Debate Continues on Use of PSA Testing for Early Detection of Prostate Cancer

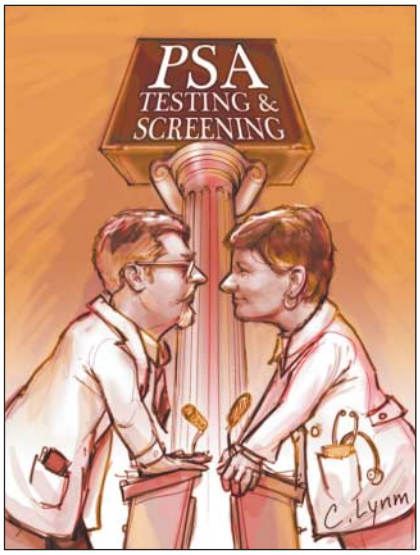
M. J. Friedrich

SERUM PROSTATE-SPECIFIC ANTIgen (PSA) testing arrived on the scene more than 20 years ago, offering great promise for the early detection and treatment of prostate cancer. Yet even after 2 decades of experience with this seemingly simple blood test, debate continues to swirl over how and when—and if—it should be used.

Prostate cancer appears in a large percentage of men as they age, but is indolent most of the time. Critics emphasize that PSA testing is an imperfect screening tool because it does not differentiate clinically significant tumors from ones that would never cause harm, and the result is overdiagnosis and overtreatment. Others defend the use of PSA testing and say that a more rational, evidence-based approach to using it can help detect and treat prostate cancer early in men who would die of the disease.

H. Gilbert Welch, MD, MPH, at Dartmouth Medical School, Hanover, NH, called PSA testing the "poster child" for the problem of overdiagnosis. "There is some benefit to screening, but it comes at a substantial human cost," he said. Surgical resection and radiation therapy can lead to such problems as incontinence, impotence, and rectal dysfunction.

PSA testing does detect more cancers earlier and at a potentially more curable stage. "However, most of these men would never develop symptoms in their lifetime, but almost all get treated," said Timothy Wilt, MD, MPD, of the Minneapolis VA Center for Chronic Disease Outcomes Research and the University of Minnesota School of Medicine. About 70% of those who are diagnosed have low-risk disease, yet 90% of these men get treated, including 80% of those older than 75 years, he said.



Clinicians and researchers continue to debate the appropriate use of prostate-specific antigen testing for detection of prostate cancer.

Others point out that clinicians should not dismiss the value of the PSA test itself, but instead recognize that it is not being used correctly. William Catalona, MD, of Northwestern University Feinberg School of Medicine, in Chicago, said, "I'm one of the biggest advocates of PSA testing because I think if it were done intelligently, it could reduce the prostate cancer death rate by half." (Catalona is a consultant for OHMX, a company that is trying to develop a new urine-based PSA assay, for which he is a coinventor.)

Two major randomized PSA screening studies published simultaneously in 2009 showed disparate results.

The US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial reported no mortality benefit from combined screening with PSA testing and digital rectal examination (DRE) during a median follow-up of 11 years (Andriole GL et al. *N Engl J Med*. 2009;360[13]:1310-1319). Yet Catalona noted that a recent article that stratified the data from the PLCO study according to comorbidity showed that PSA screening in young and healthy men reduces the risk of prostate cancer–specific mortality (Crawford ED et al. *J Clin Oncol*. 2011;29[4]:355-361).

Results from the second study, the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, showed that PSA screening without DRE was associated with an absolute reduction of 0.71 prostate cancer deaths per 1000 men after an average follow-up of 8.8 years (median, 9.0), which corresponds to a 20% relative reduction in the death rate from prostate cancer among men between the ages of 55 and 69 years at study entry (Schroder FH et al. *N Engl J Med*. 2009; 360[13]:1320-1328). A follow-up analysis that adjusted for adherence to screening showed an even higher reduction in mortality of up to 31% (Roobol MJ et al. *Eur Urol*. 2009;56[4]: 584-591).

Catalona also noted that recently reported results from the Goteborg randomized population-based screening trial came out in favor of screening, showing a cumulative relative risk reduction of 50% in the screening group (corresponding to an absolute risk reduction of 0.4%, from 0.9% in the control group to 0.5% in the screening group) during a median follow-up of

14 years (Hugosson J et al. *Lancet Oncol*. 2010;11[8]:725-732). In the trial, not all men in whom cancer was detected were treated, showing that screening can reduce mortality without requiring all patients to receive treatment.

