ORIGINAL ARTICLE

A comparison of 3 on-line nomograms with the detection of primary circulating prostate cells to predict prostate cancer at initial biopsy

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KEYWORDS  
Prostate cancer; Circulating prostate cells; Prostate biopsia; Nomograms

Abstract

Introduction: The use of nomograms which include the PSA may improve the predictive power of obtaining a prostate biopsy (PB) positive for cancer. We compare the use of three on-line nomograms with the detection of primary malignant circulating prostate cells (CPCs) to predict the results of an initial PB in men with suspicion of prostate cancer.

Methods and patients: Consecutive men with suspicion of prostate cancer underwent a 12 core TRUS prostate biopsy; age, total serum PSA, percent free PSA, family history, ethnic origin and prostate ultrasound results were used for risk assessment using the online nomograms.

Mononuclear cells were obtained by differential gel centrifugation from 8 ml of blood and CPCs were identified using double immunomarkation with anti-PSA and anti-P504S. A CPC was defined as a cell expressing PSA and P504S and defined as negative/positive. Biopsies were classified as cancer/no-cancer. Areas under the curve (AUC) for each parameter were calculated and compared and diagnostic yields were calculated.

Results: 1223 men aged >55 years participated, 467 (38.2%) had a biopsy positive for cancer of whom 114/467 (24.4%) complied with the criteria for active observation. Area under the curve analysis showed CPC detection to be superior (p < 0.001), avoiding 57% of potential biopsies while missing 4% of clinically significant prostate cancers.

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Introduction

Today, a new diagnosis of prostate cancer (PC) nearly always occurs following a patient referral for prostate biopsy (PB) as a result of an increased PSA. PSA is currently the only biomarker used for prostate cancer screening; of men aged 50–70, 10–20% will have an increased PSA, and of men with a PSA of 4–10 ng/ml, the probability of a positive initial biopsy is approximately 25%. This probability varies with age, race, family history, PSA level, PSA kinetics, prostate volume, and digital rectal examination (DRE). The ability to incorporate these parameters into risk prediction may decrease the rate of unnecessarily performed biopsies with a decrease in healthcare costs and side effects.

There is an increasing number of predictive tools based on statistical models, however, many have not been externally validated. The Montreal (Canada) predictive tool has been externally validated, it uses simple readily available markers, age, DRE, PSA, and percent free PSA to give a percent risk calculation in an individual patient. The European Randomized Study of Screening for Prostate Cancer derived Prostate Risk Indicator (SWOP-PRI) uses DRE, prostatic ultrasound findings, prostate volume, and total serum PSA, and the North American Prostate Cancer Prevention Trial derived Cancer Risk Calculator (PCPT-CRC) uses ethnic origin, age, serum PSA, DRE, and a family history of prostate cancer to calculate the risk of a positive biopsy. A direct comparison of the three nomograms in a European population of 667 patients the Montreal tool proved to be superior. However, due to the potential discrepancy in predicted outcomes with regard to the study population, genetic differences, differences in the incidence of benign hyperplasia or chronic prostatitis, a nomogram may not be applicable in all geographical zones.

The detection of malignant primary circulating prostate cells (CPC) could be one candidate for the early detection of PC. In men with prostate cancer, there is, at least, one sub-population of cancer cells that disseminate early, firstly to

Conclusions: The CPC detection was superior to the nomograms in predicting the presence of prostate cancer at initial biopsy; its high negative predictive value potentially reduces the number of biopsies while missing few significant cancers, being superior to the nomograms in this aspect. Being a positive/negative test the detection of CPCs avoids defining a cutoff value which may differ between populations.

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PALABRAS CLAVE
Cáncer prostático; Células prostáticas circulantes; Biopsia prostática; Nomogramas

Comparación de 3 nomogramas en línea con la detección de las células primarias circulantes de la próstata para predecir el cáncer de próstata en la biopsia inicial

Resumen

Introducción: Los nomogramas que incluyen el PSA para predecir los resultados de una biopsia prostática son de utilidad en la clínica diaria. En este estudio de hombres con sospecha de cáncer prostático comparamos el uso de 3 nomogramas online con la detección de células prostáticas circulantes (CPC) para predecir los resultados de la biopsia prostática.

