Prostate-specific Antigen Velocity Risk Count to Discern Significant From Indolent Prostate Cancer

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Prostate-specific antigen (PSA) velocity (PSAV) is the calculation of changes in PSA level over time, and was initially suggested more than a decade ago as a means to distinguish benign prostate enlargement from prostate cancer. Since that time, conflicting data on the value of PSA kinetics have been reported. D’Amico and colleagues showed that PSAV predicts the risk of prostate cancer-specific mortality after treatment, and the Baltimore Longitudinal Study of Aging (BLSA) demonstrated that a PSAV > 0.35 ng/mL/y more than 10 to 15 years prior to diagnosis predicts the future risk of life-threatening prostate cancer. However, other studies have questioned the utility of PSAV in clinical practice. For example, Wolters and colleagues reported that PSAV was significantly associated with significant prostate cancer on univariate analysis but was not an independent predictor in the multivariable model.

The clinical utility of PSA kinetics is an extremely important issue for many reasons. First, there is ongoing controversy regarding the over-diagnosis of indolent prostate cancer compared with a single determination of either PSA or PSAV. This review describes two recent studies on PSAV risk count.

Prostate Specific Antigen Velocity (PSAV) Risk Count Improves the Specificity of Screening for Clinically Significant Prostate Cancer

Loeb S, Metter E, Kan D, et al.
BJU Int. 2012;109;508-514.

The purpose of this study was to determine if PSAV risk count could improve the specificity of PSA screening for prostate cancer and high-grade disease. They used data from a large US prostate cancer screening study, in which PSA and digital rectal examination (DRE) were performed at 6- to 12-month intervals. Prostate biopsy was recommended for PSA levels > 4 ng/mL (before 1995) or > 2.5 ng/mL (after 1995), and/or suspicious findings on DRE.

Toward this end, 18,214 out of 35,536 men who participated in the prostate cancer screening study had sufficient PSA data as to allow calculation of PSAV risk count. In this screened population, the authors analyzed whether PSA velocity risk count could improve the specificity of PSA screening for overall and high-grade prostate cancer. Specifically, the study examined whether PSAV risk count significantly improved the discrimination of biopsy outcome compared with age and PSA alone. Multivariable models and net reclassification analysis were also reported.

In the entire study population, a PSAV risk count of 2 was associated with 40% sensitivity, 96% specificity, 40% positive predictive value, and 96% negative predictive value for prostate cancer. On multivariate analysis with age and PSA, a PSAV risk count of 2 was associated with an 8.2-fold increased risk of prostate cancer. To predict any prostate cancer diagnosis, the area under the curve (AUC) for a base model including PSA and age was 0.89, which improved significantly with the addition of PSAV risk count (AUC 0.90; P = .026).

To avoid misclassification of participants who did not undergo a prostate biopsy, and to specifically evaluate the relationship of PSAV risk count to tumor features, subset analysis was performed in 1524 men undergoing initial...
Prostate biopsy. In the biopsy subset, prostate cancer was diagnosed in 25.6%, and the Gleason score was $\geq 7$ in 17.7. On multivariate analysis, PSAV risk count (odds ratio [OR] 5.4; $P = .0002$) was more strongly associated with Gleason 8 to 10 prostate cancer than PSA (OR 1.07; $P = .29$) or age (OR 1.06; $P = .07$). Receiver operating characteristic analysis for the prediction of Gleason 8 to 10 prostate cancer on biopsy demonstrated that a model with PSA and age was significantly improved by the addition of PSAV risk count (AUC increased from 0.625 to 0.725; $P = .031$). Net reclassification analysis confirmed that PSAV risk count significantly altered the probability of detecting Gleason score $\geq 7$ and $\geq 8$ disease on biopsy.

Several stratified analyses were also performed. For example, multivariate models performed after stratification by total PSA (< 2.6, 2.6–4, and > 4 ng/mL) showed that PSAV risk count maintained a significant association with prostate cancer detection in all PSA categories (respective ORs of 4.2, 2.3, and 3.6). To determine the utility of PSAV risk count over a longer interval, a separate analysis was performed, which included 14,024 men with at least four successive PSA measurements. In this subgroup, they determined the association between risk counts ranging from 0 to 3 with prostate cancer detection, in which a risk count of 3 indicated that all three serial PSAV measurements exceeded 0.4 ng/mL/y. A risk count of 3 was found in 15% of men with prostate cancer, compared with 1% without prostate cancer ($P < .0001$). On multivariate analysis with age and PSA, a risk count of 3 (compared with a risk count of 0–2) was associated with a 7.4-fold increased odds of prostate cancer (95% CI, 5.5–10.0; $P < .0001$).

