Since its discovery in the 1970s, prostate-specific antigen (PSA) has significantly altered the medical community’s approach to prostate diseases. PSA is the most useful marker and the single best test for detecting and monitoring prostate cancer, and new data suggest it can play a role in the management of benign prostatic hyperplasia (BPH) as well.

Biochemistry of Prostate-Specific Antigen

Prostate-specific antigen is a member of the human kallikrein family of serine proteases encoded on chromosome 19, specifically denoted human kallikrein 3 (hK3), with localized expression in prostate tissue. PSA expression has been reported in nonprostate tissues, such as normal and malignant breast tissue as well as in primary lung cancer, although without clinical use. PSA primarily exists as a glycoprotein with protease activity to lyse the clotted ejaculate, thereby enhancing sperm motility, and accordingly is in high concentration in seminal fluid.

PSA in the serum is either free or bound to the serine-protease inhibitors α-1-antichymotrypsin (ACT) and α-2-macroglobulin (AMG). Most assays now measure total PSA, or free PSA, or PSA bound to ACT. PSA epitopes bound to AMG are not exposed in the large complex, so their detection is limited. It is important to recognize that total PSA results vary from different laboratories using different assays; therefore, the results are not interchangeable because they may be calibrated against different standards. Serial PSA measurements in an individual patient should ideally be obtained using a single assay. This is particularly important now that PSA velocity is considered an important tool for early prostate cancer detection and prognosis.

Factors Affecting Prostate-Specific Antigen

PSA is prostate specific; hence, prostate cancer and BPH are not the only sources of serum PSA. A variety of physiologic and pathologic processes—such as trauma, inflammation (e.g., prostatitis, prostate abscess,
Table 1: Recommendations for the Timing of Prostate-Specific Antigen Testing in Clinical Scenarios

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on Serum PSA</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheterization</td>
<td>None (atraumatic)</td>
<td>None</td>
</tr>
<tr>
<td>Ejaculation</td>
<td>Statistically significant</td>
<td>After at least 48 hours</td>
</tr>
<tr>
<td>Exercise</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>Elevation significant</td>
<td>After 4-6 weeks of antibiotics</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>None</td>
<td>Limited data</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Acute elevation of PSA</td>
<td>None</td>
</tr>
<tr>
<td>Digital rectal examination (DRE)</td>
<td>Not clinically significant</td>
<td>At least 3 days afterward</td>
</tr>
<tr>
<td>Prostatic massage</td>
<td>Elevation significant</td>
<td>At least 7 days from TRUS</td>
</tr>
<tr>
<td>Transrectal ultrasound (TRUS)</td>
<td>Statistically significant</td>
<td>At least 6 weeks from biopsy</td>
</tr>
<tr>
<td>Prostate needle biopsy</td>
<td>Elevation significant</td>
<td>None</td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>Minimal risk of elevation</td>
<td>At least 6 weeks from TURP</td>
</tr>
<tr>
<td>Transurethral resection (TURP)</td>
<td>Elevation significant</td>
<td></td>
</tr>
</tbody>
</table>

Prostate infarction), or iatrogenic manipulation of the prostate—may cause serum PSA levels to rise.² It is important for clinicians to consider these factors along with the serum half-life of PSA (2.2 to 3.2 days) to properly interpret PSA results.⁷ Table 1 shows some recommendations for the timing of PSA testing in certain clinical scenarios.⁹⁻¹²

**Prostate-Specific Antigen in BPH**

Benign prostatic hyperplasia is the hyperplastic proliferation of epithelial and stromal cells in the periurethral region of the prostate and commonly leads to lower urinary tract symptoms. Because PSA is produced by the epithelial cells, most is secreted directly into the urethra but some enters the serum.³ As the prostate enlarges, however, more PSA enters the serum, resulting in marked overlap between serum PSA values in men with BPH and men with early prostate cancer.¹³

**PSA as a Predictor of Clinical Progression of BPH**

The placebo groups of several large BPH trials have been analyzed to determine how clinicians should use PSA as a predictor for BPH progression. Those trials include the National Institute of Diabetes and Digestive and Kidney Diseases-funded Medical Therapy of Prostate Symptoms (MTOPS) study,¹⁴ the Proscar Long-term Efficacy and Safety Study (PLESS),¹⁵ and the North American dutasteride (Avodart®) data.¹⁶,¹⁷ Various progression events have been studied, but the most useful are a 4-point increase in the American Urological Association Symptom Index (AUA SI), the development of acute urinary retention (AUR), and the necessity for BPH-related surgery (Table 2).

