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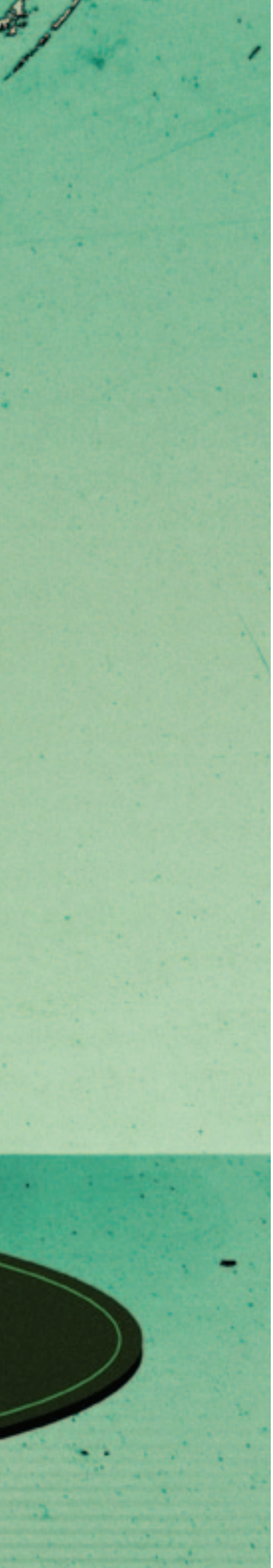

HITTING THE BULL'S-EYE IN PROSTATE CANCER

NEW IMAGING TECHNIQUES PIONEERED AT NYU LANGONE DISTINGUISH DEADLY LESIONS.

BY BRYN NELSON • ILLUSTRATIONS BY STUART BRIERS

IMAGINE A BLINDFOLDED ARCHER taking aim at a bull's-eye hung randomly in a room. A direct hit would be rare, even with 12 arrows in his quiver. For years, doctors have faced a similar challenge when using biopsy needles to probe the prostate gland in search of potentially lethal tumors.

The walnut-size gland surrounding a man's urethra is a hot spot for cancer, but notoriously difficult to access with existing imaging technology. As a result, the mostly blind biopsy technique that is still the standard of care often misses dangerous tumors while highlighting clinically insignificant ones.

New MRI–based imaging methods pioneered by NYU Langone Medical Center researchers could offer clinicians some much-needed insight, potentially transforming how tumors are detected, diagnosed, and treated. "I'm very excited and believe we can correct all the woes of screening by integrating imaging," says Samir Taneja, MD, the James M. and Janet Riha Neissa Professor of Urologic Oncology and professor of radiology.

Prostate cancer, the second leading cause of cancer-related death among men in the United States, behind only lung cancer, struck nearly 242,000 men and killed more than 28,000 in 2012, the American Cancer Society estimates. Autopsies on men over the age of 50 who died from other causes have added a startling twist, however: nearly one-third showed early signs of prostate cancer. Scientists believe that most of these slow-growing tumors never become problematic during a man's lifetime. But which ones might remain small and contained, and which ones could eventually become aggressive killers?

Tissue biopsies have long been imperfect tools for spotting signs of trouble within the prostate. The prevailing technique of inserting a dozen needles in a largely random pattern throughout the gland may reveal microscopic, nonlethal cancers that would never have harmed the patient, contributing to over-detection. At the other extreme, the biopsies may completely miss a potentially lethal cancer, contributing to under-detection through false-negative results. "So even if the patient walks out with a negative biopsy, you're never able to comfortably tell him, 'You don't have cancer,'" Dr. Taneja says.

A biopsy can also underestimate the size and aggressiveness of a prostate tumor if the needle grazes the outside edge, leading clinicians to erroneously recommend deferring treatment in favor of regular monitoring, a strategy known as active surveillance. Herbert Lepor, MD, the Martin Spatz Chair of Urology, says a recent analysis of his extensive patient database—one of the largest in the world—suggests the problem may be widespread. Since his arrival at NYU Langone in 1993, Dr. Lepor has performed thousands of surgical prostatectomies to remove a malignant prostate gland after digital rectal exams, PSA tests, and standard biopsies suggested a slow-growing cancer. Among his prostatectomy patients who might have been candidates for active surveillance because of their biopsy results, more than half actually had clinically significant disease, according to pathology exams of their removed prostates.

A more general assessment of cancer risk based on a prostate protein called prostate-specific antigen, or PSA, has also proved less than ideal. Unusually high PSA levels or a sudden spike in its production can sound the alarm and suggest that a follow-up biopsy is warranted. Although the blood-based PSA screening test is simple and inexpensive, allowing it to be widely used, the protein marker is not specific for cancer. Several major clinical studies, in fact, have reached conflicting conclusions about whether the test provides a significant survival advantage.

The uncertainty led the U.S. Preventive Services Task Force to issue a controversial recommendation last May against performing the PSA screen for men in the general population. False-positive test results, the task force reasoned, often trigger an equally unreliable biopsy, leading to over-diagnosis and overtreatment of cancers that may never become symptomatic. Bleeding and infection can occur after a biopsy, and incontinence and sexual impotency may result after a surgical or medical treatment, even with the care of highly experienced and skilled doctors.

