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Biomarkers in Prostate Cancer: A Review

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Abstract

Background: Prostate cancer (PC) is the second most common cancer in men worldwide. It's the second leading cause cancer men in death. Prognostic tests based on molecular and biomarker analysis of tumor tissue may improve risk stratification of prostate cancer [2].

Materials and methods: After a search on Pubmed for PC biomarkers, 72 papers responded to the objectives and will be included in the review.

Results: A plethora of biomarkers are predictive for the prognosis of PC and its response to certain therapies, while others, once thought to be indicative of prognosis in PC, were not.

Conclusions: This study can help in the development of diagnostic and prognostic tests of PC and contribute to the ongoing research into already existing tests.

Keywords: Prostate Cancer, Biomarkers, Diagnosis, Prognosis.

Introduction:

Prostate cancer (PC) is the second most common cancer in men worldwide. It's the second leading cause cancer men in death [1]never destined to progress or affect the patients' life. It is of utmost importance to identify which PCa are destined to progress and which would benefit from an early radical treatment. Prostate–specific antigen (PSA. PC is a heterogeneous disease, ranging from being confined to the gland, slowly developing and slightly benign to a more invasive form, progressing, aggressive, metastatic, and fatal, even when properly treated. Therefore, initial management of males with newly diagnosed prostate cancer needs to incorporate a consideration of the prolonged natural history of the disease and the risk for progression to disseminated, potentially fatal disease. It is of utmost importance to identify which PC are destined to progress, and which would benefit from an early radical treatment.

Prostate–specific antigen (PSA) remains the most used test to detect PC. It has a role in screening and management of patients with diagnosed PC. Examples of the latter include: monitoring response to therapy, surveillance following diagnosis, and in detecting recurrence. However, one of the main issues in using PSA to screen or assess the prognosis for prostate cancer is the lack of specificity [2].

In recent years, several tissue biomarkers tests have become available for determining aggressiveness and predicting outcome in patients with newly diagnosed prostate cancer. Prognostic tests based on molecular and biomarker analysis of tumor tissue may improve risk stratification of both untreated and treated males with localized prostate cancer [2].

The best validated test and clinically available include Decipher, Oncotype DX (Prostate), Prolaris and ProMark. Although these tests have been evaluated in different settings and used different end points, they all essentially provide information on tumor aggressiveness and patient outcome. Moreover, emerging therapy predictive biomarkers include BRAC1/2 mutations for predicting benefit from PARP inhibitor, AR–V7 for predicting lack of response to specific anti–androgens (enzalutamide, abiraterone), and PORTOS for predicting benefit from radiotherapy. With the increased availability of multiple biomarkers, personalized treatment for men with prostate cancer may finally see the light of day [3].

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The aim of this review is to summarizes the current implication of the most promising and clinically used PC biomarkers, large prospective studies are necessary to evaluate the real value of biomarkers in PC.

Material and Methods:

To obtain a maximum number of articles containing data on PC predictive biomarkers, an extensive electronic search of the literature was conducted in the PubMed database until the 20th of June 2021. Using Boolean Operators, the Mesh Term "Prostatic Neoplasms" was used in combination with the keywords "predictive biomarker", or "predictive" and "biomarker".

A total of 650 articles were extracted. Titles and abstracts of retrieved articles were screened for eligibility, and then entire texts were analyzed. The main objective was to include studies in English or French that contain data on prostate cancer biomarkers that can predict the tumor's response to a certain targeted therapy. Articles emphasizing on the PC without significant information on biomarkers, or papers discussing biomarkers that are not predictive to a specific treatment response, as well as the reviews that were older than one year were excluded. The 72 papers that respond to the objectives will be included in the review. The process is summarized in the PRISMA diagram below.

Results:

In the last few years, new approaches for providing significantly better biomarkers, an alternative to PSA, have been introduced. Modern biomarkers show improvement in being used as not only a diagnostic procedure, but also for staging, evaluating aggressiveness and managing the therapeutic process. We focused on multiple clinical situations in which innovative biomarkers may guide decision–making in prostate cancer therapy. In addition, we describe novel liquid biopsy approaches (circulating tumor cells, cell–free DNA) that have been described as predictive biomarkers in metastatic castration–resistant prostate cancer and might support an individual patient–centered oncological approach in the nearer future.

