ProsTAV, a novel blood-based test for biopsy decision management in significant prostate cancer

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Abstract

Background: Current pathways in early diagnosis of prostate cancer (PCa) can lead to unnecessary biopsy procedures. Here, we used telomere analysis to develop and evaluate ProsTAV®, a risk model for significant PCa (Gleason score >6), with the objective of improving the PCa diagnosis pathway.

Methods: This retrospective, multicentric study analyzed telomeres from patients with serum PSA 3–10 ng/mL. High-throughput quantitative fluorescence in-situ hybridization was used to evaluate telomere-associated variables (TAVs) in peripheral blood mononucleated cells. ProsTAV® was developed by multivariate logistics regression based on three clinical variables and six TAVs. The predictive capacity and accuracy of ProsTAV® were summarized by receiver operating characteristic (ROC) curves and its clinical benefit with decision curves analysis.

Results: Telomeres from 1043 patients were analyzed. The median age of the patients was 63 years, with a median PSA of 5.2 ng/mL and a percentage of significant PCa of 23.9%. A total of 874 patients were selected for model training and 169 patients for model validation. The area under the ROC curve of ProsTAV® was 0.71 (95% confidence interval [CI], 0.62–0.79), with a sensitivity of 0.90 (95% CI, 0.88–1.0) and specificity of 0.33 (95% CI, 0.24–0.40). The positive predictive value was 0.29 (95% CI, 0.21–0.37) and the negative predictive value was 0.91 (95% CI, 0.83–0.99). ProsTAV® would make it possible to avoid 33% of biopsies.

Conclusions: ProsTAV®, a predictive model based on telomere analysis through TAV, could be used to increase the prediction capacity of significant PCa in patients with PSA between 3 and 10 ng/mL.

KEYWORDS
biopsy, predictive model, prostate cancer, telomere
INTRODUCTION

Prostate cancer (PCA) is one of the most commonly diagnosed cancers worldwide, accounting for about 15% of the total. PCA is usually suspected based on the clinical findings of digital rectal examination (DRE) and/or prostate-specific antigen (PSA) measurements. Depending on the patient’s age, clinical variables, and medical history, a biopsy can be recommended. However, increased PSA levels appear in various conditions in addition to PCA, such as benign prostatic hyperplasia or prostatitis, resulting in unnecessary biopsies being conducted. Although a prostate biopsy is the key to diagnosis of significant PCAs, the procedure is often associated with complications, such as infection, bleeding, or both. Among all potential complications, hematuria, rectal bleeding, hematospermia, infection, pain, lower urinary tract symptoms, urinary retention, erectile dysfunction, the case of infection, is the most common reason for hospitalization after biopsy. Also, PSA has low specificity, which could result in missing cancer cases (underdiagnosis) or overdiagnosis and overtreatment, resulting in further costs and complications.

In the past decade, magnetic resonance imaging (MRI) has been increasingly used to provide visualization of potentially significant PCAs and to improve the selection of patients for biopsy. MRI is also used to facilitate targeting of lesions during biopsy and to provide information on tumor staging. The International Prostate MRI Working Group developed the prostate imaging reporting and data system to standardize prostate MRI examination performance and reporting, providing guidance on technical parameters for image acquisition and interpretation criteria for MRI data. However, general access to MRI can be limited by lack of resources and the availability of adequately trained healthcare personnel. Therefore, to improve the efficiency and accuracy of diagnosis, a large effort has been conducted in recent years to develop prediction models of PCA based on multiple biomarkers. However, to date, the diagnostic or prognostic factors that can be used during the screening and diagnosis of patients remain largely unclear as, in most cases, biomarkers lack the necessary validation to be implemented in routine clinical practice.

Telomere length measurements in peripheral blood leukocytes have been explored as potential biomarkers in a variety of cancers. In the case of PCAs, although some earlier studies showed limited or no association between telomere length (all measured in peripheral blood leukocytes) and PCA risk at diagnosis, others have found longer telomeres associated with higher PCA risk, worse metastasis-free survival, and higher overall PCA mortality. In contrast, one study found an association between shorter telomeres and worse prognosis.