PLESS showed that baseline PSA levels predicted which patients were most likely to develop AUR and/or require BPH-related surgery in the placebo arm. In that study, men with a PSA level >1.3 ng/mL had the highest risk for these adverse events.

One treatment strategy for men at high risk for BPH progression (ie, whose PSA is ≥1.4 ng/mL) is to prescribe a 5α-reductase inhibitor (5ARI—finasteride [Proscar®] or dutasteride). These agents have been shown to shrink the prostate by approximately 20% (finasteride) to 25% (dutasteride).¹⁵,¹⁷ These agents prevent BPH progression efficiently when compared to other BPH treatments (α-blockers) and to other commonly used prevention strategies in contemporary medical practice. For example, clinicians must treat about 700 patients with mild hypertension to prevent one stroke, myocardial infarction (MI), or death, and 500 patients with aspirin to prevent MI or death, while physicians using 5ARIs would only treat 35 to 45 men to prevent one from suffering AUR or from needing BPH-related surgery. Because the 5ARIs are safe, their use to prevent BPH progression in high-risk men seems reasonable.

Men receiving 5ARIs generally experience a 50% to 60% reduction in serum PSA.

**PSA and Prostate Cancer**

Annual PSA testing is recommended as a screening test for prostate cancer. The best way to use PSA, however, has been under continuous evaluation. Important potential uses of PSA as an indicator of prostate cancer include consideration of PSA threshold value, PSA velocity, and PSA density.
Prostate-Specific Antigen Threshold

The appropriate threshold to warrant biopsy of the prostate for men undergoing PSA-based prostate cancer screening is unknown. In the earliest studies, a PSA threshold of 10 ng/mL was used, but clinicians quickly recognized that this level meant the discovery of advanced prostate cancer.\textsuperscript{19} More recent large-scale studies have used a PSA threshold of 4 ng/mL to warrant prostate biopsy, and some investigators have suggested thresholds of 2.5 or 3.0 ng/mL, particularly for younger men.\textsuperscript{20,21} Moreover, several age and race adjustments have been suggested.\textsuperscript{22,23} Most recently, the results of the Prostate Cancer Prevention Trial showed that a substantial portion of men (12%) with PSA levels <2.0 ng/mL had biopsy-detectable cancer, and 11% of those men had high-grade (ie, clinically important) disease.\textsuperscript{24} Evaluation of these large data using receiver-operating characteristic curves indicated that a PSA threshold of 2.1 ng/mL should be used for biopsy because it represents the optimal trade-off between sensitivity and specificity.\textsuperscript{25} This study also reminds us that no level of PSA rules out prostate cancer because 6% of men with a PSA of 0.5 ng/mL were found to have cancer.

Collectively, these data suggest that the appropriate PSA threshold must be individualized and that multiple variables—including the patient’s age, race, and prostate size—must be considered. For most men, the PSA threshold for biopsy should probably be in the range of 2.5 to 4.0 ng/mL. However, for high-risk men (ie, African Americans or men with a positive family history) and younger men, lower values must be considered.

Current PSA Screening Recommendations

The most recent screening consensus recommendations by the National Comprehensive Cancer Network,\textsuperscript{26} a panel of prostate cancer experts including urologists, radiation oncologists, medical oncologists, internists, pathologists, and statisticians, were updated in May 2006. An algorithm for prostate cancer screening begins with a serum PSA and digital rectal examination (DRE) at age 40 and is summarized below.

Prostate-Specific Antigen Level <0.6 ng/mL

Individuals with risk factors for prostate cancer (ie, African Americans or men with a positive family history) should initiate annual screening at 40 years of age even with a PSA level <0.6 ng/mL.

Table 2: Factors Marking Progression of BPH

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-point increase in the AUA Symptom Index</td>
</tr>
<tr>
<td>Development of acute urinary retention</td>
</tr>
<tr>
<td>Necessity of BPH-related surgery</td>
</tr>
</tbody>
</table>

Prostate-Specific Antigen Level <2.5 ng/mL

If the rate of change of PSA levels, or PSA velocity (PSAV), exceeds 0.5 ng/mL/y in individuals with PSA levels <2.5 ng/mL, a prostate biopsy is recommended. To calculate the PSAV, three consecutive values during a minimum 18-month interval are used. Patients with PSA >2.6 ng/mL should also be considered for prostate biopsy.

