjected to unnecessary biopsy (Qu et al., 2002). From the literature, it is revealed that early detection plays an enormous and convincing role to treat patients. As many studies are being conducted on developing sensing mechanisms that will move, forwards along the detection limit as far down as possible. Various new biomarkers can be discovered and verified with such sensitive tools. Even though, detecting cancers at its premature stage is very fascinating for improved diagnosis. Many factors such as the possibility of accomplishment of false positive/negative data and impact of nanomaterials on human and environment should be completely understood (Bahn et al., 2002).

To avoid above limits, this review work is motivated to meet the requirements of human needs with the advances in technology. It is therefore highly expected that in the near future, nanotechnology-based biosensor could be helpful to distinguish cancer cells near the beginning stage and examine the disease with much greater precision (Grimes et al., 2005). The fast detection method with enhanced sensitivity, cost-effectiveness and easy to carry out due to its miniaturized size are attractive features of the biosensors devices that drive attention of researchers. The development of biosensors from the traditional labelled technique to more featured non-labelled technique was truly a great leap in the advanced technology. Biomarkers in relation with

Table 3
Summary of selected contemporary serum prostate cancer biomarkers.

S. No.	Biomarker	Applications	Ref.
1.	PSA	Diagnostic of PCa & follow-up	Blel et al. (2017)
2.	Free PSA (fPSA)	Diagnostic of PCa	Martin et al. (2004)
3.	Pro PSA	Diagnostic of PCa	(remove bracket Filella et al., 2013)
4.	Prostate health index (PHI)	Diagnostic of PCa	Velonas et al. (2013)
5.	4KScore	To provide an estimate of the probability of having aggressive PCa	Parekh et al. (2015)
6.	Circulating tumour cells (CTCs)	Detection media for various biomarkers	De Bono et al. (2008a,b)
7.	Chromogranin-A	For monitoring the therapeutic efficacy, staging, prognosis, tumour volume evaluation, detection of recurrent disease, screening and early diagnosis	(Khan et al., 2011)
8.	Human kallikrein 2	Splits pro-PSA to create PSA and diagnosis	Clements et al. (2004)
9.	Transforming Growth factor-β	Diagnosis at in early stage	Perry et al. (1997)
10.	Neuron-specific enolase	To determine the organ specificity	Kamiya et al. (2003)
11.	Testosterone	Prostate cancer diagnosis at re-biopsy	Fiamegos et al. (2016)
12.	Vascular endothelial growth factor (VEGF)	Prostatic biopsy at prognosis phase	Schröder et al. (2009)
13.	Huntingtin-interacting protein 1 (autoantibodies)	Diagnosis	Bradley et al. (2005)
14.	Leptin	Diagnosis	Fan et al. (2008)
15.	Zinc α2-glycoprotein (ZAG)	Diagnosis	Ganswindt et al. (2008)
16.	Prostate secretory protein of 94 amino acids (PSP94)	Diagnosis	Nam et al. (2006)

nanotechnology have opened up a new era of early cancer diagnosis and precise drug delivery (Kryscio et al., 2012). Therefore, thorough reviews on electro-biochemical sensors have been written due to their high importance.

Scientifically, nanoparticles are defined as particles on the scale of 1–100 nm in diameter. Materials reduced to the nanoscale can show different properties compared to what they exhibit on a macro scale, enabling unique applications (Barry, 2001). The small size of nanoparticles allows for a greater surface to volume ratio. This increase in ratio allows for better detection, imaging, and prognosis methods, which will further advance the treatment of PCa. These biosensors interact with human cells, tissues, nucleic acids and detect the specific diagnostic antigen explaining as a mechanistic function. These sensors generate electrical signal owing to changes in sensor properties and is responsible for measurement and detection of disease. On the basis of the condition of disease, treatment is given to the patients (Haley et al., 2008). Nanomaterials based biosensors are more sensitive, susceptible, selective and specific diagnostic agents for PCa diagnosis and detection. In addition, nanotechnological based nanoscale sensors translate into improved access to the detection of PCa biomarkers with influential and specific signals economically with high throughput detections (Jain, 2005).

Recent advances in nanotechnology have found its application in the healthcare sector, one such application is the fabrication of nanomaterial based-biosensors, for early, rapid and accurate diagnosis of diseases (Gill et al., 2019). A biosensor consists of four parts: bioreceptor, transducer, a signal processor and interface display. A biosensor is an analytical device incorporating a biological material that can detect biological or chemical analytes in solution or in the atmosphere with a physiochemical transducer, that produces discrete or continuous electrical signals proportional to the analytes. It is composed of a biological component, such as a cell, enzyme or antibody, linked to a tiny transducer, which is a device, powered by one system that then supplies power (usually in another form) to a second system (Song et al., 2012).

3.1. Carbon nanotubes (CNTs)-based biosensors

CNTs hold great potential amongst nanomaterials for several biomedical applications such as extrinsically activated hyperthermia for PCa therapy. The smart/intelligent surface engineered CNTs are still having controversy about their biodegradable/non-biodegradable nature. Multiwall carbon nanotubes (MWNTs) probed with irradiation (laser-mediated) have been reported to enhance therapeutic efficacy in the treatment of human PCa. The CNTs have potential uses to fabricate an electrochemical sensor and biosensor for the early detection and diagnosis of various cancers. Prostate antigen detection using ionic liquid carbon nanotubes (ILCNTs) modified electrode is applied as a cancer biomarker for PCa detection with high sensitivity and rapid diagnosis. DNA encased MWNTs showed to eradicate PCa safely *in vivo* following near infrared radiation (NIR) (Robinson et al., 2012). In spite of these promising findings, the toxicity of CNTs has been found to have still a reasonable query in nanotechnology such as adverse effects on human health. In brief, preparation of prostate cancer cells is the first step for cancer diagnosis using CNTs based sensor. Similarly, modified CNT's thionine (composite modified electrode) and immunosensor have been used for PSA detection. Finally, the samples (serums) are analysed for various parameters in clinical diagnosis (Zheng et al., 2005). In ILCNTs immunosensor, it is initially characterized and amplified for biocatalysis in the diagnosis of anti-PSA. Electrochemical response, reproducibility, regeneration of the immunosensor and stability of PSA are several optimized conditions before analysis of the samples. These parameters are critically evaluated in the assay and determination of antigen or antibodies (Rodriguez et al., 2018).