Recently, a study showed that combined analysis of multiple telomere-associated variables (TAVs) could be used as a new risk-score biomarker with potential to improve prediction capacity during early PCA diagnosis. Telomere Analysis Technology (TAT®) is a novel platform that integrates extended high-throughput quantitative fluorescent in situ hybridization (HT Q-FISH) with extended image capture and processing capabilities. TAT® analysis software allows the evaluation of TAV in a cell population, generating a full picture of the telomeric status of a sample, or “TAV signature,” which can be used in oncology studies. Combined with machine learning, TAV can be used to build predictive models that could help in the diagnostic pathway of PCAs. During machine learning, computers are programmed to identify patterns from the data, which can be very advantageous when analyzing large datasets. Machine learning has emerged as a powerful tool to derive predictive models for PCA screening or prognosis.

In this study, we combined analysis of TAV with machine learning to implement a predictive machine learning model, with the ultimate goal of reducing the number of unnecessary biopsies during early diagnosis of PCA.

MATERIALS AND METHODS

This retrospective, multicentric, study was carried out at the Department of Urology of seven major Spanish and United States hospitals (Hospital Universitario Reina Sofía, Córdoba, Spain; Hospital Infanta Margarita de Cabra, Córdoba, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Unidad de Patología Prostática, LYX Instituto de Urología, Madrid, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; Urological Research Network, Miami, US; and Houston Methodist, US) between 2019 and 2021. This study was not interventional nor associated with any specific therapy or drug. Patient samples of peripheral blood leukocytes derive from two studies: ONCOCHECK and ProSTAV (Figure 1). ONCOCHECK was described previously. ProSTAV was an observational, multicentric, prospective study, but, due to the severe limitations of the COVID pandemic, its samples could not be analyzed at the time of collection. The study protocol was approved by the local institutional review board and health authorities of the Reina Sofía University Hospital. All subjects provided signed consent for participation in the study.

FIGURE 1 Process of patient selection from the global cohort of the ONCOCHECK (N = 520) and PROSTAV® (N = 606) studies to the cohort used in this study for risk model generation and validation (n = 1043).
2.1 Population

Eligible patients were >18 years of age, classified as PCA-risk patients with PSA between 3 and 10 ng/mL and/or suspicious DRE, and who underwent a prostatic needle biopsy. From the global cohort, a subset of patients was selected who had no prior use of alpha-5-reductase inhibitors and PSA levels from 3 to 10 ng/mL. Patients were excluded if they had any active liver, lung or kidney disease, or severe infection; mental health disability preventing the signing of the informed consent forms or ability to follow procedures; increased risks during blood draws; or other diagnosed tumors in the previous 5 years. All patients underwent a transrectal or transperineal prostate biopsy. Specimens were evaluated by uropathologists following the recommendations of the International Society of Urological Pathology (ISUP). Each of the participating hospitals followed their local MRI protocols and the radiological reports were based on PI-RADS scoring.

2.2 Telomere analysis and TAVs

The study of telomeres from the clinical samples was performed in the laboratories of Life Length, S.L. within the scope of CLIA (99DV2112462) and ISO 15189 quality standards. TAVs were determined by TAT as described in Supporting Information: Table S1. TAT® is based on HT Q-FISH,32 a technique in which telomeres are hybridized with a fluorescent Peptide Nucleic Acid probe that recognizes telomere repeats (sequence: Alexa488-OO-CCCTAACCCTAACTTA, Panagene). The images of the nuclei and telomeres are captured by a high-content screen system (Opera Phenix, Perkin Elmer) using maximum projection images from several Z-stack individual images, to get a more reliable image of the telomere. The intensities of fluorescence translated to base pairs through a standard regression curve which is generated using control cell lines with known TL. Data were analyzed using proprietary software to generate all TAVs validated through the same CLIA and ISO15189 laboratory standards.

2.3 Model generation and validation

A multivariable logistic regression model was created for the presence of significant PCa (ISUP1 > 1), using AutoDiscovery software (Butler Scientifics). Feature selection was based on exploratory data analyses and the observed linear dependence with cancer log-odds, confirmed using the Box–Tidwell test. Ten clinical variables (PSA, free PSA %, DRE, age, DRE volume, previous biopsy, waistline, family background, PSA range, and free PSA range) and 269 TAVs were considered, but only 4 clinical variables and 6 TAVs were finally selected and used. All variables were analyzed using AutoDiscovery software under the question “Significant cancer vs no significant cancer,” and the variables were selected with better significance and strength in these two categories. AutoDiscovery applies a multiple-testing statistical procedure. Variable results were automatically classified as high significance based on the Benjamini–Hochberg false-discovery rate method. The clinical data variables were age, PSA (ng/mL), free PSA (%), and the DRE results. The telomeric variables were three “short telomere” (percentage of telomeres of a sample with a length under a specific threshold) and three “short cell” (percentage of cells of a sample whose telomeres average a length under a specific threshold) variables. Importantly, this subset of variables used as regressors, showed a low degree of auto-correlation among themselves (absolute Pearson correlation coefficient r < 0.5).

