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Review

A piece in prostate cancer puzzle: Future perspective of novel molecular signatures

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ABSTRACT

Prostate cancer (PCa) has a variable biological potential. It constitutes the second most common cancer amongst men worldwide and the fifth most common cancer in Saudi Arabia. Identifying men at higher risk of developing PCa, differentiating indolent from aggressive disease and predicting the likelihood of progression will improve decision-making and selection for active surveillance protocols. Biomarkers have been utilized for PCa screening and predicting cancer behavior and response to treatment. The prostate specific antigen (PSA) screening helps detect PCa in early stages, while implementing a plan for management and outcome. However, PSA screening is still controversial, due to the risks of over diagnosis and treatment, and its inability to detect a good proportion of advanced tumors. Alternatively, a new era of PCa biomarkers has emerged with higher PCa specificity than PSA and its isoforms hopefully improving screening methods, such as Prostate Health Index (PHI) score, Progensa Prostate Cancer Antigen 3 (PCA3), Mi-Prostate Score (MiPS), Prostate Stem Cell Antigen (PSCA), 4Kscore test, and Urokinase Plasminogen Activation (uPA and uPAR). Few novel biomarkers have shown promise in preliminary results. This review will display promising biomarkers including some important FDA approved ones, highlighting their clinical implication and future place in the PCa puzzle, along with addressing their current limitations.

Contents

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1. Introduction

Among men, globally the prostate cancer (PCa) is the 2nd most common diagnosed malignancy, while it is the 5th most commonly in Saudi Arabia. It continues to be the 5th leading cause of cancer death worldwide (Bray et al. 2018). Approximately 1.3 million new cases were diagnosed worldwide in 2018 (Bray et al. 2018), with a wide range of incidence rates of more than 25-fold (Wong et al. 2016), depending on screening programs, diagnostic tools, and predisposing risk factors among different populations (Wong et al. 2016). The lowest incidence of PCa was reported in Asia, followed by Africa, America, and Europe, with a parallel mortality to the incidence rates (apart from Africa, which has the highest mortality rate) (McGinley et al. 2016). Acid phosphatase was the first PCa biomarker known more than 80-year ago, when Gutmans et al discovered an increase in acid phosphatase activity in the serum of most men with metastatic PCa, and only in one out of 88 men with non-cancerous conditions (Gutman and Gutman, 1938). This was supported later by the decline in serum acid phosphatase following castration in men with advanced PCa, which was also associated with clinical relief (Huggins, 1942).

Recently, biomarker assays were widely used for both prediction and prognosis. Several FDA approved biomarkers became available to provide clinicians and patients with facts concerned about the risk of future disease and treatment outcomes. This review will discuss commercially available biomarkers utilized in clinical practice for PCa diagnosis, including their validity and possible shortcomings.

2. What are the prostate cancer Biomarkers?

The biomarker is defined as an indicator to evaluate the risk of a disease or it's existent, according to the US Food and Drugs Administration (FDA). Another more widespread definition which is given by the US National Institutes of Health (NIH) is measuring and evaluating an indicator related to normal biological changes, pathogenic process, and response to pharmacological or therapeutic intervention (Ilyin et al., 2004). These biomarkers result from tumor cells and / or the body's response to a malignancy process. Regardless of the definition, an ideal biomarker should be detected by a non-invasive and an inexpensive test. The test should also have high specificity and sensitivity, and it should have the ability to accurately differentiate cancerous tissues from benign tissues and aggressive tumors from inconsiderable tumors (Biomarkers Definitions Working G, 2001).

Some authors have proposed the structured, phased-model for the development and validation of biomarkers (Pepe et al., 2001), which were later adopted and modified (Bensalah et al., 2007; Paradiso et al., 2009). This structure was similar to that used in developing drugs, including introductory studies, clinical validation, longitudinal retrospective review, prospective studies and finally, cancer control research.

The current review will highlight the biomarkers which are of clinical interest for management of PCa (Table 1), such as screening and early detection, staging and/or confirmation of the disease, predicting the risk of recurrence or progression, predicting or monitoring the effectiveness of treatment and identifying patients who

Table 1
Prostate cancer biomarkers in clinical use.

