

How accurate is our prediction of biopsy outcome? PCA3-based nomograms in personalized diagnosis of prostate cancer

Maciej Salagierski², Marek Sosnowski², Jack A. Schalken¹

¹Department of Urology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands

²Urology Department, Medical University of Łódź, Poland

KEY WORDS

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ABSTRACT

Purpose. The sensitivity and specificity of prostate-specific antigen (PSA) alone to select men for prostate biopsy remain suboptimal. This review aims at presenting a review of current prostate cancer (PCa) nomograms that incorporate Prostate Cancer Gene 3 (PCA3), which was designed to outperform PSA at predicting biopsy outcome.

Materials and methods. The PubMed database and current literature search was conducted for reports on PCA3-based nomograms and tools for examining the risk of a positive prostate biopsy in a man without a known PCa diagnosis.

Results and conclusions. The introduction of PCA3 into clinical practice has led to the development of a set of PCA3-based nomograms to predict biopsy outcome. Combining PCA3 results with established PCa risk factors has produced significant improvements over PSA alone in predicting the risk of a positive prostate biopsy for cancer.

INTRODUCTION

The identification of prostate-specific antigen (PSA) as a biomarker represented a major step in the early diagnosis and monitoring of prostate cancer (PCa) in the last century. PSA was officially approved by the Food and Drug Administration (FDA) for PCa diagnosis in 1994. Although the use of PSA results in a considerable stage migration, a correlation between PSA screening and decline in mortality remains less evident, with the benefit coming at a very high cost. The European Randomized Study of Prostate Cancer (ERSPC) revealed a statistically significant 20% relative reduction in the risk of PCa specific death. However, in order to prevent one death at nine years, 1,410 men underwent PCa screening and 48 additional men were required to undergo treatment for PCa [1]. The contemporary concept of significant versus insignificant PCa remains fundamental [2]. Among the early detected tumors in a population that underwent PSA screening, there are both those requiring rapid radical intervention due to aggressive phenotype as well as a substantial number of those that will not affect patient's survival *i.e.*, low risk cancers. Therefore, due to the imperfect diagnostic accuracy of PSA, a huge number of men are subjected to the discomfort of unnecessary biopsy and patients with indolent tumors are potentially over-treated. The higher PSA

levels that are used as a biopsy indicator increase specificity, but many cases of cancer are missed due to the significant fall in sensitivity. One approach to more accurately predict an individual's risk of a positive prostate biopsy is to combine PSA with other PCa risk factors within a predictive model - a nomogram. Many PCa nomograms were created comprising different variables *e.g.* age, PSA, digital rectal examination (DRE), prostate volume, or prior biopsy among others. Some of them, being available online, have been widely utilized for a number of roles in PCa, including predicting biochemical recurrence, seminal vesicle invasion, extracapsular extension, lymph node invasion, and Gleason grade.

In recent years the advances in genetics and biotechnology have led to the development of non-invasive tests for PCa detection *i.e.* Prostate Cancer Gene 3 (PCA3). PCA3 is a non-coding RNA and the most PCa-specific marker that is clinically available to date because PCA3 RNA expression is restricted to prostate, as it is not expressed in any other normal human tissue or in any other tumor [3, 4, 5]. PCA3 RNA is highly overexpressed in 95% of tumors compared to normal or benign hyperplastic prostate tissue. Hessels et al. reported a median 66-fold upregulation of PCA3 in PCa tissue compared with normal prostate tissue. In addition, an average 11-fold upregulation was noted in prostate tissue specimens containing less than 10% of PCa cells [6]. The observation that a small number of cancer cells in a background of normal cells can be detected by the PCR assay exposed the potential of assaying PCA3 in urine. The PCA3 test, which measures the expression of PCA3 gene in urine, has already been introduced into urological practice [7, 8, 9]. Currently, the PCA3 test appears to be the best diagnostic tool for predicting biopsy outcome [10, 11, 12]. Although the PCA3 test has some limitations (the questionable aspect of the PCA3 score remains its ability to assess PCa aggressiveness) it can be considered as a useful clinical tool for biopsy making decisions. The assay, in most cases, allows avoiding unnecessary biopsies and seems very helpful in screening patients with unspecific causes of PSA elevations. Given the high diagnostic accuracy, new nomograms incorporating the PCA3 test were developed. So far, according to our knowledge, two principal risk estimators that include PCA3 have been published and validated: Chun's nomogram [13] and The Prostate Cancer Prevention Trial (PCPT) risk calculator [14]. The aim of this review is to assess the accuracy of PCA3-based nomograms designed to predict the risk of a positive prostate biopsy for cancer and to determine their value versus the previously developed PCa nomograms and/or measuring PSA levels alone.

