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PSA and beyond: alternative prostate cancer biomarkers

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Abstract

Background—The use of biomarkers for prostate cancer screening, diagnosis and prognosis has the potential to improve the clinical management of the patients. Owing to inherent limitations of the biomarker prostate-specific antigen (PSA), intensive efforts are currently directed towards a search for alternative prostate cancer biomarkers, particularly those that can predict disease aggressiveness and drive better treatment decisions.

Methods—A literature search of Medline articles focused on recent and emerging advances in prostate cancer biomarkers was performed. The most promising biomarkers that have the potential to meet the unmet clinical needs in prostate cancer patient management and/or that are clinically implemented were selected.

Conclusions—With the advent of advanced genomic and proteomic technologies, we have in recent years seen an enormous spurt in prostate cancer biomarker research with several promising alternative biomarkers being discovered that show an improved sensitivity and specificity over PSA. The new generation of biomarkers can be tested via serum, urine, or tissue-based assays that have either received regulatory approval by the US Food and Drug Administration or are available as Clinical Laboratory Improvement Amendments-based laboratory developed tests. Additional emerging novel biomarkers for prostate cancer, including circulating tumor cells, microRNAs and exosomes, are still in their infancy. Together, these biomarkers provide actionable guidance for prostate cancer risk assessment, and are expected to lead to an era of personalized medicine.

Keywords

Prostate cancer; Biomarkers; Prognostic; Predictive; Diagnostic

1 Prostate cancer: epidemiology, clinical burden and dilemmas

Prostate cancer is the most commonly diagnosed male malignancy. It is estimated that prostate cancer alone will account for about one quarter of the cancer diagnoses among men in the USA in 2015, with an estimated 220,800 new cases [1]. It is the second leading cause

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of cancer-related mortality among men with an estimate of 27,540 deaths in 2015 [1]. Although novel therapies with proven survival benefits have been developed in the last few years [2, 3], the increases in survival rates are marginal. Prostate cancer is a remarkably heterogeneous disease. Prostate tumors can be indolent or very aggressive, often metastasizing to bone and other organs, thereby causing significant morbidity and mortality [4]. A major clinical challenge in prostate cancer is the inability of current diagnostic tests, including prostate-specific antigen (PSA) screening and histopathological grading, to distinguish between aggressive and indolent tumors [5]. PSA is present in normal prostatic secretions and its levels are often elevated in prostate cancer patients [6, 7]. Serum PSA levels have been utilized as a prostate cancer biomarker for over 20 years and PSA screening has revolutionized the clinical management of the disease [8]. However, PSA has inherent limitations, including lack of specificity, leading to over-diagnosis and over-treatment of prostate cancer. In view of this, intensive efforts are currently focused on searching for alternative prostate cancer biomarkers, particularly those that can predict the aggressiveness of the disease and drive better treatment decisions.

Also, histopathological grading performed by Gleason scoring has been used as an important prognostic indicator of prostate cancer [9–11]. Gleason-based grading classifies tumors from 1 to 5 according to their relative degree of differentiation (from most to least differentiated, respectively). In prostate cancer, multifocal lesions usually exist [12] and Gleason grades can, therefore, be heterogeneous within or between different tumor foci. In view of this, a combined Gleason score that sums up the two most prevalent patterns within the prostate gland is used [9–11]. Although a Gleason score is a powerful prognostic indicator, it cannot accurately predict the aggressiveness of the disease since it has been found that tumors with similar histological patterns may have different clinical outcomes [11, 13]. Hence, there is a critical need for the development of alternative prostate cancer biomarkers with a better diagnostic and prognostic potential.

2 Prostate cancer biomarkers: a bird's eye view

The National Cancer Institute (NCI) defines ‘biomarker’ as a biological molecule found in blood, other body fluids, or tissues that can be objectively measured and evaluated as a sign of a normal/abnormal biological process and a pathogenic condition/disease. A biomarker may be used for screening purposes, for disease diagnosis and prognosis, for the evaluation of disease disposition and for the prediction/monitoring of treatment responses to various therapeutic interventions [14–16]. Since several years, the use of biomarkers for prostate cancer screening, diagnosis and prognosis has revolutionized its clinical management [8]. The first prostate cancer biomarker, prostatic acid phosphatase (PAP), was described in the 1930s and has since then been used as a clinical marker for prostate cancer progression, since serum PAP levels were found to be elevated in metastatic cases [15, 17]. This biomarker was replaced by prostate-specific antigen (PSA) in the 1980s [15, 18]. PSA is a kallikrein-related serine protease produced by the epithelial cells of the prostate gland [5] that is present in normal prostatic secretions and is often elevated in prostate cancer [6, 7]. Since the 1980s, PSA screening has significantly improved prostate cancer disease management, including its survival rates. However, owing to inherent limitations of PSA as a biomarker (see below), the field of prostate cancer biomarkers is evolving rapidly. Also,

