Point: Impact of Prostate-Specific Antigen Velocity on Management Decisions and Recommendations

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Abstract

Prostate-specific antigen (PSA) velocity predicts the presence of prostate cancer on biopsy and a greater risk of prostate cancer death after radical treatment. A new variation on PSA velocity called the *risk count* was recently shown to provide incremental reclassification for intermediate to high-grade disease on biopsy beyond PSA and age. These markers therefore have the potential to reduce overdiagnosis and overtreatment of indolent prostate cancer, and several professional guidelines support the use of PSA kinetics along with other predictors as part of the diagnostic algorithm. Among men already diagnosed with prostate cancer, PSA kinetics may also be helpful in predicting prognosis after definitive therapy. (*JNCCN* 2013;11:281–285)

Although prostate cancer screening with prostate-specific antigen (PSA) has been shown to reduce metastases and mortality from prostate cancer,[1,2] its use has numerous drawbacks. A key issue is its limited specificity for clinically significant prostate cancer, resulting in unnecessary biopsies, overdiagnosis, and overtreatment. Fortunately, the way that screening is performed has evolved considerably over the past 2 decades, and there are several variations on the PSA test itself with improved performance characteristics.

One of these variations is PSA velocity (PSAV), which is a metric of the change in PSA level over time,

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and has been known since the early 1990s to increase the specificity of PSA-based screening for prostate cancer detection.[3] This is important because prostate biopsies have potential associated risks,[4] such that reducing false-positive screening tests is an important objective. Among men aged 50 years and younger without prostate cancer, the median PSAV is approximately 0.00 to 0.03 ng/mL/y.[5,6] Recent studies have suggested that the baseline PSAV may be useful for risk stratification in young men.[7] At the other end of the spectrum, PSAV may also be useful in guiding the discontinuation of screening in elderly men.[8,9]

Another area in which improvements are needed is distinguishing indolent from aggressive disease. A large body of evidence now shows a strong relationship between PSAV and more aggressive prostate cancer features. For example, in 1073 men from a large radical prostatectomy series, insignificant tumors were present in 10% of men with a PSAV less than 0.4 ng/mL/y, and in only 5% of men with a PSAV greater than 0.4 ng/mL/y.[10] These results suggested that PSAV may be a marker for clinically significant prostate cancer. Another recent study of 219,388 US men from Kaiser Permanente showed that the annual percent change in PSA was significantly better than the total PSA for discriminating high-grade prostate cancer on biopsy (area under the receiver operating curve of 0.955 vs. 0.727, respectively).[11]

PSAV has also been shown to predict prostate cancer–specific mortality. In a landmark study, D'Amico et al[12] reported that a PSAV greater than 2 ng/mL/y predicted a greater risk of prostate cancer death after radical prostatectomy. These authors subsequently validated the relationship between a PSAV greater than 2 ng/mL/y and the risk of mortality after radiation therapy.[13] The independent relationship between PSAV and long-term treatment outcomes was also

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demonstrated by Sengupta et al.[14] These studies suggest that PSAV identifies a group that is at higher risk of ultimate disease progression and death, despite curative therapy.

Subsequently, Carter et al[15] showed that men with a PSAV greater than 0.35 ng/mL/y, even at a time when the total PSA was low, had a 5-fold increased risk of prostate cancer death more than a decade later. Thus, PSAV also has future prognostic value with regard to the likelihood of lethal prostate cancer.

Conversely, other studies have failed to show an "important" relationship between PSAV and prostate cancer–related outcomes. For example, Vickers et al[16] performed a comprehensive systematic review of studies on PSA kinetics published before March 2007, concluding that the existing evidence did not support the utility of PSA kinetics in clinical decision-making for early-stage prostate cancer.