Métodos y pacientes: Una serie de varones con sospecha de cáncer fueron sometidos a una biopsia prostática de 12 muestras. Se registraron la edad, PSA total, porcentaje de PSA libre, historia familiar de cáncer prostático, origen étnico y resultados de una ecografía transrectal. Se calculó el riesgo de cáncer prostático utilizando 3 nomogramas.

Se separaron las células mononucleares por centrifugación diferencial de 8 mL de sangre venosa e identificaron las CPC utilizando inmunocitoquímica con anti-APE y anti-P504S. Una CPC fue definida como una célula expresaendo APE y P504S y el test como positivo/negativo. La biopsia fue clasificada como cáncer/no-cáncer. Por cada parámetro el área bajo la curva fue calculada y los rendimientos diagnósticos comparados.

Resultados: Un total de 1.223 hombres > 55 años participaron, 467 (38,2%) tuvieron una biopsia positiva para cáncer, de los cuales 114/467 (24,4%) tuvieron un cáncer no-significativo. El análisis del área bajo la curva mostró que la detección de las CPC fue superior (p < 0,001), evitando el 57% de las biopsias prostáticas, mientras que no detectó el 4% de los cánceres significativos.

Conclusiones: La detección de CPC fue superior a los otros modelos para predecir los resultados de la biopsia prostática inicial, reduce potencialmente el número de biopsias innecesarias y no detecta solo una pequeña fracción de los pacientes con cáncer clínicamente significativos. Fue superior a los otros modelos en este aspecto, cuando considerados negativos los nomogramas no detectaron un número significativo de cánceres agresivos. De ser un test positivo/negativo, la detección de CPC evita la definición de un punto de corte, lo cual podría variar entre poblaciones diferentes.

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the neurovascular structures and then into the circulation. The number of these cells is very small; however, these CPCs can be detected using immunochemistry with a combination of anti-P504S (methyl-acyl-CoA racemase) and anti-PSA monoclonal antibodies. The use of the biomarker P504S, although it is not prostate specific, has facilitated the differentiation between normal, dysplastic, and malignant tissues in prostate biopsy samples. Normal or benign cells do not express P504S, whereas cells arising from prostatic intraepithelial neoplasia (PIN) or cancer are positive. The use of primary CPC detection has been reported to have a high negative predictive value, decrease the number of PB, and it does not detect low-grade small-volume tumors.\(^9,^{10}\)

We compared the performance of these three externally validated nomograms with the presence of primary CPCs to predict the outcome of transrectal ultrasound biopsies in a prospective cohort of men with suspicion of prostate cancer based on an elevated serum PSA and/or abnormal DRE.

**Methods and patients**

We studied all men undergoing an initial transrectal ultrasound-guided (TRUS) prostate biopsy at the Hospital Carabineros of Chile between January 2009 and May 2015. Indications for a TRUS biopsy were an elevated total PSA, defined as >4.0 ng/mL, or a digital rectal examination (DRE) abnormal or suspicious of cancer, defined as the presence of a nodule, areas of indurations, or asymmetry in the size of the lateral lobes.\(^11\)

