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Much of what we take for granted in medicine today—from the rigorous training of physicians and nurses to the emphasis on research and the rapid application of that research to patient care—emerged from innovations made more than a century ago at a brand new medical center in Baltimore: Johns Hopkins.

Hopkins now uses one overarching name—Johns Hopkins Medicine—to identify its whole medical enterprise. This $5 billion virtual organization unites the physicians and scientists of The Johns Hopkins University School of Medicine with the health professionals and facilities that make up the broad Johns Hopkins Health System.

A little history: Toward the end of the 19th century, American medical education was in chaos; most medical schools were little more than trade schools. Often, it was easier to gain admission to one of these than to a liberal arts college.

With the opening of The Johns Hopkins Hospital in 1889, followed four years later by The Johns Hopkins University School of Medicine, Johns Hopkins ushered in a new era marked by rigid entrance requirements for medical students, a vastly upgraded medical school curriculum with emphasis on the scientific method, the incorporation of bedside teaching and laboratory research as part of the instruction, and integration of the School of Medicine with the Hospital through joint appointments.

Hopkins medicine counts many “firsts” among its achievements during its early years: the first major medical school in the United States to admit women; the first to use rubber gloves during surgery; the first to develop renal dialysis and CPR.

Two of the most far-reaching advances in medicine during the past 25 years were made at Hopkins. The Nobel Prize-winning discovery of restriction enzymes gave birth to the genetic engineering industry and can be compared, some say, to the first splitting of an atom.

Also, the discovery of the brain’s natural opiates has triggered an explosion of interest in neurotransmitter pathways and functions. Other accomplishments include the identification of the three types of polio virus and the first “blue baby” operation, which opened the way to modern heart surgery. Hopkins also was the birthplace of many medical specialties, including neurosurgery, urology, endocrinology and pediatrics.
About the Brady Urological Institute:

America’s #1 Urological Institute

Since its inception, the mission of The Brady Urological Institute has focused on finding answers, solving problems, and coming up with medical solutions that will benefit not only its patients, but humankind as a whole.

Whether it’s developing a new therapy, fine-tuning an improved surgical technique, discovering a cure for a disease, or seeking better ways to educate patients, every time Brady medical experts set out to do something—through careful observation, study, and detailed research—they are always envisioning how improvements can be made.

As the leader in urology, the Brady Urological Institute has far more than a vision for the future. The Brady continues to create the future through discovery, intense focus, constant improvement and an ethic of service.

Patients come to The Brady for medical treatment in the following areas: prostate cancer, benign prostate hypertrophy, bladder cancer, incontinence, kidney cancer, stone disease, testis cancer, ureteropelvic junction obstruction, Peyronie’s disease, erectile dysfunction, male infertility, female urology, pediatric urology, minimally invasive surgery, robotic-assisted surgery.
Who Was Brady and Why Does the Institute Bear his Name?

James Buchanan Brady (1856-1917), the second son of a New York saloon operator, remains a legendary character from America’s “Gilded Age,” a thoughtful philanthropist whose legacy continues to fuel urological research.

Brady started working at the age of 11 to support his family, eventually getting a job selling special patented steel saws used for cutting railroad tracks. He soon developed an eye for diamonds and other jewels, and as his success as a salesman grew, so did his vast diamond collection, earning him the nickname “Diamond Jim” Brady.

As renowned as he was for his business acumen, Brady, who consumed vast quantities of food daily, was also well known for his prodigious appetite. Culinary historians note that his breakfast often started with a gallon of orange juice, a half dozen eggs, pancakes, fish cakes, and chops in a dinner including dozens of oysters and clams, terrapin, lobsters, roasted meats, and a variety of game birds.

In 1912, Brady, who was already suffering from diabetes, kidney disease, and other ailments, developed severe prostate difficulties. After undergoing successful treatment at Johns Hopkins Hospital by Dr. Hugh Hampton Young, the ever-grateful Brady endowed the urological institute that now bears his name, allowing it to flourish right from its inception.

“Diamond Jim” Brady
1856-1917
Jacek L. Mostwin, M.D., D. Phil. (Oxon)

Professor of Urology, Johns Hopkins Medicine

Medical Editor, The Johns Hopkins Prostate Disorders Bulletin
Jacek L. Mostwin, M.D., D. Phil. (Oxon)

Past, Present, and Future in Prostate Cancer Treatment

Whether you have been recently diagnosed with prostate cancer, are currently undergoing treatment or are a prostate cancer survivor concerned about the possibility of cancer recurrence, this report contains information relevant to your concerns. It provides a detailed overview of the current state of the art in prostate cancer prevention, diagnosis, treatment and research. In essence, it’s a roadmap of where we’ve come from, where we are now, and where we are headed in our ongoing battle against prostate cancer.

Fortunately, in just the past few years there has been an explosion of research and discovery in prostate cancer, with many important breakthroughs coming from the talented physicians and scientists working at the Brady Urological Institute at Johns Hopkins. Seven of those leading prostate cancer experts have contributed to this report. In addition, two other outside experts describe how their new drug and diagnostic test, respectively, will improve treatment outcomes.

Together, we hope this will serve as a valuable resource for you, not only adding to your knowledge about treatment strategies, but also helping to answer questions you may have related to the management of prostate cancer.

There is much to talk about. December 2011 marked the four-decade milestone of President Richard Nixon’s signing the United States National Cancer Act into law. With this “total national commitment for the conquest of cancer,” the president pledged to allocate whatever was necessary in terms of funding to support research efforts by the National Cancer Institute for the conquest of cancer.

How successful has this effort been with prostate cancer? Forty years later, our understanding of cancer, prostate cancer in particular, has changed greatly, thanks in part to the $90 billion spent on basic laboratory research, the hundreds of human drug trials to test novel compounds, and various treatments that have helped extend the lives of cancer patients. Yes, we have made progress, but we still have a long way to go in order to conquer this vexing cancer.

Prostate cancer is the most common cancer after skin cancer, and it is second only to lung cancer in the number of men it kills. Although we were able to land a man on the moon way back in 1969, the “war on cancer” continues as we seek cures for prostate and a host of other cancers. This year, the American Cancer Society estimates that 240,000 men will be diagnosed with prostate cancer, and 33,000 men will die from metastatic prostate cancer.
Still, there have been many major successes over the past 40 years, with some important ones achieved just recently. In the 1970s, a prostate cancer diagnosis meant a painful death for most patients when the disease reached its advanced stage. But the introduction of the prostate specific antigen (PSA) test now allows us to detect cancer in its earliest stages, when it is most treatable. The number of men diagnosed when the disease is already advanced—and the death rate from prostate cancer—have both been lowered dramatically. Two other factors that have played major roles in improving survival rates and quality of life in men with prostate cancer are the Gleason score for grading prostate biopsies and improved surgical techniques for removing the prostate introduced by Patrick C. Walsh, M.D. at Johns Hopkins.

In the 1970s, the understanding was that all prostate cancers had to be treated with surgery or radiation. However, in light of the recent discoveries about the true nature of prostate cancer, it’s now clear that we have been over-diagnosing and over-treating this cancer. Nearly half of the men diagnosed with prostate cancer in the United States have what is considered low-grade disease, which many doctors believe is unlikely to kill and may not require immediate treatment with surgery or radiation. Instead, active surveillance—close monitoring with twice yearly PSA tests and annual biopsy—is probably the best choice for most men. However, fewer than 10 percent choose this option. And for men who do need treatment for their cancer, improved surgical and radiation techniques are bringing about a reduction in death rates while helping maintain a high quality of life.

Genomics, the analysis of a cell’s DNA, is now playing a big role in prostate research, with much of the work being performed by researchers at Johns Hopkins. With novel tools to analyze the human genome, and with a $1,000 genomic test soon to be a reality in 2012, this deeper understanding of the genetic underpinnings of prostate cancer tumors is driving research even faster and it is expected to significantly increase the information that’s added to the general fund of knowledge about prostate cancer.