In summary, this study demonstrated that men with two successive PSAV measurements $> 0.4$ ng/mL/y (a risk count = 2), had approximately an eightfold increased risk for prostate cancer, and a fivefold increased risk of very high-grade disease when compared with those with a risk count of 0 or 1, after controlling for age and serum PSA concentration. Limitations to this study include the requirement for multiple serial PSA tests to calculate PSAV risk count, such that 48.8% of screening study participants could not be evaluated. There was a notably higher rate of prostate cancer diagnosis (14.1% vs 6.2%) amongst this excluded group, and similarly it will not be possible to calculate risk count for men presenting to the clinic with a high initial PSA level and limited prior PSA history. Also, the majority of this cohort was white which limits the generalizability of the results. Despite these limitations, this large series showed a robust independent association between PSAV risk count with cancer detection and biopsy Gleason score.

### Prostate Specific Antigen Velocity Risk Count Predicts Biopsy Reclassification for Men with Very Low Risk Prostate Cancer


The purpose of this study was to examine, for the first time, whether PSAV risk count could help monitor patients on active surveillance. Specifically, this study examined whether PSAV risk count predicted reclassification of disease on repeat biopsy in the Johns Hopkins active surveillance cohort, and whether it provided incremental prognostic value compared to existing clinical predictors.

In this program, men are followed by semiannual serum PSA measurements and DRE, as well as annual ≥ 12-core prostate biopsy. Using data from 1995 and 2012, 668 men met all very low-risk criteria (clinical stage T1c disease, PSA density (PSAD) less than 0.15 ng/mL/cc, Gleason score 6 or less, two or fewer biopsy cores with cancer, and 50% or less involvement of any core with cancer).10

In the primary analysis including men with at least 30 months on surveillance, higher PSAV risk count was significantly associated with biopsy progression by Gleason score and/or extent of tumor. The 5-year probability of freedom from disease reclassification on biopsy was 9.7%, 18.7%, and 39.5% for men with a risk count of 0, 1, and 2, respectively ($P < .01$).

On multivariable analysis, risk counts of 3 and 2 were associated with significant 4.63-fold and 3.73-fold increased hazard ratios for biopsy progression. Overall, they estimated that 581 (42%) of the surveillance biopsies in the cohort could have been avoided in men with a risk count of 0 or 1. Finally, they showed that the addition of PSAV risk count significantly improved discrimination compared to a base model including age, race, PSAD, and cancer on the first surveillance biopsy. Moreover, PSAV risk count was superior to overall PSAV during follow-up, suggesting that this method of calculation is more suitable for use during active surveillance.

It is important to note that PSAV risk count was less reliable during the initial 2 to 3 years on AS, given the potential for misclassification and limited PSA data, underscoring the importance of surveillance biopsies during this period. However, after this initial period, PSAV risk count had a very high negative predictive value (91.5%) and could potentially reduce the number of serial biopsies.

Finally, 35 men from this population were eventually treated with prostatectomy, of which 68.6% were due to
biopsy reclassification. At the time of surgery, Gleason ≥ 7 disease was found in 29.4% with a PSAV risk count ≤ 1, versus 68.8% with a risk count > 1. Only a single patient experienced biochemical progression during follow-up, and this patient had a PSAV risk count of 2.

In summary, PSAV risk count was associated with disease reclassification to unfavorable biopsy characteristics in men with very low risk prostate cancer on active surveillance. PSAV risk count also improved model discrimination. With additional validation of these findings in other surveillance cohorts, PSAV risk count may provide another noninvasive way to monitor patients during active surveillance. This could potentially decrease the frequency of biopsies and their associated risk for complications in the long term. A limitation of this study is that the Johns Hopkins cohort was comprised of selected very low-risk patients, which may limit the generalizability to other programs with different inclusion criteria.

Discussion
Several differences between these studies by Loeb and Patel and colleagues should be highlighted. These include sample size (18,214 vs 668), type of population (screening study vs active surveillance cohort), and primary objective (detecting overall and high-grade disease vs predicting biopsy reclassification during active surveillance).

Despite these differences, both studies provide a consistent message that PSAV risk count was independently associated with increased risk of unfavourable pathology and clinically significant prostate cancer. Additional prospective studies are warranted to examine the role of PSAV risk count as part of screening and active surveillance paradigms.

Prevalence of Infections Associated With Prostate Biopsy
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It has been estimated that approximately 1 million transrectal ultrasound (TRUS)-guided prostate biopsies are done in both the United States and Europe each year.1 Previous studies using administrative claims reported an increase in infection-related hospitalizations after biopsy over time in the United States and Canada.1 However, these studies had limited data on important factors, such as culture results and the type of prophylaxis received, which might help shed light on potential ways to reduce this problem. Accordingly, several international groups have recently undertaken detailed studies on the prevalence of postbiopsy infections that include data on the type of antimicrobial prophylaxis and resistance patterns.

Infection Related Hospitalizations After Prostate Biopsy in a Statewide Quality Improvement Collaborative

The goal of the study was to establish the rate of infection-related hospitalizations after prostate biopsy within the state of Michigan by the Michigan Urological Surgery Improvement Collaborative (MUSIC). This registry prospectively collects a variety of clinical data including detailed information on prostate biopsies. Quality assurance for the data collection is achieved by regular on-site audits of all participating practices.

For this study, exclusion criteria were individuals who were not a part of MUSIC practices and those practices

References