Considerations Regarding the Predictive Value of PSA Testing, as a Diagnostic Tool for Prostate Cancer in the Current Clinical Practice

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Short Communication

To date, more than 30 years after its discovery, serum Prostate Specific Antigen (PSA) testing, has become the most widely recommended and clinically used predictive factor for identifying men at increased risk of harbouring Prostatic Carcinoma (PCa) and is recognized as the best diagnostic tool available for early diagnosis of the disease [1-10]. However, although PSA remains the most commonly used serum biomarker for prostate cancer, in the past few years considerable ongoing controversy has emerged regarding its diagnostic performance, mainly based on evidence indicating that as currently used, this biomarker is insufficiently sensitive and specific as a diagnostic tool for accurately identifying prostate cancer [3,6,10-15]. The major and most challenging problem is the difficulty in differentiating prostate cancer from benign prostatic conditions given that, it is organ-specific rather than tumor-specific biomarker and as such, there is considerable overlap in PSA levels among men with prostate cancer and benign disease (benign prostatic hyperplasia, prostatic inflammation, certain activities such as riding a bike or having sex that can trigger a temporary increase in PSA). According to recent studies, it cannot be considered the ideal tumor marker (limited by poor specificity) for early detection of PCa as, neither an increased serum PSA is pathognomonic of prostate cancer nor, low levels necessarily confirm its absence so that, a single PSA value cannot accurately identify men with and without prostate cancer and no lower limit exists that can safely predict the absence of PCa [2,5,7,8,12,16-18]. Consequently, as there is no PSA threshold below which PCa can be ruled out with high accuracy, making thus the interpretation of an individual PSA value a distinct challenge, it is suggested that the alternative to the use of cut-points is to accept that PSA is most useful as a continuous variable (risk varies continuously) providing a spectrum of prostate cancer risk (there is a risk of PCa at all PSA values) and men with very low levels of PSA can harbour PCa [5,10,13,15,17-21].

Nowadays, increasing prostate cancer awareness motivates many patients, who after an abnormal PSA test result face the prospect of prostate biopsy, to seek the most objective information regarding their likely outcomes (probability of harboring PCa). Similarly, clinicians wish to know the odds of cancer diagnosis when prostate biopsy is recommended, in order to provide accurate estimates of those outcomes [22,23]. Furthermore, the management of patients with persistently elevated PSA levels after several negative prostate biopsies, represents a challenging daily problem for urologists, who face the dilemma to determine who needs to undergo further diagnostic procedures, depending on a greater number of biopsies with more extensive (up to saturation biopsy) protocols [24]. Especially for these men, accurate estimates of the likelihood (risk) of cancer diagnosis are important for patient counseling and informed decision-making and help physicians to make specific management recommendations. However, in current clinical practice, absolute PSA thresholds continue to be a central facet for recommending a prostate biopsy, policy resulting in a high percentage (60% - 80%) of men with elevated PSA showing negative results on initial or repeat prostate biopsy. Thus, applying a strategy of purely PSA-based indication, is associated with a high percentage of men undergoing unnecessary multiple repeated prostate biopsies [7,9,19,24-27]. Avoidance of unnecessary prostate needle biopsies is crucial because these invasive procedures may cause complications, potentially severe, such as discomfort, pain, infections, bleeding or urinary obstruction, especially in geriatric patients with co-morbidities as well as significant psychological (considerable anxiety) and emotional distress on the part of the patient and family, detrimental to patient well-being, not to mention the economic (financial) cost [6,7,9,24,25,27-29].