Prostate Cancer Gene 3 to predict prostate cancer risk – PCA3-based nomograms

Chun's nomogram

In order to increase the predictive accuracy of biopsy outcome and to identify men at risk of PCa, novel biopsy nomograms

that include PCA3 were created. Chun's nomogram combines the established risk factors of PCa (age, DRE, PSA, prior biopsy, and prostate volume) with PCA3. The authors, in a large multi-institutional study of 809 men referred for a first or repeat biopsy due to the risk of harboring PCa, observed that the incorporation of PCA3 into the base model described by Kattan and coworkers [15] while including PCa risk factors significantly improves the accuracy of the nomogram by two – 4.6%. Among the analyzed variables, PCA3 score had the highest predictive accuracy at predicting the presence of PCa at first and repeat biopsy regardless of the cut-off used. Yet, the PCA3 assay was the most efficient when a cut-off threshold of 17 was used. Notably, mean and median PCA3 scores were significantly higher in men with a positive biopsy versus those with a negative biopsy ($p < 0.001$). According to Chun and his colleagues, by increasing the predictive accuracy of prostatic biopsy, the PCA3 assay might be considered a statistically independent risk factor for PCa at biopsy. Furthermore, by better identifying men at risk for harboring PCa, the PCA3-based nomogram might be of benefit to patients and may help the clinician decide on the necessity of prostate biopsy and further prostatic evaluation.

PCPT calculator & PCA3

The objective of a risk calculator is to predict the probability of a positive biopsy for men with the suspicion of PCa. Ankerst et al. described the inclusion of the PCA3 score into the original PCPT risk calculator. The developed nomogram is already available on a website (<http://deb.uthscsa.edu/URORiskCalc/Pages/calcsPCA3.jsp>) and comprises six variables besides PCA3: age, race, family history, DRE, prior biopsy, and prostate volume. The predictive accuracy of the PCA3 score in predicting biopsy outcome was better than that of the total PSA level, PSA density, or percent of free PSA. The area under the curve (AUC) of the receiver operating characteristics (ROC) of the PCPT risk calculator incorporating PCA3 was statistically significantly higher (0.696) than that of the original PCPT risk calculator (0.653) and PSA (0.607), but not significantly different from that of PCA3 alone (0.665) (Table 1). At a specificity of 70%, the sensitivity of the PCPT risk calculator incorporating PCA3 was higher (60%) than that of the original PCPT risk calculator (56%), PCA3 (50%), and PSA (48%). Therefore, the incorporation of the PCA3 score into the classical PCPT risk calculator enhances the diagnostic accuracy of this risk calculator making it a useful tool for urologists and their patients in predicting prostate biopsy outcome and deciding whether an immediate biopsy is necessary.

Validation of PCA3-based nomograms

Perdona and coworkers in a prospective multicentre study directly compared the two nomograms incorporating PCA3: Chun's nomogram and the updated PCPT calculator in the detection of PCa within the grey zone of PSA (4-10 ng/ml) [16]. The study included 218 men referred for a first or repeat ≥ 12 core biopsy because of an elevated level of PSA and/or a suspicious DRE. The estimated risk of PCa was statistically significantly higher in men with a positive biopsy versus a negative biopsy when calculated using both the Chun's nomogram and the PCPT risk calculator. In line with previous findings, the median PCA3 score was significantly higher in men with a positive biopsy (PCA3 score = 72) versus those with a negative biopsy (PCA3 score = 22; $P < 0.001$) and an increasing PCA3 score correlated with an increasing probability of a positive biopsy ($P < 0.001$). Yet, the discriminative power of the PCPT calculator updated with PCA3 was superior to that of the Chun's nomogram - the AUC of the ROC for predicting the first biopsy outcome was

