# Biomarkers for the diagnosis of new and recurrent prostate cancer

Prostate cancer is the most prevalent cancer in men and can be managed effectively if diagnosed early and monitored. Currently, prostate-specific antigen testing in conjunction with a digital rectal exam has been utilized for screening at-risk men. However, the lack of specificity of prostate-specific antigen as a marker for prostate cancer combined with the asymptomatic and slow-growing nature of prostate tumors has resulted in many men being overdiagnosed and subjected to surgery or treatment with adverse side effects. The focus in the research community currently has been on discovering noninvasive surrogate markers such as proteins, circulating tumor cells and nucleic acids in the blood or urine of patients with prostate cancer. These markers, in combination with prostate-specific antigen, are providing promise that a personalized multiparametric approach to prostate cancer diagnosis and monitoring will aid in managing this disease.

**KEYWORDS: biomarkers ■ early detection ■ monitoring ■ predictive ■ prognosis ■ prostate cancer ■ prostate-specific antigen**

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Prostate cancer (CaP) is the most commonly occurring cancer in men in the USA and the second highest cause of deaths due to cancer in North America [1]. While CaP affects older men, with a median age atdiagnosis of 72 years, the overall lifetime risk of developing CaP is approximately one in six, and the mortality risk of CaP is approximately one in 35. Thus, while many men are diagnosed with CaP, few will die from the disease. The challenge for physicians is that the majority of diagnoses of CaP are made at the asymptomatic early stage. At this point, it is uncertain what the progression of the tumor will be due to the slow-growing nature of many prostate tumors. As a result, many patients are overdiagnosed and are unnecessarily subjected to the harmful side effects of treatment when they would potentially receive no benefit. This stage migration of detecting early tumors has created new challenges in CaP biomarker discovery as there is now a need to discover biomarkers that can accurately predict and monitor the progression of the tumor. In the past we have seen several pharmacogenomic biomarkers that have been approved by the US FDA that have helped guide treatment for oncology and other disease areas [201]. This holds promise that further biomarkers can be discovered to aid in CaP diagnosis and treatment [2–4].

To date, CaP has been managed by performing yearly digital rectal exams in at-risk men, and by two biomarkers – before 1980 by prostatic acid phosphatase and after 1985 by prostate-specific antigen (PSA). Although PSA was initially utilized for monitoring patients with CaP, it was eventually utilized for screening patients for CaP and replaced prostatic acid phosphatase as the marker of choice. The implementation of PSA as a screening biomarker has since resulted in a dramatic increase in the incidence of CaP in the North American population [5]. PSA has since been regarded as the best cancer biomarker due to its high sensitivity, although it has been shown not to be specific to CaP and is also elevated in other benign conditions of the prostate. While a PSA value of 4 ng/ml or lower is generally considered to be in the normal reference range, it is now recognized that an individual's PSA level is relative and should be monitored closely. In addition, it has been shown that there is no PSA level that can rule out CaP [6].

Mortality due to CaP has been decreasing over the last two decades and studies have shown that this is at least partially due to PSA screening [7,8]. However, the results of two randomized controlled prospective trials have caused doubt as to whether this is indeed the case. The PLCO and ERSPC studies demonstrated that PSA screening did not provide any or substantial benefit in overall patient survival [9,10]. In addition, the United States Preventive Services Task Force (USPSTF) has recommended that the population benefit of PSA screening is inconclusive and does not recommend it for men at any age [11]. The issues of high false-positive rates associated with PSA screening in these trials versus the minimal

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reduction in mortality brought to light the greater risk to patients overall for overdiagnosis if they undergo PSA screening.

PSA as a screening marker for CaP has several shortcomings that stem from it being a very good marker for detecting if there is something affecting the prostate such as benign prostate hyperplasia (BPH), prostatitis and tumors, but not being specific to any one condition. The tissue levels of PSA also do not correlate with the Gleason score, thus providing a further disconnect to CaP [12]. Rises in PSA concentrations in the circulation have been attributed to the disruption in the tissue architecture of the prostate, thus allowing PSA to leak into the circulation at an increased rate. Positive predictive values for PSA have shown it to operate at 37%, with 25% of men in the 'gray zone' (4–10 ng/ml) having CaP [13] and 15% of individuals with PSA concentrations ≤4 ng/ml having CaP [14]. Currently, the focus is on discovering diagnostic biomarkers that can distinguish benign or inflammatory prostate conditions such as BPH and prostatitis from CaP for PSA levels in the gray zone of 4–10 ng/ml, for which PSA does not function as effectively. In addition, there is a need for prognostic biomarkers to determine if tumors will progress to a metastatic stage or remain indolent. There is also a need to identify CaP that has metastasized and the sites of metastasis. The discovery of novel biomarkers for CaP with improved operating characteristics in combination with PSA will aid in guiding clinical decision-making and reduce the burden of overdiagnosis on patients and healthcare systems.

