

Prostate Specific Antigen Testing: An Update **Deborah V. Spencer, MD**

Prostate specific antigen (PSA) is an enzyme synthesized by the epithelial cells of the prostate gland under androgen receptor regulation. PSA leaks into the bloodstream when the prostatic architecture is disrupted, causing increased serum levels. Serum PSA is operationally tissue specific, but lacks cancer specificity, as it can also be elevated in conditions such as benign prostatic hyperplasia (BPH) and chronic prostatitis. PSA was introduced into clinical practice in the 1980s for prostate cancer screening,¹ and the percentage of prostate cancers discovered in the late-stages has decreased since that time, with more cancers being diagnosed at curable stages.²

PSA forms complexes with various endogenous protease inhibitors, including α_1 -antichymotrypsin (ACT), and approximately 90% of PSA in serum exists as a PSA-ACT complex. In prostate cancer, there is generally an increase in the serum concentration of bound PSA, and a corresponding decrease in unbound or free PSA. The percentage of free PSA (% fPSA) is most helpful in determining which patients with PSA levels between 4.0 to 10.0 ng/mL should be biopsied,³ although this decision is usually made based on total serum PSA levels alone.

Significant variability exists among PSA assays, with most platforms having greater than 10% relative difference for total and percent free PSA.⁴ As a result, PSA results from different assays are not interchangeable. In addition, a majority of assays are now calibrated using a reference standard that produces PSA values approximately 25% lower than the original assay used to establish the cutoff value of 4.0 ng/mL.⁵ The 4.0 ng/mL upper limit of normal is imperfect, as a significant number of men with prostate cancer have PSA values below 4.0 ng/mL.⁶ Analysis of PSA kinetics such as velocity, doubling time, and density have been used to help determine which patients between 2.5 and 4.0 ng/mL should be biopsied.

The American Cancer Society (ACS), which has not recommended regular PSA screenings since the 1990s, recently updated its prostate cancer screening guidelines to include warnings of the limitations of the PSA test, adding that PSA testing should only be offered to informed patients after receiving information about the uncertainties, risks, and potential benefits of screening.⁷ The updated ACS guidelines are in direct response to results from two large, prospective clinical trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC)⁸ and the Prostate, Lung, Colorectal, and Ovarian (PLCO)⁹ trial, which showed that prostate cancer screening may not reduce cancer specific death rates (PLCO) or may reduce death rates (by 20% in the ERSCP) only after screening and treating large numbers of men for each death prevented. These trials have prompted concern that population-based screening

may result in significant overdiagnosis and overtreatment. The American Urological Association still advocates regular PSA testing, along with digital rectal exam, although not annually.

PSA has a sensitivity of $\geq 80\%$, and specificity of $\sim 50\%$ at > 4.0 ng/mL. Approximately 20% of initially negative biopsies become positive over a three-year period, and thus specificity may be higher than 50%, assuming cancer was present at the time of the initial biopsy.¹⁰ In contrast, the sensitivity of sextant prostate biopsies is approximately 60%, with specificity of 100%.¹¹ Because of the low cancer specificity of PSA, emphasis has been placed on finding prostate-cancer specific biomarkers. Promising biomarkers include Prostate Cancer Antigen 3, Early Prostate Cancer Antigen-2 (EPCA-2), and proPSA (p2PSA) an isoform of free PSA, all of which are elevated or overexpressed in prostate cancer, and the TMPRSS2:ETS cancer specific gene fusion.¹² Although these markers are promising, there is still a need to identify biomarkers for aggressive carcinomas that would identify which patients need more aggressive treatment regimens.

References

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