Table 1. Comparison of the areas under the receiver operating characteristic (ROC) curve for the updated Prostate Cancer Prevention Trial risk calculator (PCPT + PCA3), Chun's nomogram, PCPT, prostate cancer gene 3 (PCA3), and prostate specific antigen (PSA)

	Ankerst et al. [14]	Perdona et al. [16]	Auprich et al. [17]
Diagnostic test	AUC ROC	AUC ROC	AUC ROC
PCPT+PCA3	0.696	0.840	N/A
Chun's nomogram	N/A	0.706	0.730-0.750
PCPT	0.653	N/A	N/A
PCA3 score	0.665	0.873	N/A
PSA	0.607	0.660	N/A

similar for the updated PCPT risk calculator (0.840) and PCA3 score alone (0.873), but significantly higher when compared to Chun's nomogram (0.706) (Table 1). As for the repeat biopsy, the AUC and ROC were comparable for the PCPT risk calculator, Chun's nomogram and the PCA3 Score, but significantly better than serum PSA. Importantly, the authors noticed that by using a probability threshold of 25%, no high-grade cancers would be missed. Furthermore, at this threshold, the updated PCPT risk calculator would prevent 11% of biopsies while missing no cancers, and Chun's nomogram would prevent 22% of biopsies while missing 4.1% of low-intermediate risk cancers. Therefore, both PCA3-based estimators appear helpful in biopsy making decision especially in men with PSA < 10 ng/ml. Both, the updated PCPT calculator and Chun's nomogram appear useful tools in avoiding unnecessary biopsies without missing aggressive cancers.

Auprich et al. assessed the accuracy of the previously reported PCA3-based nomogram created by Chun and coworkers in a large European cohort of men [17]. The indication for using the assay was well defined, i.e. PSA range (2.5-10 ng/mL), suspicious DRE, atypical small acinar proliferation (ASAP), and/or high-grade prostatic intraepithelial neoplasia (HGPIN). The nomogram helped to identify PCa in 255 (41.1%) of 621 men. Both in the initial and repeat biopsy set, median PCA3 scores were significantly ($P < 0.005$) higher in men with a positive biopsy (PCA3 score = 47; 53) compared to those with a negative biopsy (PCA3 score = 17; 37), respectively. This study, by externally validating the data previously reported by Chun and his colleagues, found the PCA3-based nomogram to have a high accuracy in predicting biopsy outcome with AUC ranging from 0.73 to 0.75 for the various PCA3 score cut-offs used. Therefore, it appears that the developed nomogram could assist clinicians in biopsy making decisions in European men at risk of PCa.

Some authors were trying to evaluate whether by combining novel molecular biomarkers the specificity and sensitivity of PCa detection would increase. Rigau et al., upon analyzing the urinary sediments of 215 men for the presence of both PCA3 and prostate-specific G-protein coupled receptor (PSGR) products showed that by combining two assays the sensitivity of PCa detection markedly increases (from 69% for PCA3 alone to 77% for both tests) without compromising the specificity [18]. The incorporation of prostate-specific membrane antigen (PSMA) with PCA3 and PSGR led to a further improvement in the diagnostic performance [19].

CONCLUSIONS

The introduction of PCA3-based nomograms has led to improved diagnostic accuracy of PCa over PSA alone and an

improvement in the prediction of the risk of a positive prostate biopsy for cancer over previously created PCa nomograms.

Therefore, the incorporation of PCA3 in the previously established nomograms might help clinicians to confirm biopsy indications and to avoid unnecessary biopsies. However, to safely counsel European men at risk of PCa, it remains necessary to establish the optimal PCA3 cut-off value as well as to externally validate new nomograms using other external multi-institutional patient cohorts. New biomarkers are also needed. It appears that in the future, a multiplex test incorporating several biomarkers will be used to precisely determine biopsy indication.

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Correspondence

Maciej Salagierski
1st Department of Urology
113, Żeromskiego Street
90-549 Łódź, Poland
phone: +48 42 639 35 31
maciej.salagierski@umed.lodz.pl