Researchers are already using this vital genetic information in efforts to personalize detection, diagnosis, treatment, and—someday—prevention of prostate cancer. Their goal with these “targeted therapies” is to find a weak spot in the tumor’s molecular “armor” and then hit it with continuous, precisely aimed strikes made up of novel drugs, antibodies or immunotherapies to affect certain proteins and hormones, block blood supply to the tumors and stop their growth—without damaging nearby healthy tissue.

Tests for circulating tumor cells (CTCs), which identify specific genetic traits in prostate tumors and then detect those rogue cells in the blood, are also starting to be utilized in clinical trials. The important information yielded by such tests can tell the oncologist whether a prostate therapy is working. In a research setting, this critical knowledge can help to speed up drug trials exponentially by acting as an effective biomarker of disease progression or regression.
Back in 1971, immunotherapy for prostate cancer was no more than a dream. However, the promise of a vaccine to harness the immune system and treat advanced cancer is now a reality, ushered in with the approval of Provenge (sipuleucel-T) in 2010. This therapy calls up the immune system’s disease-fighting forces to attack the advanced prostate cancer. Other novel therapies that stimulate the immune system to seek out and destroy cancer cells are now in early-phase development, as is research to find out exactly how they work to improve the immune response against advanced prostate cancer.

Until there is a cure, the alternate goal of researchers is to turn prostate cancer into a chronic disease, so that life expectancy for a man with advanced prostate cancer would be the same as that of someone without cancer. While this achievement is still far off, we are closer to accomplishing it than ever before, especially with the help of molecularly targeted treatments now in the works that zero in on tumors based on a patient’s molecular profile.

Finally, we are coming to realize that prostate cancer rates are influenced by what and how much we eat and how physically active we are. Investigations into environmental contributions to prostate cancer remain a rich area of research. For example, we now know that obesity plays a role in prostate cancer development, perhaps due to the chronic inflammation caused by an increased number of fat cells in the body. Word of this important finding, identified through rigorous clinical trials, has made its way to the medical community and the general public, and doctors are encouraging their patients to adopt serious cancer-prevention steps that include a more healthful diet and regular exercise for weight control.

I hope you are as excited as I am about the tremendous advances being made in prostate cancer prevention, detection and treatment.
Alan W. Partin, M.D., Ph.D.

CHAIRMAN, BRADY UROLOGICAL INSTITUTE
DAVID HALL MCCONNELL PROFESSOR AND CHAIR UROLOGIST-IN-CHIEF, DEPARTMENT OF UROLOGY, ONCOLOGY
JOHNS HOPKINS MEDICAL INSTITUTIONS EDITOR-IN-CHIEF, UROLOGY
W ithin a few weeks of prostate cancer surgery, a man has his first PSA test to see if there are any rogue cancer cells still circulating in his blood. What he hopes to get back from his lab report is that “the PSA is undetectable.” That means that the PSA now measures 0.1 ng/ml.

While 0.1 ng/ml has been accepted as gospel for more than 30 years, some colleagues and I at Johns Hopkins and NYU’s Langone Medical Center wondered if this “undetectable” level shouldn’t actually be lower, because many men still go on to have a rising PSA level without clinical evidence of disease, an event known as “biochemical recurrence.”

Our thinking was that the PSA test is not sensitive enough to catch the first indication of a rising PSA level, which unfortunately delays detection of recurrent cancer by months or years.

In order to validate our hunch, we recently collaborated with experts from Quanterix Corporation, a Cambridge, Massachusetts technology company that has an interesting diagnostic test called the AccuPSA. This test uses Quanterix’s proprietary SiMoA (Single Molecule Array) technology, which can capture and measure individual PSA molecules in the blood—molecules that escape standard PSA testing. Results of our small pilot study were published last year in the British Journal of Urology International. Here is a recap of what we did and what we eventually found.

We examined blood samples from 31 men whose PSA levels had initially been undetectable—0.1 ng/ml—with standard testing and who had been followed carefully for a minimum of five years after undergoing cancer surgery. One third went on to have a cancer recurrence, while the others remained cancer-free. All had negative surgical margins, which meant that the edges of removed tissue that were assessed by a pathologist after surgery were found to be negative for the presence of cancer on the edges. Similar in age and race, those who eventually relapsed had a higher pre-surgical PSA, clinical and pathological stage. Their Gleason grades were also higher than those of the men who did not relapse.

After testing all blood samples with the AccuPSA, we found that at three months following surgery, the men who eventually had a rise in their PSA had AccuPSA levels of 0.003 ng/ml or higher. Granted, that PSA number seems like an excellent level, but among the men whose PSA never went up after surgery, 75 percent had AccuPSA levels lower than 0.003 ng/ml.

Of course, our study results will have to be confirmed in much larger randomized, prospective clinical trials, but if our results are corroborated, we will then have a test that can accurately measure PSA values at 1,000 times lower than the standard PSA test—which will indicate if
The prostate is a gland located beneath the bladder, behind the pubic bone and the base of the penis and in front of the rectum. Shaped like a crabapple and weighing only about 1 ounce in young men, the prostate surrounds the urethra (the tube that carries urine away from the bladder and transports semen during ejaculation). Because the prostate surrounds the urethra at the opening of the bladder, it can affect urinary function and cause urinary symptoms in men with diseases of the prostate.

Prostate cancer tends to arise in the outer region of tissue, which is closest to the rectum. As a result, an early-stage tumor usually does not impinge upon the urethra or cause any symptoms. If the tumor continues to grow undetected and untreated, it can spread throughout the gland and ultimately produce urinary tract symptoms, including difficulty in starting to urinate, awakening during the night to urinate, and urinary urgency and frequency.

A man with prostate cancer may experience erectile dysfunction (ED) or a decrease in the firmness of erections if the cancer has invaded the nerves that control erections. In some men, the first symptoms of prostate cancer originate in areas of the body where the cancer has spread (severe back pain from cancer that has spread to the spine, for example). The diagnosis of prostate cancer at these advanced stages is unusual today because of widespread screening for the disease.
a patient is really “cured” after surgery. The AccuPSA test would then give us the ability to:

• Identify men who have a low probability of cancer recurrence (good prognosis) within a few months following surgery based on a very low PSA value

• Identify individuals at increased risk for future recurrence, enabling them to benefit from more effective treatment, such as early adjuvant or salvage therapies using radiation or cryotherapy

Granted, while a lot more work needs to be done with this test, the preliminary research looks very promising. We are now preparing the next AccuPSA clinical study protocols.

New Insights into Hormone Therapy for Advanced Cancer

About 20 to 30 percent of men experience a detectable PSA level within ten years of surgery. These recurrence figures are starting to go down and will continue to do so as more men have their cancer detected early. But what about the men who do experience a rise in their PSAs after the prostate was removed or irradiated? The only men who need to do something right away are those who have cancer that has spread to the bones, are symptomatic from disease spread, or have a prostate cancer that is obstructing the kidneys or bladder. In such cases, hormonal therapy should be started immediately to slow the progression of the cancer.

Prostate cancer cells depend on androgens (male hormones such as testosterone) in order to survive. Regular treatments with drugs called LHRH agonists (medical castration), which reduce the production of testosterone, the fuel that stimulates tumor growth, will cause tumor regression, as will surgical removal of the testicles (surgical castration, or orchiectomy).

This hormonal therapy—also called hormonal or androgen ablation—is effective at turning off the body’s supply of the male hormones, which causes the tumors to generally shrink or regress. (See the box on pages 12-13 for medications used to reduce testosterone production.) In the absence of testosterone, the prostate cancer may remain in remission for years. Unfortunately, blocking the hormones as we now do it is not the lethal blow we’d all like it to be. For many men, PSA begins to rise again, sometimes within weeks, signaling that the cancer is on the move again.