3.2. Nanoscale electro biochemical sensor for PCa biomarker detection

In recent years, chemically modified electrodes (CMEs) have made great success in biosensors and electroanalysis. It is a relatively modern technique to electrode systems which has a wide spectrum of research and clinical based applications. These includes (i) basic electrochemical investigation such as the relationship of heterogeneous electron transfer and chemical reactivity to electrode surface chemistry (Mani et al., 2009), (ii) electrostatic phenomena at electrode surfaces, and electron (Liu et al., 2008), (iii) ionic transport phenomena in polymers (Kumar et al., 2012), (iv) designing electrochemical devices and systems for applications in chemical sensing, energy conversion and storage (Fenghua et al., 2009), (v) molecular electronics, electrochromic displays, (vi) corrosion protection, and (vii) electro-organic synthesis (Kumar et al., 2010).

In research laboratory and clinics of the patients, biosensors (based on sensing techniques) play a key role after the discovery of biomarkers for early detection and diagnosis of several deadly diseases such as cancers. For early detection of prostate cancer, different types of

Table 4
Summary of selected contemporary urine PCa biomarkers.

S.No.	Biomarker	Description	Applications	Ref.
RNA-based urinary biomarkers				
1.	Prostate cancer antigen 3 (PCA3)	Nucleic acid amplification test measuring the concentration of PCA3 and PSARNA molecules in urine	To help with repeat biopsy decisions in men 50 years old	(Hessels et al., 2009)
2.	Androgen receptor (AR)	Receptor for androgen stimulation of prostate	Prognostic	Hu et al. (2011)
3.	Aurora kinase A (AURKA)	It is a centrosome-associated serine/threonine kinase involved in mitotic chromosomal segregation	Prognostic	Mosquera et al. (2013)
4.	v-raf murine sarcoma viral oncogene homolog B1 (BRAF)	Belongs to the raf/mil family of serine/threonine protein kinases.	Diagnostic and therapeutic target	Ren et al. (2012)
5.	Calcium/calmodulindependent protein Kinase 2 (CAMKK2)	AR target gene promoting biosynthesis and glycolysis	Prognostic	Karacosta et al. (2012)
6.	Kallikrein-related peptidase 4 (KLK4)	One of fifteen kallikrein subfamily members located in a cluster on chromosome 19	Prognostic	(Wang et al., 2010)
7.	Mitogen-activated protein kinase 5 (MAP3K5)	Signalling cascade	Prognostic	Pressinotti et al. (2009)
8.	Matrix metallo peptidase 26 (MMP26)	Involved in the breakdown of extracellular matrix in normal physiological processes and cancer metastasis.	Progression	Zhao et al. (2009)
9.	Protein disulfide isomerase family A, member 3 (PDIA3)	Endoplasmic reticulum that interacts with lectin chaperones calreticulin and calnexin to modulate folding of newly synthesized glycoproteins	Prognostic	Park et al. (2009)
10.	TIMP metallopeptidase inhibitor 4 (TIMP4)	Inhibitors of the matrix metallo-proteinases	Progression	Lee et al. (2006)
RNA-based urinary biomarkers				
11.	Adenomatous polyposis coli (APC)	Tumour suppressor. Promotes rapid degradation of CTNNB1 and participates in Wnt signalling as a negative regulator	Diagnostic and Prognostic	Spirio et al. (1992)
12.	Glutathione S-transferase P1 (GSTP1)	Enzyme involved in protecting DNA from free radicals	Diagnostic (indicator for repeat biopsy)	Meiers et al. (2007)
13.	Retinoic acid receptor beta (RARB)	Binds retinoic acid. Mediates signalling in embryonic morphogenesis, cell growth and differentiation	Prognostic	Li et al. (2005)
14.	Ras association (RalGDS/AF-6) domain family member 1 (RASSF1A)	Required for death receptor-dependent apoptosis	Prognostic	(Han et al., 2012a,b)
Protein-based urinary biomarkers				
15.	Calgranulin B/MRP-14	Immunochemical biomarker assays	Early detection of prostate cancer	(Schiffer et al., 2007)
16.	Proteinpolypeptide	Identification of proteins using mass spectrometry.	For diagnosis and monitoring of disease	González-Buitrago et al. (2007)
17.	Uromodulin and semenogelin I	Immunoreactivity in hematologic malignancies	Early non-invasive detection for PCa	M'Koma et al. (2007)

Table 5
Summary of selected contemporary tissue-based prostate cancer biomarkers.

S.No.	Biomarker	Description	Applications	Ref.
1.	ProMark	8-biomarker proteomic assay	To differentiate indolent from aggressive disease on intact tissue biopsies	Blume-Jensen et al. (2015)
2.	Confirm MDx	Multiplex DNA methylation assay	To help with repeat biopsy decisions	Nguyen et al. (2015)
3.	Prostate Core Mitomic Test	Genomic test measuring molecular alterations based on mitochondrial DNA	To help with repeat biopsy decisions	Saini et al., 2016
4.	Oncotype DX	Measures the expression of 17 genes related to 4 different molecular pathways	To personalize PC treatment based on assessment of disease aggressiveness	Joh et al., 2009
5.	Prolaris	Cell cycle progression (CCP) score based on the expression of 46 genes	To personalize PC treatment based on assessment of disease aggressiveness	Mohammed et al., 2014
6.	Decipher	Genomic test measuring 22 RNA biomarkers in multiple biological pathways	To classify post-surgery, intermediate- and high-risk patients into genomic risk categories for metastasis	Jordan, 2009
7.	Androgen Receptor splice variant 7 (AR-V7)	Androgen receptor variant	Possible predictive utility in patients receiving enzalutamide, abiraterone, or galaterone	Leibrand et al. (2016)
8.	PTEN/TMPRS2: ERG	Gene fusions and PTEN deletions	Predicting risk of adverse pathology or recurrence after RP based on biopsy tissue	Clinton et al. (2017)

