Biomarkers in Advanced Prostate Cancer

William Archambault and Gilles Plourde*

Department of Clinical Pharmacology and Physiology, University of Montreal, Canada

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*Corresponding author: Gilles Plourde MD, PhD Associate Professor Department of Clinical Pharmacology and Physiology, Faculty of Medicine, University of Montreal, Clinical Trial Application, Health Canada Ontario, Montreal, Quebec, Canada, Email: gilles.plourde@hc-sc.gc.ca

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Mini Review

Second to skin cancer, prostate cancer is the most common neoplastic injury in North American men. Over a lifetime, 1 out of 7 men will receive a diagnosis of prostate cancer [1-3]. Although, the 5-year survival rate is nearly 100% for stages I to III, it drops to 29% for metastatic stage IV cancers. Thankfully, more than 80% of prostate tumors are detected in the early stages, in large part due to screening using biomarkers like prostate-specific antigen (PSA) [4]. At the moment, PSA blood test is the most widely used biomarker for prostate cancer detection and is considered superior to other risk factors such as race and family history of prostate cancer [5]. However, the PSA blood test is far from being the optimal diagnostic biomarker. In fact, several groups agree that PSA has limitations in terms of specificity and sensitivity [6]. It does not seem to help reduce cancer mortality, and both the US Preventive Task Force and the Canadian Task Force on Preventive Health Care recommend against systematic screening with PSA [3,7,8]. As such, development of more sensitive and more specific biomarkers allowing for:

a. Early detection and diagnosis,

b. Treatment response and

c. Surveillance and detection of metastases is not only warranted, but necessary.

As the field of medicine is ever moving towards personalized approaches, improvements in biomarkers is the first step in tailoring treatments and follow-ups to the specific behaviors and weaknesses of individual tumors. The following case report aims to describe and review the most up-to-date evidence of the best biomarkers associated with prostate cancer, as alternative to PSA.

Case Report

A 61 year-old patient with a three-year history of stage IV prostate cancer with bone metastasis presented to the clinic questioning about the role of biomarkers in the diagnosis of his prostate cancer. Since mainly PSA level was used as the biomarker for his diagnosis, he is questioning, beside PSA, which one(s) of the following are the biomarkers that the Health Care Providers (HCPs) should have used to improve the early detection of his prostate cancer?

A. PSA derivatives;

B. PSA isoforms;

C. Prostate Health Index;

D. 4K Score;

E. PC antigen 3 and Progensa;

F. C - Reactive protein (CRP);

G. All of the above was considered useful;

H. Only A and B are correct;

I. Only A and B and F are correct.

Answer I

A. PSA derivatives

In an effort to improve sensitivity and specificity of PSA, researchers and HCPs have looked extensively at different ways to interpret PSA blood tests. Derivatives measures studied include PSA kinetics such as: PSA doubling time, PSA velocity, PSA density and age-specific PSA [9,10]. Unfortunately, scientific evidence to date concerning clinical advantages of those derivatives is pessimistic at best. None of them has demonstrated clinically relevant additional value versus or in combination with the regular PSA analysis [10,11]. However, even considering these controversies, from a clinical perspective, for our patient we used the doubling time to make the decision of introducing...
Casodex (non-steroidal antiandrogen) being already treated with Zoladex (LHRH agonist). For more than two years and half our patient had a PSA < 0.2 under treatment with Zoladex then the PSA raised to 0.9 in the following two months for a PSA doubling time of around 1 month. For a patient already under treatment with Zoladex such a doubling time was sufficient to introduce Casodex. After 3 months on the combination Zoladex and Casodex, the PSA level of our patient raised to 3.1 for a doubling time of around 1 month. This was sufficient to stop Casodex and introduce a second-line hormone therapy that includes Zytiga (an androgen biosynthesis inhibitor) and Prednisone. Therefore, A is a good answer.

B. PSA isoforms

PSA isoforms, on the other hand, seem far more promising and are already used in clinical settings. Whereas PSA derivatives are mostly kinetics of the regular PSA molecule, PSA isoforms are slightly different variants of the molecule. Example includes free PSA (fPSA) (from which we can calculate the ratio of free PSA (%fPSA)), proPSA, intact PSA (iPSA), and benign PSA (bPSA) [9-11]. Recent evidence supports the utility of %fPSA to reduce the number of biopsies in men with PSA levels between 4 and 10ng/mL [12,13]. Risk of having prostate cancer is around 56% when %fPSA is below 10% but only 8% when it is over 25% [14]. Hence biopsies would be highly recommended in those men with less than 10% free PSA, but total PSA between 4 and 10 ng/mL [15].