We may now be getting closer to understanding why some men benefit from hormone therapy, while others receive very limited help from their drugs. Thanks to the recent work of Jun Luo, Ph.D., an assistant professor at the James Buchanan Brady Urological Institute at
### Medications Used in the Hormone Treatment of Prostate Cancer 2012

<table>
<thead>
<tr>
<th>Drug type: Brand (generic)</th>
<th>Average daily dosage*</th>
<th>How to take</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premarin (estrogen, conjugated)</td>
<td>1.25-2.5 mg 3x per day</td>
<td>At the same time every day.</td>
</tr>
<tr>
<td><strong>Luteinizing hormone-releasing hormone (LHRH) agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lupron: 7.5/22.5/30 mg injected every 1, 3 or 4 months, respectively Eligard: Same as above and 45 mg injected every 6 months</td>
<td></td>
</tr>
<tr>
<td>Trelstar Depot (triptorelin)</td>
<td>3.75 mg injected every month</td>
<td>Injected intramuscularly by doctor.</td>
</tr>
<tr>
<td>Trelstar LA (triptorelin)</td>
<td>11.25 mg injected every 3 months</td>
<td></td>
</tr>
<tr>
<td>Trelstar (triptorelin)</td>
<td>22.5 mg injected every 6 months</td>
<td></td>
</tr>
<tr>
<td>Zoladex (goserelin)</td>
<td>3.6 mg injected every month or 10.8 mg injected every 3 months</td>
<td>Injected by doctor into abdomen.</td>
</tr>
<tr>
<td><strong>Luteinizing hormone-releasing hormone (LHRH) antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firmagon (degarelix)</td>
<td>240 mg, then 80 mg injected every month</td>
<td>Injected subcutaneously into abdomen by doctor.</td>
</tr>
<tr>
<td><strong>Antiandrogens</strong></td>
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<td></td>
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<tr>
<td>Casodex (bicalutamide)</td>
<td>50 mg daily</td>
<td>At the same time every day, with or without food. Used with an LHRH analog.</td>
</tr>
<tr>
<td>(flutamide) (generic only)</td>
<td>750 mg daily</td>
<td>Two 125-mg tablets every 8 hours. Used with an LHRH analog.</td>
</tr>
<tr>
<td>Nilandron (nilutamide)</td>
<td>300 mg daily for 30 days, then 150 mg daily</td>
<td>With or without food. Used in combination with LHRH analogs or surgical castration, because antiandrogens are not as effective when used alone.</td>
</tr>
<tr>
<td><strong>CYP17 inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zytiga (abiraterone)</td>
<td>1,000 mg per day</td>
<td>On an empty stomach. Do not eat two hours before or one hour after taking Zytiga. Used in combination with prednisone, 5 mg taken orally twice daily.</td>
</tr>
</tbody>
</table>

* These dosages represent an average range for the treatment of prostate cancer. The precise effective dosage varies from person to person and depends on many factors. Do not make any changes to your medication without consulting your doctor.

LHRH = luteinizing hormone-releasing hormone; LH = luteinizing hormone
**How they work** | **Precautions** | **Most common side effects** | **Call your doctor if...**
---|---|---|---
Blocks the release of (LHRH) from the hypothalamus, preventing the action of (LH), which signals the testicles to produce testosterone. | If estrogen is discontinued, testosterone levels will return to normal. Do not take if you have liver disease. May increase risk of cardiovascular problems, including heart attack and blood clots. | Breast enlargement, nausea, vomiting, fluid retention, erectile dysfunction, loss of libido. | You develop sudden changes in vision or speech, severe headaches, leg pains, dizziness or faintness.

Initially, these drugs stimulate the pituitary to release LH, prompting a jump in testosterone production. After several weeks, they block LH formation, and testosterone levels fall to castrate range. | May cause a temporary increase in cancer symptoms such as pain, urinary blockage or weakness of the legs. May increase risk of diabetes, cardiovascular disease. (Pose less cardiovascular risk than estrogens.) Your doctor should monitor you for these conditions. | Sweating, hot flashes, weight gain, fatigue, erectile dysfunction, loss of libido, loss of bone and muscle mass, headache, transient increase in cancer symptoms (see at left), mild pain, bruising or itching at injection or implant site. | Eligard, Lupron: You develop hives; rash; itching; difficulty breathing or swallowing; numbness, tingling, weakness or pain in the feet or lower legs; painful or difficult urination; blood in urine; bone pain; testicular or prostate pain; inability to move arms or legs. Trelstar and Zoladex: You develop rash, itching, swelling, severe dizziness, trouble breathing, sudden severe headache, vomiting or visual changes soon after injection.

Blocks the production of gonadotropin-releasing hormone (GnRH) by the pituitary gland, which prevents GnRH from stimulating the testes to produce testosterone. | Tell your doctor if you have any heart, kidney or liver problems or problems with the balance of your body salts or electrolytes. Can elevate liver enzymes; liver function should be tested during use. | Pain, redness and swelling around the infection site; hot flashes; flushing of the skin; weight gain; fatigue; increase in some liver enzymes. | You gain weight unexpectedly, feel more tired than usual, experience back or joint pain, develop chills or symptoms of a urinary tract infection, have decreased sex drive or erectile dysfunction.

Antiandrogens bind to the same cellular receptors that androgen hormones (including testosterone) use to stimulate prostate cells. Thus, they prevent androgen hormones from affecting the prostate. | Known to cause liver damage; liver function must be checked. May interact with several drugs, including cholesterol-lowering medications and anticoagulants such as warfarin. Nilandron: Risk of lung damage; a routine chest X-ray is required before first dose. May cause trouble adjusting to the dark. | Hot flashes, pain in the back or pelvis, diarrhea. Nilandron: constipation. | You experience nausea, vomiting, abdominal pain, fatigue, loss of appetite, flu-like symptoms, dark urine, jaundice, tenderness in your right upper abdomen. Nilandron: Seek immediate attention if you develop shortness of breath, coughing, chest pain or fever.

Inhibits an enzyme the body needs to produce testosterone from cholesterol. | Tell your doctor if you have a history of heart or liver disease, or problems affecting the adrenal or pituitary glands. Increases in liver enzymes may occur, requiring a change of dose or discontinuing use. | Joint and muscle pain, swelling, hot flashes, diarrhea, urinary tract infections, frequent urination, elevated blood pressure, abnormal heart rhythm, heartburn, cough and cold-like symptoms. | You experience dizziness, rapid heartbeats, faintness or lightheadedness, headaches, confusion, muscle weakness, pain or swelling in your legs or feet.
Johns Hopkins, we now know more about the critical differences in the hormone receptors on prostate cancer cells in those patients who no longer respond to this therapy.

Dr. Luo and his colleagues at the Johns Hopkins University School of Medicine, the University of Washington and Puget Sound VA Medical Center looked to a key player: the androgen receptors on prostate cancer cells. Using a large database, the researchers searched for variations in the nucleic acid RNA that prostate cells use to create androgen receptors. They eventually found seven specific RNA sequences different from the “normal” androgen receptor already known to scientists. When they looked for these sequences in cells isolated from 124 prostate cancer patients, they found over-production of these “outlaw” variants in prostate cancer cells taken from patients whose disease had become resistant to hormone deprivation therapy.

It was one variation, however, that caught their attention: androgen receptor variant 7, or AR-V7. AR-V7 was also prevalent in a select group of patients who had never taken hormone therapy, but whose cancer aggressively returned after surgery to remove their tumors.

To see how androgen receptors made from AR-V7 differ from others, the researchers forced lab-grown prostate cancer cells to produce only the AR-V7 sequence. Unlike cells with other androgen receptors, those with only AR-V7 receptors acted as if they were continually receiving androgens—turning on at least 20 genes that rely on androgens for activation—even though no androgens were present.

The results suggest that hormone therapy might encourage prostate cancer cells to overproduce the AR-V7 receptors over time, leading them to survive and grow aggressively even without androgens. In some patients, AR-V7 receptors might already be prevalent even without hormone therapy, predisposing them to an already-aggressive form of prostate cancer that won’t respond as well to hormone deprivation therapy.

Based on this research, we may eventually be able to develop a special test to look for this androgen receptor variant, giving us a way to determine which patients are good candidates for hormone deprivation therapy. It will also enable us to monitor disease progression in patients already on this androgen deprivation therapy. Examining the differences between AR-V7 and other androgen receptor variants may also provide researchers with new ideas for developing prostate cancer-fighting pharmaceuticals.

