PSA: Prostate-Specific Antigen, Persisting Scientific Ambiguities

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The prostate-specific antigen (PSA) test is the most important issue in men's health. It is also the most controversial. When the results of two much-anticipated studies were released in 2009, they went a long way toward focusing the debate — but scientists are still a long way from concluding the discussion.

Few could have anticipated the PSA controversy in 1966, when the protein was first identified in semen. It rapidly became a favored tool for law enforcement agencies, which used it as a marker for the presence of semen in cases of suspected sexual assault. The next important landmark in the history of PSA came in 1979, when doctors identified PSA in blood. Blood PSA levels were first used to screen for prostate cancer in 1987, and FDA approval for PSA as a screening test followed seven years later.

PSA testing caught on rapidly in the U.S. By now, most men above age 50 have been tested, and many are tested repeatedly. That's no surprise, since our society has been encouraged to value the early diagnosis of cancer along with the prompt and often aggressive treatments that follow. More surprising, perhaps, is that many experts believe that prostate cancer is the exception to the rule, and that PSA screening may actually do more harm than good. That's the crux of the controversy, and it's the very question that the two major studies were designed to answer. But to understand how this research alters the debate, it's important to understand the controversy itself. And that means starting at the beginning.

Prostate specific?

For all the uncertainties about the PSA, at least we can be sure the name is accurate.

Wrong. The protein that bears the name "prostate-specific" has also been detected in other organs, including the liver, pancreas, salivary gland, and breast (even in females). Only tiny amounts of PSA are present in these tissues. Still, purists might prefer the name Prostate Almost-Specific Antigen, while wags might suggest Perplexing Semantic Anomaly.

What is PSA?

At the center of the dispute is a simple glycoprotein (sugar-containing protein) produced by the epithelial cells of every prostate gland, benign or malignant. The prostate secretes PSA in the ejaculate, where its job is to liquefy semen, allowing sperm to swim toward their target. But although PSA is intended for the semen, some of it spills into the blood, where it can be measured by a simple blood test. Blood tests can also measure how much of the PSA is bound to other proteins and how much is unbound, or free.

One test, several roles

Doctors use blood PSA levels for several very different purposes. The test is an extremely important way to diagnose prostate cancer in men who have symptoms or laboratory abnormalities that raise suspicion of the disease. PSA levels are also used to evaluate the results of prostate cancer treatment. Some doctors even use PSA readings to estimate the severity of benign prostatic hyperplasia (BPH), non-malignant enlargement of the gland. There is no controversy about these PSA tests — but there is controversy galore about the most widespread use of PSA testing: screening for prostate cancer in men who are free of signs and symptoms of the disease.

Screening for early disease

The purpose of any screening test is to detect disease before it becomes clinically evident. Routine measurements of blood pressure and cholesterol are examples of screening tests

that have proved their worth. In the realm of cancer screening, Pap tests for cancer of the cervix, mammograms for breast cancer, and various tests for colon cancer have gained widespread acceptance.

A screening test is successful if it meets several goals:

1. It has a high *sensitivity*; that is, it detects a high percentage of cases while missing few
2. It has a high *specificity*; that is, it doesn't falsely diagnose disease when none is present
3. The test is reliable and reproducible and also safe, convenient, and inexpensive enough to gain widespread acceptance
4. Above all, the test must lead to a treatment that will improve the patient's quality of life, extend the duration of his life, or both. In a word, the test should do more good than harm.

Laboratory testing methods have improved so that PSA testing is now reliable and reproducible. Requiring only a single blood sample, the test itself is safe, convenient, and inexpensive. Coupled with the general belief that early detection is a no-brainer, these factors explain why PSA screening has become so popular. But this good news about PSA screening doesn't address the test's sensitivity and specificity, which are low (see below). And the low cost and safety of the blood test don't extend to the next steps. PSA screening often leads to prostate biopsies that are frightening, uncomfortable, and expensive. And screening may lead to treatments that do more harm than good. That's because of the limitations of the PSA itself and the very unusual natural history of prostate cancer.

