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Review Article

Prostate cancer biomarkers: Are we hitting the mark?

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1. Introduction

Prostate cancer (PCa) is among the commonest newly diagnosed cancers in the Western world, with projections for increased incidence over the following decades.[1] Prostate specific antigen (also known as PSA or human kallikrein-3) remains the first line and most commonly used serum biomarker for the detection of PCa. The introduction of PSA has resulted in the increased diagnosis of men with localized, early stage PCa.[2] In current practice, controversy remains over its suitability and efficacy as a screening tool for increasing early detection of PCa and lowering mortality.[3] An inherent limitation to PSA testing relates to lack of specificity in the setting of PCa screening.[4] There is great clinical need for accurate screening for PCa to decrease unnecessary prostate biopsies.

Additionally, PSA provides poor differentiation of PCa aggressiveness.[4] PCa presents a difficult entity to accurately risk stratify due to its highly variable clinical course. Prostate biopsy is the gold standard for PCa diagnosis, however it has diagnostic limitations and its invasive nature increases the risk of adverse events. Further, the PCa risk stratification by PSA, prostate biopsy Gleason score, or pT cancer stage may lead to understaging.[5] Accurate staging and risk stratification is critical, particularly when considering active surveillance. As such, there is a critical need for improved PCa biomarkers that are noninvasive and have improved accuracy and risk stratification properties.

This has led to the search for aids in the decision-making algorithm of PCa that may give information on prognosis, add diagnostic specificity, or act as screening tools. Over recent decades, the development of molecular biomarker assays and genetic assays has provided an avenue for PCa biomarker development. Considerable research has resulted in a new panel of tests that may improve determination of cancer presence, aggressiveness, and prognosis. Emerging biomarkers include those utilizing serum, urinary, or tissue samples as a test substrate. In clinical practice, the utility of these biomarkers is variable and may be used at different time points throughout the care of a patient with suspected or diagnosed PCa. Specifically, these biomarkers assist in diagnosis, guiding definitive treatment options, determine the risk of ongoing monitoring versus intervention, or provide risk stratification in the setting of negative initial biopsy.

There is still a need for a clear understanding of the role of each of these tests in the diagnosis, management, and prognosis of patients with PCa. This review explores the current literature on biomarkers used in PCa screening. We have reviewed the contemporary literature pertaining to different PCa biomarkers including: Pro-PSA and PHI, the 4K score test, PCa antigen 3, transmembrane serine protease protein 2 (TMPRSS2)-ERG, ExoDx Prostate Intelliscore, Second Chromosome Locus Associated with

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Prostate-1 (SChLAP1), SelectMDx, ConfirmMDx, Oncotype DX PCa assay, Prolaris, Decipher, and Embryonic Lethal, Abnormal Vision, Drosophila-Like 1 (ELAVL1). We aim to objectively review current biomarkers in PCa in order to further define the utility of these tests and their role in PCa management. Fig. 1 is a guide to the use and appropriate timing of the discussed biomarkers in the role of a patient with suspected or proven PCa.

2. Serum-based PCa biomarkers

2.1. Pro-PSA and PHI

PSA is derived from an inactive precursor enzyme that contains a pro leader sequence of seven amino acids, known as [-7] proPSA. Activation occurs through posttranslational cleavage of its ≥ 7 amino acid (AA) pro leader sequence by human kallikreins 2 and 4 to form the mature 237 amino acid PSA molecule. Partial cleavage of this leader sequence produces isoforms of proPSA depending on how many amino acids remain attached to the PSA molecule, most commonly [-4]proPSA, [-5]proPSA, and [-2] proPSA. The [-2]proPSA variant has been found to be the most prevalent in PCa extracts.[6] The Prostate Health Index (PHI, Beckman Coulter Inc., CA, USA) is a mathematical formula which relies on the differing proportions of the specific biomarkers (fPSA, tPSA, [-2]proPSA). This formula provides additional information to assist in delineating between benign prostatic conditions and PCa in men with suspected PCa. Validation was provided by a multicenter, case controlled clinical trial in which 892 patients with no history of PCa, benign digital rectal examination, and PSA between 2 ng/mL and 10 ng/mL underwent prostate biopsy. PHI was found to have greater specificity (AUC 0.73) than PSA alone or other combinations of pro PSAs.[7] Furthermore, the study displayed that increasing PHI values were associated with detection of clinically significant PCa of Gleason Grade 7 or higher. These findings were corroborated by Fossati et al,[6] who reported an association with PHI score and poorer pathological outcomes on 489 patients treated with radical prostatectomy. Whilst data regarding this test is immature, PHI appears to be a promising, noninvasive biomarker that may improve detection and provide prognostic information.