H. Ballentine Carter, MD, of Johns Hopkins University School of Medicine, in Baltimore, said that the ERSPC trial results indicate that men between the ages of 50 and 69 years will benefit from PSA screening.

"There's a disconnect between the evidence and what we do in the United States," said Carter. "I think the controversy is not so much about screening but about the downstream effects of screening. If we know that screening saves lives and we know what we're doing is not based on high levels of evidence, why not change what we're doing instead of throwing the baby out with the bathwater?"

SCREENING OLDER MEN

One of the things clinicians are doing wrong is screening older men at greater rates than younger men, said James Mohler, MD, of the Roswell Park Cancer Institute, in Buffalo, NY, where the PSA test was developed. According to recent evidence from a population-based survey taken between 2000 and 2005, almost half of all men in the United States in their 70s are being screened compared with only 24% of men in their 50s; men in their 80s were being screened at the same rate as men in their 50s (Drazer MW et al. *J Clin Oncol*. 2011;29[13]:1736-1743).

This is exactly the opposite of what clinicians should be doing, said Mohler. Men in the age group of those older than 75 years found to have prostate cancer will be overwhelmingly dominated by "autopsy-type" prostate cancer—a tumor that is not the cause of death, one that a man dies with rather than of. By contrast, men in their 40s and 50s, especially men at higher risk, such as blacks or those with a family history, are the ones who benefit most from screening, he said.

Mohler, who is chairman of the National Comprehensive Cancer Network (NCCN) Guidelines Panel for Prostate Cancer, said the NCCN guidelines recommend annual PSA testing beginning at age 40 years for men at high risk. "We don't want to miss the young man destined to die of prostate cancer," he said, noting that the NCCN is the only group that advocates beginning testing this early.

For those with a normal risk profile, the NCCN recommends that men start PSA testing at age 40 years but if the levels are low, the test only should be repeated every 5 years until age 50 years. From that point, tests should be conducted annually until age 65 years, when testing should begin to diminish in frequency and eventually stop at age 75 years.

This points to another problem with PSA testing—knowing at what age to stop. Mohler said that it makes sense to cease testing at age 75 years for most men for a number of reasons. Not only do PSA levels go up with age as a result of enlargement of the prostate, but the amount of time it takes between a prostate cancer being detected through screening and a patient turning up in the clinic is about 10 to 12 years.

Peter Albertsen, MD, of the University of Connecticut Health Center, in Farmington, pointed out that overtesting in the elderly leads to overtreatment. He and his colleagues examined the patterns of prostate cancer treatment using data from 2004 to 2005 from 2 linked population-based sources of data (the Surveillance, Epidemiology, and End Results [SEER] program and Medicare) that provide detailed information about Medicare beneficiaries with cancer (Roberts CB et al. *Am J Med*. 2011;124[3]:235-243).

Albertsen and colleagues found that the more PSA tests the patients received, the more likely they were to be diagnosed with prostate cancer, and the more likely they were to be treated—more than 80% of men diagnosed with prostate cancer in the study were treated.

"It's a public health nightmare," said Albertsen, "because we don't know when to stop PSA testing and because we treat everyone the same whether they have high-grade or low-grade disease, whether they have comorbidities or not."

REDUCING HARMS

But once a diagnosis is made, immediate treatment is not the only option. Careful monitoring of the disease with serial PSA measurements, DREs, and biopsies, which is an approach called active surveillance, is being studied in individuals with low-risk, clinically localized prostate cancer to reduce harms from early intervention while still offering interventions if the disease progresses.

In recently published work with 769 men who were 65 years or older with very low-risk prostate cancer, Carter and his group at Johns Hopkins showed that forgoing immediate radiation or surgery for active surveillance did not increase the risk of death (Tosoian JJ et al. *J Clin Oncol*. doi:10.1200/JCO.2010.32.8112 [published online ahead of print April 4, 2011]).

Watchful waiting, also called expectant management, involves even less intervention than active surveillance. Physicians observe and ask patients about signs or symptoms of disease progression, but in the absence of symptoms, treatments in response to PSA increases or a change on a DRE are not typically offered and repeat biopsies are not performed. The emphasis is on minimizing harms related to monitoring (such as a biopsy-related infection) or from treatment. If the patient reports symptoms of possible disease progression, palliative interventions are offered to reduce or eliminate symptoms or disabling signs. While treatments for cure are not typically planned or used, they are offered.