with the advent of advanced genomic and proteomic technologies, we have experienced in recent years an enormous increase in our understanding of prostate cancer biology that, in turn, has contributed to the development of novel biomarkers for prostate cancer diagnosis and prognosis. In this review, I will discuss the current state of our understanding of prostate cancer biomarkers - primarily diagnostic and predictive - thereby highlighting recent advances that have the potential to improve the clinical management of the patients. These biomarkers are blood-/urine-/tissue-based and have been either approved by the US Food and Drug Administration (FDA) or are available as Clinical Laboratory Improvement Amendments (CLIA) based laboratory developed tests (LDTs) [8, 19]. In addition, I will discuss emerging novel biomarkers for prostate cancer (including circulating tumor cells, microRNAs and exosomes) that are still in their infancy. Imaging-based tests such as computerized tomography and transrectal ultrasound have been developed as well, but these are not discussed here and are reviewed elsewhere [20, 21]. Considering the recent spurt in prostate cancer biomarker research, I foresee that promising alternative biomarkers will become available to clinicians to support a better diagnosis, prognosis and clinical management of prostate cancer patients (summarized in Fig. 1).

3 Prostate cancer biomarkers in clinical use: US FDA approved

The development of disease biomarkers as clinical diagnostic tools with US Food and Drug Administration (FDA) approval is often a long and regulated process that includes significant validations [19, 22]. Hence, only a few prostate cancer biomarkers have as yet been approved by the US FDA and these are discussed below.

3.1 Prostate-specific antigen

Currently, PSA is the most prevalently used prostate cancer biomarker by clinicians. In 1994, the US FDA approved PSA testing for prostate cancer screening in conjunction with a digital rectal exam (DRE). A PSA level of 4 ng/ml was defined as the upper normal limit. Prostate cancer cases with elevated PSA levels typically undergo biopsy for assessment of prostate cancer. However, more recent studies have shown that ∼20 % of men with PSA levels<4 ng/ml have prostate cancer and that many men with higher levels do not have prostate cancer [8, 23–25]. Although organ specific, PSA is not cancer specific and circulating PSA levels often rise in the presence of conditions that disrupt prostate basal membrane epithelial cells such as prostatitis, benign prostatic hyperplasia (BPH), prostate biopsies and surgeries [5, 8]. Owing to these shortcomings, PSA screening has led to over-diagnosis and over-treatment of low-risk prostate cancer [8, 26]. In view of this, recent changes in recommendations include later and less frequent PSA screening [27, 28]. This notion highlights the need for the development of novel improved prostate cancer biomarkers. However, despite its lack of specificity, PSA is still the most clinically accepted biomarker used for prostate cancer, especially for monitoring progression and disease recurrence after curative therapy [15, 29]. In fact, PSA screening has contributed to a significant decline (45–70 %) in age-adjusted prostate cancer mortality since the early 1990s [8, 30].

PSA exists in blood either in its free form (fPSA) or in a complex with serum protease inhibitors. fPSA accounts for 5– 35 % of total PSA (tPSA) and can occur in three molecular

forms: pro-PSA, benign PSA (bPSA) and intact PSA (iPSA) [5]. The ratio of fPSA over tPSA (percentage free PSA) has been found to be lower in prostate cancer [31] and has been shown to improve the specificity of cancer detection in men with tPSA values of 4–10 ng/ml and a normal DRE [32]. However, due to the instability of fPSA compared to complexed PSA, the percentage of fPSA exhibits a wide analytical variability and is, therefore, not used as primary screening tool [8, 33].