I. Protein biomarkers

1. Vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR)

VEGF is one of the most powerful angiogenic factors related to tumorigenesis. It is specific to endothelial cells

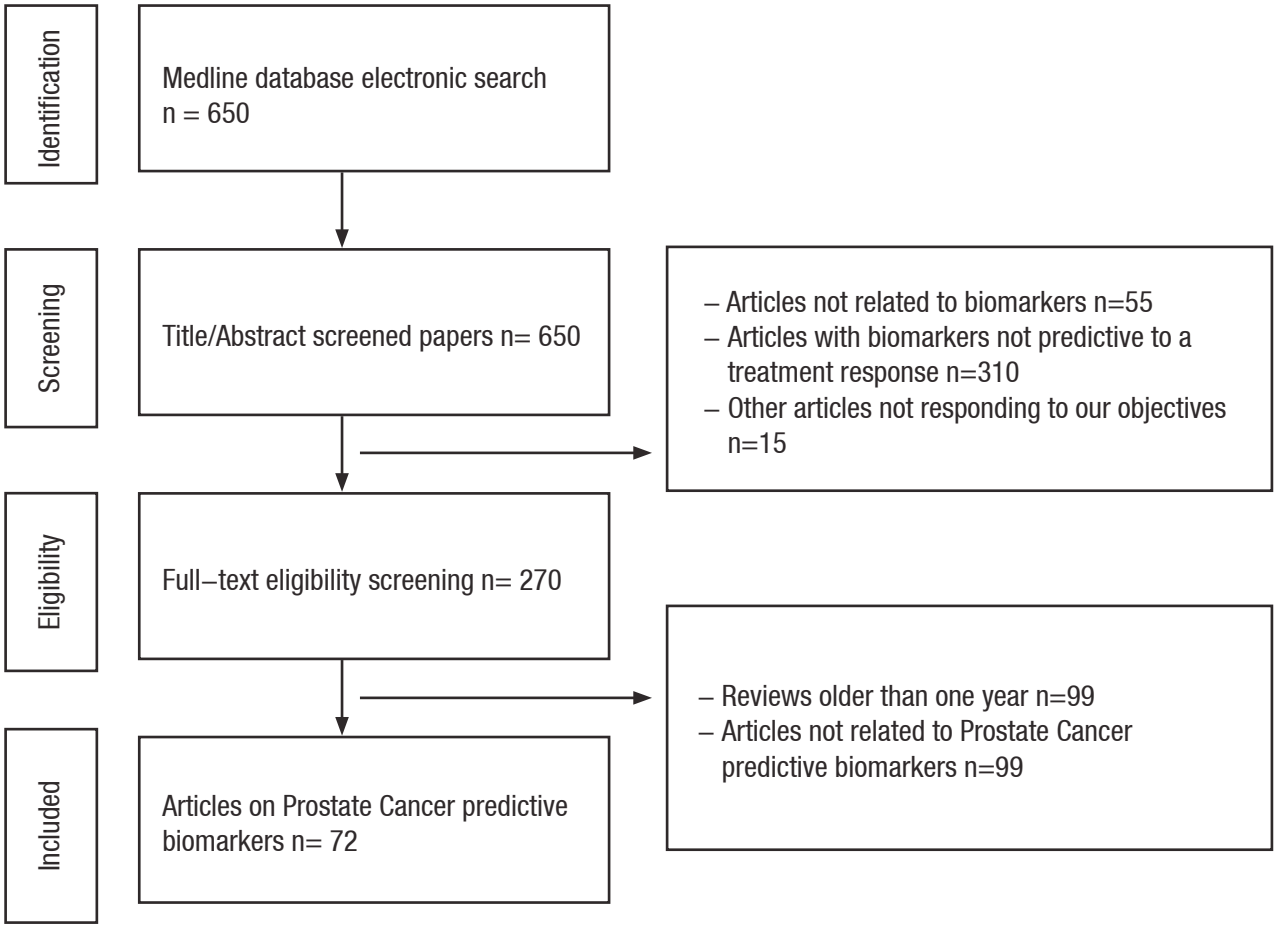

Figure 1. PRISMA flowchart for article selection process

to which it promotes proliferation and promotes vascular permeability. It has been shown that ADT may increase VEGF expression, which is demonstrated in the castrate resistant population. [4, 5, 6]

When comparing VEGF expression between both arms of the randomized controlled trials (RCTs) conducted by Larry Pan et al, no statistically significant predictive value of VEGF was found. [7]

The number and characteristics of circulating tumor cells (CTCs) in cancer patients reflect the tumor's progression, and its response to therapy. The EGFR has been reported to provide an important mechanism for the progression of CRPC. Multivariate analysis demonstrated that patients with EGFR–positive CTCs had a shorter overall survival (OS) (5.5 months) than patients with EGFR–negative CTCs (20.0 months) [8]

2. Bone metabolism biomarkers:

Two bone biomarkers C–propeptide of type I Procollagen CICP and bone alkaline phosphatase BAP were shown at the upper 25th percentile to be predictive of survival when associated with Atrasentan. In addition, Atrasentan increased OS in patients who had high levels of bone metabolism biomarkers [9]