All the predictive parameters used in the three nomograms were collected and a database was created. The variables included the following details: age, serum PSA (ng/mL) taken before the DRE and pre-biopsy using the Siemens Advia CentaurXR\(^7\) assay, serum percent free PSA, taken at the same time as the serum PSA using the Siemens Advia CentaurXR\(^8\) assay. The results of the DRE were classified as normal or abnormal and a family history of prostate cancer was defined as positive or negative. The ethnic origin was defined as ‘other’ because the current Chilean genetic pool is a result of the mix of its original Amerindian inhabitants and European settlers that colonized the country.\(^12,^{13}\) Although the Amerindian populations were genetically homogeneous, the proportion of European or African genetic contribution varies within the country.\(^14\) For this reason, the ethnic origin was classified as other in the nomogram. The prostatic volume was determined using transrectal ultrasonography with an endocavity convex probe with a 6.5 MHz transducer (Hitachi, model EVP-V33). Measures of the triaxial distances of the prostate were taken in its larger diameter and the total volume was calculated by the following formula: volume = 0.52 × transverse diameter × anteroposterior diameter × longitudinal diameter. The same prostatic ultrasound was classified as normal or abnormal, which was defined as the presence of hypoechoegenic lesions and/or capsular irregularities.

All the prostate biopsies were standard 12 core, performed transrectally under ultrasound guidance by an experienced urologist using a 18 gauge Tru-Cut needle. Each core was sampled separately, stored in formaldehyde, and sent for pathological assessment. A biopsy was defined as positive only when adenocarcinoma was observed in the final histological evaluation. In positive samples, the Gleason score, number of positive cores, and maximum percent infiltrated was recorded. The pathological analysis and reports were performed by a single dedicated uropathologist.

**Risk prediction using nomograms**

The prediction of a biopsy positive for cancer was performed using the following online based risk calculators: for the SWOP-PRI [www.prostatecancerriskcalculator.com](http://www.prostatecancerriskcalculator.com); PCTC-CRC [www.deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp](http://www.deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp) and the Montreal model [www.nomogram.org/Prostate/pros_calc.php](http://www.nomogram.org/Prostate/pros_calc.php).

**Detection of primary circulating prostate cells**

Immediately before the biopsy, an 8 mL venous blood sample was taken and collected in a tube containing EDTA (Beckinson-Vacutainer). Samples were maintained at 4°C and processed within 48 h. The prostate biopsy and CPC detection were independently evaluated with the evaluators being blinded to the clinical details and results of the biopsy or CPC test.

**Collection of CPCs**

Mononuclear cells were obtained by differential centrifugation using Histopaque 1.077 (Sigma-Aldrich), washed, and resuspended in an 100 μL aliquot of autologous plasma. 25 μL aliquots were used to make slides (silanized, DAKO, USA), were dried in air for 24 h and fixed in a solution of 70% ethanol, 5% formaldehyde, and 25% phosphate-buffered saline (PBS) pH 7.4 for 5 min and finally washed three times in PBS pH 7.4.

**Immunocytochemistry**

CPCs were detected using a monoclonal antibody directed against PSA, clone 28A4 (Novocastro Laboratory, UK), and identified using an alkaline phosphatase-anti alkaline phosphatase based system (LSAB2, DAKO, USA), with new fuchsian as the chromogen. Positive samples underwent a second process with anti-P504S clone 13H4 (DAKO, USA) and were identified with a peroxidase based system (LSAB2, DAKO, USA) with DAB (3.3 diaminobenzidine tetrahydrochloride) as the chromogen. A CPC was defined according to the criteria of ISHAGE (International Society of Hemotherapy and Genetic Engineering)\(^14\) and the expression of P504S according to the Consensus of the American Association of Pathologists.\(^15\) A CPC was defined as a cell that expressed PSA and P504S.

Slides were analyzed manually, stained cells were photographed using a digital camera, and from the digital images it was determined if CPCs were present or absent and the total number of CPCs detected by one trained observer. A test was considered positive when at least 1 cell/8 mL of blood was detected.
**A comparison of 3 on-line nomograms to predict prostate cancer**