Benign PSA appears to be a marker for Benign Prostatic Hyperplasia (BPH) [10,16], but its clinical utility for prostate cancer diagnosis is debated. Studies on intact PSA are still very sparse. One study found a correlation between lower proportions of iPSA and more advanced cancer stage and grade, which could suggest a potential role as a marker for cancer aggressiveness [17]. The best known usage of iPSA at the moment is as one of the 4 components of the 4K score test discussed below [6]. Therefore, for our patient iPSA was not very helpful.

From the 3 isoforms, proPSA has received the most attention from the scientific community. Initially interest was focused on the [-5] and [-7]proPSA, but a review by Hori et al. concluded that current evidence suggest that both of them fail to improve prostate cancer detection when compared to current PSA-based measurements [18]. The same review also suggest that [-2]proPSA seems like the most clinically relevant PSA isoform for prostate cancer detection. The authors refer to five studies where [-2]proPSA was either highly correlated with prostate cancer development or performed better than total PSA, PSA and other PSA isoforms in detecting cancer [19-23]. However, the predictive and discriminating power of [-2]proPSA seems to be most significant when it is included as part of a mathematical model such as the Prostate Health Index (PHI) [2,19]. Moreover, the velocity of certain isoforms, such as iPSA and proPSA, appears promising in increasing the detection of early prostate cancer.

However, as mentioned above the patient PSA level was already at 30.0 ng/mL (not in the range of 4.0 to 10 ng/mL), the first time our patient presented to the walking clinic with symptoms of prostate cancer. Then the PSA level increased rapidly to 175.0 ng/mL. Obviously, the %fPSA was used in our patient and the ratio was < 5% indicating a high risk of prostate cancer. Therefore, B is a correct answer.

C. Prostate Health Index

The PHI is simply the following mathematical formula: ([-2] proPSA/iPSA) x √PSA. It combines all three evidence-based PSA biomarkers into a single score. The rationale behind the formula is that men with higher levels [-2]proPSA and PSA as well as with lower levels of iPSA are more likely to have prostate cancer [24]. Recent evidence highly suggests that PHI substantially improves the screening capabilities of its individual counterparts [11,18,24]. In addition, PHI score seems to have excellent reliability across populations. In a large multicentric study, Catalona et al. [25] observed increasing detection rates with increasing PHI scores with no effect of age or race, suggesting applicability to all men irrespective of age and ethnicity [25]. Furthermore, several studies have detected a correlation between PHI scores and Gleason score on biopsies [25-27]. These findings strongly support the use of PHI scores to reduce the number of unnecessary biopsies and as a measure of cancer aggressiveness during active surveillance.

This consistent association with the Gleason scores gives PHI score an edge versus other biomarkers, such as PCA3 and TMPRSS2: ERG, who do not [28]. One study of prostate cancer surveillance using PHI had a strong model predicting which men would have a reclassification to higher-risk disease on repeat biopsies using baseline and longitudinal PHI scores (C-indices: .788 & .820 respectively; median follow-up=4.3 years). Similar results had been obtained by Isharwal et al. [29] a year prior using baseline PHI to predict unfavorable biopsy finding (c-index of .691) [30].

Today, the PHI blood test is fairly inexpensive, simple and is currently approved by the FDA and recommended by the National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer Early Detection [11]. Clinical utility is optimal for those in the diagnostic ‘gray zone’ of 4-10ng/mL PSA. PHI scores below 26 are associated with a 10% probability of cancer; approximately 17% risk for the 26-36 range; 33% risk for the 36-55 range, and the probability of cancer for scores above 55 increases above 50% [24,25]. Thus, PHI blood test following a PSA score in the gray zone range could help avoid overtreatment of low-risk prostate cancer. These would not only reduce unnecessary harmed caused to low-risk patients, but reduce overall cost of prostate cancer detection while improving quality adjusted life years (QALY). Two studies by Nichol et al. calculated
that incorporating the PHI test to the current PSA screening strategy would result in a net saving of $356,647 and $94,219 plus a gain of $0.008 and $0.003 in QALY for PSA thresholds of ≥2 and ≥4 ng/mL respectively [31,32].