Limitations of the PSA

For a test to be useful, doctors should be able to tell you whether your result is normal. Most tests have a well-established range of normal values, but for the PSA, even this apparently simple issue is controversial. Most doctors in the United States use 4.0 nanograms per milliliter (ng/mL) as a cutoff, considering results below that as normal and higher values as abnormal. But since PSA values tend to rise with age, even in healthy men, other authorities have proposed a range of normal values adjusted for age (see Table 1).

Table 1: A proposed age-adjusted PSA reference range

Age group	Proposed normal PSA range
40 – 49	0 – 2.5 ng/mL
50 – 59	0 – 3.5 ng/mL
60 – 69	0 – 4.5 ng/mL

70–79	0–6.5 ng/mL

Unfortunately, however, there is no clear-cut threshold for "normal" at any age. The likelihood that a man has prostate cancer increases as PSA levels rise, but even men with low PSAs face some risk. An important study shows how the risk rises as the PSA increases, even within the normal range (see Table 2). At higher PSA levels, the risk is even greater; according to some estimates, it may exceed 50% at PSAs above 10.

Table 2: Prostate cancer risk at low PSA levels

PSA (ng/mL)	Prevalence of prostate cancer
0.5 or less	6.6%
0.6–1.0	10.1%
1.1–2.0	17%
2.1–3.0	23.9%
3.1–4.0	26.9%

Source: Thompson, et al. *New England Journal of Medicine*, 2004, Vol. 350, pp. 2239–2246.

Even if there is no true "normal" range for the PSA, each man might have his own normal. If that were the case, then an increase in PSA might be cause for concern. Serial PSA testing measures the so-called PSA velocity, which does have value, particularly in predicting the prognosis of men who have been diagnosed with prostate cancer (see box). But many things other than cancer can produce changes in the PSA; Table 3 lists some of these factors.

Variations on a theme

Even before the PLCO and ERSPC results were unveiled in the spring of 2009, researchers were aware of limitations of PSA screening. Several modifications have been proposed, but none has proved superior to the PSA itself. One approach relies on measurements of both the total PSA and the free PSA. Cancer is more likely when the free PSA constitutes less than 25% of the total PSA; the lower the percentage of free PSA, the more likely the diagnosis of cancer. Another refinement depends on serial measurements of the PSA, typically at yearly intervals. The PSA velocity reflects the rate of change; researchers suggest that a rise of more than 0.75 ng/mL over the course of a year increases the likelihood of cancer. A similar modification, the PSA doubling time, helps doctors establish the prognosis for patients with prostate cancer; the shorter the doubling time, the worse the outlook.

The real question is not whether a PSA result is normal but what it means. And when it comes to interpreting results, the PSA's strengths and weaknesses become clear. The test's strength is its ability to detect prostate cancer in its earliest, most potentially curable form. In round numbers, PSA testing has the potential to detect about 80% of prostate cancers. Still, a normal or low reading does not rule out the disease; about 20% of men with prostate cancer have normal PSA results. A false-negative result provides false reassurance, but it's less of a problem than a false positive, which often causes great anxiety and usually leads to a prostate biopsy. In all, about 70% of men with high PSA results do *not* have cancer. And the biggest worry of all is overdiagnosis, finding prostate cancers that are so slow-growing that the treatment is worse than the disease.

Table 3: PSA variability

Many things besides prostate cancer can affect a man's PSA reading. Here are some of the common ones.

