Measuring the Importance of PSA Velocity

By Rabiya S. Tuma

Although controversial, the prostate-specific antigen (PSA) test is still widely used to determine whether a man should undergo a biopsy for prostate cancer. In recent years, PSA velocity, or how quickly the PSA level increases, is also being used to decide when to biopsy men for prostate cancer. Even though both the American Urological Association and the National Comprehensive Cancer Network (NCCN) have made PSA velocity part of their clinical guidelines, clinicians remain divided on its relevancy, and a recent study brings that debate to the fore.

In this issue of the Journal, Andrew Vickers, Ph.D., an associate attending research methodologist at Memorial Sloan-Kettering Cancer Center in New York, and colleagues use data from the large, randomized Prostate Cancer Prevention Trial (PCPT) to test PSA velocity’s diagnostic accuracy. The team concludes that using PSA velocity, as the NCCN guidelines state, would lead to many unnecessary biopsies and should therefore be removed from the guidelines. But some experts argue that this study is just one piece in a much larger body of literature that still favors PSA velocity. The one thing both sides agree on is that not only scientific data but also personal opinion influences what makes it into clinical practice guidelines, putting the onus on physicians to use their own judgment on a case-by-case basis.

Challenge Current Guidelines

Clinical practice guidelines have become more common since the 1990s as the medical community has put more emphasis on management algorithms. Yet exactly what constitutes adequate evidence to support including a given approach or technique is a matter of discussion.

The current NCCN guidelines state that physicians should use PSA velocity as part of early prostate cancer detection methods, specifically men who have a PSA below 4 ng/mL but whose PSA is rising more than 0.35 ng/mL per year should undergo a biopsy, even without other indications. In support of this approach, the guidelines cite a 2006 article in the Journal by H. Ballentine Carter, M.D., professor of urology and oncology at Johns Hopkins Medicine in Baltimore, and colleagues (see J. Natl. Cancer Inst. 2006;98:1521–7). In that study, investigators showed that in a cohort of 980 men, individuals with a PSA velocity higher than 0.35 ng/mL per year, measured 10–15 years before prostate cancer diagnosis, had a 4.7-fold-increased relative risk of cancer-specific death compared with men whose PSA velocity was 0.35 ng/mL per year or lower.

According to Vickers, the 2006 study does not support the NCCN guideline. “What Carter’s data say is that PSA velocity predicts advanced cancer 10–15 years later,” Vickers said. “That does not address the question of whether you should biopsy a man now.”

To address that question, Vickers and colleagues decided to test the NCCN guidelines by applying them to data from the PCPT—a randomized, placebo-controlled trial to test finasteride’s (Proscar’s) ability to prevent prostate cancer. All men in the trial had done multiple PSA tests and had undergone a biopsy at the end of the study, regardless of their PSA score. Using these data, Vickers and his colleagues calculated PSA velocity and estimated its sensitivity and specificity for prostate cancer detection. Of the 5,519 men in the placebo arm, PSA velocity usage would have led to 548 (almost 10% of the study population) additional biopsies, 433 (79%) of which would have been negative. Moreover, had the team added PSA velocity to existing clinical factors, including digital rectal exam, age, family history, prior biopsy, and PSA to predict prostate cancer, the predictive accuracy of the model would have increased only slightly (the area under the curve increased by just 0.007).

From these findings, Vickers concluded that the guidelines should be changed and all references to PSA velocity should be removed. “We are evaluating exactly what the guidelines say, and when we do that we end up with a very large number of unnecessary biopsies,” he said. “There are real implications of these guidelines—people getting biopsies and a lot of anxiety.”

Ongoing Debate

Not all prostate cancer experts agree with Vickers’ interpretation, however.
According to Carter, “what has been written here is another piece of evidence that PSA velocity may not be as useful as we thought it was. But I don’t think it is the end of the story, frankly.” Most important, in Carter’s view, is the absence of information about PSA velocity and detection of lethal disease. Without longer follow-up, the PCPT data can’t really address the key question of PSA velocity and its ability to help reveal lethal disease. On the other hand, Carter continues, the fact that the PCPT design included an end-of-study biopsy does make it useful for studying the association between PSA velocity and diagnosis. “PCPT is certainly as good as it gets, because PSA velocity was not used to drive a biopsy,” Carter said. “But the issue is the need for long-term follow-up, for lethality data.”