Receiver operating characteristic (ROC) curves were plotted to evaluate the discriminatory power of the model.

Given the model and number of variables, it was estimated that a minimum of 860 patients in the training cohort would be required. Patients were assigned randomly in the training and testing cohorts.

3 RESULTS

A total of 1043 samples of patients were included in the study and their characteristics are shown in Table 1. The median (interquartile range [IQR]) age was 63 (58–70), the median (IQR) PSA was 5.2 (4.2–6.7) ng/mL, and 17.4% presented suspicious DRE. Significant PCa was diagnosed in 249 patients (23.9%).

Clinical and telomeric variables presented significant differences in patients with or without significant PCa (Figure 2). For example, telomeric analysis by TAV revealed that some “Short cell” variables, representing the percentage of cells in a sample with average telomere lengths under a certain threshold, could be different in these patient groups, reflecting distinct patterns of telomere length distributions.

For the ProsTAV® predictive model development, 874 patients were selected for model training and 169 patients for model validation. Table 2 shows the relationship between ProsTAV scores and Gleason score probabilities in the validation cohort. The area under the ROC curve (AUC) was 0.71 (95% CI, 0.62–0.79; Figure 3).

The sensitivity of the logistics regression model was 0.90 (95% CI, 0.88–1.0) and the specificity was 0.33 (95% CI, 0.24–0.40), with a positive predictive value (PPV) of 0.29 (95% CI, 0.21–0.37) and a negative predictive value (NPV) of 0.91 (95% CI, 0.83–0.99; Table 3).

Compared with ProsTAV, the AUC of PSA alone was 0.52 (95% CI, 0.41–0.62), and that of free PSA% = 0.62 (95% CI, 0.52–0.73; Figure 3).
The calibration and validity of the ProsTAV® model or assessing patients at high risk of PCa were evaluated using the calibration curve and clinical decision curve analyses, respectively (Figure 4). The calibration curve shows that the predicted value was in good agreement with the actual value, and there was no deviation from the ideal model (Figure 4A). According to the calibration curve, when the prediction probability was about 20% or >80%, the ProsTAV® model slightly overestimated the risk, while the risk was underestimated if it was 25%–80%.

Figure 4B shows the decision curve analysis results of the prediction model. The x-axis represents the threshold probability, and the y-axis represents the net benefit. According to decision curve analysis, when the threshold probability was between 5% and 37%, the prediction model can achieve better net benefits. Our result shows that using the ProsTAV® model for PCa prediction has more benefits than the two extreme conditions (the treat-all-patients scheme, pink curve) and the treat-none scheme (horizontal black line).

Overall, the accuracy of the ProsTAV® prediction model was high. Based on the decision curve, the prediction model showed an acceptable net benefit and validity. With this model, 33% of biopsies would be avoided without losing any cases of significant PCa.

ProsTAV scores were compared with PIRADS scores in those patients with MRI data (Figure 5). Biopsy revealed patients with or without significant PCa. In the training cohort of 199 subjects, the prosTAV score correctly classified 100% of patients (ProsTAV score ≥ 10), while MRI classified correctly 89.5% of the patients (PIRADS ≥ 3). In the 40 patients included in the validation cohort, 9 out of 10 subjects with significant PCa were detected correctly and would be recommended a biopsy. In contrast, of the 10 patients with significant PCa, 3 subjects presented PIRADS score of 2 and would not have been recommended a biopsy.

4 | DISCUSSION

In this study, we describe the development of ProsTAV®, a predictive model for the detection of PCa, which could be useful for biopsy decision management. ProsTAV® is regression model based on a combination of clinical variables and TAVs. The model reveals an AUC of 0.71 with a sensitivity of 0.90 and a specificity of 0.33. The PPV of 0.29 and NPV of 0.91 suggest that the model could be useful in the discrimination of significant PCa cases during the diagnosis of patients with elevated PSA. Our estimation is that by using ProsTAV®, 33% of the biopsies would have been avoided, without losing any cases of aggressive significant PCa (Gleason ≥ 8), in patients with PSA between 3 and 10 ng/mL and/or suspicious DRE.