Factors that typically produce a substantial and/or sustained rise in the PSA

- Benign prostate hyperplasia (BPH)
- Prostatitis (inflammation of the gland)
- Urinary tract infections
- Prostate biopsies or surgery

Factors that sometimes produce a small and/or temporary rise in the PSA

- Ejaculation
- A doctor's digital rectal exam
- Foley (bladder) catheter and cystoscopy (bladder examination)
- Vigorous bike riding
- Warm climates
- Changes in labs or testing methods
- Hepatitis
- Bypass surgery
- Random (unexplained) variation

Factors that typically produce a substantial and/or sustained decrease in the PSA

- Therapy with finasteride (Proscar, generic) or dutasteride (Avodart)

Factors that sometimes produce a small and/or temporary decrease in the PSA

- Therapy with a statin drug
- Therapy with a nonsteroidal anti-inflammatory drug
- Obesity
- Changes in labs or testing methods
- Random (unexplained) variation

The natural history of prostate cancer

Prostate cancer is extremely common. According to estimates, about 17% of American men will be diagnosed with prostate cancer during the course of their lifetimes. That means each of us has a one-in-six chance of being diagnosed with the disease. That sounds scary, and it does underline the importance of prostate cancer. Remember, though, that the typical American man has just a 3% chance of dying from prostate cancer. In other words, only about one of every six clinically diagnosed prostate cancers will be lethal. Remember, too, that many prostate cancers never even become large enough or troublesome enough to be diagnosed clinically; Table 4 is based largely on autopsy studies from the pre-PSA era and shows that small, clinically silent prostate cancers are much more common than clinically diagnosed disease. All in all, men are substantially more likely to die *with* prostate cancer than *from* prostate cancer.

Table 4: Overall risk of developing prostate cancer

Age group	Risk of prostate cancer

50–59	10%–42%
60–69	17%–38%
70–79	25%–66%
0 and over	Up to 90%

Modified from *Report of the U.S. Preventive Services Task Force: Guide to Clinical Preventive Services*, 2nd ed. Williams and Wilkins, 1996, p. 121.

The PSA can never tell the many slow-growing, indolent, harmless prostate cancers from the less common, aggressive, potentially lethal cancers. In fact, the PSA cannot even diagnose cancer. Instead, it triggers a prostate biopsy. If doctors see cancer cells in the tissue sample, they try to estimate the cancer's aggressiveness based on its appearance. This so-called Gleason scoring system is imperfect, but it's the best we've got.

What does this have to do with PSA screening? Tests that lead to early diagnosis of aggressive prostate cancers might enable lifesaving treatment. That's the major plus for screening, and it's the upside of the PSA. But when screening identifies cancers that would never cause symptoms or harm during the patient's lifetime, it's called overdiagnosis.

Overdiagnosis is the major downside of PSA screening. A diagnosis of prostate cancer usually leads to treatment, and all prostate cancer treatments carry a substantial risk of side effects that may include sexual and urinary dysfunction. As a result, diagnosing aggressive cancers can be lifesaving, but diagnosing harmless cancers does more harm than good. The lower the PSA threshold for prostate biopsies and the more cores of tissue taken with each biopsy, the greater the risk of overdiagnosis.

The great debate

Hundreds upon hundreds of scientific papers have been written about the pros and cons of PSA screening, and debate in the public arena has often seemed even more intense than in the medical community. Until now, medical experts have divided into two broad camps, which we might call the PSAdvocates and the PSAgnostics. Here's the gist of their positions.

The case for PSA screening

The American Cancer Society (ACS) recommends that doctors discuss annual PSA testing with every man above the age of 50 who has a life expectancy of 10 years or longer; it also calls for yearly discussions to start at the age of 45 for men at increased risk, including African Americans and men with family histories of prostate cancer. The ACS says that if a man cannot decide, his doctor should recommend testing. The American Urological Association also recommends PSA screening. Until 2009, they had the same guidelines as the ACS, but their guidelines now call for doctors to offer the test to all men with a life expectancy of at least 10 years, beginning at age 40.

They have a point. Requiring only a single blood sample, PSA testing is quick, easy, and safe. With a typical cost of about $40, it is inexpensive, and technical improvements have made it reliable in most labs.

