Counterpoint: Prostate-Specific Antigen Velocity Is Not of Value for Early Detection of Cancer

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Abstract
Firm evidence shows that prostate-specific antigen (PSA) velocity is statistically associated with many prostate cancer outcomes, including those related to early detection. However, the clinical use of a marker depends on clinical and statistical significance. Before PSA velocity is used to inform decisions such as whether to perform a biopsy, evidence should be clear that doing so would improve clinical outcome. A systematic review on PSA velocity found that almost no studies had evaluated whether PSA velocity aids in clinical decision-making. Since that time, several reports have indicated that including PSA in a statistical model alongside standard predictors (eg, PSA, digital rectal examination) does not improve predictive accuracy. Specifically, performing a biopsy on men with high PSA velocity in the absence of other indications, as recommended by the NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer Early Detection, would lead to many millions of unnecessary biopsies, without a corresponding number of aggressive cancers being detected. Advocates of PSA velocity have been reduced to citing a single article claiming that PSA velocity aids in clinical decision-making. The article involves selective reporting of an unusual subgroup analysis based on an extremely limited number of events. This is not to say that, in clinical practice, urologists should ignore prior PSA values: clinical judgment can be aided by careful longitudinal evaluation of PSA changes, interpreted in the context of symptoms and treatments. However, the literature clearly shows that simplistic application of PSA velocity cutoffs is not of value for early detection of prostate cancer. (JNCCN 2013;11:286–290)

With prostate-specific antigen (PSA) velocity, as in all areas of clinical research, the first question should be, “What is the question?” It cannot reasonably be doubted that PSA velocity is statistically associated with prostate cancer outcomes, including those related to early detection. Even an article concluding that there was “little justification” for the use of PSA velocity reported that PSA velocity was a statistically significant ($P<.001$) predictor in a multivariable model. However, there is a time-honored distinction between clinical and statistical significance: what we want to know about PSA velocity does not concern null hypotheses of no association, but whether incorporating PSA velocity into clinical decision-making will improve clinical outcomes. As it turns out, clear evidence shows that using PSA velocity to make decisions about prostate biopsy does not do more good than harm.

Early Data on PSA Velocity for Early Detection of Cancer

In 2008, the author’s group analyzed data on PSA velocity from what is known as the Malmö cohort, which involves archived blood samples from more than 20,000 Swedish men followed for 20 to 30 years without PSA screening. Like prior authors, they found strong evidence that PSA velocity is associated with a long-term risk of cancer, even after adjusting for PSA ($P<.001$). However, combining both PSA and PSA velocity into a single model did not improve the predictive accuracy of PSA alone: the area-under-the-curve (AUC) for both was identical to 3 decimal places (0.771).2

The authors were surprised by this result because it seemed to contradict the prior literature. To explore this issue further, they conducted a systematic review of all prior studies on PSA velocity and doubling time in
localized prostate cancer. A total of 87 studies were identified, 42 of which had biopsy outcomes as an end point. Although many studies did report a hypothesis test for the association between PSA velocity and prostate cancer outcome, only 2 addressed the question of whether PSA velocity added predictiveness to PSA alone. One study reported that “PSA velocity did not improve the out-of-sample prediction of prostate cancer risk”\(^3\); the other reported that PSA velocity increased the AUC by a small amount (0.83 vs. 0.81) but involved the unsound assumption that patients who were never biopsied did not have prostate cancer.\(^5\) No article in the review evaluated the consequences of using PSA velocity in clinical decisions.

**Data on PSA Velocity Published After the Systematic Review**

Since publication of the review, numerous papers by the author's group and others have specifically examined whether PSA velocity adds to established predictors such as PSA. The findings have been absolutely consistent: PSA velocity does not increase the ability to predict prostate cancer outcome once PSA is known.

A particularly interesting set of articles was published by O'Brien et al.\(^6,7\) The authors first noted that changes in PSA could be defined in different ways, either in terms of velocity or doubling time, and with different rules regarding which PSAs are included and how PSA kinetics are calculated. Results showed that, for many definitions, PSA velocity cannot be calculated for a significant proportion of patients. The second major finding of the O'Brien articles is that values of PSA kinetics can vary widely among different definitions. For example, one man in the data set had PSA velocities of 0.27, 0.76, 1.47, 2.64, and 32.0 ng/mL/y, depending on the definition used. Overall, the investigators found no evidence that PSA velocity or doubling time could help predict mortality after conservative management\(^8\) or recurrence or mortality after radical prostatectomy.\(^7\) Similar findings were reported by Ross et al\(^9\) in an active surveillance cohort (in which PSA velocity was determined to be an “unreliable trigger” for intervention); the SPCG4 randomized trial of radical prostatectomy (in which PSA changes were found to be a “poor predictor of lethal prostate cancer”)\(^9\); and a study involving a large cohort of men treated surgically at academic centers.\(^10\)

These data are important because they suggest that PSA velocity is not a strong marker of cancer aggressiveness and thus is unlikely to be an important consideration in deciding whether to perform a biopsy.