Serum bone markers were assessed pre and post therapy. These included serum bone specific alkaline phosphatase (BSAP) and N–terminal telopeptide of collagen type I (NTx). Several other bone turnover markers such as osteocalcin, pyridinoline and deoxypyridinoline, have been implicated to be predictive of therapeutic response. The results reveal that the scanning methods were not predictive of efficacy. The serum and urine biomarkers tested such as CTC, BSAP and serum and urine Ntx were not distinctly indicative of early prediction of clinical benefit with cabozantinib therapy. [10]

3. Microtubule bundling

Microtubule bundling was analyzed by Gjyrez et al in samples of metastatic cancer and seen 2–3 days after the docetaxel treatment after 2–3 days for xenografts. However, that was not the case with the samples acquired resistance. These results suggest that after taxane based therapy, the microtubule bundling could be a predictive biomarker for clinical response. [11]

4. PDL–1

The expression of programmed death ligand 1 (PDL–1) was not confirmed as a predictive biomarker.[1] The absence of PD–L1 is not a predictor for immunotherapy failure, thus it does not appear to be a reliable predictive biomarker for immune checkpoint monoclonal antibodies. The positivity of PD–L1/PD–L2 is associated with enzalutamide resistance. [12]

It has been suggested that PD–L1 expression varies in the different stages of PC progression and may depend on therapies received prior to disease progression. Although the KEYNOTE–028 trial suggested that PD–L1 expression could predict response to immune checkpoint inhibitors ICIs, the larger KEYNOTE–199 trial found that the ORR in the PD–L1–negative and the PD–L1–positive cohorts was 3% and 5%, respectively.

These studies demonstrate the low accuracy of PD–L1 as a biomarker of response to ICIs in mCRPC patients. [13]

5. Serum tri– and tetra–antennary N–glycan

These N–glycans: m/z 1362, 1566, 1753, 1794, 3049, 3414, 3560, 3719, and 3865 were significantly different between PC with androgen depriving therapy ADT and CRPC groups. M/z 3049 and m/z 3414 may be associated with CRPC. [14]

6. C–Flip

c–FLIP is an anti–apoptotic protein which antagonizes caspase–8–mediated apoptosis. In vitro using a previously validated c–FLIP–targeted siRNA–strategy, with the use of droxinostat (c–flip inhibitor) or with the use of histone deacetylase HDAC inhibitors suberoylanilide hydroxamic acid (SAHA) which decreases C–flip the knockdown of C–flip has higher caspase activity and induction of apoptosis in cells treated with bicalutamide. Increased expression of C–flip causes insensitivity to SAHA and bicalutamide. [15]

Table 1. Summary of the protein biomarkers, their association and relevance with PC

II. mRNA BIOMARKERS

1. TMPRSS2–ERG:

TMPRSS2–ERG fusion is found in 50% (range: 30–70%) of newly diagnosed prostate cancers ([16], [17]). In experimental models, the TMPRSS2–ERG fusion has shown a limited role in prostate tumorigenesis [18]. A role in androgen–dependent tumor growth has been postulated [19]but how the fusion products regulate prostate cancer remains unclear. Using chromatin immunoprecipitation coupled with massively parallel sequencing, we found that ERG disrupts androgen receptor (AR, and a relationship between TMPRSS2–ERG status and degree of PSA decline was shown in chemotherapy–naive CRPC patients treated with AA, suggesting a role as a predictive biomarker of AA sensitivity [20]

However, the study found that no statistically significant difference was detected in AA success between patients

Protein biomarkers	Association and relevance
VEGF	Absence of significant predictive value [4, 5, 6]
EGFR	EGFR–positive CTCs had a shorter OS than patients with EGFR–negative CTCs [8]
Bone metabolism biomarkers	Atrasentan increased OS in patients who had high levels of bone metabolism biomarkers [9, 10]
Microtubule bundling	After taxane based therapy, it could be a predictive biomarker for clinical response. [11]
PDL–1	Low accuracy of PD–L1 as a biomarker of response to ICIs in mCRPC patients [12, 13]
Serum tri– and tetra–antennary N–glycan	M/z 3049 and m/z 3414 may be associated with CRPC [14]
C–Flip	Increased expression of C–flip causes insensitivity to SAHA and bicalutamide [15]

Table 1. Summary of the protein biomarkers, their association and relevance with PC

in whom the biomarker was present, and in those whom it was absent. [21]

TMPRSS2–ERG may hold clinical value as a predictive biomarker of ADT response, however it remains unclear whether the higher burden of driver mutations in mCRPC represents de novo mutation or results from clonal selection during ADT. [22]

2. Phosphatase and tensin homologue (PTEN)

Zinc finger and BTB domain containing 7A ZBTB7A and PTEN loss may be a better predictor of progression upon androgen deprivation than PTEN deletion alone. [23]

Biomarkers for personalized immunotherapy

Some biomarkers for immunotherapy, such as CD48, SP140, KIRREL, RHOB, FBXO17, ANAPC1, EGFR, SOCS3, ALOX15, and UBR2, are not the optimal biomarkers for the choice of anti CTLA–4 and anti PD–1 treatments, despite upregulating CTLA–4 and PD–1. [24]