Several reasons exist for these seemingly divergent results. First, the systematic review by Vickers et al[16] included heterogeneous studies of PSA kinetics both before and after a prostate cancer diagnosis to predict diverse outcomes ranging from biopsy outcome to progression on active surveillance. Studies have since shown that PSA kinetics may be more useful in certain settings than in others. For example, in the Johns Hopkins active surveillance program, PSAV (and PSA doubling time) were not reliably indicative of disease reclassification on biopsy,[17] whereas other programs have reported conflicting results.[18] Currently, a lack of consensus exists regarding the use of PSA kinetics to indicate progressive disease in active surveillance programs.[19] In the systematic review by Vickers et al,[16] combining disparate outcomes such as initial biopsy results and progression on active surveillance in a systematic review may have affected the results.

Furthermore, the systematic review included PSAV along with other types of PSA kinetics measurements involving different mathematical assumptions (eg, PSA doubling time).[20] However, this authors' group showed that PSAV is more useful than PSA doubling time in both the diagnostic setting[21] and the prediction of treatment outcomes,[22] indicating that grouping these different measurements together is inappropriate.

Perhaps the most important consideration is that several of the early studies reporting a robust association between PSAV and prostate cancer aggressiveness did not address the accuracy and predictive value of PSAV beyond that offered by total PSA and other standard predictors. In fact, the systematic review by Vickers et al[16] found that among the 87 eligible articles, only a single study reported an increase in predictive accuracy using PSA kinetics. In fact, this particular study, which was published by this article's authors' group,[23] did show an improvement in predictive accuracy with the addition of PSA kinetics to a model with race, PSA, age, and family history (area under the curve [AUC], 0.83 vs. 0.81), but was criticized for verification bias. Thus, at the time of the systematic review by Vickers et al,[16] there were numerous gaps in the evidence regarding PSAV, which hampered conclusions. Fortunately, the evidence base and statistical methodology have expanded substantially since 2007.

In one of the major studies to emerge in the past 5 years, Vickers et al[24] examined PSAV in 5519 participants from the Prostate Cancer Prevention Trial (PCPT). On multivariable analysis, they showed that PSAV was associated with a 5.2-fold increased risk of prostate cancer detection on biopsy. Furthermore, they reported on predictive accuracy using receiver operating characteristic (ROC) analysis. When added to a base model with log PSA, family history, digital rectal examination findings, and prior biopsy history, PSAV increased the AUC for the discrimination of all end points: overall cancer, clinically significant cancer, and Gleason 7 to 10 disease.

An advantage of this population from the PCPT is that empiric biopsies were performed as part of the protocol in the absence of a clinical indication, providing histologic confirmation for all participants. However, drawbacks are that the population was elderly (79% were age ≥65 years) and had been serially screened for at least 7 years, resulting in a population enriched with indolent disease. From an analytic standpoint, a limitation of this study is the reliance on ROC analysis, which has been shown to be insensitive to the incremental predictive value of new markers.[25,26] Additionally, as pointed out by Vickers et al,[16] it is "naturally difficult for a marker to add value to a predictor with which it has a strong correlation," as is the case with total PSA and PSAV. Despite these limitations, the authors stated a strong

conclusion that decisions should be based on PSA alone and that PSAV is not worth the incremental time or expense.

As this article's authors previously summarized in an editorial comment,[27] the synopsis by Vickers et al[16,24] seems to suggest little reason to maintain PSA values in the medical record. However, patients frequently present to the urology clinic with a listing of prior PSA data, and disregarding historical information is not a practicable option in the real-world clinical setting. Therefore, the real question is not whether to discard or consider the prior values, but how to make the best use of these data when available. Current evidence supports that the answer to this question is a new concept called *PSAV risk count*.[28]

This concept was initially proposed by Carter et al[29] in men from the Baltimore Longitudinal Study of Aging (BLSA). For men with several serial PSA values, the first step is to calculate 2 PSAV measurements in a row. As the name suggests, the "risk count" then involves counting the number of times in a row that the PSAV exceeds a specific threshold (eg, 0.4 ng/mL/y). Risk counts of 0, 1, and 2 indicate that neither, one, or both PSAV measurements are greater than 0.4 ng/mL/y, respectively. The initial study in the BLSA showed that the probability of high-risk prostate cancer increased significantly with increasing PSAV risk count.[29] More recently, the study by Vickers et al[24] in the PCPT similarly showed that the number of times the PSA level increased to greater than 0.4 ng/mL/y was a significant predictor of overall prostate cancer detection on biopsy, but they did not assess the relationship of risk count to aggressive disease.