Advocates of PSA screening point out that the test has the potential to detect about 80% of prostate cancers. Without screening, some 40% of prostate cancers are not diagnosed until they have spread too far to be curable. Early detection is surely the best hope for curing prostate cancer, and PSA screening is the best way to find early disease.

The case against PSA screening

The Canadian Task Force on Preventive Health Care and the Canadian Urological Association recommend against PSA testing in men who seem healthy. The U.S. Preventive Services Task Force recommends against testing for men age 75 or older as well as for men with life expectancies of 10 years or less. For other men, the task force notes that the "potential harms of screening for prostate cancer can be established, [but] the presence or magnitude of potential benefits cannot." The American College of Physicians and American

Academy of Family Physicians agree that men should be counseled about "the known risks and uncertain benefits of screening for prostate cancer" before they undergo any testing.

They, too, have a point. Even at an average cost of $40, the annual testing of all American men over 50 would cost billions of dollars. Still, it might save money if early diagnosis could reduce the need for even more expensive treatment of advanced cancer. But critics go beyond economics to consider the problem of overdiagnosis. The PSAgnostics have long argued that screening might produce more harm than good if it leads to unnecessary treatment in men who would never be harmed by their prostate cancers.

For all their differences, the PSAdvocates and PSAgnostics have agreed on one point: the only way to resolve the issue is with high-quality randomized clinical trials. And that's just why the two studies are so important.

The American study

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial began studying PSA screening in 1993. Over the next eight years, 76,693 men between the ages of 55 and 74 volunteered for the study, which was conducted at 10 medical centers around the United States. Scientists randomly assigned half the men to receive annual PSA testing for six years along with annual digital rectal exams (DREs) for four years; men who had PSA levels above 4.0 ng/mL or abnormal DREs were advised to seek diagnostic evaluation, which usually involved a prostate biopsy. Men in the comparison group continued to receive their usual medical care. Men in either group who were diagnosed with prostate cancer were treated by their personal physicians; PLCO researchers monitored the treatment methods and found they were similar in the two groups.

The PLCO scientists tracked the men to find out how many were diagnosed with prostate cancer and how many died from the disease. After seven years of observation, 22% more cases of prostate cancer were detected in the men who had regular PSA screening. However, even though PSA screening increased the diagnosis of prostate cancer, it did not improve survival. There were 50 deaths in the PSA-screened group and 44 in the comparison group; the 13% higher death rate in the PSA group was not statistically significant. About two-thirds of the men have completed another three years of follow-up in this ongoing study; the results at 10 years mirror the findings at seven years.

The PLCO study is slated to continue until all the volunteers have been evaluated for 13 years. Researchers are compiling information on treatment side effects and quality of life along with additional mortality data.

The European study

Like the American study, the European Randomized Study of Screening for Prostate Cancer (ERSPC) began in the early 1990s. A total of 162,243 men between the ages of 55 and 69 volunteered for the study. Scientists randomly assigned half the men to receive PSA screening and the other half to receive their usual medical care. Because the study was conducted in multiple medical centers spread across seven countries, the investigators followed a number of slightly different research protocols. In most cases, PSA screening was performed an average of once every four years and, in most study centers, readings of 3.0 ng/mL triggered prostate biopsies. Men who were diagnosed with prostate cancer were treated by their own physicians according to local guidelines.

After about nine years of observation, 214 men in the PSA screening group had died from prostate cancer, while 326 men in the comparison group had died from the disease. That means screening reduced the risk of dying from prostate cancer by 20%, a result that was just at the margin of statistical significance. But the reduced mortality came at a price: an additional 48 men who were not destined to die from prostate cancer had to be treated to prevent one death from the disease.

The ERSPC scientists will continue to monitor the volunteers, evaluating both deaths from prostate cancer and side effects of treatment and quality of life.