2.2. The 4Kscore test

Similar to PHI, the 4Kscore (OPKO Lab, FL, USA) test is determined on serum levels of four human kallikreins: total PSA, free PSA, intact PSA, and human kallikrein 2. These values are used in combination with clinical information (age, DRE findings, and history of previous negative biopsy result). These variables are placed into an algorithm and a patient-specific percentage risk of having Gleason score 7 or more on subsequent biopsy is provided.[8] This recent prospective study by Parekh et al[8] examined the intervention of the 4K test on 1,012 men referred for prostate biopsy for clinical suspicion of PCa regardless of PSA. The predictive accuracy of a biopsy result Gleason ≥ 3 + 4 was significantly higher with the inclusion of the 4K test (compared to PSA alone), with an AUC 0.821 [95% confidence interval (CI) 0.790–0.852] versus 0.751 (95% CI 0.714–0.789), respectively.[8] In this diagnostic setting, the 4K score has been reported to have reduced the number of prostate biopsies in a multicenter study of 611 patients.[9] Additionally, there is evidence that the 4K score may be able to identify higher risk PCas.

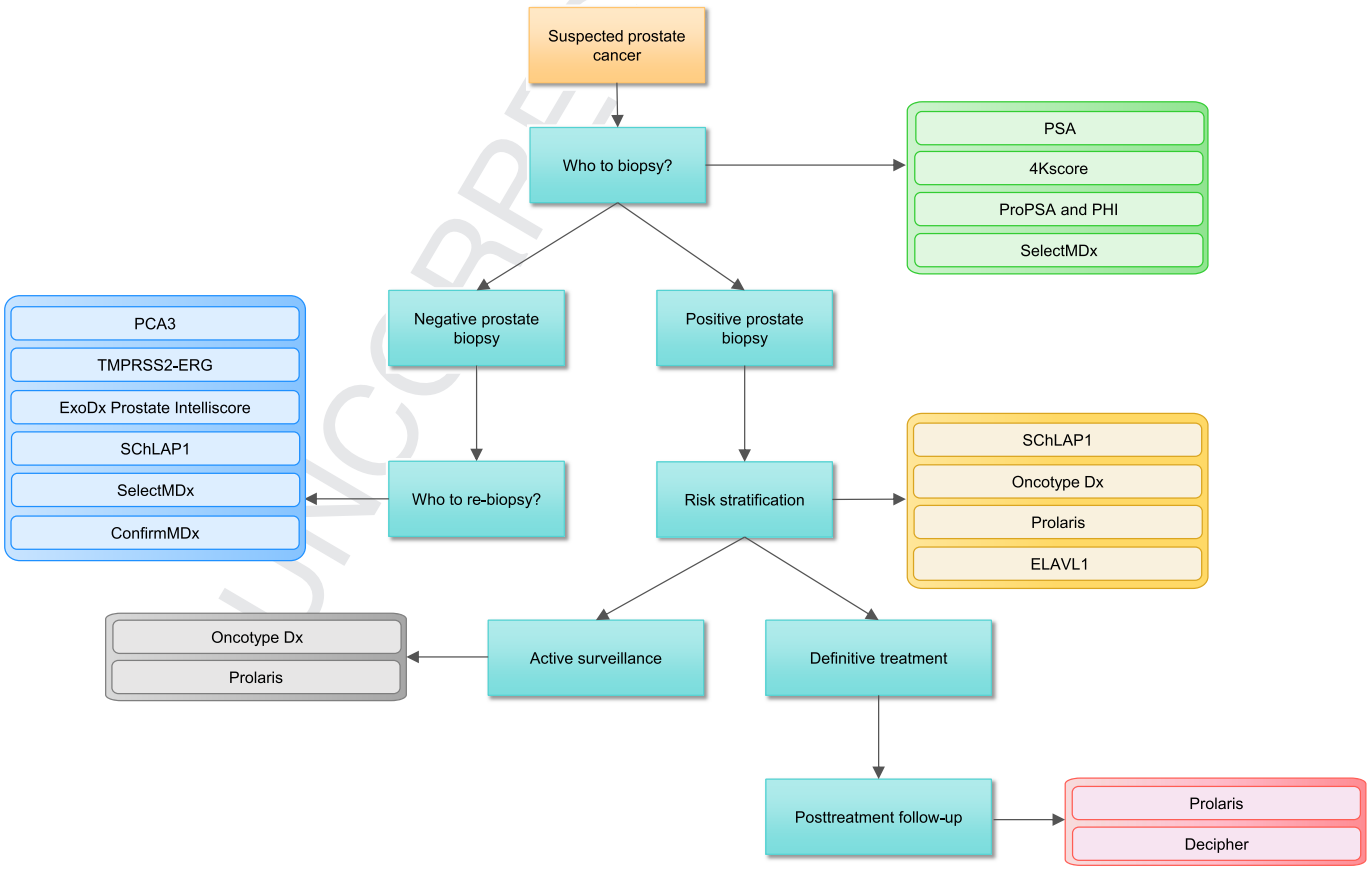

Fig. 1. Appropriate timing of the use of these biomarkers in the care of a patient with suspected or proven prostate cancer.

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