Despite the risks, Dr. Taneja and Dr. Lepor, whose research has been supported in part by the Joseph S. and Diane H. Steinberg Charitable Trust and NYU Langone Medical Center Trustee Joel Smilow, are convinced that the PSA test has saved many lives; they say they are "extremely disappointed" with the task force's recommendation. "I am a firm believer in prostate cancer screening," says Dr. Lepor. "Turning the clock back to prescreening would be absurd, based on what we know." Before doctors began embracing screening in the late '80s and early '90s, he says, "the diagnosis of prostate cancer was pretty much a death sentence." Since then, the mortality rate of prostate cancer has dropped by more than 40 percent, a dramatic decline that he and Dr. Taneja contend is almost certainly due in part to the widespread availability of early screening.

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"We've made progress. But if anyone thinks that we've optimized screening by using a nonspecific marker and randomly placing 12 needles and taking 12 specimens, then he's naive," Dr. Lepor says. "There's no doubt in my mind that we have to keep screening, but we have to screen smarter." Improved imaging, the researchers say, is the best way forward because it will likely identify many of the aggressive tumors often missed by random biopsies in the past. "It will reduce over-detection, do away with false-negatives, and potentially give us a more accurate depiction of that cancer," Dr. Taneja notes.

At NYU Langone, this ardently sought goal could spring from a technology called multiparametric MRI, developed by a collaborative team of urologists, radiologists, and other researchers. "In one exam, the patient is imaged with a variety of different MRI techniques that collectively let us better see tumors and their location in the prostate, and assess their biological potential to cause harm," says Andrew Rosenkrantz, MD, assistant professor of radiology.

One method, called a T2-weighted image, produces an anatomical view of the prostate. Another, known as diffusion-weighted imaging, assesses the motion of water molecules within cells: the more restricted the movement of the molecules, the denser the cells, and therefore the more likely that cancer is present. A third MRI–based measure, called dynamic contrast enhancement, can indicate the likelihood of cancer by assessing how blood is flowing in the prostate. Together, the data signals are helping researchers distinguish between harmful and harmless tumors.

"We're learning that the MRI is rather selective in that it typically identifies cancers that are higher grade and larger in size," Dr. Taneja says. "So therefore, those are cancers that would theoretically be lethal for the patient." In contrast, the researchers have detected clinically significant cancer in only about 5 percent of patients with negative MRI results, suggesting that the technique is missing relatively few cases. Based on the advanced imaging, Dr. Rosenkrantz is helping to validate a five-point prostate cancer suspicion score, similar to what oncologists have used for other cancers. A score of five indicates that an abnormality is almost certainly cancer, while a score of one strongly suggests that it is benign.

Within the next few years, the researchers hope to improve upon their initial results and confirm preliminary data from other centers suggesting that a patient with a negative MRI result is highly unlikely to have clinically significant disease. If a multicenter trial demonstrates that the results are reproducible, men with negative MRIs may eventually be able to forgo biopsies altogether. Such patients might remain on a form of active surveillance, with doctors monitoring their levels of PSA or other markers such as the *prostate cancer antigen 3* gene, a cancer-specific probe that has shown early potential.

For men with positive MRI test results highlighting an area of concern, subsequent biopsies can become smarter too. NYU Langone is among the few medical centers in the nation with access to a powerful navigational aid called Artemis, a robotic system that fuses MRI imaging results with ultrasound technology. The resulting guidance system allows clinicians to aim biopsy needles with unprecedented precision at areas of concern. The computer software displays a three-dimensional view of abnormalities on MRI and marks those same sites on an ultrasound image of the prostate. Robotic technology then directs the biopsy needles to those spots for the tissue sampling.

"Now with imaging, we can target not only the areas most likely to have a tumor but also the areas most likely to have aggressive tumors," Dr. Rosenkrantz says. And because ultrasound is much faster and more comfortable for the patient, targeted biopsies based on the MRI–ultrasound fusion can be performed in an office setting.

The collaborators say initial results look promising, and several team members are building their own software program to further refine the process, while others are examining the technique's cost effectiveness. Despite the added expense of multiparametric MRI imaging, Dr. Lepor and Dr. Taneja say the technology could actually save cost over time by decreasing unnecessary biopsies, surgeries, and other interventions. "I would venture to say that within two to three years, if all goes well, we'll prove it, and it will change the way we screen men," Dr. Taneja says.

In many ways, prostate cancer patients at NYU Langone are already benefiting from the loosening blindfold. Anyone with an abnormal PSA test result is now examined with the advanced MRI technique to provide a clearer view of the prostate. For now, all patients still undergo a biopsy regardless of their MRI results, but the arrival of the MRI–ultrasound fusion method in 2012 has allowed the doctors to zero in on regions of interest. In some cases, 4 guided needles have provided a better indication of the threat than the typical 12 randomly placed ones, an encouraging sign that the archers are zeroing in on the bull's-eye. "I think we're heading in the right direction," Dr. Rosenkrantz says. "This isn't just something with future potential—we're using it day in and day out now to help patients." ●

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