nanoparticles (NPs) electrobiochemical-based PCa biosensors using conventional techniques such as optical, electrical and electrochemical-based approaches have been employed since last decade. Implementing sensing techniques in the domain of nanotechnology have shown profound applications in biomarker sensing and highlighted the clinical benefits of these biomarkers (Niepa et al., 2016; Zhou et al., 2017). Therefore, thereby improving the sensitivity, selectivity and simplicity of analysis using nanoparticles (NPs) as novel sensors are gaining researcher's interest. Table 6 shows various nanomaterial-based biosensors for detection of PCa and its respective biomarkers.

3.2.1. Impedance-based miniaturized biosensors

The miniature biosensor (MB) based on impedance has been introduced as a new method and considered as ultra-sensitive, simple and rapid for PSA detection. The principle of this method is based on the impedance, and electrochemical impedance spectroscopy (EIS) is employed as a sensing technique. Electrochemical biosensors are commonly used to characterize surface modified electrodes for the investigation of the electrochemical system and process in due to unique features for sensing in miniature platforms (Nagaraj et al., 2010). In PSA detection method, PSA samples are first collected followed by reagent addition. Next, samples are stored in cancer centre of clinical diagnosis. In the EIS method, the anti-PSA/EA is used to characterize and analyse PSA content. Moreover, photolithography techniques utilize the fabricated test chip on an oxidized 4″ silicon wafer. These chips were previously cleaned and analysed for monolayer preparation, formation and antibody immobilization (Kavosi et al., 2015). It is important to note that PSA assay in phosphate buffered saline (PBS) and human plasma with biosensor are the major procedures and helpful in early diagnosis.

3.2.2. Immuno-chromatographic electrochemical biosensors

The developed nanoparticle sensor label/immuno chromatographic electrochemical biosensor performed rapid and sensitive detection of PSA. Similarly, such nanocarrier-based sensor has been reported to detect PCa in human serum wherein strips loaded with the electrochemical detector are responsible for transducing signals. It is composed of metallic elements such as Cd, Se, and ZnS with distinguished features. The sensitivity of detection is compared with a detection limit of 0.02 ng m/L (Bagalkot et al., 2007). Furthermore, nanomaterials and nanostructures based biosensor detect PSA diagnosis by employing Immunosensor comprising of the enzyme, DNA, nanoparticles, and CNTs. These are clinically used as a sensor for diagnostic purpose. Generally, diaminoheptane phosphate buffer solution and PSA is the materials used to prepare the quantum dots (QD)-anti PSA conjugates by QD conjugation Kit protocol. These are basic components for a biosensor of CNTs. It is also observed by anti-PSA-QD conjugate on glass fibre pad preparation. It is detected by lateral flow immunoassay; electrochemical detection and enzyme-linked immunosorbent assay (ELISA) (Lin et al., 2008).

3.2.3. Electrochemical transducers for prostate cancer biomarker detection

As described earlier, by different researchers that electrochemical sensors and electronic sensors are taking place at an electrode surface. It involves monitoring of changes of an electrical signal due to an electrochemical reaction at an electrode surface, because of an imposed potential, current, or frequency. The advanced biosensor technology may provide a suitable platform for real-time and personalized health monitoring (Gao et al., 2018). Electrochemical biosensors are used in point-of-care devices because they give accurate, fast, and sensitive methods for molecular sensing. In addition, they offer operating simplicity, the option for miniaturization, cost-effectiveness, and have attracted much attention in the area of point-of-care diagnostics (Han et al., 2012a,b). Fast responses, miniaturized sensor size, biocompatibility, rapid label-free detection, easy device tailoring, ultra-low detection limits, high reliability of measurements, and low development

Table 6
Summary of the best-selected nanomaterials based biosensors for detection of PCa.

Sensor platform	Method	Linearity range	LOD	Ref.
Fe_3O_4 NPs/GO sheets	CV.SWV	61 fg/mL to 3.9 pg/mL	15 fg/mL	Sharafeldin et al. (2017)
rGO-MWCNT	DPV	0.005–20 ng mL−1	1.0 pg mL−1	(Heydari-Bafrooei et al., 2017)
Thymine/CuNPs	DPV	0.05–500 fg/mL	0.020 ± 0.001 fg/mL	Zhu et al. (2016)
Si-nanowires/DNA aptamers	EIS	33 aM to 330 fM	23 aM (0.74 fg/mL)	Tzouvadaki et al. (2016)
AuNPs/glycoprofiling	EIS	4 aM to 40 nM	4 aM (0.13 fg/mL)	Pihíková et al. (2016)
CNT/AuNP/Chitosan	ECL	1 pg/mL to 50 ng/mL	0.6 pg/mL	Zhang et al. (2012)
CNT/AuNP	CV	0.01–0.5 ng/mL	7 pg/mL	Tian et al. (2012)

costs are appealing to patients, physicians, and the biomedical industry. Due to miniature small pocket size devices, it makes biosensor popular and applicable for home use. Although amperometric, voltammetric and potentiometric transducers have been commonly used. Voltammetric transducers are preferred for sensitive biomarker detection (Li et al., 2017a,b).