**Thermal Enhanced Metastatic Therapy**

Our director of research, Robert Getzenberg, Ph.D., believes that instead of finding new therapies for advanced prostate cancer, all you really need to do is find a weakness in cancer cells in order to make the therapies that we already have more effective. In 2013, we are planning to begin human trials with a new way to treat advanced prostate cancer: combining heat with chemotherapy or radiation.
Thermal enhanced metastatic therapy, or TEMT, is a new modality we are testing for advanced prostate cancer treatment that uses heat to cause changes in a cancer cell’s DNA. Heating the cells before starting a chemotherapy or radiation treatment weakens them sufficiently so the effects of the chemo or radiation become more pronounced.

What we have done is develop microscopic iron nanoparticles that will be infused into the patient and guided by a special tracking system to land on the outside of prostate cancer cells. Using a special magnetic device similar to an MRI [magnetic resonance imaging] machine, we then briefly heat the nanoparticles while not raising the temperature of the body. The iron nanoparticles will raise the temperature of the cancer cells to about 105°F, weaken them sufficiently, which then makes them susceptible to subsequent chemotherapy, immunotherapy or radiation therapy.

What heat does is change the organization of the nucleus of a cancer cell. The real value of this pioneering heat therapy is for men with metastatic disease, that is, cancer that has already escaped the prostate gland, or has recurred following surgery or radiation therapy.
Dr. Walsh was awarded the Edward L. Keyes Medal in 2011 in recognition of his lifetime contributions in the advancement of urology. This is the highest honor bestowed by the American Association of Genitourinary Surgeons and has been awarded sparingly since the citation was created in 1926. His book, *Dr. Walsh’s Guide to Surviving Prostate Cancer, Third Edition* (Warner Books) co-authored with Janet Farrar Worthington, is being published in 2012.
Hugh Hampton Young, who is regarded as the father of modern urology, performed the first radical prostatectomy surgery via the perineal approach (the area between the scrotum and anus) in 1904 at the Johns Hopkins Hospital. Despite the efficacy of the procedure in the treatment of localized prostate cancer, it remained unpopular because of its too-frequent side effects of urinary incontinence and erectile dysfunction.

When I came to Johns Hopkins in 1974 to head the Brady Urological Institute, I realized that the side effects from the procedure were keeping men from having the surgery. There was life-threatening bleeding during the surgery, many men suffered severe incontinence and all of them lost their erections afterwards. It was no surprise that radiation therapy was what men then opted for, since it had fewer side effects.

At that time, I decided to see whether these side effects could be avoided. I soon learned that they occurred because no one understood the anatomy of the structures that surrounded the prostate. Using the operating room as an anatomy laboratory, I was able to define the location of the common trunk where the blood vessels of the pelvic region could be divided, thus making it possible to operate in a relatively bloodless field. This made it possible to perform a more careful, safer and effective cancer operation. In doing so, this allowed increased preservation of the urinary sphincter, thereby improving urinary control.

Preserving erections was another issue. In 1981, while visiting Pieter Donker’s anatomy laboratory at the University of Leiden in the Netherlands, we were able to discover the location of the nerves responsible for erectile function using a dissecting microscope to examine a stillborn boy. Returning to Baltimore, I again was able to use the operating room to find and preserve these microscopic nerves on a patient. Finally, there was now a real chance to help men regain their erections after surgery. On April 26, 1982, I performed the first nerve-sparing radical prostatectomy on a 52-year-old man. Today, 30 years later, he is cancer free and has a normal life.

When it comes to curing localized early-stage prostate cancer, this improved approach—in which the entire prostate is removed, the nerves preserved (or excised when necessary to make sure all the tumor is removed), and the bladder reconnected to the urethra—is now considered to be the “gold standard.” Over the next three decades, I made 28 other important contributions to our understanding of the anatomy and surgical technique—the last one just 18 months ago. We are now at a point where, in the last year, 94 percent of the men I operated on were wearing no incontinence pads at three months, and 64 percent were already potent.

I firmly believe that if the radical prostatectomy could be performed with minimal side effects, all young men with localized prostate cancer would opt for it. I am convinced that as time goes on there will be further improvements, especially regarding erectile function. The nerves responsible

Patrick C. Walsh, M.D.

■ Advances in Radical Prostatectomy Surgery
for erectile function do not have an insulated sheath that protects them—and they are extremely sensitive to thermal injury and any movement during the surgery. I see great promise in the ongoing work of Johns Hopkins’ neuro-urologist Dr. Arthur Burnett to protect the penile nerves that affect erections. Dr. Burnett is investigating several drugs that can act as a sort of “armor” for the tiny nerves to shield them from the heat and shock that comes with prostate surgery. His preliminary work with the drug irbesartan, an angiotensin II type 1 receptor antagonist that’s used mainly for the treatment of hypertension, has yielded remarkable results in preliminary testing with his prostate surgery patients.

The promise of those innovations, and other anatomical observations, will ultimately lead to the day where the side effect profile of this surgery is better than any other treatment for prostate cancer.

On June 29, 2011, I performed my last radical prostatectomy because I wanted to stop when I was at the top. It’s best for a surgeon to cease operating a year or two too soon rather than a second too late. Over the years I’ve perfected my techniques, and the last operation I did was perhaps the best I ever performed. If I were the only one who could do this procedure well, people would accuse me of depriving patients of a chance for cancer cure with my retirement. But I have trained excellent people at Johns Hopkins who perform this surgery extremely well, and I can step away knowing that patients still have the best chance for cancer cure and few side effects.

Focal Therapy for Treating Prostate Cancer

If therapy is needed or desired for clinically localized prostate cancer, a man can choose between surgery, various radiation therapies (including brachytherapy) and active surveillance. Active surveillance, which was pioneered here at Johns Hopkins, is a method of managing prostate cancer through close monitoring with PSA testing and annual biopsies; curative treatment is not attempted unless the cancer progresses (see page 23).

Some men are now choosing to bypass these traditional cancer treatments and opting instead for cryotherapy, the minimally invasive controlled destruction of prostate tissue by the introduction of rapidly freezing temperatures within the prostate. Special cryoprobes, about the diameter of a pencil point, create iceballs that cause direct damage to all nearby tissue, including the prostate tumor cells. The procedure is also known as cryosurgery, cryosurgical ablation and cryoablation.
Cryotherapy kills cancer cells by freezing them, and it works best for men with prostates 50 cc or smaller whose cancer is localized to the gland. In the procedure, thin needles (cryoprobes) are inserted through the perineum and into the prostate. Needle placement is guided with an ultrasound probe placed in the rectum. Argon gas drops the temperature of the cryoprobes to a minimum of -40° C (and often below -135° C). The extremely low temperatures create iceballs that freeze the nearby tissue, killing the tissue and cancer cells with it. Helium is then introduced into the needles, which raises the temperature so the prostate begins to thaw. For optimal cancer cell destruction, however, a second freeze/thaw cycle is usually necessary.

While all of this sounds promising, guidelines from the National Comprehensive Cancer Network do not include cryotherapy as a standard approach for the initial treatment of clinically localized prostate cancer because there is not enough long-term data showing equivalence with surgery or radiation therapy.

High-intensity focused ultrasound, or HIFU (pronounced HIGH-foo), is another type of experimental technology for noninvasive tumor ablation and its potential clinical impact as a focal therapy could be significant one day. The term tumor ablation is defined as the direct application of chemical or thermal therapies to a specific tumor or tumors in an attempt to completely eradicate the tumor or at least achieve substantial tumor destruction. Image-guided HIFU procedures could permit the ablation of tumors and each procedure, which heats cancerous tumors to near-boiling temperatures, could be performed without the need for surgery or even an incision. This form of treatment has the potential to minimize side effects—incontinence and erectile dysfunction—and improve quality of life, while offering a rapid recovery and return to daily activities.