3. GCNT1

GCNT1 (a core 2 glycosyltransferase) expression in prostate biopsy specimen is a significant and independent predictor of recurrence after radical prostatectomy, which can be used in pre–treatment decision making for the patient. GCNT1 expression in prostate biopsy specimens was a significant and independent predictor for PSA recurrence after radical prostatectomy. [25]

4. Cytokines

The cytokine macrophage inhibitory cytokine 1 (MIC–1), a member of the transforming growth factor (TGF)β family, has been implicated widely in prostate carcinogenesis and progression. Elevated plasma/serum MIC–1 levels after initial Docetaxel treatment can predict for Docetaxel resistance in men with HRPC, indicating that further chemotherapy is not warranted and may be harmful [26].

Elevated plasma c–reactive protein (CRP) concentrations appear to be a strong predictor of poor survival and lower probability of PSA response to treatment in patients with metastatic androgen–independent prostate cancer (AIPC) who are receiving docetaxel–based therapy. Others have previously shown that higher serum IL–6 concentrations were predictive of shorter survival and lower probability of response to docetaxel in patients with AIPC. [27]

5. AGR2

In vivo anterior gradient 2 GR2–conferring pro–angiogenic and pro–metastatic effect significantly decreased bevacizumab antitumor activity, rather than cabozantinib. [28]

Table 2. Summary of the mRNA biomarkers, their association and relevance with PC

III. MicroRNAs

MicroRNAs are short, single–stranded, noncoding RNA molecules that act as posttranscriptional regulators of gene expression. They are incomparable potential biomarkers for cancer diagnosis, prediction, and prognosis, which in turn mark them as valuable targets for the clinical development of anticancer agents [29].

a) Predictive of the Onset of Docetaxel Resistance

Significant decrease of miR–34a expression ($P < 0.05$) in a cohort of prostate cancer patients experiencing

mRNA biomarkers	Association and relevance
TMPRSS2–ERG	May hold clinical value as a predictive biomarker of ADT response [30, 31, 32, 33, 34, 35, 36]
PTEN	ZBTB7A and PTEN loss may be a better predictor of progression upon androgen deprivation than PTEN deletion alone [37,38]
GCNT1	GCNT1 expression in prostate biopsy specimen is a significant and independent predictor of recurrence after radical prostatectomy, which can be used in pre–treatment decision making for the patient [39]
Cytokines	Elevated plasma MIC–1 levels after initial Docetaxel treatment can predict for Docetaxel resistance in men with HRPC, indicating that further chemotherapy is not warranted and may be harmful Elevated plasma CRP concentrations appear to be a strong predictor of poor survival and lower probability of PSA response to treatment in patients with AIPC who are receiving docetaxel–based therapy Higher serum IL–6 concentrations were predictive of shorter survival and lower probability of response to docetaxel in patients with AIPC [40], [41]
AGR2	In vivo GR2 significantly decreased bevacizumab antitumor activity, rather than cabozantinib [42]

Table 2. Summary of the mRNA biomarkers, their association and relevance with PC

biochemical recurrence compared to patients in whom this recurrence was absent. miR–34a is selected as a potential predictive biomarker for docetaxel response. [30]

It was proven that PC cells with miR–375 overexpression are resistant to docetaxel in the study conducted by Yuan Wang et al. In vivo in PC xenograft tumors in mice, using both qRT–PCR and Western blot, miR–375 transfection causes significant reduction of SEC23A and YAP1 mRNA expression and protein (also relevant in clinical samples in PC patients) which is the cause of docetaxel resistance. [31]

In addition, 22Rv1/DCTR and DU–145/DCTR clones were more resistant to docetaxel with respect to parental cell lines. [32]

b) Pterostilbene

Pterostilbene treatment significantly decelerated tumor growth in miR17/106a overexpressing xenografts without any obvious adverse effects. [29]

c) miR–34

miR–34 is a tumor suppressor in PC. Transfecting in vivo miR–34a mimic and miR–34a inhibitor into PC cell lines showed that ectopic overexpression of miR–34a induces paclitaxel–related apoptosis (arrest in G1–S phase due to overexpression) and downregulation showed resistance to paclitaxel. [33]

Table 3. Summary of the miRNA biomarkers, their association and relevance with PC

IV. GENETIC BIOMARKERS

1. BRCA1 and BRCA2

BReast CAncer genes 1 and 2 (BRCA1 and BRCA2) proteins play an important role in homologous recombination, an accurate DNA double strand break repair process. When a problem occurs in this mechanism, error–prone forms of DNA double–strand break repair predominate, which might increase a cell's mutational load, and thereby lead to tumorigenesis. [34]

miRNA	Association and relevance
MicroRNAs	miR–34a is a potential predictive biomarker for docetaxel response Pterostilbene treatment significantly decelerated tumor growth in miR17/106a overexpressing xenografts without any obvious adverse effects Ectopic overexpression of miR–34a induces paclitaxel–related apoptosis and downregulation showed resistance to paclitaxel [43, 44, 45, 13, 43, 46]

Table 3. Summary of the miRNA biomarkers, their association and relevance with PC

Poly ADP–ribose polymerase (PARP) is a nuclear enzyme with dual roles in DNA repair and transcription regulation. PARP mediates DNA single–strand break repair through the base excision repair pathway.