**PSA Velocity and Prostate Biopsy Outcomes**

Several groups have reported that PSA velocity does not significantly improve the specificity of PSA; that is, it does not aid in the decision whether to perform a biopsy in men with an elevated PSA level.\(^1,11-15\) In a study based in data from the European Randomized Trial of Screening for Prostate Cancer (ERSPC), PSA velocity increased the AUC by a small amount compared with standard predictors, but this effect was driven by a lower prostate cancer risk in men with high PSA velocities.\(^1\) This effect has been replicated independently. Exclusion of a small number of men with high PSA velocities abolished the effect of PSA velocity; moreover, PSA velocity did not help predict high-grade cancers.\(^15\)

Similar findings were found for repeat biopsy after initial negative biopsy results. In a large study based on the ERSPC, involving more than 2500 repeat biopsies and 363 cancers, PSA velocity was strongly associated with cancer risk (\(P<.001\)) but had a very low AUC (0.55). Some evidence showed that PSA velocity helped improve detection of high-grade cancer, but the confidence intervals were very wide and the clinical implications questionable, because the increase in risk with higher PSA velocity was less than 1%.\(^11\) Similar findings were reported in the REDUCE trial.\(^16\)

It has also been argued that PSA velocity could help detect prostate cancer in men with low PSA; in other words, that PSA velocity may improve the sensitivity of PSA. For many years, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection have recommended performing a biopsy in men with a PSA risk of 0.35 ng/mL/y or more even if they had no other indication for biopsy, such as positive results from a digital rectal examination (DRE) or an elevated PSA level (to view the most recent version of these guidelines, visit NCCN.org).\(^17\) The origin of this recommendation is interesting. In a study with only 20 events and no attempt to determine whether PSA velocity added predictive value to PSA alone,
Carter et al. reported a statistical association between PSA velocity and prostate cancer death 10 to 15 years before diagnosis. The cutoff point of 0.35 ng/mL was “suggested” as one reasonable choice among others based on a visual inspection of the receiver operating characteristic curve. In other words, a small study that was not about biopsy and did not examine the clinical value of PSA velocity determined a possible cutoff point based on an informal analysis, which then became hardened into a biopsy recommendation.

As it turns out, only a single data set can be used to examine whether a biopsy should be performed in men with a high PSA velocity in the absence of other indications: that from the Prostate Cancer Prevention Trial (PCPT), in which biopsies were performed in all patients at the end of the trial as part of the study protocol. The control arm of the PCPT in fact closely reflects the NCCN Guidelines recommendations because it involved yearly PSA and DRE tests. Accordingly, the data can be used to empirically test what would happen if the guidelines were implemented in practice. The results of a study on the PCPT were extremely clear. First, PSA velocity added almost nothing to the AUC of PSA alone: 0.709 versus 0.702. Second, improvements in PSA were even smaller for the end point of clinically significant or high-grade cancer. Third, the recommendation to perform a biopsy in men with low PSA and negative DRE if the PSA velocity exceeded 0.35 ng/mL/y would lead to a very large number of biopsies, in approximately 1 in 7 men of screening age. Implementation of the NCCN Guidelines would therefore lead to many millions of men in the United States every year being referred for biopsy. Fourth, the yield of biopsies based on PSA velocity was very low and PSA cutoff points had far greater sensitivity for equivalent specificity (eg, 41% vs. 25% for high-grade cancer). As a result, clinicians who believe that current PSA thresholds are insufficiently sensitive would be better off using a lower PSA threshold than performing a biopsy based on PSA velocity. Fifth, the data were independent of the method for calculating PSA; numerous different algorithms were tried, including the risk count method, and none were found to be of benefit. Finally, the data were reanalyzed excluding older men and the results were nearly identical.

### Response to the Recent Data on PSA Velocity

A summary of some of the most well-known and characteristic studies on PSA velocity in localized prostate cancer is provided in Table 1. In general, the studies supporting PSA velocity are based on clinical cohorts (ie, men who happened to be treated at a particular hospital), with small numbers of events. Most critically, none examined the marginal value of PSA velocity; that is, whether it increased the predictive accuracy of standard predictors such as PSA. In contrast, the articles suggesting that PSA velocity is not helpful are typically based on randomized trials or prospective cohort studies with large numbers of events, and did address the specific question of whether PSA velocity increases predictiveness.