### Table 1  Patient characteristics according to biopsy results.

<table>
<thead>
<tr>
<th></th>
<th>No cancer, N = 756</th>
<th>Cancer, N = 467</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean ± SD (years)</td>
<td>64.2 ± 9.1</td>
<td>65.5 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family History of Prostate cancer</td>
<td>11/756</td>
<td>7/467</td>
<td>0.86</td>
</tr>
<tr>
<td>PSA (ng/ml) median (IQR)</td>
<td>5.51 (4.40–7.51)</td>
<td>5.90 (4.80–9.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% free PSA median (IQR)</td>
<td>18 (14–24)</td>
<td>11 (9–14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DRE (+)</td>
<td>53/756 (7.0%)</td>
<td>123/467 (26.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TRUS (+)</td>
<td>121/756 (16.0%)</td>
<td>166/467 (35.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate volume (ml) mean ± SD</td>
<td>51.8 ± 21.2</td>
<td>49.7 ± 17.9</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>CPC (+)</td>
<td>143/756 (18.9%)</td>
<td>407/467 (87.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CPC (+), circulating prostate cell positive; OR, odds ratio; RR, relative risk; DRE, digital rectal examination; TRUS, transrectal ultrasound; IQR, interquartile range.

### Analysis of the results

The discrimination of the diagnostic tests was defined using the normal parameters: sensitivity, specificity, true positive (TP), false positive (FP), false negative (FN), and true negative (TN). The predictive values, positive (PPV) as well as negative (NPV), were evaluated, and the areas under the curve calculated and compared. The potential number of biopsies avoided for each method was calculated and the Gleason scores of missed cancers recorded.

In addition, using the criteria of Epstein (1994), the number of cancers needing active treatment and active observation were registered for each test, whether the test was positive or negative, in order to determine the clinical significance of each test used.

### Statistical analysis

Descriptive statistics were used for demographic variables, expressed as mean and standard deviation in the case of continuous variables with a normal distribution. In case of an asymmetrical distribution, the median and interquartile range (IQR) values were used. Non-contiguous variables were presented as frequencies. The Shapiro–Wilk test was used to determine a normal distribution. Student’s t-test was used to compare continuous variables with a normal distribution, the Mann–Whitney test for ordinate and continuous variables with a non-normal distribution, and the Chi-square test for the differences in frequency. The diagnostic yield for the test detecting CPCs and nomograms were analyzed using standard parameters. For this purpose, patients were classified as having or not having prostate cancer. Statistical significance was defined as a p value lower than 0.05; all tests were two-sided. Area under the curve analysis was performed using the online program Vassarcalc. The kappa index was calculated to analyze the degree of agreement between CPC detection and the three nonograms.

### Results

1369 men entered the study, of these men 146 were younger than 55 and thus excluded as the PCPT-CRC could not be used. Thus 1223 men were considered for the final analysis. Table 1 shows the database variables used for the risk calculators and the presence of CPCs according to the biopsy results. Although statistically significant, we considered that the differences in age and total serum PSA between the two groups were not clinically significant. Men with prostate cancer had a significantly lower median free PSA, a significantly higher frequency of abnormal DRE, abnormal prostate ultrasound, and higher frequency of CPC detection. There were no differences with regard to prostate volume or family history of prostate cancer between groups.

467/1223 (38.2%) men had a biopsy positive for prostate cancer, of which 114/467 (24.4%) complied with the Epstein criteria for active observation. 296/467 (63.2%) were Gleason 6 or less tumors, 145/467 (31.0%) were Gleason 7 tumors, and 27/267 (5.8%) were Gleason 8 or higher.

### Discriminative power of detecting prostate cancer using the three nomograms and CPC detection

The use of total serum PSA gave an area under the curve of 0.559 (95% CI 0.523–0.595), free percent PSA 0.765 (95% CI 0.725–0.801), the PCPTRC nomogram of 0.706 (95% CI 0.662–0.728), the SWOP nonogram 0.686 (95% CI 0.645–0.727), the Montreal nonogram 0.756 (95% CI 0.710–0.802), and that of CPCs 0.844 (95% CI 0.805–0.889). Comparing the areas under the curve of the different parameters; total serum PSA was inferior to all the other predictive models (p < 0.001); there was no significant difference between the PCPTRC nomogram and the SWOP nonogram (p = 0.365); there was no significant difference between the Montreal nonogram and free percent PSA (p = 0.231), and both were superior to the PCPTRC (p = 0.006 and p = 0.007 respectively) and the SWOP nonogram (p = 0.001 and p = 0.002) respectively. The CPC detection method was superior to all the other predictive models (p < 0.0001) (Fig. 1).