Biomarker	Sample	Role	Biochemical characteristic
PSA	Blood	Screening Diagnostic	Kallikrein-related peptidase 3 Secreted serine protease
fPSA **tPSA** **−2pro-PSA**	Blood	Diagnostic with better performance	Isoforms and cleavage forms of PSA
PSA density **PSA velocity** **PSA doubling time**	Blood	Diagnostic Prognostic Predictor of recurrence?	Kinetic characterization of PSA
PCA3	Urine Tissue	Diagnostic Indicator for repeat biopsy	Non-coding mRNA Highly up-regulated in PCa
4K score	Blood	Diagnostic Percent risk of high-grade cancer on biopsy	Algorithm combines clinical data with serum tPSA, fPSA, intact PSA (iPSA), and hK2.
PHI	Blood	Diagnostic	Score formula = [−2]proPSA/free PSA) × $\sqrt{}$PSA
uPA	Tissue	Prognostic	Precursor for serine protease and its receptor for degradation of extra cellular matrix
uPAR	Blood	Increased in PCa with bone metastasis	
PSCA	Tissue Blood	Prognostic Correlated with higher Gleason score, higher stage, and the presence of metastasis	Membrane glycoprotein. Specific production in the prostate and possible target for therapy Prognostic
Oncotype Dx- GPS **Prolaris** **Decipher**	Tissue	Prognostic	RNA-based genetic panels Include 85 genes

PSA: Prostate-specific antigen; fPSA: free PSA; tPSA: total PSA; PCA3: prostate cancer antigen 3; PHI: prostate health index; uPA: urokinase plasminogen activation; uPAR: urokinase plasminogen activation receptors; PSCA: prostate stem cell antigen.

will most likely respond to a given therapy, potentially identifying the molecular targets of modern therapies, and patients who will benefit from such a therapeutic regimen (Paradiso et al., 2009).

3. Diagnostic biomarkers

3.1. Prostatic specific antigen (PSA)

PSA belongs to the family of human kallikrein proteins, it is a glycoprotein, encoded by the KLK3 gene and has several isoform (Lukes et al., 2001). The FDA first approved PSA testing in 1986, where it was indicated as a prognostic marker for PCa, a function which has never been challenged. Introduction of PSA revolutionized PCa screening and diagnosis, with significant increase in the incidence of PCa due to diagnosis at earlier stages, with consequent reduction in mortality rates (Bjartell, 2013).

Despite being organ-specific, PSA is not cancer-specific. PSA levels might be increased in some non-malignant diseases such as benign enlargement and prostatitis. In men with serum PSA level of the gray zone between 4 and 10 ng/ml, makes it difficult to point out patients with cancer from those with benign changes or from patients undergoing urethral manipulation (Thompson et al., 2005). It became one of those markers routinely used to detect, stratify risk, and monitor treatment outcome (Thompson et al., 2005). PSA has a low specificity, however, it is the most commonly used diagnostic tool for PCa, especially when it is combined with digital rectal examination (DRE) and *trans*-rectal ultrasound (TRUS) (Heidenreich et al., 2011). Nevertheless, widespread use of PSA has led to a significant increase in diagnostic prostate cancer biopsies, a condition which might not be clinically significant during one's lifetime. Over-diagnosis can sometimes result in overtreatment which results in an unnecessary morbidities and psychological burden for patients Heijnsdijk et al., 2009).

PSA-based PCa screening is still a matter of controversy, and the current relevant question is to screen or not to screen. To improve its diagnostic and prognostic accuracy, PSA density, velocity and doubling time have been used. PSA velocity and doubling time are correlated with PCa diagnosis at biopsy, despite the insignificant evidence supporting the additional value of both measures to the absolute PSA alone (Vickers et al., 2009). Nevertheless, the annual percentage change in PSA can predict accurately the aggressiveness of PCa than a single PSA measurement (Wallner et al., 2013). On the other hand, PSA doubling time has a high sensitivity for recurrence prediction after radical prostatectomy or radiotherapy (Vickers and Brewster, 2012). When adding long-term PSA velocity to models with baseline PSA and age-adjusted ratio the detection and mortality of PCa increased respectively from 2.7 to 5.3 and from 2.3 to 3.4 (Orsted et al., 2013). Of interest, in men with a low PSA, biopsy is not indicated in increasing PSA velocity. Instead, in an increased PSA velocity a repeated PSA measurement should be considered within shorter period of time. Despite the fact that monitoring of PSA over time can improve decision-making, biopsy should be done when indicated regardless of PSA velocity (Vickers et al., 2014).

