

News Release

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COMPLEXED PSA TEST MORE ACCURATE THAN TRADITIONAL PSA TEST IN DETECTING PROSTATE CANCER ACCORDING TO RECENT STUDIES

Bayer Diagnostics Complexed PSA (cPSA) Test Results in Fewer False Diagnoses of Prostate Cancer

ORLANDO, Florida, May 28, 2002 – Findings released today concluded that the complexed prostate specific antigen (cPSA) test was shown to be more accurate than the total PSA (tPSA) test currently used by most physicians for prostate cancer detection and monitoring. Eight studies on cPSA were presented at the annual meeting of the American Urological Association (AUA).

A study (Partin, et al) of 737 men undergoing prostate biopsy found 40% had prostate cancer. For men whose tPSA was between 2 to 6 ng/ml, cutoff values for tPSA at 2.5 ng/ml and cPSA at 2.2 ng/ml successfully detected 95% of cancer cases (i.e., 95% sensitivity). However, the “specificity” – the percent of true negatives identified by the test (or percent of false positives avoided by the test) – cPSA was 67% more specific than tPSA (19.6% vs. 11.7%).ⁱ

Given recent studies on the incidence of prostate cancer in men with PSA values in the 2.5 to 4 ng/ml range, researchers are evaluating if the current cut-off value of 4 ng/ml should be lowered. In a study by Barstch, et al, of 191 men with tPSA values between 2 to 4 ng/ml, 29% were diagnosed with prostate cancer. Cutoff values for tPSA at 2.5 ng/ml and cPSA at 2.2 ng/ml successfully detected 86% of prostate cancer cases (i.e., 86% sensitivity); however, cPSA was 68% more specific than tPSA (34.6% vs. 20.6%).ⁱⁱ

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“The value of cPSA is that it can decrease the number of unnecessary prostate cancer biopsies,” said Herbert Lepor, M.D., Professor and Chairman, New York University School of Medicine. “Since cPSA costs the same as standard tests, and provides better results, physicians should consider using cPSA when screening for prostate cancer.”

Conventional PSA testing measures tPSA. The Bayer Diagnostic cPSA test, approved by the U.S. Food and Drug Administration in September 2000, measures the level of cPSA (PSA bound to other proteins).

Additional Findings Presented: cPSA Had More Predictive Power

A study presented by Stacy Childs, M.D., examined the power of cPSA, tPSA, digital rectal exam (DRE), age and total prostate volume to detect prostate cancer.ⁱⁱⁱ Compared to tPSA values, cPSA had more predictive power, while cPSA plus suspicious DRE findings had the highest predictive value. The findings suggest that cPSA levels together with other patient factors such as age and prostate size can help physicians better predict prostate cancer risk and the need for a biopsy.

Cost Benefit of cPSA Testing

Lars Ellison, M.D., presented results from a cost-benefit analysis of different PSA tests and resulting biopsies to determine which test was the most appropriate for population-based screening.^{iv} The study concluded that the use of cPSA, with 3.8 ng/ml positive threshold, was the most-effective screening approach because it had a strong cost-benefit ratio.

Prostate Specific Antigen

PSA is a glycoprotein produced almost exclusively by epithelial cells in the prostate. Serum PSA has proven to be an extremely useful marker for early detection of prostate cancer and in monitoring patients for disease progression and the effects of treatment. PSA serum levels of 4.0 ng/ml or less are usually considered normal; higher levels (4 to 10 ng/ml or higher) are often found in men with prostate cancer. However, current PSA testing generates up to 60% “false positives” because PSA levels can also increase due to enlargement of the prostate, a non-cancerous condition increasingly common as men get older; acute infections of the prostate (prostatitis); transurethral prostatectomy; and other factors. On the other hand, testing can also generate “false negatives” because a significant number of cases of prostate cancer have been found in men whose PSA was

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“normal,” between 2.5 to 4 ng/ml.^v As a result, much research has focused on ways to improve the accuracy of PSA testing, i.e., to reduce false negatives (making it more sensitive) and false positives (making it more specific). Data presented at the AUA shows that the cPSA test overcomes many of the shortcomings of PSA and offers physicians and patients a strong weapon in the fight against prostate cancer.

Prostate Cancer

Prostate cancer is currently the most prevalent form of cancer in men and the second leading cause of male cancer death in the U.S. The American Cancer Society estimates that 189,000 men will be diagnosed with prostate cancer this year in the U.S., with 30,200 deaths attributable to prostate cancer.