### Predictive values

The predictive values of a positive prostate biopsy for a range of nomogram scores, a range of CPCs/ml detected,
and a range of free percent PSA are shown in Table 2. The predictive values for total serum PSA were not calculated as this was the initial screening test, the other tests being sequential to a raised total serum PSA. The kappa index was 0.0071 (95% CI 0.002–0.016) (p = 0.27), which indicates that there was no agreement between the differing tests for the prediction of prostate cancer at first biopsy. This is reflected in the significantly differing predictive values between the differing methods, CPC detection versus nonograms.

Table 2a  Sensitivity, specificity and predictive values for the Montreal model at different predictive values.

<table>
<thead>
<tr>
<th>AUC = 0.765</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>98.9</td>
<td>4.8</td>
<td>39.1</td>
<td>87.8</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>92.9</td>
<td>25.7</td>
<td>43.6</td>
<td>85.5</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>88.7</td>
<td>50.8</td>
<td>52.7</td>
<td>87.9</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>71.9</td>
<td>76.9</td>
<td>65.8</td>
<td>81.6</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>45.2</td>
<td>88.1</td>
<td>70.1</td>
<td>72.2</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>28.3</td>
<td>92.7</td>
<td>70.6</td>
<td>67.7</td>
</tr>
</tbody>
</table>

Table 2b  Sensitivity, specificity and predictive values for the SWOP model at different predictive values.

<table>
<thead>
<tr>
<th>AUC = 0.686</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>97.9</td>
<td>5.3</td>
<td>39.0</td>
<td>80.0</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>71.9</td>
<td>42.5</td>
<td>43.6</td>
<td>71.0</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>42.2</td>
<td>73.1</td>
<td>49.3</td>
<td>67.2</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>24.8</td>
<td>89.9</td>
<td>60.1</td>
<td>65.9</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>13.1</td>
<td>96.4</td>
<td>69.3</td>
<td>64.2</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>4.7</td>
<td>98.7</td>
<td>68.8</td>
<td>62.6</td>
</tr>
</tbody>
</table>

Table 2c  Sensitivity, specificity and predictive values for the PCPTRC model at different predictive values.

<table>
<thead>
<tr>
<th>AUC = 0.706</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20%</td>
<td>95.5</td>
<td>7.4</td>
<td>39.7</td>
<td>88.9</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>56.2</td>
<td>64.6</td>
<td>49.5</td>
<td>70.4</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>22.1</td>
<td>91.9</td>
<td>62.8</td>
<td>65.6</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>9.2</td>
<td>97.8</td>
<td>71.7</td>
<td>63.5</td>
</tr>
</tbody>
</table>

Table 2d  Sensitivity, specificity and predictive values for the percent free PSA model at different predictive values.

<table>
<thead>
<tr>
<th>AUC = 0.765</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>37.1</td>
<td>86.1</td>
<td>72.7</td>
<td>57.8</td>
</tr>
<tr>
<td>&lt;15%</td>
<td>76.2</td>
<td>72.8</td>
<td>63.3</td>
<td>83.2</td>
</tr>
<tr>
<td>&lt;20%</td>
<td>70.2</td>
<td>42.6</td>
<td>43.0</td>
<td>69.9</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>96.2</td>
<td>22.9</td>
<td>43.5</td>
<td>90.6</td>
</tr>
</tbody>
</table>

Table 2e  Sensitivity, specificity and predictive values for the CPC detection model at different predictive values.