Pro-PSA is the inactive proenzyme form of PSA which contains a seven amino acid leader peptide that is normally cleaved by human kallikrein (hK) enzymes, i.e., hK-2 and hK-4, to PSA. However, roughly one-third of fPSA exists as pro-PSA that is more likely to be associated with prostate cancer [5, 19]. Several truncated forms/isoforms of pro-PSA exist in serum with varying lengths of the pro-leader peptide. One isoform, [-2] proPSA, consisting of PSA with a serinearginine pro-leader peptide, has emerged as a prominent biomarker for prostate cancer [8, 34, 35]. This isoform is the most prevalent biomarker that is correlated with cancer rather than BPH, and is used for the early detection and for determining the aggressiveness of the disease [34–39]. It outperforms both PSA and the percentage fPSA in terms of diagnostic ability, specificity and positive or negative predictive value [8, 40, 41]. It was shown to be the best biomarker for prostate cancer detection, particularly in cases with 2–10 ng/ml PSA [42].

3.2 Prostate health index

In 2012 the US FDA approved another test - the prostate health index (PHI) - that includes three biomarkers and is calculated for each patient as ([-2] proPSA/fPSA) × $PSA^{1/2}$. This test was developed by Beckman Coulter in partnership with the NCI Early Detection Research Network [19] and intends to distinguish cancerous and benign prostatic conditions in men aged≥50 years with a normal DRE and PSA levels of 4–10 ng/ml [42]. This test determines the need of biopsy in cases with total PSA levels between 4 and 10 ng/ml, thereby reducing unnecessary biopsies (Fig. 1). Several studies suggest that the use of PHI along with [-2] proPSA significantly improves prostate cancer detection in cases with a Gleason score≥7 [19, 38, 39] and improves the accuracy of established prostate cancer predictors at biopsy compared to PSA and fPSA [40, 41].

3.3 Prostate cancer antigen 3

Prostate cancer antigen 3 (PCA3, also referred to as DD3) is a prostate cancer-specific antigen that is encoded by a gene on chromosome 9q21-22 [5, 43, 44]. It is a long non-coding RNA of unknown function that was first reported by Bussemakers et al. in 1999 [5, 43]. PCA3 is not detected in normal prostate tissue, exhibits a low expression level in prostatic hyperplastic tissues and is highly expressed in prostate cancer [5, 43]. Owing to its restricted expression profile, PCA3 RNA serves as a useful biomarker for prostate cancer that is highly expressed in >95 % of the primary and metastatic cases. An in vitro amplification test called ‘Progensa PCA3 test’ (Hologic) was approved by the US FDA in 2012 for use in possible prostate cancer cases based on a negative biopsy result and/or negative PSA level and/or DRE results [19]. Through this assay the PCA3 score is determined in post DRE urine specimens of prostate cancer patients. The PCA3 score is obtained by dividing PCA3 RNA by PSA RNA levels. PCA3 scores less than 25 are

associated with a decreased likelihood of prostate cancer [45–47]. The PCA3 score has a higher specificity and a better predictive value (positive and negative) than serum PSA, although its sensitivity is lower [47]. The sensitivity of PCA3 is variable (ranging from 20 to 96 %) depending on the threshold cutoff used for the PCA3 levels [8, 48]. The PCA3 score, along with PSA and other risk factors, could be incorporated into a nomogram for improved risk stratification. The most widely studied utility of the PCA3 score has been its ability to predict malignancy in men with an elevated PSA and a prior negative biopsy (Fig. 1) [5, 8, 49]. Unlike PSA, the PCA3 score is independent of prostate volume [48]. Overall, PCA3 is a useful adjunct to the currently used methods for prostate cancer diagnosis, including PSA and DRE.

4 Prostate cancer biomarkers: non-FDA approved, Clinical Laboratory Improvement Amendments-based laboratory developed tests

In the following section biomarkers are discussed that have been used/developed recently and that are available as Clinical Laboratory Improvement Amendments-based laboratory developed tests [8, 19]. These tests have been commercially developed for prostate cancer but are not approved by the US FDA.