This review highlights emerging biomarkers that have been discovered for the early diagnosis, prognosis and monitoring of CaP (Table 1).

## Emerging markers & panels

### PSA derivatives

While PSA levels have been demonstrated to be a very good marker of prostate abnormalities, it has been shown that each individual's PSA levels need to be monitored closely and a personalized reference range needs be created. With this in mind, several methods of measuring PSA have been developed that include: measuring PSA changes over time (PSA velocity); the ratio of PSA to prostate volume (PSA density) determined by transrectal ultrasound; and PSA ranges that are specific to age. In addition, splice isoforms and complexed forms of PSA have been shown to provide increased clinical utility in diagnosing and predicting prostate cancer. Specifically, measuring the percentage of free PSA (fPSA) versus the total PSA in circulation has been shown to have predictive value for late-stage CaP [15]. PSA has also been found to be complexed to other binding proteins in the circulation and has been measured and shown to add clinical utility. These include PSA bound to α2-macroglobulin, α1-antichymotrypsin and α1-protease inhibitor. In addition, there are several post-translationally modified cleavage isoforms of PSA that have been measured specifically. These derivatives and isoforms have been reviewed elsewhere and will not be discussed in this review [16].

### Urinary PSA

The measurement of PSA in urine has dated back to 1985 [17] and has since been studied as a potential biomarker for CaP. Studies have shown the clinical utility of urinary PSA by itself or in conjunction with serum PSA for diagnosing CaP and predicting disease recurrence [18–21]. The clinical utility of the urine:serum PSA ratio was demonstrated in a prospective multicenter study that showed that urine PSA alone did not distinguish CaP and BPH, but when evaluated as a ratio with serum PSA, it did demonstrate significant differences, with receiver operating characteristic area under the curves (AUC) improving from 0.55 for total PSA and 0.60 for the fPSA:PSA ratio to 0.63 for the urine:serum PSA ratio [19]. In addition, another prospective study demonstrated similar findings, showing enhanced clinical utility in distinguishing CaP from BPH of the urine:serum PSA ratio for men with a serum PSA in the gray zone [20]. However, there have been studies that have shown that urinary PSA and the urine:serum PSA ratio did not distinguish or provide added clinical utility to CaP diagnosis or improvement over serum PSA alone [22,23].

### Human KLK2

Human KLK2 is a serine protease enzyme from the kallikrein family of serine proteases, of which PSA is also a member. KLK2 was initially discovered to be highly expressed in the prostate as well as in breast tumors [24]. Tissue expression of KLK2 has been shown to correlate well with CaP progression and tumor volume and has been studied as a peripheral marker in serum in combination with PSA and fPSA [25–27]. KLK2 has also been shown to have independent clinical utility as a prognostic indicator for biochemical recurrence in men with PSA ≤10 ng/ml [28]. Continued study of KLK2 as a marker to augment PSA is still warranted.

### Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is expressed predominantly in the cell membrane

**Table 1. Emerging markers for prostate cancer and their intended clinical utility.**

| Emerging CaP marker | Intended clinical utility | Ref. |
|---|---|---|
| PSA derivatives | Serum markers for diagnosis and prognosis | [15,16] |
| Urinary PSA | Urine marker for diagnosis and predicting recurrence | [17–23] |
| KLK2 | Serum marker for predicting biochemical recurrence | [25–28] |
| PSMA | Immunohistochemical diagnostic marker and target for therapy | [29,30] |
| PCA3 | Urine marker for prognostic indicator of biopsy outcome | [31–42] |
| TMPRSS2–ERG/ETS | Tissue and urine marker for diagnosis and prognosis | [43–52] |
| TGF-$\beta_1$ | Tissue and serum marker for prognosis and biochemical recurrence | [53–55] |
| AMACR | Urine marker for diagnosis and immunohistochemical marker for biopsies | [56–62] |
| EZH2 | Immunohistochemical marker for prognosis and tumor recurrence | [63,64] |
| GSTP1 | Urine marker for prognosis | [65–73] |
| ANXA3 | Tissue and urine marker for prognosis | [74,75] |
| Hepsin | Tissue marker for diagnosis | [76,77] |
| uPA/uPAR | Serum and tissue markers for prognosis and progression | [80–82] |
| GOLM1 | Tissue and urine marker for prognosis and diagnosis | [42,77,89] |
| hTERT | Tissue and urine prognostic marker | [90,91] |