The use of telomeres as biomarkers in oncology has received much attention in the past decade. In the case of PCa, the association of longer telomeres to increased risk, worse survival, or higher mortality seems well established. However, the major limitations of some of the previous studies using telomere measurements as biomarkers are the lack of accuracy and the inherent variability associated with the techniques used. Estimation of telomere length in peripheral blood leukocytes might have

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 1043)</th>
<th>Model training data set (N = 874)</th>
<th>Model validation data set (N = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>63 (58–70)</td>
<td>63 (57–70)</td>
<td>63 (56–70)</td>
</tr>
<tr>
<td>PSA, ng/mL, median (IQR)</td>
<td>5.2 (4.2–6.7)</td>
<td>5.2 (4.2–6.1)</td>
<td>5.2 (4.2–6.8)</td>
</tr>
<tr>
<td>Free PSA, ng/mL, median (IQR)</td>
<td>17 (13–23)</td>
<td>17 (13–23)</td>
<td>17 (13–23)</td>
</tr>
<tr>
<td>Suspicious DRE, N (%)</td>
<td>182 (17.4)</td>
<td>147 (16.8)</td>
<td>35 (20.7)</td>
</tr>
<tr>
<td>Significant PCa, N (%)</td>
<td>249 (23.9)</td>
<td>209 (23.9)</td>
<td>40 (23.6)</td>
</tr>
<tr>
<td>Gleason 7, N (%)</td>
<td>191 (76.7)</td>
<td>160 (76.6)</td>
<td>31 (77.5)</td>
</tr>
<tr>
<td>Gleason 8, N (%)</td>
<td>40 (16.1)</td>
<td>32 (16.3)</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>Gleason 9–10, N (%)</td>
<td>18 (7.2)</td>
<td>15 (7.2)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>mp MRI</td>
<td>N = 275</td>
<td>N = 235</td>
<td>N = 40</td>
</tr>
<tr>
<td>PIRADS, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>86 (31.3)</td>
<td>63 (32)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>3</td>
<td>59 (21.5)</td>
<td>36 (18.3)</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td>4</td>
<td>102 (37.1)</td>
<td>77 (39.1)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>5</td>
<td>28 (10.2)</td>
<td>21 (10.7)</td>
<td>4 (10.0)</td>
</tr>
</tbody>
</table>

Abbreviations: DRE, digital rectal examination; IQR, interquartile range; mp MRI, multiparametric magnetic resonance imaging; PCa, prostate cancer; PIRADS, prostate imaging reporting and data system; PSA, prostate-specific antigen.

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FIGURE 2 (See caption on next page)
TABLE 2  Relationship between the ProsTAV score and Gleason score and ISUP probabilities.

<table>
<thead>
<tr>
<th>ProsTAV score (%)</th>
<th>Gleason score probability</th>
<th>ISUP probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥7</td>
<td>&gt;8</td>
</tr>
<tr>
<td>0–10</td>
<td>8.7</td>
<td>0.0</td>
</tr>
<tr>
<td>10–40</td>
<td>26.3</td>
<td>4.2</td>
</tr>
<tr>
<td>40–70</td>
<td>33.3</td>
<td>12.5</td>
</tr>
<tr>
<td>&gt;70</td>
<td>75.0</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Note: All values are given as percentages.
Abbreviation: ISUP, International Society of Urological Pathology.

FIGURE 2  Differences in clinical (A–D) and telomeric (E–J) variables among patients with or without significant PCa. (A) Free PSA; (B) PSA; (C) age; (D) DRE; (E) variable 1 “Short cell”; (F) variable 2 “Short cell”; (G) variable 3 “Short cell”; (H) variable 1 “Short tel”; (I) variable 2 “Short tel”; and (J) variable 3 “Short tel.” Variables “Short cell” represent the percentage of telomeres of a sample with a telomere length under a certain threshold, while “Short tel” represents the percentage of cells of a sample whose telomeres average a length under a specific threshold. Differences are significant (p < 0.05) in all cases. Significance: *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3  ROC curve analysis shows the performance of the ProsTAV model in the validation cohort (N = 169).