3.2.4. Voltammetry-based biosensors for prostate cancer biomarker detection

Voltammetric experiments are carried out in an electrochemical cell consisting of a working electrode, a reference and an auxiliary (counter) electrode. In case of potentiometric devices, the amperometric biosensor can be a module of all the electrodes assembled in one capsule. However, the biosensor more commonly plays a role of the working electrode (Pohanka, 2016). Thus, the measurement is performed in a cell with an analyte solution and two other immersed electrodes. As in potentiometric, the working cell contains a constant amount of the inorganic salts (KCl, Na_2SO_4) and/or mineral acids (HCl, H_2SO_4) inactive in the measurement conditions called supporting electrolytes (Schrödle et al., 2008). This is necessary for the maintenance of the constant ionic strength and suppression of migration under the electrode polarization. In voltammetric techniques, cyclic voltammetry (CV) and differential pulse voltammetry (DPV) are versatile and the most exploited techniques for PCa-biomarker detection. CV was used for electrochemical signal measurements. It is widely used for the study of redox processes and understanding reaction intermediates. In this technique, the potential is varied over a fixed range in a forward and backward direction and current (limited by analyte diffusion at the electrode surface) is monitored (dela Escosura-Muñiz et al., 2008). In DPV, potential with a series of fixed amplitude pulses is scanned between initial and final potential. Each succeeding pulse has the same amplitude. However, it starts from a slightly higher base potential. For each pulse, current is measured at just before the application of the pulse. In addition, at the end of the pulse and the difference is estimated and plotted against potential.

3.2.4.1. DPV-based prostate cancer biomarker detection. Using the DPV technique, various researchers have reported success in fabricating sensitive biosensors for prostate cancer biomarkers. Han et al., reported DPV based PSA and free fPSA detection on dual catalysis amplification of multi-functionalized onion-like mesoporous graphene sheets. The amplification performance of the immunosensor was investigated by DPV experiments. Moreover, the immunosensor was detected in the presence of 5.0 mM AA-P to evaluate the catalytic ability of the loaded bio-AA. It can be easily seen that the peak currents obviously increases with the addition of AA-P, certifying a typical electro-catalytic process of AA for Au@PBNPs/O-GS and Au@NiNPs/O-GS nanohybrids. The catalytic DPV oxidation peak current was increased with the increasing concentration of fPSA and PSA. The calibration plots displayed good linear relationships in the ranges from 0.02 to 10 ng/mL for fPSA with a regression equation of y = 1.163x + 3.694 (ng/mL), 0.01–50 ng/mL for PSA with a regression equation of y = 0.325x + 6.369, respectively. The limit of detection values for fPSA and PSA were 6.7 pg/mL and 3.4 pg/mL, respectively (S/N = 3) (Han et al., 2012a,b). The peak currents for three folds successively simultaneous detection of fPSA and PSA at the same immunosensor array by DPV measurements and showed very small standard deviations. It could be found that the proposed immunosensor exhibited a satisfactory detection limit and linear range.

3.2.4.2. CV-based prostate cancer biomarker detection. CV is gaining interest for measurement of analytes in various biosensors and has shown promise for PCa biomarker detection. Li et al. have described the application of ultrahigh-efficient electrochemiluminesce resonance energy transfer (ECL-RET) in one nanostructure and the dual amplification for the detection of the microRNA-141 (miRNA-141) of human prostate cancer cells. To confirm the successful stepwise fabrication process of the miRNA biosensor, the CVs were employed in 5.0 mM $[Fe(CN)_6]^{3-/4-}$ from −0.2–0.6 V at a scan rate of 0.1 V/s. The bare glassy carbon electrode (GCE) exhibited a pair of quasi-reversible redox peaks of $[Fe(CN)_6].^{3-/4-}$ AuNPs were electrodeposited on the surface of bare GCE wherein an apparent increase in redox current was obtained because the well electrical conductivity of AuNPs could promote electron transfer. In contrast, the capture 2 was immobilized onto the prepared electrode and an obvious decreased current was detected due to the characteristic of impeding the electron transfer of DNA. Subsequently, the redox peak integrally decreased when the successive immobilization of HT on the electrode. After adding the reporter DNA and QDs-Ru(dcbpy)$_3^{2+}$/capture 1 to the modified sensor, a further decrease of the redox current appeared for the DNA structure could inhibit the electron transfer. The results characterized the CVs performance of the proposed electrochemiluminesce (ECL) biosensor construction (Li et al., 2017a,b).

Using the CV technique, Chang et al., established and applied in a reusable electrochemical biosensor for the detection of microRNA-182–5p (miRNA-182–5p), a prostate cancer biomarker in prostate cancer, based on the DNA cross configuration-fuelled target cycling and strand displacement reaction (SDR) amplification. They described the use of carboxyl groups (-COOH) in combination with MWCNTs for fabrication of PAMAM-CNTs-Pt Nanomaterials. After the fabrication, it was measured with square-wave voltammetry (SWV). The release of the prepared electrode was under a settled voltage applied at −0.7 V for 5 min to ensure the complete single-electron reduction of $MV2^+$ in 0.1 M PBS (pH = 7) solution for obtaining more stable complex CB-8-MV^+-MV^+. Afterwards, the electrode was measured with a CV. Subsequently, the electrode dealt with the electrochemical release was immersed into the beaker containing CB-8 and MV^{2+} under O_2 flow for 5 min to oxidize $MV^+\cdot$ to MV^{2+} for the formation of CB-8-MV^{2+} again. Next, the as-prepared electrode was modified with 20 μL of the mixture of S1-Try and S2-Try for 100 min. After that, A1, A2 and $[Ru(NH_3)_6]^{3+}$ were dropped onto the handled electrode for 120 min and then washed with ultrapure water. The fabrication process of the miRNA biosensor was characterized by CV measurement in 5 mM $[Fe(CN)_6]^{3-/4-}$ solution with a scan rate of 100 mV/s (Chang et al., 2017).

