



— DONALD DENIHAN WAS JUST 38 WHEN HE LEARNED HE HAD LOCALIZED

prostate cancer, an unusually tender age for such a diagnosis. He suspected this day might come, but not nearly so soon. A few months earlier, his brother, ten years his senior, had been diagnosed with the disease. And 12 years before that, his octogenarian father had died of advanced prostate cancer, after suffering horribly with intractable bone pain for months.

Now, as if someone had mistakenly leaned on life's fast-forward button, Mr. Denihan had to face the tough decisions that come with prostate cancer, as well as his own mortality.

"A 38-year-old does not think about prostate cancer," says Mr. Denihan, a partner in Denihan Capital, a real estate investment company. "That's the furthest thing from your mind. You're thinking about raising your family, getting your business going."

The lifetime risk for prostate cancer for all men is about one in five, but the average age at diagnosis is 70. Apparently, Mr. Denihan's fate was written in his genes.

"Men with two or more first-degree relatives with prostate cancer have a fourfold increased risk for developing the disease," explains Harry Ostrer, M.D. professor of pediatrics, pathology, and medicine at NYU, and an expert in prostate cancer genetics.

In a sense, Mr. Denihan was lucky—not to have a hereditary disposition to cancer, of course, but to have fair warning. After his brother's diagnosis, Mr. Denihan went for a screening test, which revealed a PSA (prostate specific antigen) level of 3.9 ng/

mL—just below the danger zone for the average senior, but a red flag for a 38-year-old, especially one with a checkered family history. PSA levels naturally rise with age; so a level that would be normal for an older man would be unusual for a younger man.

Following in his brother's footsteps, Mr. Denihan went to NYU Urology Associates for evaluation and advice. After a biopsy revealed he had localized cancer, he opted for a radical prostatectomy, the surgical removal of the prostate gland. Almost 10



years later, he remains cancer free, and his brother is doing well too.

“Early diagnosis probably saved his life,” says Mr. Denihan’s surgeon, Herbert Lepor, M.D., the Martin Spatz Chairman of the Department of Urology and professor of pharmacology at the School of Medicine and a pioneer in potency-preserving prostatectomy. “If he came to me in his fifties, I’d likely be telling him his disease was not curable and he would ultimately succumb to his cancer. Once prostate cancer spreads beyond the prostate, there’s no cure.”

### On the cusp of change

PERHAPS THE MOST UNUSUAL aspect of Mr. Denihan’s case was that it was relatively clear what he should do every step of the way. His family history warranted early screening, and his age at diagnosis and his father’s experience warranted aggressive treatment. For all too many men, however, figuring out how to deal with prostate cancer is a conundrum, starting with screening. PSA testing, the primary screening tool, is unreliable, leading to many false positives and needless biopsies and healthcare expenditures. As a result, medical societies disagree about the value of routine screening. The American Cancer Society supports it, but the American College of Physicians does not. Because 186,000 men will be diagnosed with prostate cancer this year, and 29,000 will die, the need for better screens and treatment is urgent.

Once prostate cancer is diagnosed, it’s hard to predict which malignancies will linger harmlessly for years or even decades and which will quickly spiral out of control. Consequently, choosing an approach to care can be a roll of the dice. Patients are left to decide whether to watch and wait, and risk missing the window when the disease is localized and potentially curable, or to pursue aggressive surgical or radiation therapy, and risk serious quality-of-life side effects.

Researchers at NYU hope to answer some of these questions by developing personalized genetic screens, a better biopsy technique, a noninvasive focal ultrasound treatment, and novel approaches to advanced cancer.

### Personalized genetic testing

WHILE MR. DENIHAN had a good idea that prostate cancer was lurking in his genes, most other men haven’t a clue. That may soon change.

