

# **Current and Emerging Biomarkers for Disease Management**

**Michael E. Karellas, MD**

**Assistant Professor of Surgery, Division of Urologic Oncology, The Cancer Institute of New Jersey, Robert Wood Johnson**

## **Current Biomarkers**

PSA was discovered in the '70s and was given FDA approval in 1986 for monitoring for prostate cancer; it was initially approved for screening. It functions to liquefy semen and circulates into two fractions in the serum, both bound and unbound. Prior to the PSA era and 1990, a majority of men were diagnosed with metastatic disease at diagnosis. Now, up to 85% of cancers are clinically localized and have a high cure rate after local therapy. There was a major spike in the late '80s to '90 in the diagnosis rate of prostate cancer, which corresponds with the increased use of PSA. Yet, PSA is organ specific but not disease specific. One can have elevation in PSA from any type of derangement of the tissue architecture, including BPH, inflammation, infection, cancer, or a diagnostic procedure. The cancer does not actually make more PSA; the cell wall leaks PSA into the bloodstream leading to a higher blood test level. Some medications lower PSA, such as finasteride and dutasteride.

There is a lack of consensus for use of PSA for routine screening. The lifetime risk of death from prostate cancer is only 3.4%. The single PSA threshold recommending a biopsy is not appropriate, and specificities can vary at different levels. There was a movement to lower the threshold but this would result in overdetection and probable overtreatment. The goal overall is to do minimal biopsies but yet detect more clinically significant cancers, cancers which would ultimately cause men to die from their disease.

As PSA does have faults, there have been many tools to try to tweak PSA in an attempt to increase the rate of positive biopsy diagnosis. PSA velocity measures rise in PSA over time; overall, this has not been shown to be a useful independent predictor of a positive prostate biopsy. Since PSA circulates as both bound and unbound portions in the plasma, there have been studies looking at the percentage of free PSA to see whether this is a way to further increase the sensitivity of PSA. Benign prostate tissue has more free PSA; therefore, men with prostate cancer should have lower ratios of free PSA relative to total PSA. Recent data have shown the percentage of free PSA only adds modest clinical value as an adjunct to using total PSA by itself for screening.

Larger prostates will have more PSA; for men who have BPH, the larger gland will make more PSA. Therefore, factoring in for the size of the prostate and adjusting for the normal value of PSA might be helpful in increasing accuracy as a biomarker. Using PSA density can often yield better results than using free PSA alone; however, this method requires an invasive transrectal ultrasound. Current AUA recommendations are a baseline PSA at age 40, and then a decision to biopsy based on DRE and PSA results, also accounting for other factors including free and total PSA, age, PSA velocity, PSA density, ethnicity, prior biopsy history, comorbidities, and family history.

## **Emerging Biomarkers**

Emerging biomarkers hopefully will allow us to have a better predictive volume with screening. The PSA3 urine test looks at a prostate specific non-coding mRNA that is overexpressed in prostate cancer as well as in metastatic prostate cancer specimens relative to benign tissue. This is a promising test to improve prostate cancer detection; it provides greater accuracy for predicting outcomes of repeat biopsy than a PSA level.

Human Kallikrein 2 is a serine protease with 80% homology with PSA. It has been found to have more intense expression in prostate cancer cells than in normal prostate tissue and has been proposed as a marker for advanced disease. Recently, Steuber reported that hK2 is the strongest predictor of extra-capsular extension as well as seminal vesicle invasion relative to other factors such as free and total PSA and free hK2. It is proposed to be predictive of locally advanced and recurrent cancer for people with PSA less than ten; preliminary results are encouraging but require further evaluation.

Plasma specific membrane antigen, or PSMA, is embedded in the prostate epithelial cells. The function is unknown, but it does show a higher expression in prostate cancer cells. This antibody is currently used in the ProstaScint scan, which is used to detect recurrent cancer. Western blot or ELISA can detect serum PSMA, yet no convincing data exists to support use for a blood test. Early prostate cancer antigen, or EPCA, is a result of an alteration of a nuclear protein, either EPCA or EPCA2, which are expressed at higher levels in prostate cancer cells. A blood test for EPCA2 demonstrated a 94% sensitivity and 92% sensitivity for prostate cancer detection, possibly elevated in extra-capsular extension or more sensitive disease. Again, data are promising but further studies are needed.

Prostate cancer, like any tumor, can express antigens to which the body makes antibodies; monoclonal antibodies to protein AMACR yields 97% sensitivity on testing. Antibodies with polyclonal ability might offer increased performance as well, but like other biomarkers, additional studies are ongoing.

Circulating tumor cells are tumor cells present in the blood of patients with metastatic epithelial cancers but often have been difficult to measure, culture and characterize. Some patients show persistence of circulating tumor cells for up to three months post-surgery, suggesting possibly disseminated tumor deposits throughout the body.

## **Nomograms**

Nomograms are used to assess risk for prostate cancer diagnosis. Useful websites include [Nomogram.org](http://Nomogram.org) and [Mskcc.org](http://Mskcc.org). Data can be entered and a subsequent permutation is made.