*CaP: Prostate cancer; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen; uPA: Urokinase plasminogen activator.*

of prostate epithelial cells in normal and CaP patients. PSMA has been found to be overexpressed in CaP tissue epithelial cells and can be detected through a commercially available immunohistochemical assay by Cytogen called ProstaScint©, which utilizes a radiolabeled antibody specific to PSMA [29]. In addition, PSMA has been investigated as a therapy target utilizing radioisotope and other toxins conjugated to antibodies directed against PSMA and by dendritic cell activation towards PSMA [30].

### *PCA3*

*PCA3*, also known as *DD3*, is a noncoding RNA that has been found to be specifically expressed in the prostate and highly expressed in over 90% of CaP tumors compared with BPH specimens [31–33]. Several studies have investigated *PCA3* mRNA levels in conjunction with *PSA* mRNA levels in the urine of CaP patients by detecting shed cells in voided urine post-digital rectal exams and have shown it to outperform serum PSA alone [34–36]. In these studies the *PCA3*:*PSA* mRNA ratio is used as a score and was shown to have higher AUC than serum PSA alone: 0.66–0.72 compared with 0.54–0.63 [34–36]. In addition, combining urine *PCA3* mRNA with serum PSA levels also showed improvements in the AUC [37]. Results from a large prospective study also showed that *PCA3* was better able to predict biopsy outcome for a first biopsy and correlated with tumor aggressiveness [38,39]. As a result of these improved characteristics, assays have been developed and are currently available that measure *PCA3* and *PSA* mRNA in urine [40,41] and the FDA has recently approved *PCA3* as a diagnostic for men who have previously had a negative biopsy, but are still considered at risk and may require a repeat biopsy. A multiparametric study of *PCA3* in combination with *GOLPH2*, *SPINK1* and the *TMPRSS2–ERG* gene fusion also showed improved receiver operating characteristics over *PCA3* alone [42].

### *TMPRSS2–ERG/ETS* gene fusions

The fusions of TMPRSS2 and the ETS transcription factors in CaP were initially discovered by cancer profile outlier analysis to be present in 80% of prostate tumors studied [43]. Since this initial discovery, many other similar gene fusions have been discovered with associations to CaP [44]. Of note are the *ERG* gene fusions, which comprise 90% of all CaP gene fusions [45] and have been found to be present in 42% of CaP tumors and much less so in prostatic intraepithelial neoplasia (PIN) and BPH tissues [46]. A watchful waiting cohort study followed men with early stages of CaP for 9 years and demonstrated that *TMPRSS2–ERG* gene fusions correlated more closely to a Gleason score >7, metastases

and CaP mortality [47]. However, there has been debate whether the *TMPRSS2–ERG* gene fusions do indeed associate with aggressive CaP and act as prognostic indicators. Some studies have shown an association [47–49] and others have not [50,51]. The discrepancies are likely due to the heterogeneity of CaP as a disease and the patient cohorts studied. The promise of the *TMPRSS2–ETS/ERG* gene fusion has prompted several studies to detect its presence in the urine of CaP patients in combination with PCA3 [49,52]. A large study of 1300 men showed that *PCA3* and *TMPRSS2–ERG* in urine (normalized to urine *PSA* mRNA) showed improved clinical utility over serum PSA for CaP diagnosis and were associated with aggressive CaP [49]. In addition, other studies have shown no significant correlation between Gleason score and the *TMPRSS2–ETS* transcripts in urine [52]. One major drawback is that if the urine *PSA* mRNA is low or undetectable, the test is of no use. Thus, additional prospective studies are warranted to determine the clinical usefulness of the *TMPRSS2–ETS/ERG* gene fusions and in combination with PSA and other biomarkers.

