Prostate specific antigen (PSA) is a glycoprotein produced by prostatic acinar cells and ductal epithelium, which is normally secreted into the prostatic ductal system, where it is present in high concentrations. PSA possesses kallikrein-like serine protease activity, which dissolves seminal gel formed immediately after ejaculation. PSA is present in seminal fluid, prostate tissue, peripheral blood, and urine. Normally, very little PSA enters the general circulation. Only after a significant derangement of prostate architecture, does PSA escape from the ductal system and enter the general circulation via the lymphatics and capillaries. PSA is detectable in the serum of almost all men and levels tend to increase with age and size of the prostate. Serum PSA concentrations increase with age at a rate of 0.04 ng/mL per year in healthy adult males.

PSA is highly specific for prostate disease, but not for prostate cancer. Many conditions other than prostate cancer may increase PSA.

| Condition or Procedure | Effect on PSA |
|---|---|
| Acute bacterial prostatitis | Increased 5 - 7 X |
| Acute urinary retention | Increased 5 - 7 X |
| BPH | Usually <10 ng/mL |
| Digital rectal exam | Disputed |
| Prostate biopsy | Increased up to 50 X |
| Prostate massage | Moderate increase |
| Transrectal ultrasound | Variable |
| TURP | Increased >50 X |
| Urethral bladder catheter | No effect |
| Cystoscopy | Increased 4X |
| Sexual activity | Variable |
| Exercise bicycle | Increased 3X |
| Treadmill stress test | None |
| Hospitalization | Decreased 20% |

The circulating half-life of PSA is three days, so PSA may not return to baseline for 10 to 40 days after these procedures. Patients should probably avoid bicycling for several days before testing. There is ongoing debate about the effect of DRE on PSA level. Some studies suggest that there is no effect on PSA levels, while others feel that DRE only effects free PSA and the free/total ratio. The effect of DRE before drawing blood for PSA testing has not been conclusively proven.

Prostate cancer is by far the most commonlydiagnosed cancer among American men and remains the second leadingcause of cancer death in men. Men in the U.S. have about one chance in six of eventually being diagnosed with prostate cancer and about one chance in 30 of eventually dying of it. African American men and men with an affected first-degree relative have an even higher risk. Numerous autopsy studies have revealed that up to 30% of men 50 years of age and older have histological evidence of prostate cancer.

## PSA Screening

Widespread screening using the PSA blood test started in 1991after the publication of a high-profile study demonstratingthat elevations in PSA in asymptomatic men were associated

witha higher risk of having prostate cancer. The FDA approved the use of PSA for early detection of prostate cancer in 1994. Prior to the widespread use of PSA screening in asymptomatic men, prostate cancer was detected by digital rectal exam (DRE) and only 25% of newly diagnosed cancers were organ-confined. Since its introduction, PSA testing has dramatically changedthe landscape of prostate cancer, creating a significant rise incancer incidence and shifting the stage of disease at the time of diagnosis to amuch earlier and potentially more curable stage. Today only 5% of men have metastatic disease at the time of diagnosis compared to 50% before the advent of PSA testing. Overall, PSA appears to detect cancer 5 to10 years sooner than DRE.

Although prostate cancer mortality has declined approximately 30% during this time, some experts argue that this decline is more attributable to improvements in treatment than screening. Two recent prospective randomized trials that were expected to resolve this issue provided conflicting results (N Engl J Med. 2009;360:1310–1319 & 1320-1328). The European Randomized Studyof Screening for Prostate Cancer (ERSPC) demonstrated a 20% reduction in prostate cancer-specificmortality in men randomized to screening comparedwith controls, while the prostate armof the Prostate, Lung, Colorectal, and Ovarian (PLCO) CancerScreening Trial in the United States did not demonstrate any benefit.