4. Summary and conclusions

This review summarized the recent ongoing developments of PCa biomarkers detection methods with an emphasis on nanotechnology. Nanomaterials based devices have been widely employed to develop early disease detection and diagnostics due to their low cost and easy scale-up in manufacturing. With the interfacing between materials scientist and biomedical engineering, nanomaterials based PCa detection are becoming simpler, ultra-sensitive, precise accuracy and reliability. We tried to highlight the importance of PCa biomarkers along with nanomaterials for fabrication of sensitive biosensors. This nanomaterial based electrochemical biosensors increase the electronic attributes, specificity, signal rate and helps in generating detectable signals for indirect detection of targets. Thus, extensive efforts have been made to identify better biomarkers in order to guide early diagnosis and prevent the disease from progression. Numerous emerging biomarkers for PCa have been discovered and been applied to clinical uses recently, bringing new insight of PCa to researchers and clinicians as well as producing plenty of novel screening tests for potential patients.

5. Future perspectives

Despite rapid advance in nanomaterial-based biosensors technology, yet there is no commercial sensor available for PCa biomarkers detection, due to few challenges still left to tackle. One such challenge faced is that many of the biosensors developed still lacking high sensitivity and specificity towards the PCa biomarkers. Another challenge is small detection range, which contribute immensely to delaying in detection, treatment and management of disease. To overcome the issue of sensitivity, selectivity and accuracy ultra-sensitive electrochemical nanobiosensors will be the best alternative. In the future, comprehensive studies are required to reconfirm assured features of the existing biomarkers and further discover novel potential ones to better predict the presence of the disease for the early detection as well as prognosis of prostate cancer. Recently, there are limited clinical trials studies are investigating the clinical application of epigenetic biomarkers in this domain of cancer patients.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Sima Singh: Conceptualization, Writing - original draft. **Atal A.S. Gill:** Writing - original draft. **Manimbulu Nlooto:** Supervision. **Rajshekhar Karpoormath:** Supervision.