### TGF-$\beta_1$

TGF-$\beta_1$ is a ubiquitous growth factor that has been implicated in several molecular processes relating to cell proliferation and differentiation, cytokine response during inflammation and new blood vessel growth. TGF-$\beta_1$ has been shown to be overexpressed in CaP tissue specimens and correlates with tumor grade and metastasis [53]. In addition, TGF-$\beta_1$ has shown to correlate with prostate tumor extravasation and biochemical recurrence [54]. Furthermore, circulating TGF-$\beta_1$ has been shown to be elevated in CaP patients [55]. In combination with other markers, TGF-$\beta_1$ could prove to have clinical utility for CaP prognosis.

### AMACR

AMACR is an enzyme involved in the synthesis and metabolism of fatty acids and has been shown to have high expression in prostate tissues. However, AMACR is also expressed in many other tissues, thus limiting its utility as a tissue marker for CaP [56], for which it is currently used to diagnose atypical biopsy specimens [57]. Specifically, *AMACR* mRNA has been shown to be overexpressed in 88% of CaP specimens [58] and has a reported 97% sensitivity and 100% specificity for CaP diagnosis in needle biopsies [59]. Similarly, a multicenter study demonstrated that AMACR staining was able to differentiate BPH from CaP with 97% sensitivity and 92% specificity [60]. AMACR has also been investigated as a urine marker for CaP. In one study, quantitative reverse transcriptase PCR was utilized to measure *AMACR* and *PSA* mRNA in urine specimens to create an AMACR score, which showed 70% sensitivity and 71% specificity and performed significantly better than PSA in diagnosing CaP [61]. In addition, the positive predictive value was 0.68 with a negative predictive value of 0.73, which was also superior to serum PSA [61]. In the same study, AMACR detection was also combined with PCA3 to create a combined test with improved sensitivities and specificities over AMACR alone. The AMACR protein has also been studied in urine and was shown to have a 100% sensitivity and 58% specificity in a small group of men [62]. AMACR has the potential to be used as a marker in a multiparametric panel for the diagnosis of CaP.

### EZH2

The *EZH2* gene produces a protein of the polycomb family that regulates gene expression. EZH2 was shown to be overexpressed in metastatic CaP upon autopsy versus organ-confined CaP and BPH, and performed better at determining tumor progression than PSA and the Gleason score [63]. E-cadherin and EZH2 tissue staining were also determined to predict tumor recurrence after therapy [64]. While detection is currently limited to tissue staining, a serum test would add value to determine its clinical utility as a noninvasive marker for CaP.

### *GSTP1* hypermethylation

Increased methylation at CpG islands of the *GSTP1* promoter has been shown to be very common in CaP [65]. Measurements in urine after prostatic massage have shown that decreased expression of *GSTP1* mRNA correlates with positive biopsies [66,67]. In addition, the promoter methylation status of *GSTP1* in urine has been measured and shown to have specificities of 93–100% for CaP detection and sensitivities of 21.4–38.9% [68–71]. However, it was shown in other studies that after prostatic massage the sensitivity increased to 75% [72,73].

### ANXA3

ANXA3 is a member of the calcium-binding annexin family and has been associated with lymphocyte activation, membrane transport and mediating the immune response. Studies on the tissue expression of ANXA3 in CaP have shown it to correlate with the prognosis of the disease, with decreased expression found in CaP versus

BPH, PIN and normal tissue [74]. In a study of 591 patients, ANXA3 was measured in urine by western blot and was shown to differentiate CaP patients with differing risk profiles [75].

### Hepsin

Hepsin is a membrane serine protease that was initially found to be expressed in the liver and has subsequently been shown to be expressed in high concentrations in the prostate, with mRNA levels shown to be overexpressed in 90% of CaP tissues [76]. Protein expression of hepsin was also shown to be higher in PIN and CaP compared with BPH [77]. The value of hepsin as a prostate cancer biomarkers needs to be further defined.

### Autoantibodies

Immune responses to antigens produced by tumors have been shown specifically with prostasomes and AMACR in CaP [78]. Detection of autoantibodies produced against AMACR in CaP patients in the gray zone of 4–10 ng/ml were shown to stratify CaP from non-CaP with a sensitivity of 62% and specificity of 72% [78]. In addition, phage display and microarray technologies have been employed to detect autoantibodies to CaP tumor peptides [79]. In this study, a phage peptide array was created to measure 22 peptides that were able to stratify CaP from non-CaP with 81.6% sensitivity and 88.2% specificity, and an AUC of 0.93, which is superior to PSA, which had and AUC of 0.80.