BRCA or homologous recombination has a synthetic lethal interaction with PARP. Therapeutic exploitation of this interaction via PARP inhibition in BRCA mutation carriers with cancer results in promising antitumor activity and has a favorable outcome. [34]

Preliminary evidence has shown that PARP inhibitors are responsible for antitumor activity in sporadic castration–resistant prostate cancer, and that the total loss of function (biallelic loss) of one of these genes BRCA1, PALB2, RAD51, and FANCA sensitizes to PARP inhibition (PARPi) [35]

Multidimensional genomic characterization of PC patients undergoing PARP inhibitor therapy will be necessary to define the entire spectrum of predictive biomarker [36]

It has been argued that biallelic BRCA2 inactivation in mCRPC warrants further exploration as a predictive biomarker for sensitivity to platinum chemotherapy, as some patients, with mCRPC, had extreme sensitivity to cisplatin. When the tumors were analyzed, these patients had a loss of BRCA2 in both alleles. [37, 38] Furthermore, patients with biallelic inactivation of BRCA 2 had good response to platinum–based chemotherapy after failure of front–line therapies

In 2016, the US Food and Drug Administration (FDA) granted Breakthrough Therapy designation (BTD) for olaparib for the treatment of BRCA1/2 (or ATM) gene mutated mCRPC patients who have received a prior taxane–based chemotherapy and abiraterone or enzalutamide [39].

In case of BRCA1/2 and ATM mutations, olaparib is associated with higher overall survival rate when compared to enzalutamide or abiraterone in CRPC. With BRCA biallelic DNA repair defect (DRD), niraparib was more effective with an objective response rate (ORR) of 41% than in other biallelic DRD. Talazoparib was most effective in BRCA than in ATM mutations. [40]

Nuclear levels of BRCA1 and RAD51 protein diminished in the radiosensitive cells while increasing in the radioresistant cells post–irradiation. These genes appear to be key in regulating radiation response, therefore these pathways, or their upstream regulators, may prove to be a good predictor of treatment outcome [41]

2. Caveolin 1

Caveolin–1 (Cav–1) is a scaffold protein of caveolae, which are 50–100 nm Ω–shaped invaginations of the plasma membrane in most cell types. Numerous studies have demonstrated that Cav–1 is overexpressed in some human tumors and is associated with poor clinical outcomes.

The study conducted by Gao et al consists in several analyses and experiments including cav–1 expression in primary PC and CRPC, the effect of cav–1 knockdown on progression to CRPC. Multiple analyses suggest that cav–1 acts on the PLCe through H–Ras to decrease factors which enhance invasion and migration in PC.

Simvastatin enhances the response to androgen receptor therapy by reducing cav–1 expression. Therefore, simvastatin opposes transformation into CRPC. [42]

3. ARV–7

Androgen receptor splice variants (AR–Vs) are truncated isoforms of the androgen receptor (AR). Two of the most abundantly expressed AR–Vs in mCRPC are AR–V7 and AR–V9. [43]

Regarding PC a significant correlation between circulating cell–free AR CNVs and treatment response to AA and enzalutamide has been shown, indicating AR gene copy number (CN) in cfDNA may be a promising biomarker capable of predicting treatment resistance [44]

Recent reports have questioned the role of CTC as a predictive biomarker given that either AR–V7 positive patients did respond to novel hormonal treatment (NHT) or AR–V7 status was not able to significantly demonstrate shorter OS compared to CTC positive yet AR–V7 negative patients [45]

Initial CTC values predict the duration and magnitude of response to hormonal therapy. CTC enumeration may identify patients at risk of progression to CRPC before initiation of ADT. [46]

Despite the correction for the epithelial signal, a significantly higher median CTC count of 25 CTCs/7.5 mL of blood was detected in AR– V7– positive patients compared with a median CTC count of 10 CTCs/7.5 mL of blood in AR– V7– negative patients ($p = 0.017$, the value of AR–V7 should be further assessed in patients with ≥5 CTCs as they have the highest need for rapidly available accurate predictive biomarkers. The predictive value of AR–V7 could not be further addressed in this study because no control group was available [47]

In addition, Antonarakis et al. found in CTCs that one splicing variant, AR–V7, is associated with resistance to enzalutamide and abiraterone. [48,62]