Bayer Diagnostics

With approximately 7,000 employees worldwide and 2001 sales of \$1.8 billion, Bayer Diagnostics (www.bayerdiag.com), based in Tarrytown, New York, USA, is one of the largest diagnostic businesses in the world. The organization supports customers in 100 countries through an extensive portfolio of central laboratory, self-testing, nucleic acid and near patient care diagnostics systems and services for use in the assessment and management of health, including the areas of cardiovascular and kidney disease, oncology, virology, women's health and diabetes. Bayer Diagnostics is a part of the worldwide Bayer Group, a \$29 billion international health care and chemicals group based in Leverkusen, Germany. Bayer Diagnostics' global headquarters in the United States operates as part of Bayer Corporation of Pittsburgh, a research-based company with major businesses in health care, life sciences and chemicals.

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DATA CORRESPOND TO ABSTRACTS #46, 834, 838, 1286.

Complexed Prostate Specific Antigen (cPSA) Assay Fact Sheet

What is Prostate Specific Antigen (PSA)?

PSA is a glycoprotein produced almost exclusively by epithelial cells in the prostate. PSA exists in the blood in two forms: “free” (fPSA) which is not bound to protein and “complexed” (cPSA) which is bound. An elevated PSA may indicate the presence of prostate cancer (CaP). A biopsy is needed to confirm if cancer is present.

How is PSA measured?

Total PSA (tPSA) is the most common PSA test used to detect CaP. However, tPSA has low specificity leading to high levels of false positives (indicating CaP is present when, in fact it was not) and false negatives (indicating CaP is not present, in fact, it was). In addition to expensive follow-up testing because of the high levels of false positives associated with PSA, and the corresponding anxiety, pain and inconvenience, research has focused on the development of enhanced serum tests.

What is cPSA?

Studies have shown that the majority of immunoreactive PSA in cancer patients is complexed with alpha-1-antichymotrypsin.¹ The Bayer Diagnostics' cPSA assay accurately measures PSA in complex with protease inhibitors. This assay has value in the discrimination of CaP from benign prostate disease and in the monitoring of CaP following primary treatment.

How does cPSA work?

Serum samples are evaluated in a laboratory to determine the level of cPSA. Concentrations of cPSA above 3.6 ng/mL are considered abnormal, which indicate the possibility of CaP.

What are the unique benefits of cPSA?

- Accuracy:** The Bayer Diagnostic cPSA assay provided a 10-22% improvement in specificity over a commercially available (tPSA), resulting in fewer false positives.²
- Basic Math:** Since tPSA is comprised of two basic components: cPSA (approximately 85% of total PSA in most cancer-free men) and fPSA (approximately 15% of total PSA in most cancer-free men) Bayer cPSA is a direct measure of the PSA form which is in greater proportion in men with CaP.¹
- Confidence:** cPSA results will remain constant over time under normal sample handling.^{3,4} The instability of fPSA can lead to inaccurate measurement of the ratio of free to total PSA (f/t PSA) and result in an increase in false-positive results.⁵

Where is the cPSA test available?

cPSA assay is currently available in laboratories nationwide.

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Prostate Specific Antigen (PSA) Background Information

Prostate cancer (CaP) is the most common cancer, excluding skin cancers, in American men, and is the second leading cause of male cancer deaths in the United States, exceeded only by lung cancer.¹ This year it is estimated that 189,000 new cases of CaP will be diagnosed and 30,200 men will die from CaP in United States.¹

A man's risk of developing CaP increases significantly after the age of 50, and more than 75% of prostate tumors are found in men over the age of 65.² However, CaP can occur at any age. Since the introduction of the prostate specific antigen (PSA) blood test in 1986, there has been a shift towards the identification of earlier-stage cancers and better short-term outcomes.³ Today the American Cancer Society recommends that men over the age of 50 be screened for CaP by digital rectal examination (DRE), that includes a physician feeling the prostate to check for abnormalities, in conjunction with a yearly PSA blood test.¹

The Evolution of PSA

PSA has revolutionized the detection and management of CaP like no other tumor marker in the history of oncology. First discovered in 1970s, applied in the 1980s and used widely in the 1990s, PSA has profoundly impacted the way in which CaP is treated.⁴

PSA is a glycoprotein produced almost exclusively by epithelial cells in the prostate. Men with CaP have high serum PSA levels because of enhanced production of PSA and changes in the size and shape of the prostate gland that allows PSA greater access to the circulation system. PSA in the circulation system serves as a tumor marker. CaP, however, is not the only reason for an elevation in PSA. Biopsy of the prostate, transurethral prostatectomy, acute urinary retention and acute prostatitis can all increase PSA levels. Additionally, many false-positive elevations (false positive as there is actually no CaP present) in PSA are attributable to benign prostatic hyperplasia (BPH) or enlargement of the prostate, a non-cancerous condition.