These recommendations increase the overall screening intensity for younger men. This is the ideal population to screen, because data have shown that radical prostatectomy in men younger than 65 years of age significantly reduces prostate cancer mortality.\textsuperscript{27} Randomized, large-scale studies are underway to identify whether screening for prostate cancer decreases overall mortality. The Prostate, Lung, Colon, and Ovarian Cancer screening trial\textsuperscript{28} in the United States, as well as the European Randomized Study of Screening for Prostate Cancer,\textsuperscript{29} will provide more data about the efficacy of various screening protocols.

PSA Density

PSA density (PSAD) is defined as the ratio of serum PSA concentration to the volume of the prostate gland. It was originally proposed as a tool to distinguish prostate cancer from BPH. Initially, a PSAD value >0.15 ng/mL/cc was recommended as a prostate biopsy trigger point; however, further studies demonstrated that lowering the limit to 0.08 ng/mL/cc increased sensitivity for detecting prostate cancer.\textsuperscript{30} PSAD has been shown to correlate with the presence of prostate cancer, progression-free survival, pathologic stage, and aggressiveness of prostate cancer.\textsuperscript{31}

While the concept of measuring prostate volume and PSAD is logical, there are practical limitations. Differences in the ratio of PSA-producing epithelium to stroma within the prostate have limited the utility of PSAD. Some clinicians have proposed calculating PSAD using transition zone volume instead of total prostate volume, because this is the source of PSA in BPH.\textsuperscript{32} These calculations are cumbersome and inexact; hence, most clinicians use PSA as a ‘‘tethering’’ tool (after consideration of PSA threshold and velocity) to determine whether a prostate biopsy is needed.

PSAV to Diagnose Prostate Cancer

Screening patients with PSA beginning at 40 years of age allows a clinician to obtain a baseline level. As described earlier, PSAV is the rate of change of PSA calculated using at least three serial measurements collected over at least 18 months. As first demonstrated by Carter et al in 1992,\textsuperscript{33} men with BPH had a median PSAV of 0.12 ng/mL/y, while men with prostate cancer had a median PSAV of 0.88 ng/mL/y. This study showed that a PSAV >0.75 ng/mL/y for men with PSA levels in the range of 4 to 10 ng/mL had a sensitivity for detecting prostate cancer of 72%, with a 90% specificity for those without cancer. For

Individuals with risk factors for prostate cancer (ie, African Americans or men with a positive family history) should initiate annual screening at 40 years of age even with a PSA level <0.6 ng/mL.
patients with PSA <4, conflicting evidence exists regarding PSAV. However, lowering PSAV threshold to 0.5 ng/mL/y in men younger than 60 years was recently suggested because prostate cancers may be missed in these younger patients with a cutoff point of 0.75 ng/mL/y.

**PSA to Predict Prostate Cancer Outcome**

Pretreatment PSAV is emerging as a powerful tool for predicting the course of prostate cancer. Early studies correlated PSAV to tumor grade, stage, and time to biochemical failure following radical prostatectomy. More recently, pretreatment PSAV of 2 ng/mL in the year before prostate cancer diagnosis demonstrated a high risk of death from prostate cancer and overall mortality following radical prostatectomy and external beam radiation therapy, even in classically low-risk patients.

Other studies have shown that high PSAV correlates with identification of high Gleason score cancers on prostate biopsy. Prostatitis and other variables must be taken into account when using PSAV. Serial use of the same assay is the best way to limit laboratory variability that may obscure PSAV findings.

**Other PSA Parameters**

PSA doubling time (PSADT) is best calculated using at least three serum PSA values, each separated by 3 months or more with increases of at least 0.2 ng/mL. The calculation assumes first-order kinetics and has been evaluated as a surrogate marker for prostate-cancer specific and overall mortality following radical prostatectomy as well as external beam radiation therapy. PSA doubling times of <10 months following biochemical failure after radical prostatectomy inversely correlate with survival. Also, PSADTs of <3 months following biochemical failure after surgery or radiation therapy inversely correlate with prostate-cancer-specific and overall mortality. Thus, PSA doubling time remains a useful prognostic tool before and after therapy.