The variant AR–V7 has been discussed as a predictive biomarker to nonresponse to next–generation ADT in

patients with CRPC. AR–V7 status in CTC cannot entirely predict nonresponse to next generation ADT and AR–V7–positive patients should not be systematically denied abiraterone or enzalutamide treatment, especially as effective alternative treatment options are still limited. [49]

AR–V7 measured in CTC for predicting resistance to enzalutamide and abiraterone [50]

Reverse transcriptase–polymerase chain reaction detection of AR–V7 transcripts in whole blood was associated with inferior outcomes in patients treated with abiraterone [51]

AR–splice variants lack the C–terminal ligand–binding domain (LBD), a key regulator region of the full–length AR (AR–FL). The LBD is responsible for androgen–dependent receptor activity and the target of flutamide, bicalutamide, and enzalutamide. Therefore, LBD deletion results in loss of the antiandrogen binding site and constitutive activation of AR–V7. AR–V7 positivity is associated with reduced OS (median 8 months for AR–V7+ and not reached for AR–V7–) and PFS (20 months for AR–V7– vs 3 months for AR–V7+). [52]. Same results found a lack of response to AR (enzalutamide, abiraterone) treatment was significantly associated with high expression of AR, TSPAN8, PSCA, WNT5B, and NKX3–1. NKX3–1 is an AR–regulated homeobox gene and well–known marker of AR signalling. NKX3–1 has been shown to co–localise with AR and acts with other downstream pathways to promote cell survival in advanced prostate cancer [53]

Another study aimed to confirm the predictive value of AR–V7 measured in plasma samples as a predictive biomarker for hormonal therapy in metastatic PC. However, AR–V7 + was not associated to poorer or better clinical outcomes in mCRPC patients receiving abiraterone or enzalutamide. Both AR–V7 and AR–V9 were not associated with a lack of efficacy of abiraterone or enzalutamide in mCRPC. [43]

Regarding AR–V7, there was no significant difference in PFS between the groups Treated with Enzalutamide, Abiraterone, hormone therapies, or Taxane–Based Therapies [54]

While AR–V7 expression above the digital threshold of 14.7 transcripts per mL blood is highly specific for prediction of progression on first line abiraterone therapy, HOXB13 expression identifies additional non–responding patients, in whom suppression of androgen production is insufficient to achieve a sustained tumor response. [55]

Moreover, patients treated with AR signalization inhibitors had the most favorable survival outcome, if they were AR–V7 negative, and had the least favorable survival outcome, if they were AR–V7 positive. Patients with AR–V7–positive CTCs receiving taxanes had longer observed median survival times than those treated with AR inhibitors (not statistically significant). High–risk patients negative for AR–V7 treated with AR inhibitors had a longer median OS than those treated with taxanes, whereas for the high–risk patients positive for AR–V7, receiving AR inhibitors, had a shorter median OS than those receiving taxanes. [56]

4. LTZS1

The LZTS1 gene was previously described as a tumor suppressor gene [57], and chromosomal deletions on chromosome 8p encompassing LZTS1 are frequently observed in a variety of human cancers [58] including prostate cancer [59]. LZTS1 is a regulator of mitosis by maintaining high levels of CDC25C and CDK1 activity to prevent chromosomes missegregation [60].

Nakouzi et al conducted a study on cultured cells to try and distinguish the role of LTZS1 as predictive biomarker for docetaxel resistance. LTZS1 turned out to be downregulated in resistant cells (to docetaxel) compared to non–resistant ones. Further explorations showed increased methylation of the promoter which could then be the mechanism of downregulation. Moreover, knockdown of LTZS1 showed an advantage in survival, reinforcing the idea that LTZS1 is implicated in resistance to docetaxel. [61]

5. Stanniocalcine 1

Stanniocalcine 1 (STC1) may regulate growth and metastasis of prostate carcinoma, and may aid as a predictive biomarker. [62]

6. Nuclear Eg5 (kinesin spindle protein)

Eg5 separates spindle poles of a mitotic cell by crosslinking two antiparallel microtubules and moving to the plus–ends of both microtubules. Due to its essential function in mitosis, multiple Eg5–inhibitors have been developed for anti–cancer therapy, such as ispinesib.

