Outcomes of expanded use of PCA3 testing in a Spanish population with clinical suspicion of prostate cancer


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Received 5 April 2011; accepted 7 April 2011
Available online 16 February 2012

KEYWORDS
PCA3 score; Prediction; Prostate cancer; PSA; Prostatic biopsy

Abstract
Objectives: DD3PCA3 (PCA3) gene expression is prostate cancer-specific. Routine use of this biomarker has resulted in a 35–67% reduction in the number of required biopsies. The aim of this study is to evaluate our outcomes in its routine use and to establish in which group of patients this is the most efficient, depending on the number of previous PCA3 biopsies.

Material and methods: A total of 474 consecutive patients who had previously undergone a biopsy (group A, n = 337) or not (group B, n = 134) for whom a PCA3 was requested were analyzed. We subdivided group A into A1 (a previous biopsy, n = 182) and A2 (<1 previous biopsy, n = 155). The recommendation of whether to perform a biopsy or not was made independently by each of the 11 clinicians and guided by prostatic specific antigen (PSA) levels and digital rectal examination.

Results: Median age was 65 years (range 38–84). PCA3 score had an informative ratio of 99.6%, with a median of 29 (range 1–3245). The percentage of biopsy sparing was 49% of the cases. ROC analysis demonstrated an AUC for PSA and PCA3 of 0.532 (p = 0.417) and 0.672 (p < 0.0001), respectively. Sensitivities of PSA ≥4 and PCA3 ≥35 were 87% vs. 85%, with specificities of 12% vs. 33%, PPV 34% vs. 39% and NPV 63% vs. 81%, respectively. The PCA3 score showed direct correlation with the percentage of positive biopsies (p < 0.0001).

Conclusions: Routine use of PCA3, due to its high NPV, results in a significant reduction in the number of biopsies. PCA3 appears to be more efficient in biopsy-naive patients. Among patients already biopsied, the results are superior in those biopsied only once.

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Introduction

The universalization as 'tumor marker' of the prostate specific antigen (PSA) is a fact reflected in the rates of contamination of 20 and 60% in studies of ERSPC and PLCO prostate cancer (PCa) screening, respectively,1,2 as a result of opportunistic use of this biomarker. The reality in our country is that the PSA is demanded by the patient who comes to the family doctor for a health check. Although there is not yet scientific evidence at the highest level (Ia) that the early diagnosis of PCa is capable of decreasing cancer-specific mortality, the emergence of PSA has migrated the stages with a significant decrease in locally advanced and metastatic tumors compared to patients received in the pre-PSA era. In addition, the partial results with longer follow-up (14 years) of the ERSPC study report a number of 293 patients who need to undergo screening (95% CI 177–799) and 12 PCa diagnosed to prevent death from PCa, data comparable to breast cancer screening.3

Therefore, we are probably facing the regularization of PCa screening programs, concealed or organized by the Health System, which can face the consistent problem of overdiagnosis of indolent PCa.4

In addition, data such as the fact that 15% of patients with PSA <4 ng/ml and normal rectal examination diagnosed with PCa in the control arm of the Prostate Cancer Prevention Trial,5 or 74% of negative biopsies of the ERSPC with PSA between 4 and 10 ng/ml6 require us to test new markers, with the aim of improving the profitability of our biopsies and detecting clinically significant PCa.

DD3PCa gene (abbreviated as PCA3 in the literature) was discovered by Bussemakers et al. in 1999 as highly overexpressed a gene in PCa analyzing normal prostate populations, benign prostatic hyperplasia (BPH) and PCa of radical prostatectomy pieces using the technique of differential display analysis.7 The same as the PSA, it was organ-specific and its presence in different cell lines from other tissues and organs could not be proved. The big difference with the PSA is that its median expression was 66 times higher in 95% of the PCa tissue analyzed compared to normal tissue or BPH in each patient, with a clear overexpression in samples from metastatic PCa.

Basic research began from the discovery of this new biomarker to the development of a commercial kit (Progena18 PCA3 test) for clinical application to detect the expression of this gene in urine.