In the 1990s geneticists were hot on the trail of a prostate cancer gene, buoyed by the discovery of individual genes for breast and colon cancer. “A whole bunch of candidate genes were identified, but all the studies had flaws,” says Dr. Ostrer. “We don’t know of any single gene that

represents a high risk for developing prostate cancer. That whole line of inquiry has been put on the shelf for now.”

Instead, researchers are looking for subtle genetic variations that distinguish which individuals are at greater risk for prostate cancer. Over the last year, 33 risk variants have been identified using DNA arrays, or gene chips, which have dramatically accelerated the analysis of gene expression across large swaths of the genome.

In a new study Dr. Ostrer and his colleagues are assessing the role of these risk variants in prostate cancer. To do so, they are tapping into a trove of tissue samples and clinical data collected from 1,800 of Dr. Lepor’s patients since 2000, and correlating the expression of the variant genes with clinical outcomes.

“Because there are so many risk variants, every man is likely to have some,” Dr. Ostrer says. “But we may be able to link certain combinations of these variants to different levels of risk.” If so, this data could form the basis of a personalized genetic screening test, highlighting which men need to be especially vigilant about getting regular PSA tests and rectal exams.

DNA arrays might also prove valuable in characterizing the genetic signatures of cancers that are likely to progress, which would provide an invaluable guide to treatment.

In another project, a collaborative effort with Mount Sinai School of Medicine, Dr. Ostrer is studying whether genetic makeup can be used to predict the risk of incontinence, impotence, and other complications following brachytherapy, a popular alternative to prostatectomy in which radioactive seeds are implanted in the gland.

“We are at the very beginning of personalized genetic testing for prostate cancer,” adds Dr. Ostrer. “We had 10 or 15 years of false starts looking for the single gene. But I imagine that in another 10 years, we will be using these risk variants all the time for making predictions and guiding therapy.”

### Better biopsies

AFTER ALMOST A DECADE, Mr. Denihan still cringes at the thought of his prostate biopsy, which he remembers as “uncomfortable” at best. Certainly, there’s nothing pleasant about having a biopsy gun inserted in your rectum, followed by the firing of a dozen or so tiny needles, one of several approaches for obtaining tissue samples. But at least the test worked as intended. Too often, biopsies miss malignant tissue, giving patients a false sense of security.

A new device called TargetScan may reduce this uncertainty. TargetScan employs a stationary rectal ultrasound probe and three-dimensional imaging to map the prostate. The system records exactly where biopsy samples are taken, ensuring accurate sampling of the entire gland, reports

Samir Taneja, M.D., the James M. Neissa and Janet Riha Neissa Associate Professor of Urologic Oncology and director of the Division of Urologic Oncology, who is leading a nationwide trial of the device.

TargetScan may make “watchful waiting” (i.e., active surveillance) less of a gamble. “If I find a small, nonaggressive cancer in a 70-year-old man, I’m probably going to offer the patient the option to observe the cancer. With this device, I can go back a year later and biopsy exactly the same spot and determine whether the cancer is progressing,” says Dr. Taneja, who also serves as a scientific adviser for TargetScan’s manufacturer, Envisioneering Medical Technologies.

TargetScan’s mapping capabilities could also allow for focal therapy, in which only the cancerous portion of the prostate is treated, potentially minimizing side effects.

### Focal therapy

WHEN IT CAME TIME to select a treatment, Mr. Denihan chose radical prostatectomy, even though it carries a small risk of urinary incontinence and a significant risk of impotence. “Seeing firsthand what my father experienced—the bleeding, the constant pain—I wanted the cancer out immediately, no matter what the consequences were,” he says.

For Mr. Denihan, the consequences were relatively minor. His bladder control returned within days, and his potency within months. “It’s not the same as it was before,” he says, referring to his erectile function. “But I have nothing to complain about.”

However, many other patients do, especially older men, who tend to have the most trouble with erectile dysfunction after prostatectomy. About four in 10 patients suffer this indignity, even with highly experienced surgeons like Dr. Lepor, who has performed the operation some 3,600 times. “That is where I have to do better,” he says.