Further studies are warranted to improve specificity of the score ranges as well as to clarify the accuracy of PHI in active surveillance, but PHI use is resting on solid preliminary evidence at the moment. As mentioned above, the patient presented with a PSA level that we cannot considered in the “gray zone” on his first visit to the walking clinic suggesting that it was already too late for him to perform this score and this measure becomes irrelevant. A prostate biopsy was performed in our patient in combination with the transrectal ultrasound. The Gleason index (index commonly used to study the prostate cancer severity which is done by examining the appearance of prostate cells under a microscope) shown a result of 9/10 (5 + 4) strongly suggesting the presence of an aggressive and intrusive prostatic adenocarcinoma which means that the use of this biomarker would not have add much value to his diagnosis. Therefore C is not a good answer.

D. 4K Score

4KS is another blood test looking to discriminate between indolent and aggressive prostate cancer by yielding a % risk of a high-grade cancer on subsequent biopsy (Gleason score ≥ 7). It differs from PHI as it incorporates total PSA, fPSA, intact PSA and the kallikrein-related peptide hK2 into the equation. In addition, 4KS considers clinical information like age, prior negative biopsy status and negative digital rectal examination to provide its % risk score [33]. The rationale for using these four kallikreins proteins as cancer detection and active surveillance tools comes from evidence that their levels increases with cancer cell undifferentiating and, either directly or indirectly, promote prostate cancer progression and metastasis [34,35].

A review of 4KSevidence by Punnen et al. list several studies including close to 10,000 subjects who looked at the % reduction of biopsies using 4KS. The % reduction in biopsies ranged from 36-82% [33]. Among those studies, there is the recent prospective US validation study. Enrolling 1012 subjects, researchers prospectively analyzed the 4KS of subjects who had low-grade Gleason score 6 versus those that had Gleason score ≥ 7. Using a cut-off of 7.5% risk of Gleason score ≥ 7 would result in 36% reduction of unnecessary biopsies while delaying the diagnosis of 1.7% of Gleason score 7 and missing 0 Gleason score 8 and above cancers. Additionally, 4KS performance did not differ between white and black American men [36]. As such, 4KS could provide a valuable personalization of probability thresholds depending on the individual.

A healthy risk averse patient could opt for a lower risk score (say 5% instead of 7.5) whereas someone more risk-taker or with an already low life-expectancy could choose a higher risk score (say 15%) before undergoing an invasive and costly procedure.

Indeed, similarly to PHI, a research group performed a meta-analysis to evaluate the screening efficacy and substantial cost saving potential of the kallikrein panel. They concluded that 48-56% of biopsies could be avoided via a 8-10 % improvement in predictive accuracy resulting in annual savings close to 1 billion US$ [37]. Future research comparing the predictive value of PHI vs. 4KS would be interesting as they could determine if one of the two is superior in discriminating between aggressive and low-risk prostate cancer. However, the 4K Score is not yet FDA or Health Canada approved.

Based on the biopsies results (above) and radiology exams, the HCP confirms that the patient has an aggressive and intrusive prostate adenocarcinoma of stage T3c (meaning that the tumor has extended outside the prostate and its capsule). In addition, the seminal vesicles are affected with a notation N3 [+N] (confirming several adenopathies located in the abdominal, pelvic and thoracic areas) as well as M1 [confirming the presence of metastases in other organs far away from the prostate such as lungs, bones but not the liver]. Because the PSA level was already high (not in the gray zone) at presentation and because the biopsies were strongly positive for an advanced prostate cancer from the beginning, using this biomarker becomes irrelevant for our patient. Therefore D is not a good answer.

E. PC antigen 3 and Progensa

The Progensa PCA3 assay is a nucleic acid amplification test that measures the urine concentration of prostate cancer antigen 3 (PCA3) and PSA RNA molecules, following a digital rectal examination (DRE). The ratio of PCA3 to PSA RNA yields the PCA3 score [11,38]. A PCA3 score below 25 associated with a decrease in likelihood of prostate cancer, but decreasing the cut-off to a score of 10 reduced false positives by a little more than a third while false negatives increased only by 5.6%. Two different reviews summarizing 11 clinical studies determined that the overall accuracy of PCA3 was around 66% [39,40]. This promising result combined with easy specimen collection following DRE has prompted the FDA to grant approval to the Progensa assay in 2012 [38]. The assay is also part of the European Association of Urology guidelines for repeat biopsy decision making [41].