Free PSA (fPSA) circulating unbound to AMG or ACT has been demonstrated to correlate with prostate cancer, especially in the PSA range of 4 to 10 ng/mL. A multi-center, prospective, clinical trial using percentage fPSA determined that a cutoff point of 25% fPSA diagnosed 95% of prostate cancers. This threshold prevented 20% of unnecessary biopsies, and percentage fPSA was an independent predictor of prostate cancer in men with normal DRE and PSA levels from 4 to 10 ng/mL. However, fPSA exists in at least three isoforms: pro-PSA, b-PSA, and i-PSA. The current assays variably measure each one and for this reason, measurement of fPSA is not routinely recommended. When assays for the three separate isoforms become available and are evaluated, it is possible fPSA will become a useful tool to aid in prostate cancer detection.

Complexed PSA-ACT (cPSA) has been investigated to improve specificity for prostate cancer detection. Total PSA (tPSA) in the range of 2.5 to 6 ng/mL remains a diagnostic gray zone. Recent analysis using a cPSA threshold for biopsy of 2.2 ng/mL for tPSA in the 2.5 to 6 ng/mL range decreased unnecessary biopsies by 11%, while maintaining 98% sensitivity. Further investigation may support cPSA as a more specific marker using a cutoff point of 2.2 ng/mL than tPSA with a cutoff point of 2.5 ng/mL. Percent cPSA is now used in the National Comprehensive Cancer Network prostate cancer screening guidelines to guide prostate biopsy recommendations as an alternative to percent fPSA.

**Summary**

We now know that there is a strong relationship between prostate volume, age, and serum PSA in men with symptomatic BPH (but without prostate cancer). Both prostate volume and PSA can be used to estimate the degree of prostate hyperplasia. Consequently, both can be used in making decisions about appropriate patient therapy, especially since treatment outcomes and the risks of long-term complications depend on prostate volume.

PSA has revolutionized our ability to identify and manage prostate disease. For BPH, men with PSA levels >1.4 ng/mL have a high risk of progression and should be considered for preventive therapy.

**References**


35. Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: results of second screening round of ERSPC (ROTTERDAM).


Self Test

This self-assessment test is presented as an educational adjunct to the monograph. Completion of this brief test will help reinforce the material you have read. Answers are elsewhere on this page.

1. The placebo data from several large studies (PLESS, MTOPS, dutasteride) investigating 5ARI therapy for men with BPH demonstrate that:
   a. progression to AUR or BPH-related surgery was increased among men with PSA levels <1.4 ng/mL.
   b. baseline PSA correlates with response to 5ARI treatment but not with BPH progression in placebo patients.
   c. baseline PSA is correlated with need for BPH-related surgery but not with risk of AUR.
   d. a baseline PSA >1.4 ng/mL indicates a higher risk of BPH-related events and may benefit from 5ARI treatment.

2. When determining PSA values in patients treated with 5ARI therapy for BPH:
   a. age- and volume-related PSA ranges are not useful.
   b. PSA thresholds are of limited value because the serum PSA is significantly decreased.
   c. a doubling algorithm is needed and maintains (or improves) sensitivity and specificity for prostate cancer detection after 6 to 12 months of 5AR therapy.
   d. prostate cancer screening using PSA is not reliable in men treated with finasteride or dutasteride.

3. PSA velocity is:
   a. useful in determining biopsy indications when it is >0.5 ng/mL/y in young individuals; however, its use in predicting prostate cancer treatment outcomes is limited.
   b. calculated by three serial serum PSA measurements at least 24 months apart.
   c. reliable in cases of prostatic inflammation or iatrogenic manipulation, although these must be taken into account.
   d. used to predict prostate cancer mortality following radical prostatectomy or radiation therapy even in low-risk patients.

4. Current recommendations for prostate screening using serum PSA:
   a. should begin at 50 years of age unless the patient is African American or has a family history of prostate cancer.
   b. would not include a prostate biopsy recommendation at a PSA level of 2.0 ng/mL because minimal chance of prostate cancer detection exists.
   c. begin at age 40 for all men with DRE and serum PSA; the median PSA value at this age is 0.6 ng/mL.
   d. no longer incorporates DRE into the algorithm to recommend prostate biopsy.

5. Use of PSA doubling time (PSADT):
   a. correlates with prostate cancer-specific and overall mortality after radical prostatectomy and external beam radiotherapy.
   b. has fallen out of favor as a prognostic tool with the use of percent free and complexed PSA.
   c. is less useful than PSA density in evaluating treatment outcomes for prostate cancer.
   d. may be calculated using any three measurements of PSA.

Self Test Answers for This Issue:
1. d
2. c
3. d
4. c
5. a
Coming in the next issue:

Prevention of BPH: Are medications effective?

—Leonard S. Marks, MD