That said, the author’s own systematic review on PSA velocity was conducted some time ago, and therefore, in preparation for this paper, several noted advocates of PSA velocity were asked for any recent data suggesting that PSA velocity added predictiveness to PSA alone. A single article by Loeb et al. was referred. This article compares the predictive accuracy of PSA velocity, calculated in terms of risk count, plus PSA with that of PSA alone, showing that PSA velocity increased the AUC by 0.01. However, such a trivial increase in AUC is hardly a ringing endorsement of the clinical value of PSA velocity. Moreover, the analysis is badly flawed by the assumption that men who never underwent a biopsy did not have prostate cancer. Because men with elevated PSA levels are referred for biopsy, and are therefore at risk of having cancer detected, the findings are no more than a demonstration that men with high PSA velocities end up with high PSA levels. The authors are not unaware of this problem and, in the methods section, state that they planned a subgroup analysis including only those men who underwent biopsies. Remarkably, the results of this analysis are not presented, and the AUC of PSA plus PSA velocity for biopsy outcomes is never reported. The authors do present a subgroup of a subgroup analysis, claiming that the AUC of PSA increases dramatically when PSA velocity is incorporated for the prediction of high-grade disease, wherein, unconventionally, high grade is defined as Gleason score 8 to 10. This analysis is based on only 21 cases, which is highly problematic given the context of multivariable modeling.
Conclusions

Little question exists that PSA velocity has a statistical association with prostate biopsy outcomes, even after adjusting for PSA. However, a systematic review including studies published to March 2007 found that essentially no papers had answered the

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Table 1 Examples of the Results of Typical Studies on Prostate-Specific Antigen Velocity in Men Before Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Events</th>
<th>End Point</th>
<th>Examined Marginal Value?</th>
<th>PSA Velocity Helpful?</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLSA</td>
<td>Prospective cohort study</td>
<td>20</td>
<td>Prostate cancer death in men before diagnosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Malmö, Sweden</td>
<td>Prospective cohort study</td>
<td>82</td>
<td>Advanced cancer in men before diagnosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Loeb et al</td>
<td>Prospective cohort</td>
<td>346</td>
<td>Diagnosis of prostate cancer during screening</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PCPT</td>
<td>Randomized trial</td>
<td>1211 (any) 256 (high-grade)</td>
<td>Prostate cancer on biopsy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ERSPC</td>
<td>Randomized trial</td>
<td>710 (any) 144 (high-grade)</td>
<td>Prostate cancer on biopsy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ERSPC</td>
<td>Randomized trial</td>
<td>363 (any) 44 (high-grade)</td>
<td>Prostate cancer on repeat biopsy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>D’Amico et al</td>
<td>Clinical cohort</td>
<td>28</td>
<td>Prostate cancer death in men treated with radiotherapy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>D’Amico et al</td>
<td>Clinical cohort</td>
<td>27</td>
<td>Prostate cancer death in men treated with surgery</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stephenson et al</td>
<td>Clinical cohort</td>
<td>117</td>
<td>Prostate cancer death in men treated with surgery</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Khatami et al</td>
<td>Clinical cohort</td>
<td>104</td>
<td>Progression on active surveillance</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ross et al</td>
<td>Prospective cohort study</td>
<td>102</td>
<td>Progression on active surveillance</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SPCG4</td>
<td>Randomized trial</td>
<td>34</td>
<td>Prostate cancer death in men managed conservatively after diagnosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>O’Brien et al</td>
<td>Prospective cohort study</td>
<td>119</td>
<td>Prostate cancer death in men treated conservatively</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: BLSA, Baltimore Longitudinal Study of Aging; ERSPC, European Randomized Trial of Screening for Prostate Cancer; PCPT, Prostate Cancer Prevention Trial; PSA, prostate-specific antigen; SPCG4, Scandinavian Prostate Cancer Group Study No. 4.
critical question of whether use of PSA velocity aids prediction or clinical decision-making once PSA is known. Numerous papers published since that time have clearly addressed this question in the negative: statistical models including both PSA and PSA velocity do not importantly predict prostate cancer any better than models based on PSA alone, and clinical decisions based on PSA velocity do not improve clinical outcome. Advocates of PSA velocity have been reduced to citing a single paper purporting to show that PSA velocity aids clinical decision-making. The paper involves selective reporting of an unusual subgroup analysis based on an extremely limited number of events.

This is not to say that, in clinical practice, urologists should ignore prior PSA values. Clinical judgment can be aided by careful longitudinal evaluation of PSA changes, interpreted in the context of symptoms and treatments. As a simple example, a PSA of 5 ng/mL may be considered very differently in a man who has experienced a gradual rise over time compared with a man experiencing a decrease from 12 ng/mL after treatment for signs of prostatitis. However, the literature clearly shows that simplistic application of PSA velocity cutoffs is not of value for early detection of prostate cancer.

References