HIFU treatment is straightforward and typically no hospital stay is required. After receiving a spinal or epidural anesthesia, as well as intravenous sedation, the small probe—encased in a latex

Cryotherapy for Prostate Cancer

The National Comprehensive Cancer Network (NCCN), an alliance of 21 of the world’s leading cancer centers (including the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins), is dedicated to improving the quality and effectiveness of care provided to patients with cancer. The NCCN regularly publishes their clinical practice guidelines for prostate cancer to provide information that many doctors follow to make sure their decisions for cancer patients are well informed. Here is what the NCCN says about cryotherapy for prostate cancer:

“Cancer cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that achieves damage to tumor tissue through local freezing. Based on different definitions of biochemical failure, the reported 5-year biochemical disease-free rate following cryotherapy ranged from 65 percent to 92 percent in low-risk patients. However, this technique is not recommended as primary therapy due to lack of data from long-term studies for comparison with radiation and radical prostatectomy.”
# The Pros and Cons of Prostate Cancer Treatment Options

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active surveillance</strong></td>
<td>• Avoids side effects from radiation therapy or radical prostatectomy</td>
<td>• Requires close monitoring (regular digital rectal exams, PSA* tests, and prostate biopsy) to monitor for signs of progression</td>
</tr>
<tr>
<td></td>
<td>• No hospitalization or surgical risks</td>
<td>• May be psychologically stressful knowing that cancer will not be actively treated until it progresses</td>
</tr>
<tr>
<td><strong>Radical prostatectomy</strong></td>
<td>• Proven to reduce prostate cancer death rates</td>
<td>• General risks of surgery</td>
</tr>
<tr>
<td></td>
<td>• Removed tissue allows accurate staging</td>
<td>• Hospitalization required</td>
</tr>
<tr>
<td></td>
<td>• PSA levels reliably predict recurrence</td>
<td>• Catheter in place for 1-2 weeks</td>
</tr>
<tr>
<td></td>
<td>• Fewer bowel/rectal problems than with EBRT</td>
<td>• Recovery period: at least 1 month</td>
</tr>
<tr>
<td></td>
<td>• Less urinary urgency and frequency than with EBRT or brachytherapy</td>
<td>• Incontinence: 5-20% (mostly stress incontinence)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Erectile dysfunction: 30-50% at 5 years (with nerve preservation)</td>
</tr>
<tr>
<td><strong>External beam radiation therapy</strong></td>
<td>• No hospitalization or surgical risks</td>
<td>• No post-treatment staging information</td>
</tr>
<tr>
<td>(EBRT)</td>
<td>• Activities unrestricted</td>
<td>• Daily treatments for 6-8 weeks</td>
</tr>
<tr>
<td></td>
<td>• Low risk of urinary incontinence (1-2%)</td>
<td>• Fatigue may occur when treatment ends</td>
</tr>
<tr>
<td></td>
<td>• Less urinary retention than with brachytherapy</td>
<td>• Erectile dysfunction: 30-50% at 5 years (with nerve preservation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bowel/rectal problems: 5-10% (urgency, pain, diarrhea, or bleeding) but typically improve after treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bladder irritation: 5% (urinary frequency, urgency, discomfort)</td>
</tr>
<tr>
<td><strong>Brachytherapy</strong></td>
<td>• No hospitalization or surgical risks</td>
<td>• No post-treatment staging information</td>
</tr>
<tr>
<td></td>
<td>• Less radiation damage to healthy tissue</td>
<td>• Less favorable option for men with intermediate- or high-risk disease</td>
</tr>
<tr>
<td></td>
<td>• One treatment</td>
<td>• Urinary retention, urgency, and frequency more common than with other treatments, especially in men with lower urinary tract symptoms before treatment</td>
</tr>
<tr>
<td></td>
<td>• Low risk of urinary incontinence (1-2%)</td>
<td></td>
</tr>
</tbody>
</table>

* PSA = prostate-specific antigen.
balloon filled with cooling liquid—is placed into the rectum. Using ultrasound, the urologist then locates the parts of the prostate he wishes to treat. Pressing a button emits a computer-controlled beam of high-intensity focused ultrasound, raising the temperature at the desired (focal) point in the prostate to 85º C to 100º C for three seconds. The beam heats up a portion of tissue equal to about the size of a few grains of rice stacked end to end; this results in eventual tissue death. By repeating the process 400 to 600 times as the probe is moved around the prostate, it is possible to destroy most of the prostate tissue.

As I mentioned, HIFU is still an experimental procedure in the United States. Some men, however, opt to have the procedure performed out of the country, where the procedure is approved for treating prostate cancer. The results, unfortunately, are not always good. I recently treated a 52-year-old man who had HIFU performed in the Dominican Republic. Initially ecstatic with the procedure, he told me that he had intercourse with his wife several hours after undergoing the procedure. Unfortunately, his PSA started rising two years later and his biopsy was positive for cancer.

HIFU was a treatment he never should have been offered. In order to treat his recurrent cancer, I had to perform one of the most difficult radical prostatectomy surgeries I have ever done in my life. Although his doctor in the Dominican Republic told him that he had been given a “whole gland treatment,” the post-surgery pathology report I received after completing his surgery showed there were many skipped areas in the gland and that only 30 percent of the cancers in his prostate had actually been treated with the HIFU therapy. Luckily, I was able to maintain his urinary continence and erectile abilities and his PSA has so far remained undetectable.

Most prostate cancers detected today are very small and pose little risk, which is why the idea of focal therapy is starting to gain some level of popularity in the United States. But without being able to image the prostate properly with MRI (magnetic resonance imaging) scans and without being able to tell the exact location and extent of cancer in the prostate, focal therapy will remain an experimental procedure for the treatment of prostate cancer.

■ A Word About Robot-assisted Radical Prostatectomy

What do men like? Toys, new things and electronic gizmos. They also want the newest and latest, whether it is a smartphone or a novel medical technology. When it comes to the robotic-assisted radical prostatectomy, it’s the same thing. Men and hospital administrators have embraced the technology for prostate cancer treatment even though there have been no studies showing its equivalence to standard surgery with a scalpel.

The surgical robot is a tool but nothing more than that. There are advantages to it in some people's hands. If the robot helps the surgeon perform the operation better, then so be it. I am not a negative person when it comes to the robot. I just think that it’s being oversold and overapplied in this country. There are now 80-year-old men getting robotic-assisted procedures that they don’t need because of their advanced age and low-risk cancer, and this has to stop.
H. Ballentine Carter, M.D.

Professor of Urology, Oncology
Johns Hopkins Medicine

Director, Division of Adult Urology, Brady Urological Institute
H. Ballentine Carter, M.D.

**Considering Active Surveillance for Low-Risk Prostate Cancer**

Prostate cancer in today’s PSA-era is over-treated, and a growing number of doctors and patients believe that a low-grade cancer detected early is more likely to never cause problems and is only a concern because it has been detected and brought to the patient’s attention. Consequently, *appropriately selected men should consider active surveillance for low-risk prostate cancer.*

Physicians know that most men over age 60 harbor some cancerous cells in the prostate, and that many of the small cancers within the prostate can be detected using current biopsy techniques, even in men with low PSA levels (less than 4 ng/ml). Nevertheless, most of these small cancers will not cause harm during the lifetime of the patient. From birth to age 90, there is an approximate 17 percent chance of being diagnosed with prostate cancer, and a 3 percent chance of dying of the disease. It’s evident that most older men are more likely to die with prostate cancer than from the disease. Therefore, deferring treatment may actually be the best approach for the carefully selected individual who is thought to have an early cancer.

However, how long do you defer? How can you identify the lucky man whose prostate cancer will do no harm? And how can you determine which man has a cancer that will lie dormant for years, but then suddenly start to grow, metastasize and ultimately prove fatal? These are the important questions that prostate researchers continue to grapple with. At this point, we still can’t accurately predict who has a cancer that will remain small and harmless, nor can we tell who has a cancer that will grow very rapidly, spread quickly out of the prostate and move to nearby bone, forever immune from curative treatment.