Recently, a meta-analysis has been published by the Agency for Health Technology Assessment in Andalusia, in which a selection of 14 articles from 403 citations about PCA3 in the literature is analyzed. The sensitivity provided is estimated in a range of 46.9–82.3%, the specificity from 56.3 to 89%, the positive predictive value (PPV) between 59.4 and 97.4%, and the negative predictive value (NPV) between 87.8 and 98%, recognizing acceptable diagnostic accuracy rates for the use of PCA3 in the diagnosis of PCa.8

In our institution, we have introduced the routine use of PCA3 score since October 2009. After an initial phase of internal validation, we have aimed at recognizing the saving rate of biopsies, the reliability of the test in routine use, and establishing in which subgroup of patients it is more profitable depending on the number of previous biopsies performed.
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Methods

Patients

After approval by the Ethics Committee of the Valencian Institute of Oncology of the use of the Progensa™ PCA3 test, we looked at 474 patients referred to or controlled in our Department for PCa screening due to elevated PSA and/or suspicious rectal examination. After consent, patients underwent the test, regardless of whether they had been previously biopsied (group A, n = 337) or not (group B, n = 134).

We subdivided the A group into A₁ (a previous biopsy, n = 182) and A₂ (>1 previous biopsy, n = 155). The period included in the review is from October 2009 to January 2011; during the first 3 months, the biopsy was performed to all patients regardless of the PCA3 value, as an optimization and validation phase in our centre of the results provided by the test in the literature. After the same, and once these results were confirmed, the recommendation for biopsy or not was taken independently by each of the 11 urologists of the department, together with the PSA and rectal examination, the final decision being taken by the patient once the risks of the biopsy and individual risk of harboring PCa were explained. The biopsy was transrectal ultrasound-guided according to the usual technique.

Determination of PCA3 using the Progensa™ PCA3 test (Gene Probe, San Diego, USA)

For the collection of urine samples, prostatic massage was performed to patients, consisting of three pressures for each lobe from the base toward the apex and from the lateral to the middle lobe using enough strength to gently depress the gland. The first 20–30 ml of the post-massage urination were collected in a sterile container. Approximately 2.5 ml of this urine were deposited in a collection tube (Urine specimen transport kit, Progensa) with transportation included. This tube constitutes the sample processed and it is stored at −80°C until it is used. For the analysis of the specimen, the Progensa™ PCA3 kit (Gene Probe, San Diego, USA) was used, consisting of a first step in which the PCA3 and PSA messenger RNA (mRNA) is isolated by magnetic separation with oligonucleotides. Then, both mRNA molecules are amplified by the PCR transcription-mediated amplification (TMA) test. Finally, the products of that amplification are hybridized with a specific fluorescent probe labeled with acridinium ester. The results are presented as the ratio between the number of copies of PCA3 and PSA copies in a milliliter multiplied by one thousand [(PCA3mRNA/PSAmRNA) × 1000], after which we obtain the so-called PCA3 score. A ratio above the cut-off point set at 35 is correlated with a greater likelihood of a positive prostate biopsy. The cases in which the expression of PSA is undetectable due mainly to the low cellularity of the sample were considered as not evaluable and were excluded from the study.

Statistical methods

The performance characteristics of both PCA3 and PSA in the total cohorts of the study were evaluated by determining the parameters of sensitivity, specificity, PPV and NPV. Different cut-off points were taken into account for the evaluation of these parameters: values of 35 and 20 for PCA3 score, and the value of 4 ng/ml for PSA. Representations of ROC curves were performed with the histological findings of biopsies for both PCA3 and PSA. The comparison between groups were performed using the χ² test for categorical variables (Fisher’s test for 2 × 2 tables and Spearman’s correlation for linear associations). We used the Kruskal–Wallis’ or Mann–Whitney’s U tests to compare categorical variables with continuous variables. All these tests were performed using SPSS v.15 (SPSS Inc., Chicago, IL, USA).