Although the evidence remains conflicted regardingwhether prostate cancer screening is associated with a reductionin mortality, it is clear thatany benefit is accompanied by a significant rate of overdetection and overtreatment. Overdetection increases with age, rising from about 27% in men age 55 to about 56% at age 75. The ERSPC study demonstrated that 1410 men would need to be screened and 48 cases of prostate cancer would need to be treated to prevent one death over 10 years. Despite the fact that active surveillance is an option, more than 90% of men in the United States choose to undergo aggressive treatment, even if they have low grade cancer. This degreeof potential overdetection and overtreatmentis greater than that for anyother cancer for which routine screening occurs. Potential adverse effects of overtreatment includebleeding, infection, erectile dysfunction and urinary and fecal incontinence. Moreover, the harms of screening accrue immediately, whereas potential benefits are realized only many years later.

The cloud of controversy surrounding overdetection and overtreatment exists at least partially because there is no evidence-based, standardized threshold for a clinically actionable PSA level. Amid this continuing controversy regarding the merits of early detection of prostate cancer, the Prostate Cancer Advisory Committee of the American Cancer Society (ACS) revised its guideline on the early detection of prostatecancer (CA Cancer J Clin 2010;60:70-98). The revision states that prostate cancer screening shouldnot occur without an informed discussion about risks and benefits. If the patient decides to undergo screening, PSA is the recommended screening test with or without digital rectal exam (DRE). The age at which screening should be initiated depends on the patient’s estimated risk of developing prostate cancer:

- Age 50 years for men ataverage risk
- Age 45 years for men at higher risk including African American menand men who have a father or brotherdiagnosed with prostate cancer before age 65 years
- Age 40 years for men at appreciablyhigher risk such as those with multiple family members diagnosed with prostatecancer before age 65 years

Asymptomatic men who have less than a 10-year life expectancybased on age and health status should not be offered prostatecancer screening. At age 75 years, only about half of men havea life expectancy of 10 years or more. Men in this age groupwith significant comorbidities, as well as younger men withlife-limiting comorbid conditions, are not likely to benefitfrom screening.

ACS recommends the following PSA thresholds to guide test frequency and referral for further evaluation:

- Screening should be conducted yearly for men whose PSA levelis 2.5 ng/mL or greater
- Screening can be extended to every 2 years formen whose PSA is less than 2.5 ng/mL
- A PSA level of 4.0 ng/mL remains a reasonable level to recommend referral forfurther evaluation or biopsy in men at average risk for prostatecancer
- PSA levelsbetween 2.5 ng/mL and 4.0 ng/mL may be used to recommend biopsy in individuals at increased risk of high-grade cancer.

The American Urological Association (AUA) also recently published their Prostate Specific Antigen Best Practice Policy in November 2009 (J Urol 2009;182:2232-2241). This policy differs significantly from the ACS guideline. AUA stated that prostate cancer testing is an individual decision that patients of any age should make in conjunction with their physician or urologist. It recommended that prostate cancer screening with both PSA and DRE should be offered to men beginning at age 40 years and repeated annually. AUA no longer recommends a single PSA threshold value to prompt prostate biopsy. The decision to proceed to biopsy should be based primarily on PSA and DRE results but should also consider free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history and comorbidities. The AUA guidelines have been criticized because they are not supported by any convincing evidence.

At the other extreme, the US Preventive Services Task Force (USPSTF) concluded in 2008 that for men younger than age 75 years, the benefit of screening for prostate cancer was uncertain and the balance of benefits and harms could not be determined (http://www.ahrq.gov). They recommended against screening men age 75 years or older. If screening was eventually shown to reduce deaths, the USPSTF concluded that PSA screening as infrequently as every 4 years would yield as much of a benefit as annual screening.

These 3 sets of discordant guidelines have done little to quell the controversy regarding prostate cancer screening. Physicians are still left with a bewildering array of disparate guidelines. Despite all of these ambiguities, PSA testing will remain the mainstay of prostate cancer screening for the foreseeable future.

## Methods to Improve PSA Sensitivity and Specificity

The substantial overlap in serum PSA levels between men with BPH and prostate cancer coupled with low sensitivity and specificity for detecting early cancer has prompted a search for ways to improve the clinical usefulness of PSA. Four methods have been proposed so far; PSA velocity, PSA density, age specific PSA reference ranges and free PSA/total PSA ratio.