Yet most men today—even those whose age gives them a life expectancy of less than 15 to 20 years—undergo treatment for their prostate cancer shortly after being diagnosed, even though the disease might have been so insignificant that the risks of treatment and damage to quality of life far surpass the risk posed by the cancer. For the most part, the reason this is done is that men and their doctors have no assurances that the cancer will not one day become significant and lethal.

Nevertheless, active surveillance is an acceptable alternative for select older men who want to carefully monitor the disease rather than undergo immediate treatment. More and more
people with prostate cancer are beginning to step back and take a more measured assessment of their cancer instead of automatically reacting with, “I am going to treat this cancer immediately.” Men today are more educated about prostate cancer. They recognize that we are over-detecting small tumors that may never cause harm, and they are beginning to understand that not every cancer needs immediate treatment—if indeed it requires any treatment at all.

**DO YOU WANT TO PURSUE ACTIVE SURVEILLANCE?**

Based on data from the ongoing active surveillance study at Johns Hopkins that was initiated 16 years ago by Drs. Patrick Walsh, H. Ballentine Carter and Jonathan Epstein, active surveillance is most appropriate for men age 65 and older with an expected lifespan of 15 to 20 years. Younger men with underlying medical ailments that will limit their life expectancy are also reasonable candidates.

To join the Hopkins active surveillance program, a man should have very low- to low-risk prostate cancer. Very-low-risk cancer meets all of the following criteria:

- stage T1c
- PSA less than 10 ng/ml
- Gleason score of 6 or less
- no more than two cores (biopsy tissue samples) with cancer, and with cancer involving less than 50 percent of any core
- PSA density less than 0.15

Low-risk cancer meets the following criteria:

- stage T1c or T2a
- PSA less than 10 ng/ml
- Gleason score less than 6

In addition, the man must agree to have a digital rectal exam (DRE) and PSA test every six months and a 14-core prostate biopsy once a year, with two biopsy samples taken from the area of the prostate located farthest from the rectum. Other active surveillance programs may have slightly different criteria for admission and follow-up.

If you’re thinking about the active surveillance option, it’s important to consider your emotional tolerance level. For example, will you be able to live indefinitely with an untreated cancer without excessive worry? Another question to ask yourself: Will you be able to stick to the recommended surveillance schedule? If the honest answer to either question is no, do not be afraid to tell your doctor. Only then will you be able to determine the course of treatment that’s best for you.

For more information about enrolling in the active surveillance program at Johns Hopkins, contact Dr. H. Ballentine Carter at 410-955-0351.
Today, with extensive PSA screening and improved biopsy sampling, it is now possible to detect prostate cancers on average a decade earlier than in the era when screening was just being implemented. Many of these cancers will not progress during the remaining years of an individual’s life. Thus, active surveillance would certainly be rational for those men with low-risk cancer if they would agree to be monitored twice a year so any disease progression could be detected while they were still within what we term the “window of curability.”

At Johns Hopkins, we believe this is achievable today. I also believe that active surveillance will become a more popular option within the urological community (and among patients) as more information becomes available about the natural history of the prostate cancers that are being detected today with PSA screening.

A man thinking about active surveillance should understand that it entails close monitoring by a physician. At Johns Hopkins, we generally monitor men with regular PSA measurements, digital rectal exams and an annual biopsy. Active surveillance also requires that a person be able to live with the understanding that he has cancer and not be overcome by the anxiety produced by the need for careful monitoring.

The greatest risk with surveillance is that a man could possibly have a high-grade tumor that had been missed on a prostate biopsy. We have estimated this risk to be about 4 percent per year. Hopefully, the future will bring new blood markers or imaging techniques that could lower this risk. Nevertheless, at present, men who have a cancer grade above Gleason score 6 should consider treatment with surgery or radiation unless their life expectancy is limited.
Prostate cancer in today’s PSA-era is over-treated, and a growing number of doctors and patients believe that a low-grade cancer detected early is more likely to never cause problems and is only a concern because it has been detected and brought to the patient’s attention. Consequently, appropriately selected men should consider active surveillance for low-risk prostate cancer.

Many men diagnosed with prostate cancer don’t know anything about cancer when first diagnosed. Suddenly the man is asked to take on a very complex issue and make treatment decisions that could forever affect his quality of life—even the very length of his life. There are many gray areas when it comes to prostate cancer treatment decisions and a man must decide, with the help of his doctor and the support of his loved ones, what he wants to do.

By the time a man enters my office, mine may be the second or third opinion that he has sought, and I often see an informed patient sitting across the desk from me. On the other hand, I also see some who are not well informed about treatment possibilities.

I am a big believer in knowledge, and an informed patient is always a plus. I spend quality time with each of my patients and look closely at each diagnosis to see if there are other confounding factors that may affect the very-low- or low-risk diagnosis he may have received.

I don’t want to panic the patient. Many fear they need to do something right away, whether it is surgery or radiation. I explain, however, that with very-low risk and low-risk cancers, they have plenty of time to absorb the facts and consider what to do.

I try to be as optimistic as possible. Let’s say the patient is a 65-year-old man with a Gleason 6 cancer and a PSA below 10 ng/ml. There is no “better” cancer than this Gleason 6 diagnosis. I could treat the man and he would be cured. We could also observe the cancer and pursue active surveillance. This choice will not irrevocably alter the patient’s life, nor will it shorten it, and we have compelling data to back this up. This patient has very low risk, which is why I would recommend active surveillance unless the psychological concerns of living with cancer threaten to overwhelm the patient.
I tell men that prostate cancer has lethal and non-lethal forms. As cancers do, it may, over time, become more aggressive and try to spread. My job is to keep the patient healthy in mind and body while he is living with cancer, and to keep close tabs on it. We don’t have a good way to follow prostate cancer with an ultrasound or MRI, so a PSA test is given twice a year and a biopsy yearly so we can monitor it that way.

If a man falls comfortably into the very-low-risk or low-risk category, I will feel comfortable surveilling him—as long as I get the sense that he will come back to see me every six months for testing.

My job as a physician is to work with my patients and guide them. If they choose active surveillance, I am there for them, helping them maximize their quality of life. If a man with
The choice of prostate cancer treatment is based in part on the likelihood, or risk, that your tumor will grow and spread to other parts of your body. The lower your risk, the lower your chances that the prostate cancer will spread and that you will die of it.

### NCCN Risk Classification and Management Options

The following table outlines the risk groups, newly diagnosed cases, and NCCN management recommendations:

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Newly diagnosed cases (%)</th>
<th>NCCN management recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Low</strong></td>
<td>15</td>
<td>• Active surveillance when life expectancy is less than 20 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stage T1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prostate-specific antigen (PSA) less than 10 ng/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gleason score 6 or less and not more than two cores with cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Less than 50 percent of core involved with cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PSA density less than 0.15</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>35</td>
<td>• Active surveillance when life expectancy is less than 10 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stage T1c or T2a, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PSA less than 10 ng/mL and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gleason score less than 6</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>40</td>
<td>• Active surveillance or external radiation with/without hormonal therapy, with/without brachytherapy or surgery if life expectancy is less than 10 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery or external radiation with/without hormonal therapy, with/without brachytherapy if life expectancy is 10 or more years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stage T2b-T2c or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PSA 10 to 20 ng/mL or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gleason score 7</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>10</td>
<td>• Surgery or radiation plus hormonal therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stage T3a or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PSA 20 ng/mL or higher or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gleason score 8 or higher</td>
</tr>
</tbody>
</table>

low-risk disease opts for surgery, we have now reached the point where cure is likely and we can treat the worst side effects of incontinence and erectile dysfunction.

**Proton Beam Therapy and HIFU for Prostate Cancer**

Right now, we have a 95 percent prostate cancer cure rate with surgery. You can’t say that about proton beam therapy or HIFU. Proton beam therapy, which uses proton particles instead of X-rays, targets radiation more directly to tumors and spares healthy tissue, which should lead to fewer side effects. Its value is established for treating eye and certain pediatric tumors, but it’s now heavily marketed for prostate cancer. Although it has been in use for treating prostate cancer at some medical centers for more than a decade, it has not proven any better than standard external beam radiation therapy. I really don’t think that it’s worth the time or expense for patients to go for treatment at one of the nine centers around the country that have the $150 million machines.