4.1 *TMPRSS2-ERG* gene fusion test

Recurrent gene fusions involving ETS transcription factor family member genes (usually *ERG,* a v-ets erythroblastosis virus E26 oncogene homolog) with the androgen regulated gene *TMPRSS2* (transmembrane serine protease isoform 2) are frequently encountered in prostate tumors (∼50 % tumors) [42, 43]. Laxman et al. demonstrated the occurrence of these gene fusions in urine of clinically localized prostate cancer patients post-DRE [44]. These gene fusions serve as potential non-invasive urinary biomarkers that have subsequently been tested in additional studies. *TMPRSS2-ERG* fusions in urinary sediments have been associated with a high specificity (93 %) and positive predictive value (94 %), although its sensitivity has been reported to be low (37 %) [12, 45]. The drawback of this fusion gene as a biomarker is the associated tumor heterogeneity, as most prostate tumors contain multiple foci [12]. Also, the prognostic implications of this gene fusion are not clearly defined. Some studies suggest that *TMPRSS2-ERG* gene fusion-positive cases are associated with a higher prostate cancer aggressiveness, metastasis and mortality [13, 46], while others have reported a lack of correlation between this fusion and clinical outcome [47]. Also, the frequency of this gene fusion is low in some populations. Hence, it is difficult to identify an appropriate cutoff across populations [13]. In view of its shortcomings, this prostate cancer-specific biomarker has been combined with PCA3 for developing a urine-based test for prostate cancer. Combining *TMPRSS2-ERG* and PCA3 has been shown to significantly improve the sensitivity for prostate cancer diagnosis [49, 50], with the sensitivity of PCA3 increasing from 68 to 76 % [45]. Additionally, combined *TMPRSS2-ERG* and PCA3 scores have been reported to improve the performance of serum PSA for predicting prostate cancer and high-grade prostate cancer at biopsy [50].

4.2 Mi-Prostate score test

Considering the inherent heterogeneity of prostate cancer, a panel of markers rather than a single marker has been suggested to be more suitable for its diagnosis and prognosis [51]. Mi-Prostate Score (MiPS) is a test offered by the University of Michigan MLabs that incorporates blood PSA levels and urinary levels of *TMPRSS2-ERG* and PCA3 for prostate cancer risk assessment [19]. This validated test improves the utility of the PSA blood test and allows risk stratification of prostate cancer, while avoiding unnecessary biopsies [19, 52].

4.3 Oncotype DX test

Genomic Health Inc. offers the Oncotype DX prostate cancer test, which is a multi-gene expression assay developed for formalin-fixed paraffin-embedded (FFPE) diagnostic prostate needle biopsies containing as little as 1 mm of prostate tumor. This assay assesses the activity of a set of 12 cancer-related genes to reveal the underlying biology of the tumor. The 12 cancer-related genes represented in the assay are involved in four different biological pathways, including the androgen pathway (*AZGP1, KLK2, SRD5A2, RAM13C*), proliferation (*TPX2*), cellular organization (*FLNC, GSN, TPM2, GSTM2*) and stromal response (*BGN, COL1A1* and *SFRP4*). Five reference genes have been included to normalize the data and to control for variability. These measurements are algorithmically combined to calculate a Genomic Prostate Score (GPS). This assay has been analytically and clinically validated as a predictor of aggressive prostate cancer [19, 53] and enables prostate cancer risk stratification to guide clinicians in making treatment decisions.

4.4 ProMark test

ProMark, offered by Metamark, is a protein based prognostic test for predicting prostate cancer aggressiveness, particularly in patients with Gleason scores 3 + 3 or 3 + 4 [54]. This test measures the expression of eight proteins (DERL1, CUL2, SMAD4, PDSS2, HSPA9, FUS, phosphorylated S6, YBOX1) in biopsy tissue sections employing an automated immunofluorescence method. Based on the expression levels of these eight proteins, an independent risk score is calculated on a scale of 0–1 that provides a personalized prediction of disease aggressiveness. A risk score of ≤0.33 is ‘favorable’ and a score of >0.80 is ‘unfavorable’. These scores are associated with false negative and false positive rates of 10 % and 5 %, respectively. This risk score was clinically validated as an independent predictor of prostate cancer aggressiveness relative to current risk stratification tools [54] and can aid in stratifying patients for active surveillance versus therapeutic intervention.

4.5 ConfirmMDx test

ConfirmMDx, offered by MDx Health Inc., is a test that detects an epigenetic field effect or “halo” associated with a cancerization process at the DNA methylation level in cells adjacent to cancer foci [19, 50, 52, 55]. This test has the ability to diagnose prostate cancer cases that are histologically normal/benign. For this test, core specimens collected during a 12-core biopsy are employed with a minimum requirement of eight cores derived from the apex, mid and left/right base, and two additional locations of the prostate [19]. This test helps to distinguish patients who have a true-negative biopsy from those who may have

occult cancer with a 90 % negative predictive value (NPV). Its further clinical utility includes the identification of high-risk men who may need a repeat biopsy and, potentially, treatment.