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References

Adam, B.-L., Qu, Y., Davis, J.W., Ward, M.D., Clements, M.A., Cazares, L.H., Semmes, O.J., Schellhammer, P.F., Yasui, Y., Feng, Z., 2002. Cancer Res. 62, 3609–3614.
Armstrong, A.J., Eisenberger, M.A., Halabi, S., Oudard, S., Nanus, D.M., Petrylak, D.P., Sartor, A.O., Scher, H.I., 2012. Eur. Urol. 61, 549–559.
Bagalkot, V., Zhang, L., Levy-Nissenbaum, E., Jon, S., Kantoff, P.W., Langer, R., Farokhzad, O.C., 2007. Nano Lett. 7, 3065–3070.
Bahn, D.K., Lee, F., Badalament, R., Kumar, A., Greski, J., Chernick, M., 2002. Urology 60, 3–11.
Barry, M.J., 2001. N. Engl. J. Med. 344, 1373–1377.
Blel, N., Fourati, N., Souiri, M., Zerrouki, C., Omezzine, A., Bouslama, A., Othmane, A., 2017. Curr. Top. Med. Chem. 17, 2913–2925.
Blume-Jensen, P., Berman, D.M., Rimm, D.L., Shipitsin, M., Putzi, M., Nifong, T.P., Small, C., Choudhury, S., Capela, T., Coupal, L., 2015. Clin. Cancer Res. 21, 2591–2600.
Bradley, S.V., Oravecz-Wilson, K.I., Bougeard, G., Mizukami, I., Li, L., Munaco, A.J., Sreekumar, A., Corradetti, M.N., Chinnaiyan, A.M., Sanda, M.G., 2005. Cancer Res. 65, 4126–4133.
Bussemakers, M.J., Van Bokhoven, A., Verhaegh, G.W., Smit, F.P., Karthaus, H.F., Schalken, J.A., Debruyne, F.M., Ru, N., Isaacs, W.B., 1999. Can. Res. 59, 5975–5979.
Carter, H.B., Pearson, J.D., 1999. Urology 54, 780–786.
Chang, Y., Zhuo, Y., Chai, Y., Yuan, R., 2017. Anal. Chem. 89, 8266–8272.
Cho, W.C., Cheng, C.H., 2007. Expert Rev. Proteom 4, 401–410.
Clements, J.A., Willemsen, N.M., Myers, S.A., Dong, Y., 2004. Crit. Rev. Clin. Lab. Sci. 41, 265–312.
Clinton, T.N., Bagrodia, A., Lotan, Y., Margulis, V., Raj, G.V., Woldu, S.L., 2017. Expert Rev. Precis. Med. Drug Dev. 2, 249–260.
Damborska, D., Bertok, T., Dosekova, E., Holazova, A., Lorencova, L., Kasak, P., Tkac, J., 2017. Microchim. Acta 184, 3049–3067.
De Bono, J.S., Scher, H.I., Montgomery, R.B., Parker, C., Miller, M.C., Tissing, H., Doyle, G.V., Terstappen, L.W., Pienta, K.J., Raghavan, D., 2008a. Clin. Cancer Res. 14, 6302–6309.
DeGrado, T.R., Coleman, R.E., Wang, S., Baldwin, S.W., Orr, M.D., Robertson, C.N., Polascik, T.J., Price, D.T., 2001. Can. Res. 61, 110–117.
dela Escosura-Muñiz, A., Ambrosi, A., Merkoçi, A., 2008. Trac. Trends Anal. Chem. 27, 568–584.
DeMarzo, A.M., Platz, E.A., Sutcliffe, S., Xu, J., Grönberg, H., Drake, C.G., Nakai, Y., Isaacs, W.B., Nelson, W.G., 2007. Nat. Rev. Canc. 7, 256–269.
DePinho, R.A., 2000. Nature 408, 248.
Diamandis, E.P., 2003. Clin. Chem. 49, 1272–1275.
Dickinson, L., Ahmed, H.U., Allen, C., Barentsz, J.O., Carey, B., Futterer, J.J., Heijmink, S.W., Hoskin, P.J., Kirkham, A., Padhani, A.R., 2011. Eur. Urol. 59, 477–494.
Dijkstra, S., Mulders, P., Schalken, J., 2014. Clin. Biochem. 47, 889–896.
Engers, R., 2007. World J. Urol. 25, 595–605.
Fan, R., Vermesh, O., Srivastava, A., Yen, B.K., Qin, L., Ahmad, H., Kwong, G.A., Liu, C.-C., Gould, J., Hood, L., 2008. Nat. Biotechnol. 26, 1373–1378.
Fan, T., Du, Y., Yao, Y., Wu, J., Meng, S., Luo, J., Zhang, X., Yang, D., Wang, C., Qian, Y., Gao, F., 2018. Sensor. Actuator. B Chem. 266, 9–18.
Fenghua, L., Jiangfeng, S., Huafeng, Y., Shiyu, G., Qixian, Z., Dongxue, H., Ari, I., Li, N., 2009. Nanotechnology 20, 455602–455608.
Fiamegos, A., Varkarakis, J., Kontraros, M., Karagiannis, A., Chrisofos, M., Barbalias, D., Deliveliotis, C., 2016. Int. Braz J. Urol. 42, 925–931.
Filella, X., Giménez, N., 2013. Clin. Chem. Lab. Med. 51, 729–739.
Fuchsjäger, M., Shukla-Dave, A., Akin, O., Barentsz, J., Hricak, H., 2008. Acta Radiol. 49, 107–120.
Gabrilovich, D., 2004. Nat. Rev. Immunol. 4, 941–952.
Gambhir, S.S., 2002. Nat. Rev. Canc. 2, 683.
Ganswindt, U., Stenzl, A., Bamberg, M., Belka, C., 2008. Eur. Urol. 54, 528–542.
Gao, F., Fan, T., Ou, S., Wu, J., Zhang, X., Luo, J., Li, N., Yao, Y., Mou, Y., Liao, X., Geng, D., 2018. Biosens. Bioelectron. 99, 201–208.
Gill, A.A., Singh, S., Thapliyal, N., Karpoormath, R., 2019. Microchimica Acta 186, 114–133.
González-Buitrago, J.M., Ferreira, L., Lorenzo, I., 2007. Clin. Chim. Acta 375, 49–56.
Grimes, D.A., Schulz, K.F., 2005. Lancet 365, 1500–1505.
Haley, B., Frenkel, E., 2008. Nanoparticles for drug delivery in cancer treatment. Urol. Oncol. Semin. Ori. 26, 57–64.
Han, J., Zhuo, Y., Chai, Y., Yuan, R., Zhang, W., Zhu, Q., 2012a. Anal. Chim. Acta 746, 70–76.
Heinisch, M., Dirisamer, A., Loidl, W., Stoiber, F., Gruy, B., Haim, S., Langsteger, W., 2006. Mol. Imaging Biol. 8, 43–48.
Herr, H.W., Kornblith, A.B., Ofman, U., 1993. Cancer 71, 1143–1150.
Hessels, D., Schalken, J.A., 2009. Nat. Rev. Urol. 6, 255–261.
Hessels, D., Gunnewiek, J.M.K., van Oort, I., Karthaus, H.F., van Leenders, G.J., van Balken, B., Kiemeney, L.A., Witjes, J.A., Schalken, J.A., 2003. Eur. Urol. 44, 8–16.
Heydari-Bafrooei, E., Shamszadeh, N.S., 2017. Biosens. Bioelectron. 91, 284–292.
Hövels, A., Heesakkers, R., Adang, E., Jager, G., Strum, S., Hoogeveen, Y., Severens, J., Barentsz, J., 2008. Clin. Radiol. 63, 387–395.
Hu, R., Isaacs, W.B., Luo, J., 2011. Prostate 71, 1656–1667.
Jain, K.K., 2005. Clin. Chim. Acta 358, 37–54.
Jensen, H.K., Donskov, F., Marcussen, N., Nordsmark, M., Lundbeck, F., von der Maase, H., 2009. J. Clin. Oncol. 27, 4709–4717.
Joh, J.E., Esposito, N.N., Kiluk, J.V., Laronga, C., Lee, M.C., Loftus, L., Soliman, H., Boughey, J.C., Reynolds, C., Lawton, T.J., Acs, P.I., 2011. Oncologist 16, 1520–1526.
Jordan, V.C., 2009. Cancer Res. 69, 1243–1254.
Kamiya, N., Akakura, K., Suzuki, H., Isshiki, S., Komiya, A., Ueda, T., Ito, H., 2003. Eur. Urol. 44, 309–314.
Karacosta, L.G., Foster, B.A., Azabdaftari, G., Feliciano, D.M., Edelman, A.M., 2012. J. Biol. Chem. 287, 24832–24843.
Kavosi, B., Salimi, A., Hallaj, R., Moradi, F., 2015. Biosens. Bioelectron. 74, 915–923.
Khan, M.O., Ather, M.H., 2011. J. Pak. Med. Assoc. 61, 108–111.
Kryscio, D.R., Peppas, N.A., 2012. Acta Biomater. 8, 461–473.
Kulasingam, V., Diamandis, E.P., 2008. Nat. Rev. Clin. Oncol. 5, 588.
Kumar, A., Sharma, S., Maurya, R.A., Sarkar, J., 2010. J. Comb. Chem. 12, 20–24.
Kumar, M., Kumar, N., Bhalla, V., Sharma, P.R., Kaur, T., 2012. Org. Lett. 14, 406–409.
Landers, K.A., Burger, M.J., Tebay, M.A., Purdie, D.M., Scells, B., Samaratunga, H., Lavin, M.F., Gardiner, R.A., 2005. Int. J. Cancer 114, 950–956.
Lawrence, M.G., Lai, J., Clements, J.A., 2010. Endocr. Rev. 31, 407–446.
Lecouvet, F.E., Geukens, D., Stainier, A., Jamar, F., Jamart, J., d'Othée, B.J., Therasse, P., Berg, B.V., Tombal, B., 2007. J. Clin. Oncol. 25, 3281–3287.

