UNFLAPPABLE PSA

Is An Improved PSA Screening Test In Sight?

By Liz Savage

A fter decades of searching for a replacement for prostate-specific antigen (PSA) in prostate cancer screening, many researchers are once again examining variations on the long-beleaguered biomarker.

PSA has withstood years of skepticism from critics who blame it for the overdiagnosis and overtreatment of millions of men since it became the favorite prostate cancer screening test in the early 1990s. But PSA is staying put in the clinic. Now, instead of focusing on new markers of prostate cancer, many researchers are looking for ways to enhance PSA’s predictive powers.

“PSA has been very effective in changing the landscape of prostate cancer, but it still has a number of significant limitations that need to be addressed,” said Robert Getzenberg, Ph.D., director of research at Johns Hopkins University’s urological institute.

PSA was first identified in 1966 and quickly proved useful for identifying semen in criminal cases of sexual assault. Further studies in the 1980s suggested its utility as a prostate cancer screening tool, but physicians were skeptical of a test with such low sensitivity and specificity. Prostate cancer causes elevated PSA levels, but so do benign conditions like prostate enlargement or inflammation. Even though PSA wasn’t a marker of cancer, it was associated with the risk of cancer. In 1994, the U.S. Food and Drug Administration approved PSA screening for the early detection of prostate cancer.

Today PSA remains controversial and is being tested in large randomized screening trials. One such trial, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, is trying to determine whether screening tests like PSA reduce cancer deaths. But results of the trial won’t be available for several years. In the meantime, the PSA test will probably remain the primary screening test. “For prostate cancer, it’s still our good old PSA,” said Sudhir Srivastava, Ph.D., chief of the cancer biomarkers research group at the National Cancer Institute. “There are some candidate biomarkers for prostate cancer, but nothing really compares to PSA at this point in time. All the data we know of are very preliminary and need to be validated.”

Researchers have been looking for a new prostate cancer biomarker throughout PSA’s screening career. There has been no shortage of promising rising stars, but none has withstood the test of time and validation. “The problem isn’t with coming up with biomarker X, Y, or Z. ... It’s finding the one that’s worth doing a clinical trial on and then validating it,” said Thomas Flaig, M.D., a medical oncologist at the
University of Colorado Health Sciences Center in Aurora. What looks promising in the lab has yet to hold up in real-world conditions. Aside from the tremendous time and money that it takes to validate a marker, a major problem with finding new biomarkers is PSA itself. Often, when trying to show that a marker is effective, researchers conduct a trial comparing the biomarker in patients with prostate cancer and those without. Ideally, researchers will find the marker in the cancer patients and not the healthy people. The problem is that the healthy group is often not given a biopsy, said Ian Thompson, M.D., professor and chair of urology at the University of Texas Health Science Center in San Antonio. According to the results of the Prostate Cancer Prevention Trial, which Thompson led, about 15% of “healthy” men with low PSA levels have prostate cancer. If men with prostate cancer are in the control group, the results of the Prostate Cancer Prevention Trial, which Thompson led, about 15% of “healthy” men with low PSA levels have prostate cancer. If men with prostate cancer are in the control group, the promising results suddenly become much less so.

Because two decades of biomarker research has still not yielded a new prostate cancer marker that can be used in the clinic today, the spotlight remains on PSA. The trick then, experts say, is figuring out how to improve on it. PSA is good at indicating advanced cancers because PSA levels rise as cancer advances, but a high PSA level does not necessarily mean that a man has cancer. Nor does a low level mean that a patient is cancer free. In fact, while the current standard is to take a biopsy sample from a man with a PSA level of 4.0 ng/mL or higher, there really is no cutoff point below which a physician can guarantee that there is no cancer. Because so many men fall into the gray area around 4.0, “this has created a large group of men who don’t know what’s going on in their prostates,” Getzenberg said. What’s needed is a marker that can augment PSA and reduce the number of men who receive an unnecessary biopsy.

Several other ways to measure PSA have been proposed and studied since PSA testing came into common use (see sidebar), but none has been widely accepted yet. PSA velocity, the change in PSA over time, has attracted the most attention, even though some question its usefulness in the clinic. In this issue of JNCI (see p. 1510), Ruth Etzioni, Ph.D., a biostatistician at the Fred Hutchinson Cancer Research Center in Seattle and colleagues reviewed the inconsistent results from studies on PSA velocity. Some studies may have suggested that PSA velocity is more useful as a screening tool than it actually is, she said. Etzioni is concerned that adding PSA velocity to screening regimens could result in more men being biopsied with little improvement in prostate cancer mortality.

“How many more men are we actually going to detect and cure if we add PSA velocity, and how many more men are we falsely going to declare positive or overdiagnose?” Etzioni asked. “This is what we should be evaluating before we try to make inferences from a variety of studies, some of which are overoptimistic, none of which weigh the cost and benefits.”

Another way to use PSA is to combine it with other known risk factors—such as age, family history, or race—to calculate a man’s prostate cancer risk. Thompson and his colleagues developed the risk calculator (http://www.compass.fhcrc.org/edrmnci/bin/calculator/main.asp) based on data from more than 5,500 men in the placebo group of the Prostate Cancer Prevention Trial. The calculator helps to put the PSA number in perspective. Take, for example, two men with a PSA level of 4.0 ng/mL. The first, a 55-year-old white man with no family history of the disease, has a 35% risk of getting prostate cancer and a 6% risk of high-grade disease. On the other hand, the second man, a 75-year-old African American man whose father had prostate cancer, has a 41% risk of cancer and a 23% risk of high-grade cancer with the same reading. If PSA and a rectal examination are the only criteria for a biopsy, then both men would undergo the procedure. But with the calculator, their risks look different. “The evidence is compelling that these other risk factors dramatically alter a person’s risk.” Thompson said.

The need for new prostate cancer biomarkers is clear. But, Thompson said, PSA isn’t going away. “In the absence of [the results of the screening trials], men as a group have decided that they want be screened. ... With that kind of ongoing natural experiment, how do we make it better?”

**The Many Faces of PSA**

**PSA velocity:** the rate of change in PSA over time
**Free PSA:** the percentage of PSA that is free in the blood versus PSA that is bound to carrier proteins
**Age-adjusted PSA:** an adjusted cutoff level for biopsying based on age—because PSA increases with age
**Pro-PSA:** an inactive PSA precursor thought to be more strongly associated with cancer than prostate enlargement
**PSA density:** the PSA level divided by the prostate volume—accounts for prostate size because larger prostates have higher PSA levels

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