However, recent analysis indicates that PCA3 to be inferior to other biomarkers such as PHI and 4KS for malignant prostate cancer detection [42]. It seems that the most optimal gains of Progensa were obtained when used in combination with other biomarkers like TMPRSS2: ERG or within a multivariable model [43,44]. Despite being available commercially and approved by regulatory agencies, PCA3 is not commonly used as a first-line test in clinical practices. Therefore, E is not a correct answer.

F. C - Reactive protein (CRP)

C-reactive protein (CRP) is an acute-phase protein released primarily by hepatocytes and is involved in processes of
inflammation, necrosis and carcinogenesis. It has been associated with poor prognosis of survival in several types of cancers [45]. Recent studies have looked into its potential predictive role in assessing prostate cancer severity and survival outcomes. Several of them, including a meta-analysis, have concluded that elevated CRP is associated with poor survival in prostate cancer patient with a cut-off value around 8.6 mg/L [46,47]. A single study of 261 patients has found a decrease in cancer-specific survival for those with elevated CRP (Hazard Ratio (HR) = 3.34) while the meta-analysis pooling 9 studies with more than 1400 patients obtained a HR of 1.91 for the same conclusion [45,48].

It is important to mention, however, that given the known association of CRP with several diseases related to survival (ex: cardiovascular and pulmonary diseases), the above results should be interpreted with caution. Not all of those studies assessed potential comorbidities that could confound the relationship of high levels of CRP and low survival. In addition, different types of treatment (radiotherapy, chemotherapy, etc.) can trigger differential intensities of inflammation and could also play a role in the increase CRP levels observed [45]. Despite those limitations, it seems that, for whatever reason, a CRP count above 8.6 mg/L represents bad news for prostate cancer patients and should be interpreted accordingly.

For our patient, this biomarker was very useful and has been measured from the beginning. It was at 75.0 mg/L at his first visit to his oncologist. Considering that our patient was not known for any cardiovascular, pulmonary or other inflammatory diseases, his high CRP level was therefore predictive of a severe prostate cancer disease. In fact, from the beginning (at the time of his biopsies) our patient was already having a grade IV prostate cancer with a Gleason score of 9. Therefore E, is a good answer.

Then the patient received anti-inflammatory drugs that gradually decrease the CRP level to normal. Therefore, by taking anti-inflammatory drugs, the CRP level becomes useless for the follow up of treatment in our patient. Which means that CRP is a strong positive predictor of cancer severity at the time of diagnosis but becomes less useful for assessing the response to treatment?

Question #2: For his stage IV prostate cancer our patient was treated with hormone therapy that includes Zoladex then Casodex. He was also treated with Xgeva to help with the treatment of his bone metastasis. Among the following which treatment?

A. Circulating tumor cells (CTCs);
B. Neutrophil-to-Lymphocyte Ratio (NLR);
C. Circulating testosterone levels;
D. Androgen receptor splice variant 7;
E. All of the above

Answer E

A. Circulating tumor cells (CTCs)

CTCs are cells that have detached from a primary tumor and are circulating within the lymphatic or systemic blood vessels and have been associated with increased risk of metastases [49]. A study from de Bono and his group has determined that patients with metastatic castrate-resistant prostate cancer (mCRPC) with a CTC count ≥ 5 (within a 7.5 ml sample of blood) had much worse overall survival than those with lower CTC count (11.5 vs. 21.7 months). In addition, the survival predictive value of CTC surpassed that of monitoring PSA decrease [50]. One of the most interesting potential applications of CTCs as biomarkers being studied is its use as a treatment response indicator. A recent study analyzed the treatment outcome of 486 patients from two major studies, all with CTC ≥ 5, and concluded that a ≥30% decline in CTC was associated with increased survival, compared to those with a stable or increased CTC [51].

The cut-off value of 5 has been questioned recently by several studies who suggest that it would be best to simply interpret CTC as a continuous variable with a greater number representing a worse prognosis at all time points. Indeed, it seems that the relationship between CTC count and survival is inversely proportional, regardless of the cut-off value chosen [52]. Unfortunately, the CTC was not measured in our patient, but it is not a bad idea to start using it in our patient and for other patients with prostate cancer. Therefore A is a good answer.