Therefore, additional, accurate and noninvasive clinical tools (tests) to increase the probability...
of detecting PCa at biopsy and reduce the number of unnecessary repeat biopsies, are needed [7,19,22,25,26,28,30]. These tools should be based on patient stratification techniques (risk-based strategy) as, currently, risk stratification is considered essential to identify those men who are at increased risk of having PCa and therefore are proper candidates for biopsy, as well as to reduce unnecessary biopsies and over-diagnoses help physicians in making specific management recommendations (evidence-based decision making) To this aim, researchers developed several different risk based strategies in the form of predictive statistical models, aiming to improve the diagnostic performance of total PSA values ranging between 2.5 to 10.0 ng/mL (extended diagnostic “gray zone”) [4,19,22,25,26,31]. All these tools include serum total PSA in combination with several additional PCa risk factors such as age, race, family history, number and histology of previous negative biopsies, prostate volume, various molecular forms of PSA (free PSA, % free/total PSA ratio) and PSA derivatives such as age-specific (age-adjusted) total PSA, PSA velocity (PSA kinetics) and total PSA Density (PSAD) [4,12,14,17,18,23,26,27,31]. These predictive “systems” (mathematical models) use statistical techniques and/or advanced medical informatics to analyze data from past clinical experience trying to make predictions about future outcomes and include: Kattan-type nomograms, risk groupings, Artificial Neural Networks (ANNs), probability tables (“Partin staging tables”), Classification And Regression Tree (CART) analyses, probability formulas, look-up and propensity scoring tables, risk-class stratification models and multivariate risk calculators [4,23,26,31,32]. Other technologies currently being utilized to improve the diagnosis of PCa in case of abnormal PSA values, include: 1) The PCA3 test, a molecular biology assay that measures the expression of PCA3 (prostate cancer gene 3) mRNA in urine samples. PCA3 is specific to the prostate and is significantly up-regulated in prostatic cancerous cells. The test quantitatively measures PCA3 mRNA as well as PSA mRNA and determines their ratio. High ratios have been shown to be indicative of prostate cancer [33] the Prostate Health Index (phi), a new simple, noninvasive blood test that results in a score, or “phi score.” This score gives more accurate information (3X more specific for prostate cancer than PSA) on what an elevated PSA level might mean and the probability of finding cancer on biopsy [34] the Confirm MDx test, an epigenetic assay to help distinguish patients who have a true-negative biopsy from those at risk for occult cancer. The test helps urologists rule out prostate cancer-free men from undergoing unnecessary repeat biopsies and, helps rule in high risk patients who may require repeat biopsies and potential treatment [34,35] the multiparametric (mp) prostate MRI, a rapidly evolving imaging technology—diagnostic test, that can detect significant prostate cancer as well as can, with high degree of safety, exclude indolent disease. By enabling targeted biopsies that exclusively detect significant cancer, mpMRI may provide the diagnostic accuracy that has been so sorely lacking [36].

With the intention of increasing our clinical ability in making individualized predictions (impact on biopsy decision making) regarding the outcome of prostate biopsy in men at risk for prostate cancer (abnormal serum PSA values) and in determining the need (weighing the magnitude of effort required) to perform repeat biopsies (avoiding unnecessary procedures), by stratifying individuals in those who need intensive follow-up and those who do not, in cases with negative initial prostate biopsies, we developed the PCP-SMART model. The Prostate Cancer Risk - Simulation Modelling, Assessing the Risk, Technique (PCP-SMART) is a novel, linear regression-based multivariable mathematical, simulation modelling method, designed to estimate the probability of detecting PCa (predict the outcome) on prostate needle biopsy. It was constructed by incorporating routinely available and easily determined clinical variables (patient age, total PSA, free/total PSA ratio, prostate volume, PSA Density [PSAD]), all established independent risk factors of prostatic carcinoma. Key derivative of this multivariable model is the PCRD (Prostate Cancer Risk Determinator), a novel mathematical index for estimating the risk of PCa, which has shown promising results, increasing the potential of better identifying men with PCa and equally important, those who may avoid unnecessary biopsy as it exhibited good diagnostic performance characteristics and high discriminative accuracy for predicting the outcome of prostate biopsy, correctly identifying 9 out of 10 patients with prostate cancer as well as, 9 in 10 of those without the disease. Also, it outperformed other, clinically established and commonly used variables in predicting prostate biopsy outcome in the initial and repeat settings as well as, it added significant information to combinations with PCa risk factors highly improving risk stratification of men prior to biopsy. By further employing multiple variable logistic regression model analysis, we formulated a mainly PCRD based mathematical equation, that allows calculation of a single value, enabling measurement of the probability of finding prostate cancer on biopsy, in an individual basis. The formulated logistic regression based mathematical equation, allowed calculation with 91% accuracy of a single probability value, enabling individualized measurement of the risk of finding prostate cancer on biopsy. In conclusion, our model was shown to be promising, simple and practical, exhibiting good diagnostic performance characteristics and high overall discriminative accuracy, providing significantly improved ability in predicting an individual’s risk of prostate cancer on biopsy. However, it lacks external validation while, meaningful interpretation has yet to be uniformly accepted within clinical practice. Thus, as generalizability of our results to community practice populations remains to be determined, larger and multi-institutional studies will be needed and external validation of the PCRD index is recommended prior to its routine clinical use. Regardless of these limitations, we anticipate that our model and its key derivatives will become a widely used tool providing highly accurate, reproducible and individualized disease related risk estimations to facilitate management decisions in clinical practice, possibly easily accessible via web application, that might aid urologists in selecting most suitable candidates for initial or repeat prostate biopsy [37].

References


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