



## A NEW GENERATION OF PSA TESTING

A decade has elapsed since PSA became available for the detection and staging of prostate cancer. The initial upper limit of normal was set at 4.0 ng/ml based on an evaluation of approximately 1,000 healthy men over the age of 40. Since then, efforts have been made to make the test more sensitive so as to detect more cancers and more specific so as to avoid positive tests in men without cancer. Therefore, a new generation of PSA evaluations has emerged. They include age-specific reference range, PSA velocity, PSA doubling time, PSA density, PSA ratio and, most recently, reverse transcriptase-polymerase chain reaction (Rt-PCR) for PSA. A description of these tests and their roles follows:

### Age-specific Reference Range (ASRR):

Because PSA is produced by the normal prostate, and because prostatic enlargement provides a bigger factory for PSA production, it is expected that PSA levels rise as men age. Therefore, men over the age of 70 can have a PSA up to 6.5 ng/ml and still be considered within normal limits. The age-specific reference range is not accepted by all urologists, but it does emphasize the need for some latitude for slightly elevated PSAs in the older age group as a result of prostatic enlargement.

### PSA velocity (PSAV):

A study that made use of banked serum was able to measure PSA levels retrospectively over a 10- to 20-year interval in men who were known to have prostate cancer and those who were known to have benign prostatic hypertrophy (BPH). The PSA slope accelerated 5

to 7 years before the diagnosis of cancer. The rate of rise was significantly greater than for BPH patients, in whom the minimal rise over time due to increased prostate volume occurred (see above age-specific reference ranges). Thus, patients whose annual PSA demonstrates progressive rises need to be evaluated for the presence of cancer.

### PSA Density (PSAD):

This concept is related to age-specific reference ranges in that it poses a correction for PSA based on prostate volume. The formula "PSA divided by prostate volume" is used. Obviously if a patient has a very large prostate with an elevated PSA, the PSA density might be entirely within normal range. One of the difficulties with PSA density measurement is the fact that PSA volume measurement reproducibility can be quite unreliable.

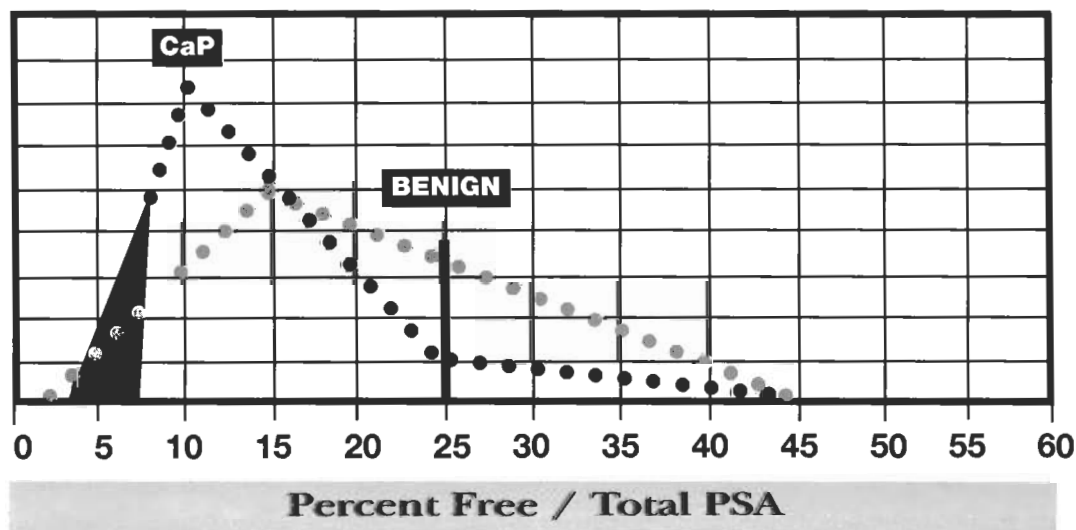
### PSA Doubling Time (PSADT):

This calculation projects the time span for the PSA to double. The longer the doubling time, the less likely the presence of cancer. It is, therefore, related in some degree to PSA velocity.

### PSA Ratio:

It has become clear that there is more than one form of PSA in the serum. "Complexed" PSA is produced to a greater degree in patients with cancer, and "free" PSA is produced to a greater degree in patients with BPH. Therefore, ratios can be developed. Very low ratios of free to complexed or free to total PSA are associated with

**Distribution of free to total PSA in serum. Patients with prostate cancer have lower free/total ratios, whereas patients with benign disease have higher ratios.**



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cancer, whereas high ratios are associated with benign enlargement as shown in the figure. The free to total PSA (also called PSA-2) evaluation is still in the process of evolution to determine the most accurate ratio levels associated with cancer and BPH. More testing and analysis will be necessary to reach appropriate conclusions.

#### RT-PCR:

The newest and most sophisticated (high-tech) test is RT-PCR for PSA. This test measures the presence or absence of a prostate cancer cell in the bloodstream. RT-PCR for PSA actually measures the presence of a PSA-producing prostate cell. The presence of circulating prostate cancer cells would appear ominous. However, it has been clearly demonstrated that circulating cells are cleared from the body by a number of mechanisms and do not imply successful spread of the tumor. However, the presence of such cells does place the patient at higher risk for eventual metastases. Determining the real significance of RT-PCR will require a significant amount of further laboratory investigation. It is at present not appropriate for clinical use.

Eastern Virginia Medical School is collecting both PSA ratios and RT-PCR data in collaboration with other centers across the country so that appropriate analysis and clarification of the role of these two assays will be possible.♦

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