3.2. Prostate Health index (PHI)

PSA is found in 2 forms; free (fPSA) and complex. Around 75%, 10% and 2% of serum PSA is bound to α1-antichymotrypsin, α2-macroglobulin, and α1-proteinase inhibitor, respectively. To improve the diagnostic accuracy of the PSA test alone for tPSA concentration between 4 and 10 ng/ml, the FDA has approved the use of fPSA ratio (%fPSA) [(fPSA/tPSA) × 100] as a useful tool (Graefen et al., 2002). A high total PSA with a low fPSA level generally indicates a risk of more aggressive PCa (Catalona et al., 2000).

The BPH-associated PSA (BPSA), pro-PSA, and intact fPSA are 3 unique isoforms of PSA [25]. The PSA is activated by the effect of human glandular kallikrein-2 over the inactive pro-PSA. Truncated forms of pro-PSA [−2] (proPSA) are a pro-PSA with the remaining non-cleaved amino acids, which are increased in cancerous cells (Mikolajczyk et al., 2002). They have the highest specificity for PCa screening, and are considered efficient predictors of PCa aggressiveness (Catalona et al., 2004).

PCa detection significantly improved when utilizing the PSA isoform [−2] (proPSA) and its derivatives ratio: %proPSA [proPSA devided by (fPSA × 1000) × 100 (Sokoll et al., 2008a, 2008b; Stephan et al., 2009). The PHI formula can improve the diagnosis of PCa by combining tPSA, fPSA and [−2] (proPSA); (PHI = [−2]proPSA/free PSA) × $\sqrt{}$PSA).This single PHI score improves the clinical decision-making, screening and prediction of aggressiveness of PCa (Catalona et al., 2011; Jansen et al., 2010; Guazzoni et al., 2011). Of interest, %p2PSA and further modified PHI, using respectively 2- and 3-PSA markers, revealed better detection of PCa than tPSA and %fPSA, as shown by better specificities at high sensitivities. This can reduce unnecessary prostate biopsies. Moreover, these biomarkers may detect aggressive PCa more accurately due to the significant correlations between %p2PSA and PHI with Gleason score (Jansen et al., 2010; Guazzoni et al., 2012).

Furthermore, in a multicenter prospective study of more than 650 men underwent prostate biopsy the PHI has been validated. They were over 50-years of age with PSA of 4–10 ng/ml and normal DRE (Loeb et al., 2015). The PHI was able to detect clinically significant PCa with more accurate than PSA alone, %fPSA, or [−2] proPSA. Therefore, PHI seems to reduce prostate biopsies and the overdiagnosis of indolent diseases. The FDA has approved two biomarkers recently, including proPSA (as part of the PHI) and PCa antigen 3 (PCA3) (Sartori and Chan, 2014).

3.3. Prostate cancer antigen 3 (PCA3)

This is an FDA approved urine-based assay to test for PCa. It is designed to evaluate the need to repeat the biopsy in previous negative specimen. It is a noncoding messenger RNA (mRNA), which shows overexpression in 95% of PCa with a median 66-fold upregulation. Being prostate-specific, its expression is not impacted by non-prostatic cancers or benign non-prostate tissue, and it is independent of prostate volume (Bussemakers et al., 1999; Hessels et al., 2003). Its significant overexpression in primary specimen and metastatic PCa highlights its importance as a promising diagnostic tool in urine and tissue (Hessels et al., 2003; de Kok et al., 2002).

Groskopf and colleagues developed a urinary assay, transcription-mediated amplification (TMA) method (PCA3, Gen-Probe Incorporated) for PCA3 assessment (Groskopf et al., 2006). This method depends on measuring both PCA3-mRNA and PSA-mRNA in first-catch urine samples collected after DRE, thus providing higher instructive rates compared to samples obtained without performing DRE (Sokoll et al., 2008a, 2008b). This is because DRE induces pressure within the prostate with the consequent shedding and release of prostate cells through the prostatic ducts and into the urethra. The PCA3 score is a ratio between PCA3-mRNA and PSA-mRNA [(PCA3-mRNA divided by PSA-mRNA) × 1000)] (Sokoll et al., 2008a, 2008b). PCA3 score is significantly correlated with tumor volume and Gleason score in prostatectomy specimens, therefore, it may be a novel molecular marker for classification of PCa patients (Nakanishi et al., 2008). Furthermore, the urinary PCA3 score was also correlated with the probability of a positive biopsy (Deras et al., 2008). However, the prognostic value of PAC3 and its ability to predict the presence of PCa still lacks clinical validation. Nevertheless, PCA3 urine assay improves specificity and accuracy of PCa detection in the PSA gray zone (Marks et al.,

2007; van Gils et al., 2007a), thus preventing unnecessary prostate biopsies (van Gils et al., 2007b).