Results

PCA3 test informative rate

Following the recommendations of the Progensa™ PCA3 kit (Gene Probe, San Diego, USA), we obtained a result of the test in 472 of the 474 patients included in the study (99.6%). The median PCA3 score obtained was 29 (range 1–3245).

Relation of the test with the prostate volume

The mean prostate volume calculated for PCA3 cases of 35 (45cc) and cases with PCA3 >35 (42cc) showed no statistically significant differences (p = 0.270). Nor did they using a PCA3 cut-off point of 20 (49.3cc vs. 42cc, p = 0.378).

Rate of biopsies performed-not performed

We performed a total of 242 biopsies (median of 10 cylinders, range 2–49) and dismissed it in 232 patients. The overall biopsy sparing rate was 48.9% (232/474). Of the biopsies performed, 158 were negative (66%) and 82 positive for PCa (34%).

In group A, biopsies were performed in 150 patients (44.5%), which means a 55.5% repeated biopsy sparing rate, and 47 were positive for PCa (31.5%). In group B, 91 biopsies were performed (68%), which translates into an initial biopsy sparing rate of 32%, and 34 were positive for PCa (37%).

PCA3 diagnostic yield in the global series

Fig. 1 shows the percentage increase of positive biopsies based on PCA3 intervals reflected for each column, while Fig. 2 shows the areas under the curve for PSA and PCA3 score in the global series.

Of the 64 biopsies performed with a PCA3 score <35, 52 were negative. Likewise, of the 175 biopsies performed with a PCA3 score >35, 69 (39%) were positive for PCa.

The overall sensitivity for the PCA3 score (cut-off point of 35) and the PSA (cut-off point of 4 ng/ml) was 85 and 87%, the specificity 33 and 12%, the PPV 39 and 34%, and the NPV 81 and 63%, respectively. Lowering the cut-off point of the PCA3 score to 20, the sensitivity was 95%, the specificity 20%, the PPV 38%, and the NPV 89.
PCA3 diagnostic yield for patients with previous biopsy

Of the 28 biopsies performed in the group with PCA3 score <35, 25 were negative, whereas in 43 (36%) of the 120 biopsies performed in the group with PCA3 score ≥35 were PCa (p = 0.009). The sensitivity for the PCA3 score 35 was 93%, specificity 31%, PPV 36%, and NPV 89%. Fig. 3 shows the areas under the curve for PSA and PCA3 in this group A. Lowering the cut-off point of the PCA3 score to 20, the parameters of sensitivity, specificity, PPV, and NPV did not change much with respect to the cut-off point of 35, these being 96%, 16%, 34%, and 89%, respectively.

Diagnostic yield of the PCA3 score for patients without previous biopsy

Of the 36 biopsies performed with PCA3 score <35 in this subgroup, 28 were negative for PCa, whereas of the 55 biopsies performed with PCA3 score ≥35, 26 (47%) were PCa (p = 0.15). The sensitivity for PCA3 score 35 in this group of patients was 76%, the specificity 49%, the PPV 47%, and the NPV 78%. Fig. 4 shows the areas under the curve for PSA and PCA3 for patients not biopsied. When using a PCA3 with a cut-off point at 20, we increase the sensitivity (97%) at the expense of decreasing the specificity (30%); for its part, the PPV is 45% and the NPV 94%.

Diagnostic yield of the PCA3 score depending on the number of previous biopsies

We subdivided group A into A1 (a previous biopsy, n = 182) and A2 (>1 previous biopsy, n = 155). In group A1, of the 16 biopsies performed with PCA3 score ≥35, 15 were normal, while 24 of the 68 (35%) biopsies performed in patients with PCA3 score ≥35 were PCa (p = 0.022). The sensitivity for the PCA3 score 35 in the group A1 was 96%, the specificity 25%, the PPV 35%, and the NPV 94%. For a cut-off point of the

![Figure 1](http://www.elsevier.es) Percentage of positive biopsies of the 271 performed according to the value of the PCA3 score. The number of patients included in each interval reflected by each column appears at the bottom of the figure.