Recent results from the randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) comparing radical prostatectomy to observation demonstrated a reduction in cancer deaths with surgery (Bill-Axelson A et al. *N Engl J Med*. 2011;364[18]:1708-1717). In contrast, findings from the Prostate Intervention

vs Observation Trial (PIVOT) reported last month at the American Urological Association's annual meeting, which compared surgery vs observation in men diagnosed in the early era of widespread PSA testing (1994-2002), indicated that surgery did not significantly reduce mortality compared with observation over 12 years in men with lower PSA levels or low-risk tumors. PIVOT findings did suggest a modest benefit from surgery for men with higher PSA levels (greater than 10) or high-risk tumors.

Andrew Vickers, PhD, of Memorial Sloan-Kettering Cancer Center, in New York City, said that while he sees both sides of the controversy, he does think that what researchers have learned in the last 15 to 20 years could be put to use to make PSA screening work well. Among the useful things learned, he said, is that although people usually think of PSA as a diagnostic tool, PSA levels also have a prognostic value, a result he and others have demonstrated. His group found that the PSA level at age 60 years predicts the lifetime risk of metastasis and death from prostate cancer (Vickers AJ et al. *BMJ*. 2010: 341:c4521).

A rational, evidence-based screening program for prostate cancer is possible, said Vickers. He proposes testing men at an early age, but not repeating the test annually in men with low readings and not performing a biopsy for a high level on a first reading because PSA levels fluctuate. For many men, with persistently high PSA levels, particularly older men, he suggests using active surveillance and sending those who would need to be treated immediately to high-volume centers, where outcomes for prostate surgery are better.

"You can push PSA testing," said Vickers. "You just have to do it in the right way." □

Retinoblastoma Therapy Delivers Power of Chemotherapy With Surgical Precision

M. J. Friedrich

THE PAST CENTURY HAS SEEN GREAT strides in the treatment of retinoblastoma, with more than 95% of US patients now being cured of this rare childhood malignancy. Building on this success, ophthalmologists have sought to minimize the adverse effects from radiation and systemic chemotherapy, hoping not only to cure the disease but also to save the eye and preserve vision.

Radiation can achieve this end, but it also can give rise to secondary cancers. And while systemic chemotherapy—which replaced radiation in the 1990s as first-line treatment for retinoblastoma—is effective in shrinking tumors, it has many adverse effects, including hearing impairment, development of second cancers, and long-term fertility issues. Systemic chemotherapy also does not fully eradicate the tumor, necessitating additional focal techniques such as laser therapy or cryotherapy that require the patient to undergo numerous examinations, procedures, and treatments.

An alternative to these therapies is superselective ophthalmic artery infusion of chemotherapy, a novel approach that delivers a chemotherapeutic agent directly to the eye while minimizing systemic exposure. It is proving to be a simple and superior technique that not only destroys tumors but also can preserve and even restore vision in some cases, said David Abramson, MD, chief of the Ophthalmic Oncology Service at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City, whose team has developed this approach.

The technique is called superselective because the clinician injects the chemotherapeutic agent directly into the ophthalmic artery—the only blood vessel supplying the eye. Performed on an outpatient basis with the patient under general anesthesia, the procedure involves feeding a microcatheter 450 μm in diameter into the carotid artery closest to the eye being treated and extending it into the ophthalmic artery by fluoroscopic control. A small amount—about 1 mL—of the agent is then delivered in pulses over a 30-minute period.

In the 1990s, Japanese investigators pioneered a similar but less selective technique that involves injecting the chemotherapy agent melphalan into the internal carotid artery. Inspired by the Japanese approach, Abramson and his colleagues put together an institutional review board–approved clinical protocol in May 2006 to test the delivery of melphalan directly into the ophthalmic artery, an approach that he calls chemosurgery because the precise technique used to deliver the drug is similar to a surgical procedure.

The trial included 10 patients who had advanced disease and whose eyes were scheduled for removal. One child could not be treated because of an anomaly in the ophthalmic artery that prevented cannulation. The procedure was done without local complications or significant systemic adverse effects in 9 patients. Among the 9 treated eyes, 2 have been enucleated for suspected tumor recurrence, although no tumor was found on histopathologic examination (Abramson D et al. *Ophthalmology*. 2008;115[8]: 1398-1404). In 3 patients, retinal function improved due to partial resolu-