3.4. Mi-Prostate score (MiPS)

This test screens for the presence of two PCa biomarkers; the PCA3 gene and an RNA biomarker resulted from abnormal fusion of TMPRSS2 and ERG (T2-ERG) (Salami et al., 2013). The T2-ERG gene fusion is present in 50% of PCa patients, but its role in the development of disease is not known. The new urine multiplex test is an algorithm that better assesses for T2-ERG gene fusion assay, PCA3, as well as serum PSA (University of Michigan MLabs) to predict the risk of detecting PCa on biopsy. The combined MiPS multivariable algorithm was found to be more specific than any of the individual variables, with 80% and 90% sensitivity and specificity, respectively (Salami et al., 2013). This algorithm was validated in 1225 men in detecting PCa on biopsy or higher Gleason scores ($\geq$7) and was significantly better than PSA alone (Tomlins et al., 2016). Therefore, MiPS can reduce unnecessary prostate biopsies.

3.5. 4Kscore panel Algorithm

The 4Kscore test (OPKO Lab, Miami, FL) is another promising serum-based biomarker that combines clinical data of age, DRE, previous biopsy results, with serum concentrations of 4 kallikreins (4k), including tPSA, fPSA, intact PSA (iPSA), and human kallikrein 2 (hK2). It can be used in patients considering an initial prostate biopsy due to an elevated PSA level, an abnormal DRE or in men with prior negative biopsy with a currently elevated PSA. It can predict the possibility of detecting high-grade disease (GS $\geq$ 7) on prostate biopsy. Patients with a 4Kscore of 1%-7.5% are considered low risk, thus deferring biopsy safely while following-up by PSA. On the other hand, a score of $\geq$20 indicates high-risk disease necessitating prostate biopsy.

The European Randomized Study of Prostate Cancer Screening (ERSPC) has developed the test where measurements of these four kallikreins were correlated with a positive biopsy (Vickers et al., 2010; Benchikh et al., 2010; Vickers et al., 2008). In patients with PSA $\geq$ 3.0, the 4k panel increased the sensitivity of high-grade PCa detection compared to clinical variables alone (Benchikh et al., 2010; Salagierski and Schalken, 2012). The diagnostic performance of the 4k panel was comparable to that of PHI for predicting GS $\geq$ 7 cancer with PSA levels between 3 and 15 ng/ml, and both tests performed better than age-stratified PSA in the prediction of high-grade cancer (Salagierski and Schalken, 2012).

In the cohort of 1012 men undergoing prostate biopsy at 26 US independent sites, a 4Kscore cutoff of 7.5% risk spares 360 biopsies while missing 16 of 215 aggressive PCa detected on biopsy (Lin et al., 2017). In addition, the 4k panel has been studied in men on active surveillance, but it did not show much better results than PSA when combined with a clinical model considering age, BMI, prostate volume, previous negative biopsies, and amount of positive biopsy cores (Lin et al., 2017).

4. Prognostic biomarkers

4.1. Urokinase plasminogen activation (uPA and uPAR)

The urokinase plasminogen activation system represents a potential target for PCa biomarkers due to its vital role in the process of extracellular matrix degradation. It is involved in different phases of cancer initiation and progression. uPA is an inactive precursor of serine protease. It is secreted as a zymogen (pro-uPA) then binds to its specific soluble cell-surface receptor (uPAR), leading to the transformation into plasmin from plasminogen (Andreasen et al., 2000). Due to its wide range of substrate specificities plasmin activates a proteases cascade involved in multiple degradation process of various forms of extracellular matrix proteins. Binding of uPA to its receptor results in the activating a cascade of events which results in angiogenesis, cell proliferation, migration and tissue (Andreasen et al., 2000; Basire et al., 2006).

Increased serum levels of uPAR has been associated with distant metastases and poor prognosis (Duffy, 2002; Stephens et al., 1999). Similarly, increased serum levels of uPA is significantly correlated with tumor progression, and it is considered to be a poor prognostic marker of PCa (Shariat et al., 2007; Lilja et al., 2007; Miyake et al., 1999a, 1999b). The expression of uPA and uPAR is upregulated in aggressive prostate cancer. Furthermore, both markers are correlated with metastatic potential of PCa (Cozzi et al., 2006). In the specimen of PCa post radical surgery the overexpression of both uPA and its inhibitor (PAI-1) were found related to aggressive disease and recurrence (Miyake et al., 1999a, 1999b).