![Figure 2](http://www.elsevier.es) Areas under the curve for the PSA and PCA3 score of the overall series.

![Figure 3](http://www.elsevier.es) Areas under the curve for the PSA and PCA3 score for the patients previously biopsied (group A).
Table 1  Sensitivity (SE), specificity (S), PPV, and NPV values for the overall series and the different subgroups of patients for the PCA3 score with cut-off points of 35 and 20.

<table>
<thead>
<tr>
<th>Series</th>
<th>PCA3 score 35 (%)</th>
<th></th>
<th>PCA3 score 20 (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE</td>
<td>S</td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
<td>Overall</td>
<td>85</td>
<td>33</td>
<td>39</td>
<td>81</td>
</tr>
<tr>
<td>No previous biopsy</td>
<td>76</td>
<td>49</td>
<td>47</td>
<td>78</td>
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<td>96</td>
<td>25</td>
<td>35</td>
<td>94</td>
</tr>
<tr>
<td>+1 previous biopsy</td>
<td>90</td>
<td>23</td>
<td>37</td>
<td>83</td>
</tr>
<tr>
<td>Some biopsy</td>
<td>93</td>
<td>31</td>
<td>36</td>
<td>89</td>
</tr>
</tbody>
</table>

**PCA3 score of 20**, these parameters were 96, 14, 32 and 89%, respectively.

In group A2, of the 12 biopsies performed with a PCA3 score <35, 10 were normal, with 19 out of the 52 biopsies performed in patients with a PCA3 score ≥35 (p = 0.196) being positive. The sensitivity for the PCA3 score 35 in this group of patients was 90%, the specificity 23%, the PPV 37%, and the NPV 83%. Lowering the cut-off point of the PCA3 score to 20, the sensitivity was 95%, the specificity dropped to 19%, the PPV was 36%, and the NPV remains 89%.

In **Tables 1–3** the sensitivity, specificity, PPV, and NPV values are summarized for the overall series and the different subgroups of patients for the PCA3 with cut-off points of 35 and 20, for the total PSA with cut-off point at 4 ng/ml, and for the ratio free PSA/total PSA (% f/t PSA) with cut-off points of 10 and 20%, knowing that the median f/t PSA was in the overall series of 17.4% (range 1–44%). In **Table 4**, these parameters are also described in relation to the rectal examination of the 242 cases who underwent biopsy, being 183 (76%) an anodyne and suspicious rectal examination in the remaining 24%.

**Discussion**

In the **European Randomized Study of Screening for Prostate Cancer**, it was observed that only 26% of the biopsies performed with a PSA between 4 and 10 ng/ml are positive for PCA3, which means that 74% of the individuals included in the study have been performed unnecessarily or insufficiently. This observation confirms the reality of the large number of biopsies that in clinical practice are unnecessarily made, not free of morbidity and constituting important social and health costs. The main purpose of the use of new biomarkers is precisely focused on the optimization of the biopsies performed; with this aim, the use of the **PCA3 score** provides a biopsy sparing rate between 40 and 67%, according to the literature. The study that we present here includes an initial validation phase of 3 months in which biopsies were performed regardless of the outcome of the PCA3. After the individual assessment of each PSA/PCA3 score, we get an overall biopsy sparing rate of 48.9%, which makes this biomarker an aid that does not replace but it does complement the information we had prior to its use to make the decision to biopsy or not, justifying, thus, its cost.

The routine use of the new test by the 11 urologists of the department has demonstrated that its determination was possible in 99.6% of the cases, within the range of 95–100% reported in the literature. Since its release, the new marker has been tested in parallel in the U.S.A. and Europe with independent studies that initially showed the independence of the **PCA3 score** against the prostate volume and the serum PSA observations that we have been able to confirm in our results. These studies were performed on patients with or without prior biopsy. The summary of all these articles is that a **PCA3 score ≥35** provides a chance of 2–2.5 times higher positive repeated biopsy than a **PCA3 score <35**, offering areas under the ROC curve around 0.7.

**Table 2**  Sensitivity (SE), specificity (S), PPV, and NPV values for the overall series and the different subgroups of patients for PSA 4 ng/ml.