4.6 Prolaris test

Myriad Genetics Inc. offers Prolaris, a genomic test for predicting prostate cancer aggressiveness in conjunction with clinical parameters such as Gleason score and PSA. This test measures the expression of a set of 31 cell cycle progression genes and 15 housekeeping genes to predict disease progression [56–58]. The expression of the cell cycle-related genes is correlated with the proliferation of prostate cancer and serves as a risk stratification tool enabling a better treatment/monitoring strategy for patients at the time of diagnosis. A low expression of these genes is associated with a low risk of progression and those men may be candidates for active surveillance, while a high expression is associated with a higher risk of disease progression in men who may be treated. This test is significantly more prognostic than the currently used clinicopathological variables. It may also be useful in estimating the disease recurrence risk in post-prostatectomy patients.

4.7 Prostate Core Mitomic test

The Prostate Core Mitomic test offered by Mitomics is based on mitochondrial DNA (mtDNA) alterations in prostate cancer biopsies. It is a highly sensitive test that yields accurate and reliable results. This test can detect large-scale mtDNA deletions (3.4 kb) in normal/benign appearing tissues obtained by biopsy via a ‘cancerization’ field effect [19, 59, 60]. In this assay, a section of the needle core sample from the negative biopsy is employed to assess the occurrence of 3.4 kb mtDNA deletions using real time PCR. The sensitivity of the assay is 85 % and the specificity is 54 %, with a negative predictive value of 92 %. This test helps to identify men who do not require a repeat biopsy [61].

4.8 4K score test

The 4K score test, offered by Opko Health Inc., measures the blood plasma levels of a panel of four prostate-derived kallikrein proteins, i.e., total PSA, fPSA, intact PSA and human kallikrein 2 (hK2) [19, 62, 63]. These biomarkers are combined with other parameters such as age, DRE status and prior biopsy status to calculate the risk of pathologically insignificant versus aggressive prostate cancer. This test helps to identify patients eligible for biopsy based on the probability of having aggressive prostate cancer, and helps to avoid unnecessary biopsies in low-risk patients.

4.9 Prostarix test

Prostarix is a test developed by Metabolon Inc. and marketed by Bostwick Laboratories. This test is based on a panel of four metabolites excreted into urine, including sarcosine, that are increased during prostate cancer progression [64]. This metabolic test uses a quantitative liquid chromatography-mass spectroscopy (LC-MS) method to accurately measure the concentrations of four amino acids in urine samples collected after DRE. From these measurements, a Prostarix score is generated. In clinical trials, the Prostarix test has shown an increased sensitivity and specificity compared to PSA. This test provides physicians with

a better risk stratification tool leading to more informed patient management decisions, especially for patients with a negative DRE or a modestly elevated serum PSA level.

4.10 Decipher test

Decipher is a genomic test offered by Genome Dx Biosciences that assesses the disease progression risk after radical prostatectomy. This test evaluates the expression levels of a set of 22 RNA biomarkers involved in multiple biological pathways related to the development and progression of prostate cancer. The expression of these biomarkers is used to calculate the probability of clinical metastasis within 5 years after radical prostatectomy, and within 3 years after biochemical recurrence. The prognostic value of this test has been validated in a high risk surgical cohort where a high genomic classifier (GC) score was associated with metastasis incidence rates of>25 %. Conversely, a low GC score was found to be associated with a good prognosis in over 70 % of the high risk patients [65, 66].

5 Other prostate cancer biomarkers

5.1 α-Methylacyl coenzyme A racemase (AMACR)

α-Methylacyl coenzyme A racemase (AMACR) is over-expressed in prostate cancer and has been used as a biomarker in needle biopsy specimens [67]. AMACR protein expression analysis in 94 prostate needle biopsy specimens revealed a 97 % sensitivity and a 100 % specificity for detecting prostate cancer [67]. In addition, AMACR expression has been found to be down-regulated in prostate cancer recurrences and metastases [68]. It is useful as a tissue biomarker in interpreting prostate needle biopsy specimens that are diagnostically challenging [67]. Although it is used as a biomarker, it is not specific to prostate cancer [15, 69].