Lee, F., McLeary, R., Kumasaka, G., Borlaza, G., Straub, W., Gray, J., Meadows, T., Lee Jr., F., Solomon, M., McHugh, T., 1985. Prostate 7, 117–129.
Lee, S., Desai, K.K., Iczkowski, K.A., Newcomer, R.G., Wu, K.J., Zhao, Y.-G., Tan, W.W., Roycik, M.D., Sang, Q.-X.A., 2006. Cell Res. 16, 750.
Lee, D.-E., Koo, H., Sun, I.-C., Ryu, J.H., Kim, K., Kwon, I.C., 2012. Chem. Soc. Rev. 41, 2656–2672.
Leibrand, C.R., Price, D.K., Figg, W.D., 2016. Cancer Biol. Ther. 17, 467–469.
Leyten, G.H., Hessels, D., Jannink, S.A., Smit, F.P., de Jong, H., Cornel, E.B., de Reijke, T.M., Vergunst, H., Kil, P., Knipscheer, B.C., 2014. Eur. Urol. 65, 534–542.
Li, L.-C., Carroll, P.R., Dahiya, R., 2005. J. Natl. Cancer Inst. 97, 103–115.
Li, Z., Lin, Z., Wu, X., Chen, H., Chai, Y., Yuan, R., 2017a. Anal. Chem. 89, 6029–6035.
Lin, Y.-Y., Wang, J., Liu, G., Wu, H., Wai, C.M., Lin, Y., 2008. Biosens. Bioelectron. 23, 1659–1665.
Liu, Y., 2014. Oncol. Lett. 7, 2013–2018.
Liu, I.J., Zafar, M.B., Lai, Y.-H., Segall, G.M., Terris, M.K., 2001. Urology 57, 108–111.
Liu, X., Dai, Q., Austin, L., Coutts, J., Knowles, G., Zou, J., Chen, H., Huo, Q., 2008. J. Am. Chem. Soc. 130, 2780–2782.
Mani, V., Chikkaveeraiah, B.V., Patel, V., Gutkind, J.S., Rusling, J.F., 2009. ACS Nano 3, 585–594.
Martin, B., Finlay, J., Sterling, K., Ward, M., Lifsey, D., Mercante, D., Jainto, J., Martin, L., Rayford, W., 2004. Prostate Cancer Prostatic Dis. 7, 132–137.
Meiers, I., Shanks, J.H., Bostwick, D.G., 2007. Pathology 39, 299–304.
Mohammed, A.A., 2014. Med. Oncol. 31, 140–146.
Mosquera, J.M., Beltran, H., Park, K., MacDonald, T.Y., Robinson, B.D., Tagawa, S.T., Perner, S., Bismar, T.A., Erbersdobler, A., Dhir, R., 2013. Neoplasia 15, IN1–IN4.
Mousavi, S.M., Sundquist, J., Hemminki, K., 2010. Eur. J. Cancer Prev. 19, 275–279.
M'Koma, A.E., Blum, D.L., Norris, J.L., Koyama, T., Billheimer, D., Motley, S., Ghiassi, M., Ferdowsi, N., Bhowmick, I., Chang, S.S., 2007. Biochem. Biophys. Res. Commun. 353, 829–834.
Nagaraj, V.J., Aithal, S., Eaton, S., Bothara, M., Wiktor, P., Prasad, S., 2010. Nanomedicine 5, 369–378.
Nam, R.K., Reeves, J.R., Toi, A., Dulude, H., Trachtenberg, J., Emami, M., Daigneault, L., Panchal, C., Sugar, L., Jewett, M.A., 2006. J. Urol. 175, 1291–1297.
Nguyen, H.G., Welty, C.J., Cooperberg, M.R., 2015. Curr. Opin. Urol. 25, 65–70.
Niepa, T.H.R., Wang, H., Dabrowiak, J.C., Gilbert, J.L., Ren, D., 2016. Acta Biomater. 36, 286–295.
Parekh, D.J., Punnen, S., Sjoberg, D.D., Asroff, S.W., Bailen, J.L., Cochran, J.S., Concepcion, R., David, R.D., Deck, K.B., Dumbadze, I., 2015. Eur. Urol. 68, 464–470.
Park, S.-W., Zhen, G., Verhaeghe, C., Nakagami, Y., Nguyenvu, L.T., Barczak, A.J., Killeen, N., Erle, D.J., 2009. Proc. Natl. Acad. Sci. Unit. States Am. 106, 6950–6955.
Perry, K.T., Anthony, C.T., Case, T., Steiner, M.S., 1997. Urology 49, 151–155.
Picchio, M., Briganti, A., Fanti, S., Heidenreich, A., Krause, B.J., Messa, C., Montorsi, F., Reske, S.N., Thalmann, G.N., 2011. Eur. Urol. 59, 51–60.
Pihíková, D., Belicky, Š., Kasák, P., Bertok, T., Tkac, J., 2016. Analyst 141 (3), 1044–1051.
Ploussard, G., De La Taille, A., 2010. Nat. Rev. Urol. 7, 101–109.
Pohanka, M., 2016. Anal. Lett. 49, 2865–2882.
Pressinotti, N.C., Klocker, H., Schäfer, G., Luu, V.-D., Ruschhaupt, M., Kuner, R., Steiner, E., Poustka, A., Bartsch, G., Sültmann, H., 2009. Mol. Canc. 8, 1–12.
Qu, Y., Adam, B.-L., Yasui, Y., Ward, M.D., Cazares, L.H., Schellhammer, P.F., Feng, Z., Semmes, O.J., Wright, G.L., 2002. Clin. Chem. 48, 1835–1843.
Ren, G., Liu, X., Mao, X., Zhang, Y., Stankiewicz, E., Hylands, L., Song, R., Berney, D.M., Clark, J., Cooper, C., 2012. Genes Chromosomes Cancer 51, 1014–1023.
Renehan, A.G., Zwahlen, M., Minder, C., T O'Dwyer, S., Shalet, S.M., Egger, M., 2004. Lancet 363, 1346–1353.