### Urokinase plasminogen activator & receptor

Urokinase plasminogen activator (uPA) is a serine protease involved in converting plasminogen to plasmin through binding of its membrane-bound receptor uPAR. This complex has also been shown to be involved in extracellular matrix degradation and tumor cell invasion. Multiparametric detection of uPAR isoforms with PSA and KLK2 was able to predict biopsy outcomes in patients with elevated PSA levels [80], and elevated tissue levels of uPAR in CaP tumors have been shown to correlate with bone metastases and CaP progression [81]. Preoperative serum concentrations of uPA and uPAR were also shown to be increased in patients with CaP bone metastases, thus showing that uPA and uPAR could be predictors of metastatic progression [82].

### Circulating tumor cells

As a tumor progresses it sheds its cells into the bloodstream and these cells may form distant metastases. Detecting and measuring circulating tumor cells (CTCs) by isolating them and performing reverse transcriptase PCR of CaP-specific genes has shown promise in the diagnosis and prognosis of CaP. Prostate tumor markers such as TMPRSS2–ERG, androgen receptor and phosphatase and tensin homolog copy number have been detected in CTCs in CaP patients and aided in their detection [83]. A study has shown that CaP patients with castrate-resistant CaP with more than five CTCs per 7.5 ml of blood had a significantly decreased overall survival [84]. In addition, another study evaluating the effect of chemotherapy in castrate-resistant CaP also showed that increased levels of CTCs correlated with decreased survival [85].

### Prostasomes

Prostasomes are exosomes that are derived from the prostate epithelium and originate as vesicles from internalized pieces of the cell membrane that contain proteins and RNA from the prostate cell. These vesicles are subsequently shed into the circulation and have been detected in blood, seminal plasma and urine [86]. Increased amounts of Prostasomes have been detected in serum of men with CaP and have shown correlation with the Gleason score [87]. In addition, *PCA3* and *TMPRSS2–ERG* RNA transcripts have been detected in prostasomes isolated from urine of CaP patients, where elevated levels were associated with CaP [88].

### GOLM1

GOLM1, also known as Golgi membrane protein GP73 and Golgi phosphoprotein 2, is a membrane protein expressed in the Golgi apparatus that aids in transport of proteins through the Golgi. GOLM1 has been studied at the protein [77] and the transcript level in CaP tissues, both of which have shown to be increased in CaP and show diagnostic clinical utility [42]. Initial findings of the clinical utility of GOLM1 were confirmed when *GOLM1* mRNA was evaluated in the urine of men with CaP and biopsy-negative men. GOLM1 outperformed serum PSA, with AUCs of 0.622 and 0.495, respectively, for diagnosing CaP. In addition, GOLM1 protein was also detected in urine and was shown to have increased levels in men with CaP versus controls [89].

### hTERT

The lengths of the telomeric ends of chromosomes are maintained by the enzyme hTERT. Overactivity of hTERT has been shown to be present in 90% of CaP tissues [90]. In addition, hTERT activity has been measured through a

telomeric repeat amplification assay in the urine of CaP patients and controls and has demonstrated a sensitivity of 58% with 100% specificity and shown prognostic utility [91]. A larger study has demonstrated that hTERT activity in urine has a sensitivity of 90% with 76% specificity.