5.2 *PTEN* gene deletions

PTEN is a tumor suppressor gene located on chromosome 10 that is commonly lost in prostate cancer. This loss leads to activation of the phosphoinositide-3-kinase (PI3K) signaling pathway, which plays a cardinal role in cell growth, proliferation and metastasis and, in addition, to inhibition of the androgen receptor (AR) signaling pathway [70, 71]. *PTEN* deletions are associated with a poor prognosis and a hormone-refractory disease, and are used as a predictive biomarker for response to therapy [72, 73]. *PTEN* deletions combined with *TMPRSS2-ERG* gene fusions have a better prognostic potential. Tumors with *PTEN* loss and ERG gene fusions are associated with a poor outcome, while those with only *PTEN* loss or an *ERG* fusion exhibit intermediate-poor or intermediate outcomes, respectively [72, 74–76].

6 Promising alternative prostate cancer biomarkers: in infancy

Apart from the biomarkers described in the preceding sections, recent studies suggest the potential utility of additional novel biomarkers in prostate cancer as discussed in this section.

6.1 Circulating tumor cells

Circulating tumor cells (CTCs) in whole blood are emerging biomarkers for cancer detection and prognosis [15, 77–79]. CTCs are malignant in origin and carry information about molecular alterations such as *TMPRSS2-ERG* fusions, *PTEN* deletions and *AR* copy number changes [15, 80]. An increased level of CTCs in blood of castration-resistant prostate cancer patients may predict a worse overall survival [15, 78, 81]. Though CTCs yield useful information, current CTC detection techniques are labor-intensive, expensive and lack sensitivity [15, 66]. Based on current detection techniques, ∼50 % of the patients present with undetectable CTC levels [66] pointing at a need for a further improvement of these techniques.

6.2 MicroRNA biomarkers

Prominent among alternative prostate cancer biomarkers are microRNAs (miRNAs) that constitute an evolutionarily conserved class of small (18–25 nt long) regulatory RNAs [82]. miRNA expression patterns have been found to serve as phenotypic signatures of various cancers [83], including prostate cancer. In primary prostate cancers, widespread deregulation of miRNAs has been reported compared to normal prostate tissues. Altered miRNA expression profiles have been associated with prostate cancer progression, aggressiveness, metastasis and recurrence, thereby highlighting the prognostic potential of miRNAs [83–86]. miRNAs have emerged as putative diagnostic and prognostic biomarkers that can distinguish tumor from normal tissues, aid in stratification of tumors and monitor treatment responses [83, 87]. Owing to their small size and resistance to endogenous RNase activity, miRNAs are stable biomarkers that can be readily detected in formalin-fixed tissues [88], as also in body fluids such as serum, plasma and urine [89]. Due to these attributes, miRNAs can be potentially used as both tissue biomarkers and as non-invasive cancer biomarkers [83, 90, 91]. It has been found that expression profiles of a set of 15 miRNAs (up-regulated: miR-16, -31, -125b, -145, -149, -181b, -184, -205, -221, -222; down-regulated: miR-96, -182, -182*, -183, -375) can discriminate benign prostate tissue from prostate cancer with 84 % accuracy [92], and that serum miR-141 levels can distinguish prostate cancer patients from healthy individuals [93]. miRNA profiling in sera from healthy men and untreated prostate cancer patients of low, intermediate and high risk groups based on CAPRA scores revealed miRNA signatures for prostate cancer diagnosis and prognosis [94]. miR-107 and miR-574-3p levels were found to be higher in urine of men with prostate cancer compared to controls [95]. Clearly, miRNAs are emerging as promising alternative biomarkers for prostate cancer, although further studies are required to ultimately develop miRNAs into clinically useful biomarkers [83, 85].