Roach, M., Bae, K., Speight, J., Wolkov, H.B., Rubin, P., Lee, R.J., Lawton, C., Valicenti, R., Grignon, D., Pilepich, M.V., 2008. J. Clin. Oncol. 26, 585–591.
Robert, G., Descazeaud, A., Nicolaïew, N., Terry, S., Sirab, N., Vacherot, F., Maillé, P., Allory, Y., De La Taille, A., 2009. Prostate 69, 1774–1780.
Robinson, J.T., Hong, G., Liang, Y., Zhang, B., Yaghi, O.K., Dai, H., 2012. J. Am. Chem. Soc. 134, 10664–10669.
Roddam, A.W., Duffy, M.J., Hamdy, F.C., Ward, A.M., Patnick, J., Price, C.P., Rimmer, J., Sturgeon, C., White, P., Allen, N.E., 2005. Eur. Urol. 48, 386–399.
Rodriguez, C., Torres-Costa, V., Ahumada, O., Cebrián, V., Gómez-Abad, C., Díaz, A., Manso Silván, M., 2018. Sensor. Actuator. B Chem. 267, 559–564.
Saini, S., 2016. PSA and beyond: alternative prostate cancer biomarkers. Cell. Oncol. 39, 97–106.
Sawyers, C.L., 2008. Nature 452, 548–552.
Schiffer, E., 2007. World J. Urol. 25, 557–562.
Schröder, F.H., Hugosson, J., Roobol, M.J., Tammela, T.L., Ciatto, S., Nelen, V., Kwiatkowski, M., Lujan, M., Lilja, H., Zappa, M., 2009. N. Engl. J. Med. 360, 1320–1328.
Schrödle, S., Richmond, G.L., 2008. J. Am. Chem. Soc. 130, 5072–5085.
Sharafeldin, M., Bishop, G.W., Bhakta, S., El-Sawy, A., Suib, S.L., Rusling, J.F., 2017. Biosens. Bioelectron. 91, 359–366.
Sharifi, M., Avadi, M.R., Attar, F., Dashtestani, F., Ghorchian, H., Rezayat, S.M., Saboury, A.A., Falahati, M., 2019. Biosens. Bioelectron. 126, 773–784.
Siddiqui, M.M., Rais-Bahrami, S., Truong, H., Stamatakis, L., Vourganti, S., Nix, J., Hoang, A.N., Walton-Diaz, A., Shuch, B., Weintraub, M., 2013. Eur. Urol. 64, 713–719.
Siegel, R., Ma, J., Zou, Z., Jemal, A., 2014. CA A Cancer J. Clin. 64, 9–29.
Song, K.-M., Lee, S., Ban, C., 2012. Sensors 12, 612.
Spirio, L., Otterud, B., Stauffer, D., Lynch, H., Lynch, P., Watson, P., Lanspa, S., Smyrk, T., Cavalieri, J., Howard, L., 1992. Am. J. Hum. Genet. 51, 92–100.
Stewart, C.S., Leibovich, B.C., Weaver, A.L., Lieber, M.M., 2001. J. Urol. 166, 86–92.
Tian, J., Huang, J., Zhao, Y., Zhao, S., 2012. Microchim. Acta 178, 81–88.
Trotman, J., Fournier, M., Lamy, T., Seymour, J.F., Sonet, A., Janikova, A., Shpilberg, O., Gyan, E., Tilly, H., Estell, J., 2011. J. Clin. Oncol. 29, 3194–3200.
Turkbey, B., Pinto, P.A., Choyke, P.L., 2009. Nat. Rev. Urol. 6, 191–203.
Tzouvadaki, I., Jolly, P., Lu, X., Ingebrandt, S., de Micheli, G., Estrela, P., Carrara, S., 2016. Nano Lett. 16, 4472–4476.
Varambally, S., Dhanasekaran, S.M., Zhou, M., Barrette, T.R., Kumar-Sinha, C., Sanda, M.G., Ghosh, D., Pienta, K.J., Sewalt, R.G., Otte, A.P., 2002. Nature 419, 624–629.
Velonas, V., Woo, H., Remedios, C., Assinder, S., 2013. Int. J. Mol. Sci. 14, 11034–11060.
Wang, W., Mize, G.J., Zhang, X., Takayama, T.K., 2010. Int. J. Cancer 126, 599–610.
The WHO 2018 database available at: https://www.who.int/news-room/fact-sheets/detail/cancer.
Willmann, J.K., Van Bruggen, N., Dinkelborg, L.M., Gambhir, S.S., 2008. Nat. Rev. Drug Discov. 7, 591.
Zhang, M., Dai, W., Yan, M., Ge, S., Yu, J., Song, X., Xua, W., 2012. Analyst 137, 2112–2118.
Zhao, Y., Xiao, A., Ni, J., Man, Y., Sang, Q., 2009. Chin. J. Canc. 28, 1168–1175.
Zheng, G., Patolsky, F., Cui, Y., Wang, W.U., Lieber, C.M., 2005. Nat. Biotechnol. 23, 1294–1301.
Zhou, F., Yao, Y., Luo, J., Zhang, X., Zhang, Y., Yin, D., Gao, F., Wang, P., 2017. Anal. Chim. Acta 969, 8–17 2017.
Zhu, Y., Wang, H., Wang, L., Zhu, J., Jiang, W., 2016. ACS Appl. Mater. Interfaces 8, 2573–2581.
DeBono, J.S., Scher, H.I., Montgomery, R.B., Parker, C., Miller, M.C., Tissing, H., Doyle, G.V., Terstappen, L.W., Pienta, K.J., Raghavan, D., 2008b. Clin. Cancer Res. 14, 6302–6309.
Han, J., Zhuo, Y., Chai, Y., Yuan, R., Zhang, W., Zhu, Q., 2012b. Anal. Chim. Acta 746, 70–76.
Li, Z., Lin, Z., Wu, X., Chen, H., Chai, Y., Yuan, R., 2017b. Anal. Chem. 89, 6029–6035.