B. Neutrophil-to-Lymphocyte Ratio (NLR)

Similarly to CTCs, the tumor microenvironment, the mix of local cells and immune cells around the tumor, is known to influence on cancer progression and treatment outcome. For example, higher levels of M1 macrophage and CD8+ infiltrating lymphocytes correlate with more positive clinical outcome in solid tumors. On the other hand, presence of B-Cells, M2 Macrophage or Regulatory T-Cells is indicative of tumor growth [53]. More recently, the NLR has gained accrued interest from researchers for its prognostic value specifically for CRPC. First two independent studies, one with CYP17 inhibitor ketoconazole and the other with docetaxel chemotherapy, stratified their patients using a cut-off NLR value of 3. In both cases, pre-treatment NLR > 3 patients had a worse progression-free survival and overall survival, respectively, compared to patients with NLR ≤ 3 [54,55].

The interest generated by those findings led to the recent publishing of a meta-analysis on the matter. Compiling 22 studies, Cao et al. observed that a high NLR predicts a lower PSA response, a higher risk of recurrence and a worse overall survival, progression-free survival and recurrence-free survival in both mCRPC and localized prostate cancer [56]. Even though the meta-analysis revealed that there is still no clearly defined NLR cut-off value (most studies used NLR >3 or >5), the body of evidence to date supports the use of NLR value for risk
stratification and personalization of treatment interventions for all types of prostate cancer patients. A patient with CTC and NLR scores above 5 might benefit from a more aggressive regimen early on to maximize its survival whereas a patient with low scores and no metastasis yet could decide to withhold treatment for a while and improve his/her quality of life.

For our patient this NLR score was already at 2.1 from the beginning and was suggestive that our patient had a good progression-free survival and overall survival. As per September 2017, his NLR score goes down to 1 suggesting that the first line hormone therapy was an appropriate treatment even though our patient becomes less responsive to hormone therapy. Therefore, this biomarker can be used to follow the response to hormone therapy and is useful as a biomarker to indicate whether or not a more aggressive treatment regimen should be provided to our patient and other patients. Therefore B, is a good answer.

C. Circulating testosterone levels

Hormonal therapy is, along with surgery and radiation therapy, the first-line treatment for locally advanced prostate cancer. Prostate tumor cells are particularly responsive to androgens (testosterone and dihydrotestosterone). As such, several drugs lowering testosterone levels are approved by the FDA for hormone therapy of prostate cancer [57]. Circulating testosterone levels would then be an obvious choice of biomarker to monitor the success and efficacy of those therapies as well as to predict the chances of recurrence.

However, the association between serum testosterone and prostate cancer growth is weak at best. Some studies have found a correlation between increased cancer growth and higher levels of serum free testosterone [58], but several independent groups have found contradicting evidence [59,60]. Indeed, in study of 168 patients, lower testosterone and estrogen levels were associated with a higher Gleason score suggesting the opposite association [47,61].

Our patient noticed that his testosterone level decreased at the first months of hormone therapy, suggesting, at some point that the hormone therapy was able to sufficiently suppress the testosterone. However, currently his testosterone level is still very low but our patient is responding less well to hormone therapy. This confirms that other androgenic hormones might be involved in his prostate cancer. Therefore, going for a second line hormone therapy might be sufficient to re-establish the treatment response to hormone therapy by inhibiting similar androgenic hormones but at different level. Therefore, the circulating testosterone level is a good marker to the response to hormone therapy and when the patient becomes resistant to hormone therapy; it is not specifically due to an absence of suppression of the testosterone but rather due to the actions from other androgenic hormones that can be secreted by the adrenals or by the cancer itself. Therefore C is a good answer.

D. Androgen receptor splice variant 7

On the brighter side, a new promising biomarker, AR-V7 (Androgen-Receptor Splice Variant 7), seems excellent to predict response to anti-androgen treatments. In an important study of 31 patients treated with Zytiga (abiraterone) (a CYP17A1 inhibitor anti-androgen) and 31 patients treated with enzalutamide (an androgen receptor antagonist), the CTCs were analyzed for presence of AR-V7. The biomarker was detected in 19% of abiraterone patients and 39% of enzalutamide patients. Of all those AR-V7 positive patients, none had a decreased in PSA levels and significantly lower overall survival compared to AR-V7 negative patients [62]. The same group pursued their analysis and observed the response to treatment for taxane chemotherapy in AR-V7 positive versus negative patients and found no difference in taxane efficacy between groups [63]. Hence, they concluded that CTCs analysis for presence AR-V7 could be a first step in personalisation of treatment option where AR-V7 positive patients would be started on taxane chemotherapy instead of anti-androgen drugs. This recent research also further supports the importance of evaluating CTCs in our attempt to move towards an even more evidence-based personalized medicine. Since our patient is now becoming resistant to hormone therapy and since he is now treated with Zytiga, this biomarker becomes highly relevant for him. Therefore D is a good answer.