Nuclear Eg5 expression and docetaxel response are positively correlated in patients in whom the eg5 expression was proven within 3 years before docetaxel therapy. [63]

7. Platelet biomarkers:

In the docetaxel treated patient group, none of the platelet biomarkers (KLK2, KLK3, FOLH1, and NPY transcripts) were associated with time for PFS. Patients positive for KLK3, FOLH1, and NPY showed a 4.2–fold increased risk of therapy failure ($P < 0.01$) and 3.2 times shorter PFS ($P < 0.001$) compared to biomarker negative patients. [64]

8. Gene Polymorphism:

Men heterozygous for rs12422149 (SLCO2B1) had significantly improved median PFS on first–line AA compared with the homozygous wild type and difference not seen in rs1789693 genotype. Germline variant alleles in rs12422149 of SLCO2B1 predict improved response to first–line AA for mCRPC. [65]

On the other hand, no association was found between CYP17A1 c.–362T>C and biochemical response to abiraterone [52]. The genetic variant rs2486758 (T>C) in CYP17A1 is negatively associated with biochemical response to AA, a more–than–four–fold decrease in the odds of biochemical response to AA per minor allele. [66]

Enzalutamide resistance was demonstrated in 2 patients with CTCs that were characterized by a gain of CYP11A1, ERG, and BRD4 and loss of CDK12 and cMET, and a gain in MLL2/3, FGFR2, and ERG and loss of MYC, RAF1, and AURK–A. [67]

Additionally, single nucleotide polymorphisms (SNP) in SULT1E1 were significantly associated with time to treatment failure in men on abiraterone acetate therapy. The SNP may serve as predictive markers for treatment with abiraterone acetate. [68]

Moreover, it was discussed that NBN, a DDR gene, correlates with radioresistance. [69]

Monica Cojoc et al. showed that radioresistant prostate cancer cell sublines DU145–RR, PC3–RR, and LNCaP–RR have an increased baseline phosphorylation of Chk2 (Thr68) and AKT (Ser473), therefore suggesting the existence of potential molecular mechanisms precipitating acquired radioresistance in these tumor cells.

9. Secreted Frizzled Related Protein (SFRP1)

Results revealed that SFRP1–negative patients showed a significantly poorer OS rate than SFRP1–positive patients P = 0.016. SFRP1 (hazard ratio, 0.429; 95% confidence intervals, 0.227–0.812; P = 0.009) may serve as an independent predictive and prognostic factor for PC. [70]

10. TSP–1

Baseline level below median of systemic thrombospondin–1 (TSP–1) had greater OS with tasquinimod compared to placebo. Upregulation of TSP–1 in bone marrow–derived myeloid cells can create a metastasis–resistant environment in prostate cancer. [71]

Table 4. Summary of the genetic biomarkers, their association and relevance with PC

V. HORMONAL BIOMARKERS

1. Serum testosterone

Testosterone can be a possible predictive biomarker. Analyses with docetaxel showed a progression–free survival (PFS) significantly inferior in men with levels of testosterone >0.05ng/ml as well as a trend for inferior overall survival (OS). On multivariate analysis, serum testosterone was a significant factor of progression. Similar results were found with Cabazitaxel. [73]

Lower levels of pre–treatment androgens (serum testosterone and serum androstenedione) were associated with primary resistance to abiraterone acetate (AA) (p=0.001). [74]

2. TSH

Responders to treatment developed a significant increase in thyroid stimulating hormone (TSH) compared to non–responders (p=0.03). TSH increase is predictive of therapy response. Hypothyroidism may serve as a simple predictive biomarker for therapy response under AA therapy. [75]

Table 5. Summary of the hormonal biomarkers, their association and relevance with PC

VI. Others

1. NLR

The neutrophil–to–leukocyte ratio (NLR) is the proportion of systemic neutrophils and lymphocytes, and it is a recognized circulating biomarker in multiple cancer. Baseline NLR may predict response to AA in this population of men with asymptomatic or mild symptomatic mCRPC. In addition, NLR holds a significant predictive value and strongly suggests, as others have reported, the prognostic value of NLR in mCRPC patients. [76]

Table 6. Summary of the NLR's association and relevance with PC

Conclusions

A plethora of biomarkers are predictive for the prognosis of PC and its response to certain therapies. These include Cav 1, that can be targeted by simvastatin, and high levels of bone metabolism biomarkers, such as CICP and BAP, are associated with increased OS when treated with atrasentan, AR–V7 negative status is indicative of an increased OS with taxanes therapy, and LTZS1 are implicated in resistance to docetaxel. In addition, TMPRSS2–ERG is a predictive biomarker of ADT response, while miR–34a is a potential predictive