### Proteomic, genomic & metabolomic approaches to CaP biomarker discovery

The emergence of the 'omics' era has created great insight into the mechanisms and networks involved in disease progression and etiology. Specifically, proteomics has provided information on the post-translational fate of genes, through the analysis of protein expression levels and post-translational modifications [92]. A challenge with proteomic analysis of biological fluids such as plasma and serum is the large dynamic range of protein concentrations ($10^{10}$) [93]. However, even in the presence of such challenges, proteomic signatures have been identified through mass spectrometry-based analysis of serum proteins that can predict biochemical recurrence [94] and response to chemotherapies [95]. Cell line model systems have also shown promise for the identification of novel markers for CaP through proteomic analysis of conditioned media [96]. Increasing improvements in genomic technologies facilitated the migration from array-based methods to 'next-generation' sequencing platforms. Such platforms are able to identify noncoding RNAs, such as *PCA3*, in a *de novo* fashion [97]. Novel sequencing platforms have also been able to identify transcriptomic patterns in CaP correlating with metastases within 4 weeks of biopsy [98]. In the urine, detection of nucleic acids requires cell shedding from the site of origin. However, proteins are more readily secreted, and identification of proteins in urine may be detected earlier and thus provide a greater lead time for diagnosis. In addition, proteins in urine are not as susceptible to proteolytic degradation as in serum and plasma [99]. Proteomic analysis of urine has uncovered several CaP markers including Calgranulin B (S100-A9/MRP-14), which was found to be diagnostic for CaP [100]. A larger multicenter study has utilized mass spectrometry for the analysis of peptides in urine. A training set of 86 patients and a validation set of 264 patients were used and a 12-peptide panel was developed that had an 89% sensitivity and 51% specificity. In combination with age-specific intervals and fPSA, the performance increased to 91% sensitivity and 69% specificity [99]. Metabolomic analysis of CaP tissues and urine identified that sarcosine tissue levels correlate with CaP progression and metastasis [101]. In this study, CaP tissues and urine specimens were analyzed and 1126 metabolites were monitored by gas and liquid chromatography-based mass spectrometry in 262 specimens. Metabolomic profiles were identified that could differentiate BPH, localized CaP and metastatic CaP. Specifically, sarcosine was shown to be the best predictor of CaP progression and metastasis, with elevated levels present in 79% of metastatic specimens, 42% in localized CaP and no elevation in BPH specimens. Monitoring of metabolites such as sarcosine in combination with other markers should aid in the early diagnosis and prognosis of CaP.

## Conclusion & future perspective

Early diagnosis and accurate prognosis of organ-confined CaP coupled with identification of predictive markers that can be identified to guide treatment options is still the goal that the CaP research community is striving towards. The introduction of PSA testing has forever changed the way in which CaP is managed; however, it is still not able to distinguish clinically relevant tumors from indolent ones. The cost of overdiagnosis of CaP and other diseases has created a great deal of attention in this area in order to bring healthcare costs down [102]. The discovery of novel noninvasive markers would aid in this effort tremendously by reducing biopsy procedures, surgeries and treatments for men who would not see a benefit. The promise of new 'omics' platforms in addition to proper study design, specimen collection and data analysis tools should bring us closer to this goal. In this respect, the PRoBE design is the most ideal approach for biomarker verification and validation [103]. This approach consists of four main components that a biomarker must be evaluated under in order to determine its overall suitability for clinical implementation, namely, clinical context, performance criteria, study design and study size. The PRoBE approach provides a robust framework for overall biomarker development and should be utilized.

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## Executive summary

***Prostate cancer is the most prevalent cancer in men in the USA***

- The expected number of new cases of prostate cancer (CaP) in 2012 in the USA is 241,740 and the expected number of deaths is 28,170.
- The overall mortality risk of CaP is approximately one in 35.

***Management of prostate cancer***

- Currently, prostate-specific antigen (PSA) is the marker of choice for screening patients for CaP; however, it has come under much scrutiny after the results of two large independent clinical trials have shown that screening does not significantly decrease mortality.
- PSA measurements are now recognized as a relative level of risk for each individual person.
- PSA does not distinguish indolent versus aggressive forms of CaP in the early stages where PSA serum levels are in the 'gray zone' of 4–10 ng/ml.
- Novel markers used in conjunction with PSA that can increase the overall specificity of CaP diagnosis and prognosis is the focus of current CaP biomarker research.

***Emerging markers for CaP***

- Several markers have shown promise for the noninvasive detection of CaP in urine, serum and plasma.
- Markers have been shown to work synergistically in multiparametric panels and through the use of mathematical algorithms.
- Tissue markers are also available and show clinical utility but require a patient to undergo needle biopsy.

***'Omics' approaches to CaP biomarker discovery***

- Recent advances in mass spectrometry and genomic sequencing platforms have enabled researchers to uncover novel markers and panels of genes and proteins that show diagnostic and prognostic significance.
- Caution needs to be taken with 'omics' approaches as overfitting of data can be a hazard and lead to erroneous results.

***Conclusion & future perspective***

- Multiparametric approaches to CaP diagnosis and prognosis will provide a personalized approach to managing this disease.

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