HIFU, or high-intensity focused ultrasound, is not FDA approved for treating prostate cancer and may not be for years. Although a man may opt to enter a study with HIFU, in my estimation there is no need to do so for a treatable condition that responds to the standard of care, which is surgery.
Jonathan I. Epstein, M.D.

How Should We Designate Low-Risk Cancers?

There are those who believe that low-risk Gleason 6 cancers—since they generally pose no danger—should not be treated with surgery, and that they should be called something other than “cancer.” In my opinion, we still need to continue to call this cancer. There are plenty of cases of small cancers that, due to biopsy sampling error, turn out to be significant cancers. And if we didn’t call them cancer and didn’t follow them carefully, there would be some men who would lose the chance of getting cured.

Cancer is a powerful word; it’s not as if simply changing the name of Gleason 6 cancer to “precancer” or “neoplasia” would suddenly eliminate the many concerns surrounding very-low and low-risk cancer. What about the man with a Gleason 6 cancer who has a PSA of 15 ng/ml and an irregular digital rectal exam? Pathologists and surgeons would admit that he probably has a fairly aggressive cancer and that the biopsy needle just didn’t locate the more aggressive area in the prostate.

Do we then say, “Well, we’re going to call it cancer if it’s a Gleason 6 with an abnormal rectal exam and a PSA greater than 10 ng/ml?” Does a patient then say, “I have a Gleason 6 cancer, but it’s nothing to worry about?” It gets so complicated and illogical when you start putting this into practice. The real answer is “Yes, it is cancer, even if it’s a Gleason 6.”

We need to educate prostate cancer patients to understand that not all prostate cancers are horribly aggressive but some of them are. It’s a matter of separating them out to determine as best we can which type of disease a man has.

As for these very-low and low-risk cancers, we have to look at the whole package in order to decide if this is a cancer that has to be treated. The decision will be based on the patient’s age, underlying illnesses, and factors like the rectal exam, PSA and how much cancer is present on the biopsy.

Educating the Patient about Prostate Cancer

There are many men who know nothing of prostate cancer, and understand very little about the differences between doctors and the treatment options for prostate cancer. After being told that he has prostate cancer, a man is suddenly cast into a maelstrom.

Can the typical American man understand all of the nuances he is being asked to comprehend in making the decision about what to do about his cancer? Definitely not.
Two things do have to happen in order for a man to achieve the best outcomes after being diagnosed with prostate cancer. First, he has to have a highly educated physician who is up on all the latest treatment issues and will take the time to answer all of his questions. That doctor is not always easy to find. Second, the patient has to be his own advocate in seeking second opinions—and that includes getting a second opinion on his prostate biopsy. There is the possibility that he was misdiagnosed based on the biopsy and doesn’t have cancer at all. And if he does, the grade of the cancer could change upon review, which would affect his decision about which therapy to consider.

Once a biopsy is taken, the specimen is typically sent to a commercial laboratory or a hospital’s in-house lab. In some cases, spotting a prostate cancer is easy, but in others, the clues that tell a pathologist a cell is cancerous are not so clear. A little less than 1 percent of men are totally misdiagnosed and told that they have cancer when they don’t. It’s far more common—up to 20 percent of cases—that an incorrect Gleason grade is assigned. For example, when a biopsy specimen is sent to us for a second opinion, we often change the grade of the cancer, which significantly impacts the prognosis and treatment decisions.

One of the problems today is that pathologists used to work in a hospital setting and were accredited by hospitals. Now, many urologists or urology groups looking to manage costs are hiring their own pathologists to work for them. These pathologists do not have to go through the same accreditation screening that they would in a hospital. While there are some excellent pathologists working in such settings, I am aware of some who are abysmal—who made so many misdiagnoses that I had to contact the urologist with these concerns.

As a patient, you don’t know if your biopsy will be reviewed by one of the vast majority of pathologists who are good, or by one of the few who are not. That’s why a second opinion is so important. To get a second opinion on your biopsy report at Johns Hopkins, your physician or hospital must send your slides and a summary of your case to us, where pathologists with expertise in prostate cancer will review it. The review process normally takes several days, after which Johns Hopkins sends a report of all findings to your physician and/or others you may designate; your slides and other materials are returned.

The costs of a second opinion from Johns Hopkins may be covered by your insurance. If you have an HMO or PPO coverage, you will need an authorization to have a second opinion. Medicare will cover a second opinion requested by a physician. For more on second opinions at Johns Hopkins, go to www.hopkinsconsults.org
Understanding and Considering Active Surveillance

Active surveillance entails accepting that you have prostate cancer but choosing instead to test it regularly to see if it is becoming more aggressive; you will decide on treatment only if and when it does. This is a tough concept to accept for doctors and patients alike. Following cancer and not actively treating it is an emotionally charged concept, and it will take more time to gain widespread acceptance. The concept of active surveillance is slowly moving into the mainstream, however, and it’s something patients are becoming more aware of. There are some who bring it up with their doctors. Five years ago, virtually no one did this.

Focal Therapy for Treating Prostate Cancer

Focal therapy is an experimental procedure in which only the part of the prostate deemed to have cancer is treated. I don't recommend focal therapies—HIFU, cryotherapy, brachytherapy—unless the man is part of an ongoing study. Once MRI is improved to the point where it can actually detect and differentiate Gleason 3 from Gleason 4 tumors, focal therapy will eventually play a role in prostate cancer treatment. After that, the number of focal therapy cases will increase over the years, especially because some men are not comfortable doing active surveillance; they’d rather treat their cancer in some more aggressive fashion. They may be amenable to treat half of the prostate with a focal therapy and following up with annual tests as one would with active surveillance.

Before that can happen, however, we need well-controlled, long-term studies looking at the outcomes of focal therapies in medical centers that follow the patients carefully. We won’t have real answers about the utility of focal therapy until these studies are completed.

The Use of Novel Diagnostic Tests to Differentiate Cancer Aggressiveness

There is now a global hunt in progress using a variety of prostate cancer fingerprints—scientists call them biomarkers—that have been discovered or created to help identify the initiation, development, and ongoing cascade of damage caused by the cancer. Granted, the search has been painstakingly slow, especially when compared to the great successes achieved in the past two decades by heart-disease. Everyone is familiar with the most common biomarker for heart disease, the blood test for cholesterol levels. In the search for additional ways to predict the risk of heart disease, considerable evidence indicates that a molecule called C-reactive protein (CRP)—a protein made by the blood in response to inflammation of any kind—tends to be elevated in people who go on to develop heart disease and suffer a heart attack.

Without the prostate specific antigen (PSA) test, we never would have made such great strides at diagnosing prostate cancer and monitoring its aggressiveness if it recurs. Researchers are
now looking at biomarkers for TMPRSS2-ERG fusion prostate cancer, which may be the most common genetic rearrangement in human cancer. These genetic rearrangements, which are thought to play a role in prostate cancer development, comprise about 50 percent of the PSA-screened prostate cancers we see today.

There is conflicting data on the relation of TMPRSS2-ERG to tumor aggressiveness. TMPRSS2-ERG can’t be measured in the blood, but when a urologist does a vigorous rectal exam it can be calculated in the urine. The hope is that one day this marker will have the possibility to complement PSA and biopsy findings to help determine the presence of an undetected aggressive cancer. Knowing this would be of great benefit to men considering active surveillance as their treatment choice.

**The Future of Prostate Cancer Treatment**

I think the outlook now for men with prostate cancer compared to when I first started in the field three decades ago is much more complicated—but in a positive way—because we now understand much more about the biology of prostate cancer and because there are many more treatment choices.

We have active surveillance, whereas in the past if a man had cancer, the prostate was removed or irradiated. That’s because most of the cancers I saw before the advent of PSA testing were large, advanced cancers. Now, the pendulum has swung the other way and we are over-diagnosing and over-treating the smaller cancers that we now find.