<table>
<thead>
<tr>
<th>AUC = 0.844</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>87.2</td>
<td>84.1</td>
<td>77.2</td>
<td>91.4</td>
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<tr>
<td>&gt;3</td>
<td>65.1</td>
<td>95.6</td>
<td>90.2</td>
<td>81.6</td>
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<tr>
<td>&gt;5</td>
<td>45.6</td>
<td>96.1</td>
<td>88.0</td>
<td>74.1</td>
</tr>
<tr>
<td>&gt;7</td>
<td>39.2</td>
<td>96.8</td>
<td>88.4</td>
<td>72.0</td>
</tr>
<tr>
<td>&gt;8</td>
<td>24.8</td>
<td>98.8</td>
<td>92.8</td>
<td>68.0</td>
</tr>
</tbody>
</table>

Detection of clinically significant prostate cancer

Of the 467 cancers, 114 complied with the criteria of Epstein for active surveillance, 353 being considered clinically significant and needing active treatment. For the analysis, the following cut-off values were used; for the PCPTRC nonogram a cut-off value of >20% probability was used to recommend a biopsy, for the SWOP nonogram, >20% probability was used to recommend a biopsy, and if the risk of high grade was >3% in the 12.5–20% risk group, biopsy was also recommended, for the Montreal nomogram >20% was used to recommend a biopsy, and for CPC detection, at least 1 cell detected was used to recommend a biopsy. The number of biopsies that theoretically could be avoided and the number of significant cancers missed are shown in Table 3 for each predictive model.

a) in men with a test considered positive, that is, indicating the need for a prostate biopsy, the diagnostic yield ranged from a low of 38% for the Montreal model to a high of 77% for CPC detection. Of those cancers detected in these men, the percentage of cancers needing treatment compared with those requiring observation was similar, with between 76 and 86% of cancers detected requiring treatment.
Thus, in men with a test considered negative, that is, a biopsy is not required, there were differences, approximately 30% of men with a free percent PSA or SWOP model considered negative had a cancer detected on biopsy. More importantly, 70% of these cancers would be considered to need active treatment. Of men considered negative for the Montreal, PCPTRC and CPC tests, 11% of these men would have cancer detected. In both the Montreal and PCPTRC, more than 50% of these cancers would be clinically significant, differing from the CTC test, where only 20% were clinically significant. Table 4 summarizes the number of biopsies avoided and significant cancer missed or detected.

### Table 4  Number of biopsies potentially avoided and significant cancers missed or detected according to predictive model.

<table>
<thead>
<tr>
<th>Biopsies avoided, N=1223</th>
<th>Significant cancer missed</th>
<th>Significant cancer detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>% free PSA</td>
<td>985 (81%)</td>
<td>205 (58%)</td>
</tr>
<tr>
<td>SWOP</td>
<td>452 (37%)</td>
<td>91 (26%)</td>
</tr>
<tr>
<td>PCPTRC</td>
<td>63 (5%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Montreal</td>
<td>217 (18%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>CPC</td>
<td>696 (57%)</td>
<td>12 (4%)</td>
</tr>
</tbody>
</table>

#### Discussion

An ideal prostate cancer screening test or using a nomogram incorporating various predictive markers is not to detect all prostate cancers, but to detect clinically significant cancers which have the potential to cause harm to the patient. At present, the only widely used screening test is serum total PSA, which in a range 4–10 ng/ml is associated with a positive biopsy rate for all cancers of approximately 30%, of which it has been estimated that 23–42% of screen detected prostate cancers are overtreated. Men with clinically insignificant prostate cancers that were never meant to have symptoms or to affect their life expectancy may not benefit from knowing that they have the ‘disease’. The detection of clinically insignificant prostate cancer could be considered an adverse effect of the prostate biopsy. As such, there is considerable anxiety and distress found in men undergoing active surveillance. In addition, a prostate biopsy is not without side effects, approximately 1% require hospitalization for sepsis or hemorrhage. Thus, the use of new biomarkers or nomograms may reduce this number of ‘unnecessary prostate biopsies’; that is to say, they do not detect indolent or cancer that does not require treatment. There were two recently published studies. That by Borque-Fernando et al. compared the ability of the 4Kscore test with the PCPTRC and ERSPC-RC4 (European Research Screening Prostate Cancer Risk Calculator 4); the three models presented AUCs above 0.7 with no significant differences between the three nomograms. The second compared the prostate health index with the prostate biopsy results, with an area under the curve of 0.749 and proved to be superior to the percent free PSA and PSA density in predicting all prostate cancers detected at biopsy. However,
when comparing the detection of only aggressive tumors, there was no significant difference between the prostate health index and the two PSA based parameters. The AUC for percent free PSA and the PCPTRC reported in these two studies are similar to that obtained in our cohort of patients.

