

One study found that the PCA3 assay had a **negative predictive value of 0.73** and that the assay ratios correlated with rising Gleason scores.

Assay is gene marker, not surrogate marker

New PCa assay aids critical diagnostic decisions } Prostate Cancer {

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Atlanta—A new prostate cancer test known as the PCA3 assay (Gen-Probe Inc., San Diego) remains a work in progress, but at this stage of development, it appears to offer significant utility in men with subtly elevated serum PSA (ie, ≥ 2.5 ng/mL) but a negative initial biopsy.

The question these men raise is whether to watch and wait or to proceed to a second biopsy. Urologists now have a third option: the PCA3 assay.

One of a series of studies presented here at the AUA annual meeting showed that in a cohort of 225 men with PSAs ≥ 2.5 ng/mL and one negative biopsy, the PCA3 ratio had a sensitivity of 58%, a specificity of 74%, and an odds ratio of 3.9. By comparison, PSA with a cutoff of 4.0 ng/mL has an odds ratio of 1.2, which means that PSA has negligible diagnostic value at best.

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Dr. Marks

“This is the problem,” said Jack Schalken, PhD, research director in the department of urology, Radboud University Nijmegen Medical Center, the Netherlands. “The patient has an elevated PSA but a negative biopsy, so there is a concern as to what to do next. We have five clinics in the Netherlands that have been using this assay for 3 years now in these circumstances. In fact, now that they are familiar with the assay and data, they are turning to the PCA3 assay in selected cases to indicate a need for the first biopsy.”

Dr. Schalken and his team are credited with being the first to publish a description of the PCA3 gene in 1999. The assay that evolved from their discovery measures the mRNA of the prostate cancer-associated gene in urine expressed following a digital rectal exam.

“It is not perfect, but it is a new tool and, in

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JACK SCHALKEN, PhD

combination with PSA and biopsy, it can be very useful,” said Yves Fradet, MD, professor of surgery, University Laval, Quebec, and a co-author of one of the studies presented here.

Dr. Fradet explained that the assay works by quantifying PCA3 mRNA in voided urine and normalizing PCA3 levels to the amount of prostate RNA in the same sample using a prostate-specific “house-keeping” gene. The resulting ratio is then reduced by a multiplier (10^{-3}) to yield the PCA3 score. The PCA3 score is correlated with prostate biopsy results, and different cutoff points yield varied specificities and sensitivities. Dr. Fradet’s team calculated that a PCA3 score of 35×10^{-3} represented the optimal balance of specificity and sensitivity. In other words, a cutoff of 35 produced the greatest diagnostic accuracy.

Specific to prostate tissue

Whereas the study presented by Dr. Fradet showed the PCA3 test to have immediate applications, the other studies presented suggest a broader role for the assay in the future.

Leonard S. Marks, MD, medical director of the Urological Sciences Research Foundation, Culver City, CA, presented data suggesting that PCA3 is specific to prostate tissue and no other cancer tissue and that PCA3 scores are significantly different among patients with cancer and patients with presumed normal prostates, those with biopsy-negative tissue, those with tissue showing prostatic intraepithelial neoplasia, or those with atypical small gland proliferation. In addition to helping establish the specificity of the assay, Dr. Marks’ study also found that PCA3 was not influenced by prostate volume. BPH is known to influence PSA levels and complicate decisions as to whether to pursue a biopsy.

Another related study from Radboud University showed the assay to have a negative predictive value of 0.73, and it also found that the assay ratios correlated to a degree with rising Gleason scores.

Jack Groskopf, PhD, senior research scientist for Gen-Probe Inc. and a co-author on one of the studies, told *Urology Times* that although the test is currently directed to a specific population of men with elevated PSA and negative biopsies, the number of men who fall within that range is not small.

“It is estimated that there may be between 10 and 20 million men in the United States alone with elevated serum PSA and at least one negative biopsy. We think the urologist will get the

UT Table

PCA3 vs. PSA: Data in men with at least one negative Bx

	PCA3 assay	Serum PSA
Cutoff	PCA3/PSA= 35×10^{-3}	4.0 ng/mL
Sensitivity	58%	83%
Specificity	74%	17%
Odds ratio	3.9	1.2

Source: Jack Groskopf, PhD



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YVES FRADET, MD

most benefit from the PCA3 assay in this initial target population,” Dr. Groskopf said.

“It is important to note that this test directly detects PCA3 mRNA from cancer cells. It is not a surrogate marker like serum PSA.”

Then there is the mystery of the gene’s function. It is not now known.

“This is a whole new class of genes. Dr. Coffey at Johns Hopkins has observed that this is one of the first examples of a gene with a practical application, but we have no clue as to what it does,” Dr. Fradet said.

The assay as developed by Gen-Probe is relatively simple to use.

First, voided urine is collected following an “attentive” digital rectal exam. An attentive exam is described as applying firm digital pressure to the prostate from base to apex and from the lateral to the median line for each lobe with exactly three strokes per lobe.

The urine is then placed in a medium that can be shipped overnight to labs in cold packs or stored up to 6 months at -70°C .

The PCA3 assay is currently offered commercially by two U.S. laboratories: Bostwick Laboratories, Richmond, VA, and AmeriPath, Palm Beach Gardens, FL. **UT**