<table>
<thead>
<tr>
<th>Series</th>
<th>SE</th>
<th>S</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>87</td>
<td>12</td>
<td>34</td>
<td>63</td>
</tr>
<tr>
<td>No previous biopsy</td>
<td>74</td>
<td>25</td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>1 previous biopsy</td>
<td>96</td>
<td>5</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>+1 previous biopsy</td>
<td>100</td>
<td>5</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>Some biopsy</td>
<td>98</td>
<td>5</td>
<td>32</td>
<td>83</td>
</tr>
</tbody>
</table>

**Figure 4**  Areas under the curve for the PSA and PCA3 for the patients without previous biopsy (group B).
Table 3  Sensitivity (SE), specificity (S), PPV, and NPV values for the overall series and the different subgroups of patients for the free/total PSA ratio with cut-off points of 10 and 20%.

<table>
<thead>
<tr>
<th>Series</th>
<th>Free/total PSA ratio 10 (%)</th>
<th>Free/total PSA ratio 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE</td>
<td>S</td>
</tr>
<tr>
<td>Overall</td>
<td>33</td>
<td>83</td>
</tr>
<tr>
<td>No previous biopsy</td>
<td>38</td>
<td>84</td>
</tr>
<tr>
<td>1 previous biopsy</td>
<td>14</td>
<td>85</td>
</tr>
<tr>
<td>+1 previous biopsy</td>
<td>56</td>
<td>76</td>
</tr>
<tr>
<td>Some biopsy</td>
<td>27</td>
<td>82</td>
</tr>
</tbody>
</table>

In the meta-analysis published, the different areas under the curve for the PCA3 score are in the range 0.63–0.87, which includes ours. Our results of overall sensitivity of the test (85%) would be slightly above the aforementioned meta-analysis range (46.9–82.3%). Our results in specificity (33%), and PPV (39%) are significantly lower than the ranges given by the meta-analysis (56.3–89% and 59.4–97.4%, respectively); we think that this could be because, in the first place, we have performed a median of 10 cylinders, lower than the number currently being raised in many other series, and secondly, because patients that are not biopsied, with figures of 49% specificity, and 47% PPV, constituted only a third of the series.

However, we confirm with our observations of NPV (81%) for a PCA3 score with cut-off of 35, near the range published in the literature of 87.8–98%, that when this test was negative, the biopsy could be avoided by not diagnosing PCa in very few cases. On the other hand, although the ratio of the PCA3 score with the Gleason score offers conflicting results in the literature, a clear ratio of the value of the PCA3 score with the tumor volume and multifocality has been published, so we would expect these biopsies would diagnose insignificant PCa, especially if the PCA3 score is <25.

Recently, it has been reported that the addition of the PCA3 score may improve predictive models of low tumor volume (+2.4–5.5%) and of insignificant PCa (+3–3.9%), while it does not improve the predictive ability of extracapsular disease or seminal vesicle invasion.

As mentioned above, our parameters of sensitivity, specificity, PPV, and NPV are better for the subgroup of patients without previous biopsy, which has some logic given that patients who have been biopsied one or more times somehow have ‘fewer’ chances of hosting a PCa. This trend continues in the biopsied group among which some only have a biopsy done while others have more than one, although the differences are not so important now. It is worth mentioning that in the group of more than one biopsy, the specificity of the % f/t PSA <10% (56%, Table 3) is frankly better than that of the PCA3 score = 35 (26%, Table 1). In 301 previously biopsied men with PSA between 2.5 and 10 ng/ml with a number of cylinders similar to ours, no PCA3 cut-off point offered statistically significant differences if the f/t PSA was lower than 10%. In the placebo arm of the REDUCE study, the differences in the areas under the curve between PCA3 and % f/t PSA did not reach statistically significant differences (p = 0.064). All this has made us rethink about the need for request of the PCA3 score in patients with more than one previous biopsy when the free/total PSA rate is <10%, admitting that this is not conclusive in patients with no biopsy or with only one biopsy due to its low sensitivity in our environment (Table 3), and its known dependence on the tumor volume.