Finally, the utility of PSAV risk count was recently externally validated in a larger independent population of 18,214 men from an established screening cohort.[30] After adjusting for age and PSA, men with a risk count of 2 had an 8-fold increased risk of prostate cancer diagnosis and a 5.4-fold increased risk of Gleason 8 to 10 disease on biopsy. On ROC analysis, PSAV risk count significantly improved predictive accuracy for overall prostate cancer compared with a base model of age and PSA alone ($P=.026$). It also led to a significant increase in the discrimination of Gleason 8 to 10 disease (AUC, 0.725 with risk count plus age and PSA vs. 0.625 for age and PSA alone; $P=.031$). As discussed

earlier, ROC analysis has limitations in evaluating new markers.[26] Thus, as in major studies from other disciplines,[31] net reclassification analysis was also used to evaluate risk count and high-grade disease. For this analysis, 2 different definitions of high-grade disease were used: Gleason 7 to 10 (which spans a more heterogeneous group but includes a larger number of events) and Gleason 8 to 10 (the most life-threatening group but is limited by a smaller number of events). Regardless of the definition, PSAV risk count led to a statistically and clinically significant reclassification in the risk of Gleason 7 or greater ($z=6.5$; $P<.001$) and Gleason 8 or greater disease on biopsy ($z=3.5$; $P<.001$), when compared with age and PSA.[30] These results suggest that, compared with age and PSA alone, PSAV risk count may be useful to reduce unnecessary biopsies and the diagnosis of low-risk prostate cancer. Correspondingly, PSAV risk count was recently added as a talking point in the 2012 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection (to view the most recent version of these guidelines, visit NCCN.org).[32]

Despite this robust evidence supporting PSAV, several important considerations exist. As with a single PSA measurement, confounding of PSAV is possible. For example, studies from the United States and Europe have shown that sudden high spikes in PSA that impact PSAV often reflect prostatitis rather than prostate cancer.[33,34] This is where the art of medicine and clinical judgement play a key role. Park et al[35] recently showed how recalculating PSAV after eliminating confounding factors reduced false-positive and false-negative results. Although these considerations form a routine part of judicious clinical practice when making decisions regarding biopsy and treatment, retrospective analyses of PSA kinetics in existing large-scale databases may show less favorable results by ignoring these patient-specific factors. Certainly, these issues highlight the sensibility of using a calculation such as PSAV risk count, which helps to single out the individuals with sustained PSA increases with a higher risk for life-threatening disease.[29,30]

Additionally, no randomized trial has ever compared the outcomes of PSAV- or risk count–based screening versus traditional screening approaches. In randomized screening trials, such as the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer

screening trial,[36] European Randomized Study of Screening for Prostate Cancer (ERSPC),[1] and the Goteborg population-based randomized screening trial,[2] biopsy recommendations were based on total PSA levels rather than PSA kinetics. This article's authors believe that PSAV may help maximize the benefits of screening (ie, early detection of life-threatening disease, leading to reduced morbidity and mortality) and reduce the harms (ie, unnecessary biopsies, overdiagnosis, and overtreatment of insignificant disease); however, this concept has not been tested in a randomized fashion, and such a trial is unlikely to occur.

Although additional observational evidence continues to accumulate on the incremental value of PSAV and risk count, the bulk of contemporary data supports their clinical utility. Therefore, PSAV has been incorporated into several screening guidelines. The 2012 NCCN Guidelines for Prostate Cancer Early Detection recommend considering a biopsy for a suspicious digital rectal examination, PSA level greater than 2.5, or PSAV of 0.35 ng/mL/y or greater, and also discuss the use of PSAV risk count as a talking point.[32] In the best practice statement on PSA, the American Urological Association also recommends PSAV among the factors that should be considered along with PSA in determining the need for biopsy.[37] For men diagnosed with prostate cancer, PSAV should also be used in risk stratification and the assessment of recurrence risks after treatment.

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