Genetic Biomarkers	Association and relevance
BRCA1/2	Biallelic inactivation of BRCA 2 had good response to platinum–based chemotherapy after failure of front–line therapies, and more sensitivity for cisplatine Olaparib is associated with higher OS rate when compared to enzalutamide or abiraterone in CRPC with BRCA1/2 and ATM mutations [47,48,49, 50, 51,52,53,54]
Caveolin 1	Helps in progression to CRPC Simvastatin enhances the response to AR therapy by reducing cav–1 expression, therefore opposing transformation to CRPC[55]
ARV–7/9	Both AR–V7 and AR–V9 were not associated with a lack of efficacy of abiraterone or enzalutamide in mCRPC. Patients, treated by taxanes, having ARS inhibition, had the most favorable survival outcome, if they were AR–V7 negative, and had the least favorable survival outcome, if they were AR–V7 positive. [56,57,58,59,60,62, 63,64,65,66 ,67,68,69,70]
LTZS1	Implicated in resistance to docetaxel [71,72,73,74,75]
PDL–1	Low accuracy of PD–L1 as a biomarker of response to ICIs in mCRPC patients [26,27]
Stanniocalcine 1	STC1 may regulate growth and metastasis of prostate carcinoma, and may aid as a predictive biomarker[76]
Nuclear Eg5 (kinesin spindle protein)	Nuclear Eg5 expression and docetaxel response are positively correlated in patients in whom the eg5 expression was proven within 3 years before docetaxel therapy[77]
Platelet biomarkers	In the docetaxel treated patient group, patients positive for KLK3, FOLH1, and NPY showed an increased risk of therapy failure and shorter PFS compared to biomarker negative patients[78]
Gene Polymorphism	Men heterozygous for rs12422149 (SLCO2B1) had significantly improved median PFS on first–line AA compared with the homozygous wild type and difference not seen in rs1789693 genotype. Germline variant alleles in rs12422149 of SLCO2B1 predict improved response to first–line AA for mCRPC SNP in SULT1E1 were significantly associated with time to treatment failure in men on AA therapy. SNP may serve as predictive markers for treatment with AA NBN correlates with radioresistance [79,62, 80,81, 82,83]
HSDB1	Men with variant type in HSD3B1 with higher activity of 3β–HSD–1 showed favorable response and prognosis in abiraterone treatment HSD3B1 (1245C) allele is a potential biomarker for predicting ADT resistance and rapid development of CRPC
SFRP1	SFRP1–negative patients showed a significantly poorer OS than SFRP1–positive patients. SFRP1 may serve as an independent predictive and prognostic factor for PC[84]
TSP–1	Baseline level below median of systemic TSP–1 had greater OS with tasquinimod compared to placebo [85]

Table 4. Summary of the genetic biomarkers, their association and relevance with PC

biomarker for docetaxel response. SNP may serve as predictive markers for treatment with abiraterone acetate, while HSD3B1 (1245C) allele is also a potential biomarker for predicting ADT resistance and rapid development of CRPC, and tasquinimod had a greater OS with compared to placebo when TSP–1 is positive. Moreover, cytokines can also play a role as biomarkers, such as MIC–1, as its elevated plasma levels after initial docetaxel treatment can predict for docetaxel resistance in men with HRPC, indicating that further chemotherapy is not warranted and might be harmful. BRCA 1/2 positive cancers can be treated by Olaparib, and GCNT1 expression in prostate biopsy specimen is a significant and independent predictor of recurrence after radical prostatectomy. Additional biomarkers are also predictive for prognosis, such as EGFR, serum testosterone, microtubule bundling, Nuclear Eg5, C–Flip, NLR, TSH, CRP, SFRP1, and PTEN. On the other hand, certain biomarkers, once thought to be indicative of prognosis in PC, were not, such as VEGF and PSA, and others have been shown in limited studies to be

Hormonal biomarkers	Association and relevance
Serum Testosterone	Lower PFS and OS with higher levels of testosterone with docetaxel and cabazitaxel Lower levels of pre–treatment androgens were associated with primary resistance to AA [86, 87]
TSH	TSH increase is predictive of therapy response. Hypothyroidism may serve as a simple predictive biomarker for therapy response under AA therapy [88]

Table 5. Summary of the hormonal biomarkers, their association and relevance with PC

Neutrophil–to–Leukocyte Ratio (NLR)	Baseline NLR may predict response to AA in this population of men with asymptomatic or mild symptomatic mCRPC [89]

Table 6. Summary of the NLR's association and relevance with PC

indicative of it, like Stanniocalcine 1 and Serum tri– and tetra–antennary N–glycan.

Many advancements have been made to integrate biomarkers in the diagnosis and/or management of PC. The available biomarker tests that can be used for consideration of initial biopsy, are either serum–based (PHI and 4KScore) or urine–based (ExoDX Prostate IntelliScore, MiPS Mi(chigan) Prostate Score, Progensa (PCA3) and SelectMDX), or can also be tissue based (ConfirmMDx, Prolaris, OncotypeDx, Decipher and ProMark), used in this case as a confirmatory test. They are classified as prognostics (Prolaris, Decipher and OncotypeDx) or diagnostics (PCA3, 4KScore, PHI and SelectMDx). [77] This study can help in the development of diagnostic and prognostic tests of PC and contribute to the ongoing research into already existing tests. Large prospective studies comparing the biomarkers are needed. Moreover, with the potential discovery of new biomarkers and with the recent advancements in bioinformatic, a new horizon can open up for the management of PC.

Conflicts of interest

The authors report there are no competing interests to declare.

Data sharing statement.

Data sharing is not applicable to this article as no new data was created or analyzed in this study.

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