An alternative to surgery may be a new noninvasive therapy called high-intensity focused ultrasound (HIFU), which uses high-frequency sound waves to destroy prostate tissue. The sound waves, which are generated with a rectal probe, can be focused anywhere in the prostate within 3 mm of precision, an area slightly bigger than the head of a pin.

“With TargetScan information, we would be able to do focal treatment and remove only cancerous portions of the gland,” says Dr. Lepor, who is heading the first nationwide study of HIFU, which will compare it to brachytherapy. Moreover, HIFU can be repeated if more cancerous tissue is detected at a later date, which is not true with either brachytherapy or external beam radiation.

Dr. Lepor suspects that HIFU will be



less effective than prostatectomy in curing the more aggressive cancers, but it will likely be associated with quicker recovery and better preservation of potency. “Today, radical prostatectomy is largely reserved for the treatment of men with low-risk cancers, and the survival of these men may not be compromised if they choose to undergo HIFU,” he says. “If studies at NYU and other institutions confirm these predictions, some patients will find HIFU an attractive option. But HIFU won’t be for everyone.”

### Androgen deprivation alternative

LEFT UNCHECKED, prostate cancer usually proceeds slowly, and sometimes silently. Eventually, symptoms begin to appear—such as frequent urination, increased urination at night, difficulty starting and maintaining a steady stream of urine, and blood in the urine. Unfortunately, these are also the symptoms of benign prostatic hyperplasia, or BPH, the annoying but not dangerous enlargement of the gland common in men after age 50; distinguishing cancer from BPH can be difficult. When prostate cancer metastasizes, it typically spreads to the bones, lymph nodes, rectum, and bladder. At this point, the most common symptom is bone pain, often in the pelvis, ribs, or spine. Prostate cancer can also compress the spinal cord, leading to leg weakness and

urinary and fecal incontinence.

By the time Mr. Denihan’s father was diagnosed, the cancer had already spread far and wide. His main recourse was surgical castration to stem the flow of male hormones called androgens, which accelerate the growth of cancer cells. The therapy did little good for his cancer or his quality of life. Within two years, he was gone.

A quarter-century later, androgen deprivation remains the standard therapy for advanced cancer, though it is now accomplished by the administration of hormones. “We’ve been using the same basic approach for 65 years,” says Anna Ferrari, M.D., associate professor of medicine (oncology). “We need better therapies.”

Androgen deprivation does work for a time, yet it ultimately fails as the surviving cancer cells develop resistance. To make matters worse, patients invariably suffer from hot flashes, fatigue, or sexual dysfunction, as well as other serious side effects. The elder Mr. Denihan was no exception.

An alternative approach, being developed by Dr. Ferrari and her colleagues at NYU, is to block the function of the androgen receptor, rather than depriving the body of androgen. Blocking the activity of this key molecule seems to debilitate prostate cancer cells more than other androgen-dependent cells in the body, thereby lessening side effects. To strengthen the

▲ Prostate cancer survivor **Donald Denihan** (second from right) places his arm around his surgeon, **Dr. Herbert Lepor**. From left to right: brother **Benjamin (Patrick)**, cousin **Daniel** and brother **Laurence**.

therapy, the researchers are adding agents that disrupt the resistance pathways that tumor cells develop. Clinical trials in men with recurrent prostate cancer after primary therapy and in men who are no longer responding to hormone therapy will be launched within the year.

Dr. Ferrari is also experimenting with immunotherapies for men with different stages of prostate cancer, including at least three different vaccines. She is testing new chemotherapy regimens, some in combination with cancer vaccines, for men with metastatic disease.

### The next generation

THESE DAYS, MR. DENIHAN is back to thinking about raising his family and growing his business, not about prostate cancer. But as he inches into middle age there comes a new worry: Have his three young sons inherited the family predisposition for the disease? If so, will physicians be able to do anything to stop it? More than a few fathers have the same worry, and the same hope. ●