Imperfect but important

Both the PLCO and ERSPC trials are large, high-quality randomized clinical trials, but like all such research, they have potential shortcomings. Neither study provides information beyond 10 years, but both are ongoing, which is important because many prostate cancers grow very slowly. The PLCO study has the advantage of following a single uniform nationwide protocol, but only 85% of the men assigned to screening underwent the recommended testing, and 52% of the men in the comparison group chose to have PSA tests on their own. Still, the differences in screening rates are large enough that if testing

produced a benefit, it should show up in a study this big. Some experts are likely to assert that the PSA cutoff of 4.0 ng/mL was too high (see Tables 1 and 2), but it is the level in general use in the United States. The ERSPC study generally used a PSA cutoff of 3.0 ng/mL, but has the disadvantage of incorporating slightly different standards and research protocols in each of the seven participating countries.

The American study found that PSA screening did not prevent death from prostate cancer during the first decade of screening. The European investigators reported a small mortality benefit, but at substantial cost of overdiagnosis and overtreatment. They found that a man whose prostate cancer was diagnosed by screening would have a one-in-49 chance of gaining a lifesaving benefit from prostate cancer treatment. Looked at another way, since an average American man's risk of dying from prostate cancer is 3%, the 20% reduction in relative risk reported by ERSPC would translate to an absolute risk of 2.4%, or a 0.6% reduction in a typical man's personal risk of dying from prostate cancer.

Experts have already begun debating the merits and significance of PLCO and ERSPC. Limitations in the studies ensure that a healthy discussion will continue, and we are all looking forward to results from additional research, such as PIVOT (Prostate Cancer Intervention Versus Observation Trial) in the U.S. and the PROTECT (Prostate Testing for Cancer and Treatment) study in Britain. But in science, as in politics, the perfect should not become the enemy of the good. PSAdvocates and PSAgnostics have long called for large, high-quality randomized clinical trials of PSA screening, and now they have two. Attention must be paid.

Should you have a PSA test?

Medical researchers and policymakers need to know if mass screening programs prevent death. In the case of PSA screening, the best available evidence is that testing produces little or no reduction in prostate cancer mortality. And although the PLCO and ERSPC studies have not yet released data on the side effects of treatment, it is likely that since screening does not substantially reduce the risk of death, the side effects of overdiagnosis and overtreatment will mean that screening does more harm than good.

Public policy is one thing, personal preference quite another. We have long maintained in these pages that while there is no right answer about PSA screening, there are two wrong

answers: you must be tested, and you should never be tested. As before, each man should consult with his physician (and often his spouse), then decide for himself. And the decision can change from year to year as new information comes in.

Despite these major studies, PSA testing remains a personal decision. But things *have* changed. Before PLCO and ERSPC, the PSAgnostics said there was no evidence that PSA screening saves lives. Now, they can say there is good evidence that screening does not save lives. Before PLCO and ERSPC, the PSAdvocates said that if a man could not decide whether or not to have a PSA, the default recommendation was in favor of testing. Now they may come to say that unless a man has a particular reason to request a test, the default recommendation might be against screening.

The contest will continue, but the playing field has tilted.

Looking ahead

Prostate cancer is the most common internal malignancy in American men; about 186,000 cases will be diagnosed this year alone. And in the course of this year, about 29,000 men will die from prostate cancer, making the disease the second most common cause of cancer deaths in American men. And whatever doctors think about PSA screening, they all agree that 29,000 deaths are far too many.

Enormous amounts of brainpower, effort, time, and money have been devoted to research on PSA screening. And even after PLCO and ERSPC, more study is needed. Still, the studies suggest it may be time to redirect some energy and effort to other crucial issues, starting with ways to prevent the disease. We also have a desperate need for good markers to tell if a man is at risk for aggressive prostate cancer, for better ways to distinguish harmless cancers from potential killers, and for research to find treatments that can cure aggressive tumors. The PLCO and ERSPC studies have not resolved all the questions about PSA screening, but they have opened a new chapter in research on the often harmless, sometimes lethal, always perplexing disease we call prostate cancer.

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