The uPAR can significantly predict PCa biopsy specimens in patients with elevated PSA, improving the regression model accuracy for PCa prediction (Steuber et al., 2007). Higher levels of uPA have been also associated with advancing PCa stage and bone metastases (Duffy, 2002; Hienert et al., 1988; Miyake et al., 1999a, 1999b), and may strongly predict biochemical and/or aggressive recurrence and distant metastasis (Gupta et al., 2009). However, uPAR only seems to be helpful in predicting the presence of poor pathologic characteristics, rather than significant prediction of PCa (Milanese et al., 2009).

4.2. Prostate stem cell antigen (PSCA)

PSCA was identified in LAPC-4 xenograft model of prostate cancer cells after analysis of genes upregulation. It is a cell surface antigen with 30% homology to stem cell antigen type-2 (SCA-2). It is located on chromosome 8q24.2 and encodes a 123 amino acid glycoprotein, a glycosyl phosphatidylinositol- anchored cell surface protein related to the Ly-6/Thy-1 family of cell surface antigens (Reiter et al., 1998). The PSCA is a misnomer, where it is neither an exclusive protein in prostate cells nor a marker for stem cells (Antica et al., 1997). PSCA overexpression in PCa may result from gene amplification due to its genetic location on chromosome 8q24.2, especially in metastatic and recurrent PCa, indicating poor prognosis (Sato et al., 1999). Its located near to the c-myc oncogene, which is more active in recurrent and metastatic disease (Nupponen et al., 1998), may also explain the overexpression of PSCA in PCa patients.

PSCA is expressed in basal and secretory epithelial cells as well as neuroendocrine cells of the prostate (Gu et al., 2000). Immunohistochemical studies show that PCSA is detected in more than 80% of primary PCa tissues and metastatic lesions as well (Gu et al., 2000); Lam et al., 2005). Increased PSCA expression in PCa is more related to aggressive PCa: higher score and stage, distant metastases and risk of biochemical failure (Gu et al., 2000; Han et al., 2004; Joung et al., 2010). Patients with advanced PCa, who expressed PSCA, had worse disease-free survival than those who do not express PSCA (Raff et al., 2009; Hara et al., 2002).

Reverse transcription polymerase chain reaction (RT-PCR) analysis for PSCA revealed a positive correlation between greater levels of PSCA mRNA expression and metastatic PCa (Lam et al., 2005; Dannull et al., 2000). Therefore, the PSCA expression in PCa patients can be a predictor of poor prognosis (Reiter et al., 1998; Cher et al., 1994), an indicator of high-risk disease and metastasis, making it a promising aid in molecular staging (Joung et al., 2007). Of interest, PSCA seems to be an important biomarker for predicting benign prostate hyperplasia (BPH) in patients who are at a higher risk of developing PCa (Fawzy et al., 2015).

4.3. Genetic panels in PCa prognosis

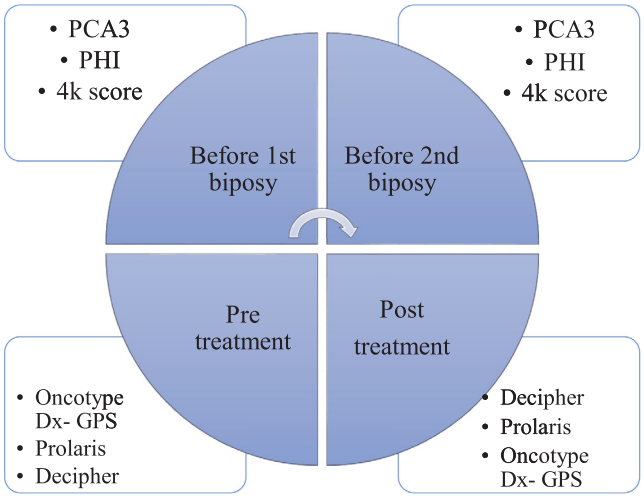
Currently, three commercially available RNA-based genetic panels have been validated in men with PCa, including Prolaris®, Oncotype DX®, and Decipher®. However, the commercial assays have their own difficulties to be used effectively due to the variable tumor bulk present in needle cores at first diagnosis. In addition, these expression panels lack head-to-head prospective comparison in a given patient cohort. Nevertheless, they include 85 genes, where there is virtually no interference among these panels, also such tissue-based tests require no additional biopsy, owing to the fact that the individual's existing biopsy is used. Results can be generated from as little as 1-mm of cancerous tissue.