6.3 Exosomal biomarkers

Exosomes are small extracellular vesicles (30–100 nm in size) [96] that are gaining significant interest as alternative disease biomarkers that can be detected non-invasively in blood, urine or semen [87]. Exosomes are a promising source of protein and RNA/miRNA biomarkers for the early diagnosis and prognosis of prostate cancer [97]. Prostate-derived microvesicles (50–150 nm) or prostasomes [98] have been reported to be higher in prostate cancer patients and to correlate with increasing Gleason scores [15, 98]. Two known prostate

cancer biomarkers, PCA3 and *TMPRSS2-ERG* (see above), could be detected in exosomes isolated from urine of prostate cancer patients, showing its potential for prostate cancer diagnosis [99]. Plasma-derived exosomal survivin has been found to be high in prostate cancer patients, suggesting its use as a biomarker for the early detection of prostate cancer [100]. Increasing evidence indicates that also circulating miRNAs in body fluids are present in exosomes [101, 102]. An analysis of miRNAs in serum-derived exosomes revealed an association of miR-141 and miR-375 with metastatic prostate cancer [95].

7 Conclusions and perspectives

Since several years, serum PSA has been used as a prostate cancer biomarker [8]. However, due to its inherent limitations, including lack of specificity, PSA screening has proven controversial leading to an intensive search for alternative prostate cancer biomarkers with a better diagnostic and predictive potential. In particular, there is a quest for biomarkers that can distinguish between aggressive and indolent tumors, thereby leading to better treatment decisions. With the advent of advanced genomic and proteomic technologies, we have in recent years experienced an enormous increase in our understanding of prostate cancer biology. As a result, prostate cancer biomarker research has expanded its horizons with several promising alternative biomarkers being discovered. Several US FDA approved and clinical laboratory-based tests have been developed that show an improved sensitivity and specificity over PSA. However, in most recently developed tests, serum PSA is still being used in conjunction with other parameters, highlighting the fact that PSA remains an indispensable tool in the clinical management of prostate cancer. The emerging alternative biomarkers may continue to supplement or, possibly, replace PSA over time. These alternative biomarkers appear to have better detection/diagnostic and prognostic abilities/predictive values (summarized in Fig. 1). The new generation of prostate cancer biomarkers seems promising and provides actionable guidance to risk assessment and treatment decisions. The clinical implementation of several newly discovered biomarkers has, however, often been hindered by the erroneous design of preclinical trials, inappropriate statistical analyses etc. [15]. Careful validation of emerging biomarkers such as exosomal biomarkers, CTCs and miRNAs may help to fulfill the so far unmet clinical challenges and guide clinicians to better diagnoses and better treatment options for prostate cancer. With the armamentarium of novel alternative biomarkers, prostate cancer is poised to enter an era of personalized medicine.

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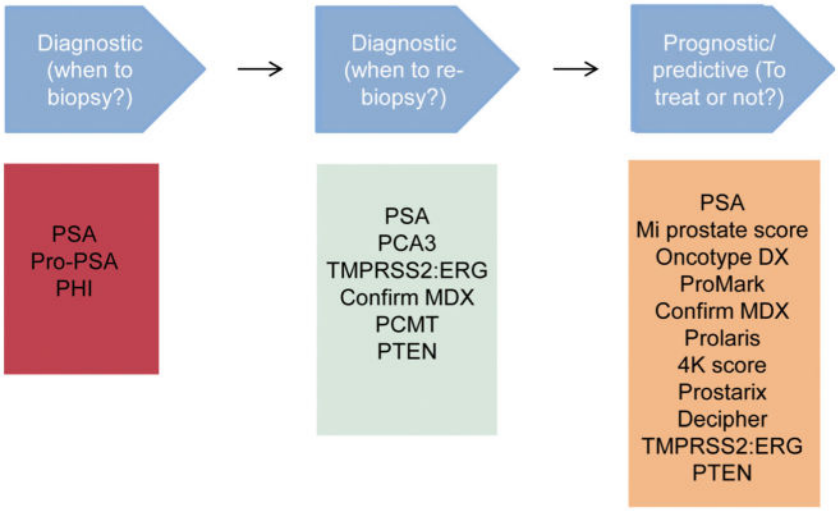

Fig. 1.

Overview of clinically validated and emerging prostate cancer biomarkers that are either approved by the US FDA or are available as Clinical Laboratory Improvement Amendments (CLIA)-based laboratory developed tests. These are blood-/urine-/tissue-based biomarkers that have a diagnostic and/or prognostic/predictive potential. Diagnostic biomarkers include those that help clinicians to decide on when to biopsy or to re-biopsy. In addition, some recently developed biomarkers may have prognostic/predictive potential and may help to guide treatment decisions