Anthony D’Amico, M.D., Ph.D., chair of genitourinary radiation oncology at the Dana–Farber Cancer Institute in Boston, said the PCPT data are inadequate for addressing questions about PSA velocity because the trial had no quality assurance for PSA tests. Physicians know that benign disease can increase PSA protein level, but they appreciate less, according to D’Amico, that pretest behavior, such as bicycle riding, sexual activity, or medical procedures, can temporarily increase PSA as well. Also, different laboratories use different assays to measure the protein, which can alter the score.

“Because the PSAs are not quality assured, there is no way of knowing [whether] the PSA velocities are accurate,” he said. “And this doesn’t just speak to the paper; this speaks to the guidelines. Calculations of velocity should only really be done on a data set where the values are collected on the same assay and where patients are educated prior to the sample being collected. Otherwise, you end up with a situation where you really don’t know what you are measuring.” D’Amico’s group recently completed a study looking at how these confounding factors continued on pages 460–461
affected PSA and found a substantial effect on PSA velocity calculation, although he declined to elaborate on the unpublished data.

Vickers, though, doesn’t buy these arguments. “Do we really think that in clinical practice out there in the community, the way that PSA is measured is really going to be better than in a randomized trial?” And though he acknowledges that the PCPT data set may not be perfect, he is confident about its value for addressing the issue of whether the guidelines should include PSA velocity. “The guidelines say to biopsy a man if he has a high PSA velocity but no other indication, so what possible data set do you have?” he asked. “We don’t have data sets for biopsy of men with no indication. This is the only possible data set to address the question.”

What Makes Good Guidelines?
When asked whether Vickers’ new data should lead to a reevaluation of the guidelines, Otis Brawley, M.D., chief medical officer for the American Cancer Society in Atlanta, and an expert on prostate cancer screening, did not answer directly—but he noted that data are not the only factor driving guidelines. “There are guidelines that are based on scientific findings from prospective, randomized, controlled trials, and then there are guidelines out there that are based on opinion,” he said. “These are guidelines based on opinion, not on prospective, randomized trials.”

Carter, who along with D’Amico sits on the committee that writes the NCCN guidelines, concurs: “A lot of it has to do with who is on the NCCN [committee] and who has the loudest voice,” he said. “And frankly, like everything else in life, there are a lot of politics here. It is not all about data.”

Although Carter thinks these new data should be weighed into the debate, he said that he and other experts would be hard pressed to get physicians to ignore changes in PSA over time. “There is not a urologist in the world who is going to have a patient walk in whose PSA went from 1 to 3 over the last 2 years and not pay attention to it.”
strictly on the strongest level of evidence, PSA velocity probably wouldn’t be included. “On the other hand, if it is going to be a group of people who review the data and then make points about the data or point out the limitations of the data, well then I think it is perfectly appropriate to include it,” he said.

For his part, Vickers is careful to say that he is not advocating that clinicians ignore PSA trends or changes over time. Rather, he thinks that calculating PSA velocity is unnecessary and even problematic if used in the way the guidelines specify. “They have these incredibly simplistic statements: ‘If the PSA velocity is above 0.35 ng/mL per year, do a biopsy; if it is not above that, don’t do a biopsy.’ Those are the guidelines we evaluated,” Vickers said. “I think when we start producing guidelines, we need to think a little bit more carefully and have a pretty solid reason to put things in there.”

He continued that even if his new study were wrong, that still wouldn’t substantiate the guidelines because, thus far, the studies have not tested the use of PSA velocity as specified in the guidelines.

D’Amico, like Carter, acknowledges that no level-one, randomized, controlled trial data exist to support using PSA velocity for prostate cancer detection. In fact, D’Amico said, the strongest data supporting the use of PSA velocity in any setting come from his own group: a 2004 report in the New England Journal of Medicine showing that PSA velocity was valuable for prostate cancer prognosis. But even that is a single-institution finding. Therefore, until stronger data come in supporting or refuting PSA velocity’s value in early detection, the guidelines should qualify its usage, and clinicians should rely on it with caution.

“That is something I don’t think practitioners appreciate,” D’Amico said. “They look at the guideline and say, ‘Okay, there it is,’ instead of saying, ‘Okay, but what level of evidence is that based on?’ People take what they hear as truth and don’t question the facts on which it is based. We have to use clinical common sense. That is the most important rule here with [PSA] velocity.”