The Prolaris test (Myriad Genetics, UT, USA) assesses the expression of 31 genes that is part of cell-cycle progression (CCP), an essential regulatory step in cancer development, and a stronger prognostic factor than PSA. The CCP score independently predicts biochemical recurrence (BCR) after radical prostatectomy on univariate and multivariate analysis, HR: 1.89 and 1.77 respectively. It is also related to the time of death from PCa on univariate and multivariate analysis, HR: 2.92 and 2.57 respectively (Cuzick et al., 2011). Prolaris test generates a score ranging from −3 to +3, based on gene expression levels; higher scores correlate with increasing probability of adverse events following treatment. The test was separately evaluated in over 2500 patients at different institutions, with a concordance index of 0.72 and 0.85 for biochemical recurrence and cancer specific mortality (Punnen et al., 2014).

The Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score is based on the histopathological examination of the prostate post radical surgery to predict risks of future relapse and mortality. Furthermore, when combining both the CAPRA-S and CCP scores the new index is better for both the overall cohort as well as the low-risk subset than each score alone. Of interest, the Prolaris test affected the physician decision of management in 65% of cases, with a 40% reduction in treatment to less interventional options (Crawford et al., 2014).

The Oncotype DX® test (Genomic Health, CA, USA) includes 17-gene-expression panels through PCR and it analyzes tissue samples from prostate biopsy. It yields a Genomic Prostate Score (GPS), a measurement of gene expression within prostate tumors, on a scale of 1–100, where higher scores indicate a more suggestive pathology. Of note, GPS score should be utilized together with of other related clinical factors. The GPS predicted high-grade (Gleason ≥4 + 3; OR: 2.3) and high-stage (≥pT3; OR: 1.9) disease on radical prostatectomy specimens after controlling other clinical variables (Klein et al., 2014; Cullen et al., 2014). The Oncotype DX test of the prostate needle biopsy can predict the aggressiveness of the cancer and facilitate making better decision of earlier intervention versus active surveillance (Fig. 1).

Decipher® (GenomeDX Biosciences, BC, USA) is a genomic classifier, which tests 22-gene-expression signatures that have been identified and associated with PCa aggressiveness after radical prostatectomy and is approved to assess the risk of metastasis after treatment. The test generates a score between 0 and 1 in increments of 0.1. In a multivariable analysis the only significant prognostic factor for both early metastasis and PCa-specific death was found is the Decipher test. It has a good correlation to disease-specific survival (AUC = 0.75) (Erho et al., 2013). The higher the scores the earlier death from PCa. Decipher genomic classifier has been compared with the CAPRA-S score as a predictor of PCa-specific mortality in 185 men at a higher risk of recurrence after radical prostatectomy of whom 25 experienced PCa-associated death. For patient with aggressive disease Decipher reclassified many high-risk PCa patients based on the CAPRA-S score ≥ 6. Decipher scores can predict PCa-specific mortality (HR: 11.26) independently, with a collective incidence of death linked to prostate cancer of 45% at 10 years (Cooperberg et al., 2015). The AUC for Decipher was 0.79 for predicting 5-year metastasis after radical prostatectomy, exceeding that of clinical models (Karnes et al., 2013). These finding can improve decisions of introducing adjuvant radiotherapy to PCa patients with higher Decipher scores, while preserving salvage radiotherapy to low scores patients (Den et al., 2015).



PCA3: Prostate cancer antigen 3; PHI: Prostate health index; GPS: Genome prostate score

Fig. 1. Prostate cancer biomarker assays and the clinical decision-making.

5. Conclusion

Prostate cancer is a heterogeneous disease with variations within a single tumor and among different tumor deposits; therefore, tissue sampling is critical. Multiple novel promising biomarkers are commercially available to improve prediction of PCa in men with an elevated PSA and guide management, such as PSA isoforms, PHI score, PCA3, MiPS, 4Kscore Panel Algorithm, uPA, uPAR and PSCA. They improve screening methods and diagnosis, monitoring PCa patients, assessment of therapeutic response and guiding molecular targeted therapy. The commercially approved gene-expression profiles can predict disease prognosis and clinical response to treatment. Of interest, despite the fact that these biomarkers can provide valuable information about the disease, these markers should not be used as a first line in the diagnosis of PCa. Currently, no single biomarker seems to be superior, and all these genetic signatures should be considered as only one piece of the puzzle in the decision-making process.

Declaration of Competing Interest

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.

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