<table>
<thead>
<tr>
<th>Biopsy-confirmed result</th>
<th>Significant PCa</th>
<th>No significant PCa</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>36</td>
<td>87</td>
<td>123</td>
</tr>
<tr>
<td>Low risk</td>
<td>4</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>129</td>
<td>169</td>
</tr>
</tbody>
</table>

Note: Sensitivity = 0.90 (95% CI, 0.88–1.0); Specificity = 0.33 (95% CI, 0.24–0.40); PPV = 0.29 (95% CI, 0.21–0.37); NPV = 0.91 (95% CI, 0.83–0.99).
Abbreviations: CI, confidence interval; NPV, negative predictive value; PCa, prostate cancer; PPV, positive predictive value; TAV, telomere-associated variable.

The combination of these technologies results in highly reproducible telomeric studies for cancer research. This study was conducted under ISO15189 accreditation, which is an absolute requirement for biomarker development and ensures the analytical performance of the methods.

Numerous biomarkers are under development and clinical testing for their potential use in PCa diagnosis. However, their direct comparison with ProsTAV® is uncertain due to differences in the cohorts evaluated. However, the predictive power of ProsTAV® is in the range of other proposed models, such as STHLM3, which is based on plasma protein biomarkers and genetic polymorphisms (AUC = 0.74), capillary electrophoresis/mass spectrometry of urinary biomarkers (AUC = 0.81), or other plasma protein biomarkers panels. In a previous study from our laboratory on the application of TAV as biomarkers for PCa diagnosis, we developed two predictive models with AUC > 0.76. Some methodological differences can explain the differences observed with the model described here. First, the earlier study was based on a smaller population (N = 401) derived from two centers (incidence of PCa, 19.2%), and used principal component analysis and random forest to generate the models. Here we used a much larger population (N = 1043) from seven centers in Spain and the United States (incidence of PCa, 23.9%), and used regression to generate the model, improving its accuracy.

Although for ProsTAV®, the specificity is relatively low, it should be noted that, as a biomarker in early diagnosis of PCa, the goal for the urologist is to avoid unnecessary biopsies without misclassifying some difficulties because to obtain reliable values, it is necessary to measure precisely and reproducibly a large number of telomeres in the cell population. For example, quantitative PCR is known to have variation coefficients of as much as 10%. Also, some techniques, such as Q-PCR, do not provide information on very short telomeres and comparisons between studies are often not possible. In this study, we used TAT®, a platform based on Q-FISH, which can obtain highly detailed and robust data from individual telomeres, individual cells, and cell populations. Additionally, the recent development of imaging technologies, such as the high-content screen system used in this study, has permitted much higher sensitivity and the analysis of images in different Z-stacks, allowing for a more robust telomere analysis.
significant cancer. However, neither ProsTAV® nor any of the alternatives can avoid all unnecessary biopsies. The results of this kind of biomarker are a balance between not having more than 10% of misclassified significant cancers and avoiding the maximum possible number of biopsies, identified as specificity. Additional efficacy studies are being conducted to evaluate ProsTAV® in routine clinical practice. However, the results of the current study confirm the utility of a telomere-based approach such as ProsTAV® in PCa prediction.

Multiparametric MRI has been established in recent years as a highly useful tool for the diagnosis of PCa. However, its use in early screening is not fully implemented due to lack of resources. Some studies show that combination of biomarkers and MRI can lead to higher detection of clinically significant PCas and reduced number of biopsy procedures. In our study, ProsTAV® analysis combined with MRI on a limited number of 40 patients of the same validation cohort showed that ProsTAV® could help discriminate those patients with high PSA and low PIRADS (scores 2 or 3) who otherwise would not be recommended a biopsy. Given the low number of patients in our study, the results of this preliminary analysis must be interpreted with caution. The possible benefits of combination of ProsTAV® with multiparametric MRI should be further evaluated in future studies with larger cohorts.

5 | CONCLUSIONS

The results of this study suggest that there is a potential utility for highly sensitive telomere analysis in oncology. ProsTAV® could be useful in the detection pathway of significant PCAs during the early...
diagnosis of patients with PSA between 3 and 10 ng/mL. Our preliminary analysis also suggests that ProsTAV® in combination with multiparametric MRI could be of benefit to patients with low PI-RAD scores to facilitate the decision to conduct a biopsy. A larger study is currently underway to test this possibility.

ACKNOWLEDGMENTS
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CONFLICT OF INTEREST STATEMENT
EGG has received funding for research from Ferrer, Opko, and Life Length. LF and NdP are current employees of Life Length. IC was an employee of Life Length from 2021 to 2022. All other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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