The rate of change in PSA over time, which is referred to as PSA velocity, can be calculated using sequential PSA measurements. To correctly measure PSA velocity, at least three PSA

values over a time period of at least 18 months is recommended. Some investigators have suggested that a PSA increase of 0.75 ng/mL or greater in a year is reason for concern in patients with a PSA level >4.0 ng/mL. Other studies have suggested that a lower PSA velocity threshold of 0.4 ng/mL per year may improve prostate cancer detection for younger men and for those with PSA levels below 4.0 ng/mL. Age adjusted PSA velocities with threshold values of 0.25 ng/mL/year in men ages 40 to 59, 0.5 ng/mL/year in men ages 60 to 69, and 0.75 ng/mL/year for men over 70 years of age have been proposed. However, the ESPRC study failed to demonstrate that PSA velocity was an independent predictor of positive biopsy.

PSA concentration increases with size of the prostate, but the degree of increase differs for benign versus malignant tissue. PSA increases ~0.2 ng/mL per gram of normal tissue versus 3.5 ng/mL per gram of cancerous tissue. The dimensions of the prostate can be determined by transrectal ultrasound and then converted to prostate volume. PSA density is calculated by dividing PSA concentration by prostate volume. PSA density is especially useful in distinguishing BPH from early cancer, when the PSA concentration is between 4.1 and 10 ng/mL and the DRE is negative. PSA density averages 0.28 for men with cancer and 0.19 for men without cancer. The probability that a patient has cancer is 15% if the PSA density is >0.15 and and increases to 90% if the PSA density is 0.50 ng/mL per cc of prostate. Unfortunately, the excellent predictive values for PSA density that have been reported in the literature have not been realized in clinical practice, largely due to interoperator irreproducibility.

PSA levels tend to increase with age. Median PSA values are 0.7 ng/mL for men in their 40s, 0.9 ng/mL for men in their 50s, 1.2 for men in their 60s and 1.5 for men in their 70s. For this reason, some investigators have suggested the adoption of age adjusted reference ranges. The following table summarizes several published age adjusted reference ranges for different ethnic groups of men.

**Age Adjusted PSA Reference Ranges (ng/mL)**

| Age in Years | Asian Americans | African Americans | Whites |
|---|---|---|---|
| 40 - 49 | 0 - 2.0 | 0 - 2.0 | 0 - 2.5 |
| 50 - 59 | 0 - 3.0 | 0 – 4.0 | 0 - 3.5 |
| 60 - 69 | 0 - 4.0 | 0 - 4.5 | 0 - 4.5 |
| 70 - 79 | 0 – 5.0 | 0 – 5.5 | 0 – 6.5 |

The use of age adjusted reference ranges for older men results in fewer biopsies but also increases the risk of missing high grade cancers in older men. They also increase the likelihood of over-detecting smaller volume and lower grade tumors in younger men.

## PSA for Risk Stratification and Prognosis

PSA levels are extremely useful in the management of patients with established prostate cancer. The percent of patients with PSA levels >4 ng/mL progressively increases with clinical stage. The proportion of men with organ-confined cancer is about 80% when the PSA level at diagnosis is <4.0 ng/mL, about 70% when PSA is between 4 and 10 ng/mL and abut 50% when PSA is >10 ng/mL. In addition, the proportion of men with metastases to the

pelvic lymph nodes is around 5% when PSA level at diagnosis is 10 ng/mL or less, 18% when PSA is between 10 and 20 ng/mL, and 36% when PSA is above 20 ng/mL.

PSA can be used to predict the presence of skeletal metastases. If a patient with untreated prostate cancer does not have skeletal symptoms and has a PSA less than 10 ng/mL, they most likely do not have skeletal metastases. One scans are generally not necessary in patients with newly diagnosed prostate cancer who have a PSA of less than 20 ng/mL unless the history or clinical examination suggests bony involvement.