It is not yet clear which the cut-off point offering more profitability to the test is; if the goal is to detect more tumors, we confirm that with a cut-off point of 20, the sensitivity is increased by 10 points, at the expense of a loss of 13 points in specificity. Only one of the PCas detected in our series with PCA3 score <35 had a Gleason score of 7 on biopsy (data not shown). Therefore, if the goal is to detect more clinically significant tumors, we believe that a PCA3 score cut-off point of 35 is acceptable, although our low specificity makes us agree with other authors on the importance of understanding the PCA3 score as a continuous variable, the need to validate the optimal cut-off point for each population, and the fact that the reason for its daily use is to add another source of information, along with the PSA, the rectal examination, and the patient’s history, to decide whether or not to biopsy. In this regard, the nomograms used for the detection of PCa are reinforced if they include the PCA3 score.

Like other previous tumor markers, only its routine and massive use determines what the indications and diagnostic yield are. We believe that the PCA3 has been a substantial help in the early diagnosis of PCa, being a PCa specific mRNA and being determined in urine that can be collected in the same doctor’s office. It will probably be complemented in the medium term with a broader panel of molecular biomarkers in urine, in which an improvement of the diagnostic yield is objectified to using a PCA3 score alone, one of the markers used being the fusion gene TMPRSS2-ERG, which may also offer prognostic value.

The limitations of the study come along with the routine use of a new marker and the type of study. Although in a first phase of 3 months we did not consider the value of the PCA3 and all patients with suspected PCa were biopsied.

Table 4  Sensitivity (SE), specificity (S), PPV, and NPV values for the overall series and the different subgroups of patients for the rectal examination.

<table>
<thead>
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<th>Series</th>
<th>S</th>
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<th>PPV</th>
<th>NPV</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td>20</td>
<td>75</td>
<td>29</td>
<td>64</td>
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<td>No previous biopsy</td>
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<td>24</td>
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<td>32</td>
<td>70</td>
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<td>+1 previous biopsy</td>
<td>14</td>
<td>62</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>Some biopsy</td>
<td>19</td>
<td>73</td>
<td>25</td>
<td>66</td>
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</tbody>
</table>
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by PSA and/or rectal examination, confirming the statistics that the marker had offered in the literature, afterwards, it was the urologist’s recommendation based on the 3 factors and personal history of each patient that has finally made the patient decide to undergo biopsy or not. On the other hand, only since July 2010, has the number of cylinders been notarized at 10 in the first one, and at 14 or more (depending on prostate volume) in the second or future; previously, the number of biopsies was lower (data not shown). All this can clarify our results, but we wanted to present them as this marker has been introduced into our daily routines.

We would have to investigate the PCA3 value as the first diagnostic test, given that its use and standardization has been developed always preceded by PSA or in patients within a pre-screening framework, or in populations at risk of PCa.10

Conclusions

Our results confirm that the routine use of the PCA3 score both as a continuous and categorical variable, complementary to the PSA and rectal examination, can advise a patient with suspected PCs whether to undergo biopsy or not and make biopsies profitable. If the goal is biopsy sparing, we believe that the PCA3 score is a good tool because the potential not biopsied PCs are few, probably not clinically significant, and a rational follow-up could detect them later without compromising the patient’s life. Its use could probably be avoided in patients with more than one biopsy and with a% f/t PSA <10%. Further studies should be carried out along with other molecular markers to improve the diagnostic yield of these new biomarkers.

Funding

This work was supported by grants PI061619, PI101206 from the Instituto Carlos III (Madrid, Spain), ACOMP/2009/176 of the Generalitat Valenciana and the Research Grants from Astra Zeneca Spain.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work would not have been possible without the technical assistance of the Data Manager of the Urology Department of the IVO, Vanesa Pérez and the administrative assistance of Nuria López. We thank the Instituto Carlos III of Madrid for their support (PI061619, PI101206) for various studies on prostate cancer that has benefited from this work.

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