

Detecting the undetectable in prostate cancer screening

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A team of Northwestern University researchers, using an extremely sensitive tool based on nanotechnology, has detected previously undetectable levels of prostate-specific antigen (PSA) in patients who have undergone radical prostatectomy.

The researchers found measureable PSA levels in each post-operative patient in its study, thanks to the power of the nanoparticle-based bio-barcode assay developed at Northwestern. The technology is 300 times more sensitive than commercially available PSA tests. After the removal of the prostate gland, patients typically have PSA levels that are undetectable when measured using conventional diagnostic tools.

This ability to easily and quickly detect very low levels of PSA may enable doctors to diagnose men with [prostate cancer](#) recurrence years earlier than is currently possible. Prostate cancer is the second leading cause of cancer death for men in the United States. (Only lung cancer is more deadly.)

"We have defined a new zero for PSA," said Chad A. Mirkin, George B. Rathmann Professor of Chemistry in the Weinberg College of Arts and Sciences, professor of medicine and professor of materials science and engineering. "This level of sensitivity in detecting low concentrations of PSA will take the blinders off the medical community, especially when it comes to tracking residual disease."

The study will be published online during the week of Oct. 19 by the

[Proceedings of the National Academy of Sciences](#) (PNAS). Mirkin and C. Shad Thaxton, M.D., assistant professor of urology in Northwestern's Feinberg School of Medicine, led the study. (Both are members of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.)

"This new PSA assay may alter the management of patients who have been treated with surgery for prostate cancer," said William J. Catalona, M.D., professor of urology at the Feinberg School and director of the Clinical Prostate Cancer Program at the Lurie Cancer Center. He was the first to demonstrate that the [PSA test](#), a simple blood test, could be used as a screening tool for prostate cancer.

"Studies have shown that postoperative radiation therapy given early to patients with adverse pathology, called adjuvant radiation, reduces the recurrence rate and improves survival," Catalona said. "Because the 'nano-PSA assay' is more sensitive than the current commercially available PSA tests, it may allow physicians to target adjuvant radiation for patients destined to have a life-threatening tumor recurrence."

The study is an early indicator of how nanotechnology can be used to improve medical diagnostics and early cancer detection. In the case of prostate [cancer recurrence](#) following primary surgical treatment, patients with detectable but non-rising PSA levels could be reassured that their cancer will not recur. This reassurance potentially could be delivered much earlier than with conventional diagnostic tools. For patients with increasing levels of PSA, detected before conventional tools are able, doctors could diagnose a recurrence and intervene accordingly.

Furthermore, the effectiveness of post-operative treatment could be assessed by monitoring a patient's PSA levels. Tracking PSA levels early, before conventional tools are able, may allow doctors to validate treatments for recurrent cancer, such as radiation, hormone therapies and

chemotherapies. The most effective will be able to keep down PSA levels.

"The first route to a new therapeutic is a good diagnostic tool, and that's what we have here," said Mirkin, director of Northwestern's International Institute for Nanotechnology. "This bio-barcode assay, or a variant of it, could be a commercial tool in as little as 18 months. The technology is there. Now it's a business decision."

PSA is a protein produced by the cells of the prostate gland and found in the bloodstream. This pilot study looked at serum samples from 18 post-prostatectomy patients collected over the course of a number of years.

The researchers were able to reliably and accurately quantify PSA values at less than 0.1 nanograms per milliliter, the clinical limit of detection for commercial assays. The lower limit of detection for PSA using the bio-barcode assay is approximately 300 times lower than the lower limit of detection for commercial tests. The PSA measurements were used to classify the patients as either having no evidence of disease or having a relapse of disease.

The Northwestern team is now conducting a similar retrospective study of 260 patients and eventually plans to do a large prospective study.

The ultra-sensitive technology is based on gold nanoparticle probes, decorated with DNA and antibodies that can recognize and bind to PSA when present at extremely low levels in a blood sample. A magnetic microparticle, outfitted with a second antibody for PSA, also is used in the assay. When in solution, the antibody-functionalized particles "recognize" and bind to PSA, sandwiching the protein between the two particles.

The key is that attached to each tiny gold nanoparticle (just 30

nanometers in diameter) are hundreds of identical strands of DNA. Mirkin calls this "bar-code DNA" because they have designed it as a label specific to the PSA target. After the "particle-protein-particle" sandwich is removed magnetically from solution, the DNA is removed from the sandwich and read using a Verigene® ID system, a nanotechnology platform designed to detect and quantify DNA.

The amount of PSA present is calculated based on the amount of bar-code DNA. For each molecule of captured PSA, hundreds of DNA strands are released, which is one of the ways the PSA signal is amplified.

More information: The title of the *PNAS* paper is "The Nanoparticle-Based Bio-Barcode Assay Re-Defines 'Undetectable' [PSA](#) and Biochemical Recurrence Following Radical Prostatectomy." In addition to Mirkin and Thaxton, other authors of the paper are Robert Elghanian, Audrey D. Thomas, Savka I. Stoeva, Jae-Seung Lee, Norm D. Smith and Anthony J. Schaeffer of Northwestern, and Helmut Klocker, Wolfgang Horninger and Georg Bartsch of Innsbruck Medical University in Austria.

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