PSA level is significantly associated with the risk of biochemical failure after surgical treatment of prostate cancer. Biochemical occurrence of cancer is evident within 10 years of surgery in approximately 10% of men with a preoperative PSA level below 2.6 ng/mL, 20% when the PSA level is between 2.6 and 10.0 ng/mL, and 50% when PSA level is above 10.0 ng/mL.

PSA velocity prior to treatment of prostate cancer is also associated with the risk of prostate cancer death after treatment. A PSA velocity above 2.0 ng/mL/year in the year before diagnosis is associated with a 10 fold greater risk of death in the decade following radical prostatectomy than a velocity of 2.0 or less.

**PSA in Posttreatment Management of Prostate Cancer**

PSA levels are most useful for monitoring patients with established cancer for residual disease after radical prostatectomy. When the entire prostate is removed for cancer, serum PSA should become <0.05 ng/mL. Half-life of serum PSA is three days. A serum PSA level of 50 ng/mL should become undetectable 30 days after curative radical prostatectomy.When PSA values fall to less than 0.05 ng/mL, 92% of patients remain disease free for up to 70 months. If post-operative PSA levels remain greater than 0.4 ng/mL, residual cancer should be suspected.

PSA is a very sensitive indicator of recurrence after radical prostatectomy. Levels begin to rise 6 to 23 months (mean lead-time of 12 months) before there is clinical evidence of recurrence. The American Urological Association defines biochemical recurrence after prostatectomy as a PSA value of 0.2 ng/mL. This value should be confirmed by at least 2 PSA measurements.

Patients may be treated with radiation therapy for clinically localized cancer. PSA levels may increase slightly (1.2 times baseline) immediately after beginning radiation therapy. Following radiation therapy, PSA should fall to a low level and then remain stable. PSA values <0.2 ng/mL are uncommon after external beam radiotherapy, which does not ablate all prostate tissue. Interpreting PSA values after brachytherapy is complicated because of intermittent rises. The median PSA level of these patients is 0.1 ng/mL. A consistently rising PSA value after radiation therapy usually indicates cancer recurrence. A PSA rise of 2.0 ng/mL or more over and above the nadir usually indicates recurrence.

Serial PSA levels are also helpful in monitoring androgen deprivation therapy which includes bilateral orchiectomy, luteinizing hormone releasing hormone (LHRH) agonist, or 5 alpha reductase inhibitor (finasteride) therapy. Nearly all men have a dramatic initial response to therapy with PSA levels decreasing rapidly in the first six months of treatment. In patients treated with androgen suppression therapy for metastatic disease, failure to achieve a PSA

nadir <4.0 ng/mL seven months after initiation of therapy is associated with a median survival of one year. . Patients with a PSA nadir of <0.2 ng/mL have a much longer median survival of 6 years.

**PSA Performance and Orders**

PSA values can differ by 25% from laboratory to laboratory depending on the type of instrumentation and reagent used. Assays using the 1999 World Health Organization standard yield results 20-25% lower than those using the Hybritech standard. The same assay should be used for serial testing because PSA assays are not interchangeable and there is no conversion factor between them.

An individual patient's PSA level can fluctuate at least 6% over time in the absence of prostate disease. Serial PSA measurements should change at least 21% to be considered clinically significant.

PSA concentrations decrease almost 20% within 24 hours after hospitalization, possibly because the patient has become sedentary and remains primarily in the supine position. Serial monitoring should be performed on sera collected when patients are ambulatory.

Serum PSA appears to be a relatively stable analyte. Specimens can be stored up to 3 days at room temperature, 14 days in a refrigerator, or more than 6 months in a freezer without significantly affecting concentration.

Medicare covers a screening PSA test for beneficiaries every twelve (12) months.If the interval between tests is less than 12 months, Medicare denies payment and holds the beneficiary responsible. To avoid payment denials, annual physical exams that include a PSA should not be scheduled until twelve months have elapsed.

Reference range is 0 - 4 ng/mL. The lower limit of detection for third generation assays is 0.01 ng/mL.

Specimen requirement is one SST tube of blood.

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