Question #3: True or False, The used on bone turnovers biomarkers is highly relevant for patients with bone metastatic prostate cancer.

Response: True

The skeleton is the preferred location of prostate cancer metastases, affecting up to 90% of advanced CRPCs [64]. Once in the bones, tumor cells disturb the equilibrium between bone formation by osteoblasts and bone resorption by osteoclasts [65]. As such, bone metastasis from prostate cancer is responsible for complications known as Skeletal-Related Events (SREs). Examples of SREs include pathologic fractures, chronic bone pain, and spinal cord compression [66]. On top of a decreased quality of life and increased cost of treatment, patients experiencing SREs also have decreased survival odds versus those who have not had SREs [67].

Evidence for the use of bone biomarkers for diagnosis and screening metastases progression remains unclear due to lack of solid prospective studies. However, data is more optimistic for usage of bone biomarkers as proxy for the response to treatment of bone metastases [68]. A superiority study of the anti-RANKL monoclonal antibody denosumab (Xgeva), commonly used in the treatment of metastatic bone tumors, over zoledronic acid for delay of SREs noticed a significant suppression of bone turnover markers with Xgeva. For example, the median bone-specific alkaline phosphatase and the N-telopeptide decreased significantly more, compared to baseline, in the denosumab group than in the zoledronic group [69].
Radium-223 (Ra-223; Xofigo) is another approved treatment for prostate cancer bone metastases and is included in the treatment program of our patient with bone metastasis. In a phase II study prior to its approval, Ra-223 had significantly decreased or slowed down the increase in the risk of death. On the other hand, the normalization of the same bone biomarker were associated with reduced risks of skeletal complications, but Ntx has never been tested in our patient. Therefore, we can easily assume that these biomarkers are relevant for our patient with bone metastatic prostate cancer treated with hormone therapy in combination with Xgeva. This biomarker will also very useful when the patient will have to be treated with Xofigo, if necessary.

Conclusion

This case report reviewed the evidence concerning prostate cancer biomarkers currently available and with the greatest potential clinical utility in three distinct areas: Detection & Diagnosis; Treatment & Prognosis and Metastasis Surveillance & Detection. However, it is by no means an exhaustive list of all the potential prostate cancer biomarkers in the literature. Several other biomarkers not discussed in this case report are also very promising.

The fusion gene TMPRSS2: ERG is harnessing interest at the moment, especially for its predictive value for both tumor progression and response to treatment [11]. The immune response regulator PD-1 (Programmed cell-death receptor 1) is another biomarker gathering research attention. In a 2017 study of 535 prostate cancer patient, high density of PD-1+ lymphocytes was associated with worse survival outcomes, especially in patients with high initial Gleason scores (≥9) as in our patient [73]. Tumor-infiltrating lymphocytes, tumor-associated macrophages and the tumor microenvironment are also under scrutiny as potential negative predictors of survival and personalization of therapy. The list is growing and there is no doubt that, as our understanding of immunotherapy grows, so will be our ability to detect and use other relevant biomarkers. Advancement in technology is making new types of analysis possible while decreasing the cost of existent clinical tests. Although novel and original research should never be discouraged, the pursuit of strong, solid, multi-centered, randomized comparative studies comparing the efficacy of already available and useful biomarkers is warranted. As highlighted by this case report, several biomarkers already used clinically seem to provide benefits for patients and for the healthcare system.

Unfortunately, the ever increasing number of possible test to perform gradually creates a difficult decisional puzzle for HCPs when it comes the time to choose which diagnostic test to perform or which biomarkers to evaluate. Establishing the superiority of a biomarker over another or demonstrating their additive prognosis power could make the decisional algorithms much simpler for HCPs, save money to the health care system by decreasing the necessity for multiple tests and improve substantially the quality of life of prostate cancer patients via an improved individualized therapy.
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