In our study cohort, total PSA alone had an inferior predictive accuracy, an AUC of 0.559, which is similar to that reported in other studies. In order of ascending predictive power were the SWOP model, PCPTRC model, Montreal model, free percent PSA, and finally the CPC model. However, the predictive power to detect all cancers, may not translate into biopsies avoided and clinically important cancers missed. This will depend on the cut-off values used to define a positive or negative test, which is dependent on the population at risk.

In our study, using the recommended cut-off values, the clinical utility of the various models differed significantly from the predictive power of the individual model. The use of free percent PSA with the cut-off of <10% would avoid 81% of possible biopsies but would miss 58% of the significant cancers. Thus, although it has a high predictive value, in the clinical reality, it does not differentiate between who to biopsy or not to biopsy. Both the PCPTRC and the Montreal models missed few clinically significant cancers, 4% and 5% respectively. However, few biopsies were avoided, 5% and 18%, respectively. The SWOP model was intermediate avoiding 37% of biopsies but at a cost of missing 26% of significant cancers. The best fit to the clinical reality in our study population was the primary CPC detection, where 57% of biopsies could be avoided and missing only 4% of significant cancers.

The use of CPCs depends on the methodology used, using the EpCAM (Epithelial Cell Adhesion Molecule) based CellSearch™ system, the frequency of patients positive for CPC is less than 25% in men with localized cancer, and it was similar in controls and men with cancer. However, using an anti-Ber-4 and telomerase based method, CPCs were detected in 80% of men with localized cancer, similar to the method using anti-PSA, anti-P504S used in our study. One explanation of the failure of EpCAM based systems to detect CPCs is the failure to include tumor cells that have reduced or absent EpCAM expression secondary to the epithelial mesenchymal transition, and fails to detect between benign and malignant circulating tumor cells.

Our results suggest that the use of primary CPCs when used as a sequential test in men with suspicion of prostate cancer is superior to the other models, not only in its predictive power of a positive biopsy but it does not detect low-grade small-volume tumors. Its role is not in detecting a significant cancer; it had a similar performance to the other models, but in predicting when there is not a clinically significant cancer. In other words, in clinical practice, CPC negative men may not require biopsy but could be followed up.

We admit that our study has various limitations; firstly, it is a single-center study, where the immunocytologist has the experience and training to perform the tests and has been internally validated as to pre-analytical, analytical, and post- analytical variables as described in the methods section. That this study is focussed on patients with suspicion of prostate cancer (abnormal PSA and/or DRE) and may not reflect the general prostate cancer screening population. However, we consider that the study population represents ‘real life’ practice where the patient has been referred from primary care services for consideration of a prostate biopsy. Currently, a definitive acceptable threshold for the differing models in recommending a prostate biopsy does not exist. The CPC test avoids this problem by being a positive/negative test and, thus, it is easier to use.

Conclusions

The use of predictive models to determine the need for prostate biopsy is limited by the effects of differing populations, with differing incidences of benign disease and the lack of clear cut-off values. The use of CPC detection using an adequate biomarker could be used to exclude men from undergoing a prostate biopsy, decreasing adverse effects, and decreasing costs. We believe it warrants further multicenter studies to validate its use as a sequential test in men with suspicion of prostate cancer.

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Conflict of interest

Dr. Nigel P Murray receives consultancy fees from ViatarCTC-solutions, Boston, USA. Viatar did not participate in any form in the study. The other authors do not report conflicts of interest.

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