Conventional PSA testing measures total PSA (tPSA), and results are reported in ng/ml or nanograms per milliliter. Results under 4ng/ml are usually considered normal, values between 4-10ng/ml are considered borderline and results over 10ng/ml strongly suggest CaP. Recent studies have shown an appreciable incidence of CaP in men whose PSA were between 2.5-4ng/ml.⁵ Given these findings, researchers are evaluating whether the values associated with normal levels, should be reviewed.⁶

Despite the widespread use of PSA in the early detection and monitoring of CaP, the specificity of PSA is low. The ideal test for CaP would be one that is 100% sensitive, i.e., it detects all causes of cancer in a group (no false negatives) and is 100% specific, i.e., it does not diagnose CaP when it is not present (% of true negatives identified by the test). PSA, at the traditional level of 4.0ng/ml, misses 18-25% of CaP and provides false-positive results in approximately 60% of patients free of CaP.⁷

To improve the specificity of PSA testing and reduce the number of negative biopsies, several approaches have been introduced including:

Percent free PSA ratio, a blood test that measures how much PSA circulates by itself (unbound) in the blood and how much is bound together with other blood proteins. If PSA results are borderline and percent free PSA ratio is low (25% or less), then CaP is more likely to be present. A biopsy is necessary to confirm. If the results of fPSA ratio are normal (greater than 25%), even with a borderline PSA, a biopsy may be avoided.⁸ Studies have shown that free or unbound PSA in blood samples can become unstable and falsely decrease over time when storage conditions are not optimal, leading to false positives and unnecessary biopsies.^{9,10}

Age-specific PSA, a comparison of PSA levels in people with similar ages. Higher PSA levels are typically more common in older men compared to younger men, even without cancer. If a man's PSA level is higher than the upper limit of normal of the age group, there is a greater chance of CaP. Although, in older men with borderline PSA levels, the comparison oftentimes leads to confusion.⁸

PSA density (PSAD), an option for patients who have had a PSA test and a transrectal ultrasound (TRUS). By dividing the PSA number by the size or volume of the prostate (from the TRUS results), the PSAD can be determined. The chance that CaP is present is greater with a high PSAD.⁸

PSA velocity, a measurement of how quickly PSA levels rise over a period of time, although, two or more PSA tests may be required over the course of several months. Additionally, PSA velocity may be helpful in terms of interpreting borderline results. It is not used to diagnose CaP.⁸

The Future of PSA Testing

Because tPSA is comprised of PSA which is bound to α 1antichymotrypsin (ACT) or complexed PSA (cPSA) and unbound or free PSA (fPSA), scientists recently began to examine the benefits of evaluating various PSA forms in relation to an increased risk of CaP. Studies have established that the cPSA proportion is the form that is increased in patients with CaP.¹¹

Test refinements, including cPSA, are improving the specificity, resulting in more accurate detection of CaP. Multiple studies have recently demonstrated the benefits of cPSA over tPSA as an initial diagnostic and monitoring marker for CaP in conjunction with DRE.^{12, 13, 14}

Benefits of Bayer Diagnostic cPSA

- Accuracy:** cPSA provides a 10-22% improvement in specificity over commercially available tPSA, resulting in fewer false positives.¹² cPSA has been shown to enhance detection of CaP in men with total PSA between 2.5-4ng/ml.⁶
- Basic Math:** Since tPSA is comprised of two basic components: complexed PSA (approximately 85% of total PSA in most cancer-free men) and free PSA (approximately 15% of total PSA in most cancer-free men), cPSA is a direct measure of the PSA form which is in greater proportion in men with CaP.¹¹
- Confidence:** cPSA results will remain constant over time under normal sample handling.^{15, 16} The instability of fPSA can lead to inaccurate measurement of the ratio of free to total PSA (f/t PSA) and result in an increase in false positive results.⁹

Multiple studies have demonstrated that cPSA offers improved specificity over tPSA and improved performance over the instability and variability found with fPSA. cPSA can completely replace total PSA as the initial diagnostic marker for CaP.

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