On the other hand, we are still diagnosing many aggressive cancers, treating them and saving lives, which we could not have done without PSA testing. The prostate cancer death rate is coming down, most likely due to PSA screening but at the expense of over-treating some cancers. We are trying to reduce over-treatment but doing it in a very intelligent way based on data from long-term studies from around the world.
William G. Nelson, M.D., Ph.D.

Marion I. Knott Professor of Oncology
Johns Hopkins Medicine

Director, The Sidney Kimmel Comprehensive Cancer Center

Professor of Oncology, Urology, Pharmacology, Medicine, Pathology, and Radiation Oncology
The goal of focal therapy is to destroy an area of the prostate that has cancer instead of removing the entire prostate through surgery. Focal therapy for prostate cancer with a less invasive heat, cold or a radiation source only makes sense if you know precisely where to aim it. There are ongoing international initiatives to find ways to use MRI scans as a way to pinpoint exactly where cancer is located within the prostate. If we could actually see where the cancer was lurking, focal therapy could be very effective. Although we are not there yet with these diagnostic scans, I would not bet against a technological breakthrough. When it comes to prostate cancer treatment, I think focal therapy would be transformative.

The Problem with Provenge for Advanced Prostate Cancer

Provenge is a vaccine that is currently indicated for patients who have failed hormone therapies and their PSAs are rising. The vaccine is given in three separate infusions over a one-month span. One of the paradoxes of Provenge is that because it stimulates the immune system, it doesn’t produce PSA declines and visible tumor shrinkages. No one knows how it works. While it is an interesting cancer vaccine that was shown in a clinical trial to extend life, without a biomarker such as PSA that indicates that the drug is working, Provenge defeats the rationale of all anticancer drugs, which is that you either get a reduction in PSA, which indicates that the therapy is killing cancer cells, or there is no PSA response, indicating the therapy is not working.

Men with advanced cancer know what their PSA is, and if they take a drug like Zytiga or MDV3100 and their PSA falls, they will continue to take those drugs. Provenge does not work that way and I think that is going to be the ultimate downfall of this vaccine.

Androgen Deprivation and Beyond for Advanced Prostate Cancer

Prostate cancer cells need androgens such as testosterone in order to thrive. Knowing that, men with recurrent cancer are prescribed drugs called leuteinizing hormone-releasing hormone (LHRH) agonists to prevent the testicles from producing testosterone. Commonly used injectable LHRH drugs include leuprolide (Lupron) and goserelin (Zoladex).

This hormonal therapy is very effective in lowering PSA, causing reduction in tumors, and improvement in pain for some time. Unfortunately, for reasons we don’t really understand, most patients eventually develop resistance to hormonal treatment. The cancer cells are able
The goal with ongoing androgen deprivation drug research is to find ways to cripple androgen signaling and remove it completely from the cancer equation. We are getting closer to that with our new wave of drugs, especially abiraterone, which is called Zytiga, and a new drug that awaits FDA approval called MDV3100 (see page 47). Both of these drugs work well when other hormone therapies have failed. For example, 90 percent of patients taking Zytiga experience a dramatic reduction in PSA, and many have a significant shrinkage of tumors and improvement in bone pain due to bone metastases.

If cancer is going to eventually outfox these drugs and continue to proliferate, it will have to accomplish that by doing something very different from what we currently understand. That, I think, will be the next wave of castration-resistant prostate cancer that we will have to treat. Researchers will have to find what is still fueling the growth of this cancer and stop it, which is the aim of ongoing research at Johns Hopkins.

### Autopsy Results to Aid in Cancer Research

Autopsies, especially of men who have died from advanced prostate cancer, are not regularly performed anymore for a variety of reasons, including changing cultural norms and rising costs. Recently, however, there has been a renewed interest in autopsies to find out exactly what happens during the course of metastatic prostate cancer and see why treatments did or did not work. We are now performing autopsies at Johns Hopkins because we feel that this information we get from examining tissue will allow us to better understand what is going on metabolically within the cancer cells. With this knowledge, we hope that we will then be able to develop better treatment of advanced prostate cancer. Here is an example of a recent autopsy case that started with my involvement with a patient I had first seen 17 years ago.

As part of an annual physical, this 48-year-old man had been given a PSA test, which came back with a highly elevated level of 40 ng/ml. A subsequent Gleason 8 biopsy indicated an aggressive prostate cancer, while a bone scan indicated no metastases. The man soon underwent a radical prostatectomy and three months following surgery, his PSA had dropped to 0.13 ng/ml, which was a good sign that the cancer had most likely been removed.

Six months later, however, the man’s PSA had risen to over 6 ng/ml, an indicator that some of the cancer must have already escaped the prostate before surgery. In order to try and hold his
cancer in check, he immediately agreed to enroll in a clinical trial with an experimental prostate cancer vaccine for recurrent cancer, and this soon dropped his PSA down to 1.2 ng/ml.

About twelve and a half years after he was diagnosed with his cancer recurrence, metastases were first noted in his prostate bed, bones and lymph nodes. Treatment with androgen deprivation therapy was initiated to cut off the supply of testosterone to the cancer cells, followed by chemotherapy with Taxotere and radiation treatments to treat the metastasis discovered in his skull.

The cancer was held in place with these therapies for three additional years before other metastases were uncovered in his lung and throat. At this point, the patient was enrolled in a clinical drug trial with abiraterone, a drug that has since been approved by the FDA and is now called Zytiga. This oral medication is designed to reduce PSA, shrink tumors and reduce bone pain. His symptoms improved and his PSA fell to as low as 0.3 ng/ml. However, a little more than a year later, liver metastases were discovered, which then had to be treated.

Despite all of these interventions over the course of 17 years, the patient finally died from castration-resistant prostate cancer. What was so special about this patient was that he wanted to help us unravel the mysteries surrounding advanced cancer and assist us in finding answers about castration-resistant disease in order to keep other men from going through what he had. He agreed to donate his body to science immediately upon his death so that we could perform an autopsy and complete a genetic sequencing of all his metastatic tissues. An anonymous donor who was interested in helping us uncover the biological underpinnings of prostate cancer paid for these expensive and time-consuming procedures.

Autopsy results revealed metastases in my former patient’s lymph nodes and vertebrae as well as an enlarged liver that was riddled with cancer. We are continuing to examine the prostate tissue that was taken from the man’s body after his radical prostatectomy 17 years earlier and compare it with the tumor cells found in various places throughout his body after his death. We hope to discover if the cancer cells that originally migrated from the prostate before surgery were the same cells that eventually killed him. Or, were the mutated cells found in the metastases the actual cause of his death?

Unraveling the unique molecular makeup of his cancer and getting answers to these important questions will help us to better understand the role of the changes in the prostate tumor progression process and how the metastatic pathways work. It will also help us to eventually develop better diagnostic tests and treatments that may be able to prevent or mitigate advanced prostate cancer.
It seems unfair that treating your advanced prostate cancer can make you vulnerable to bone loss and fractures, but that's exactly what could happen with long-term hormone therapy. Also known as androgen deprivation therapy, or ADT, hormone therapy reduces levels of testosterone and estrogen, both of which help maintain bone density in men.

Although not all men using ADT will develop osteoporosis (bone loss), an estimated 50 percent will be affected by their fourth year of treatment and more than 80 percent will be affected after 10 years. Using ADT for a year or more increases fracture risk as well. A 2005 study in *The New England Journal of Medicine* reported that among men with prostate cancer who lived for at least five years after their diagnosis, the risk of a fracture was nearly 20 percent among ADT users, compared with 13 percent for nonusers.

The most widely used BMD test is dual-energy x-ray absorptiometry (DXA). It takes 20 minutes and uses two x-ray beams to scan your bones for signs of bone loss. The results are expressed as a T-score. A score of -1 or above is considered normal, and a score of -2.5 or below indicates osteoporosis. A score between -1 and -2.5 is called osteopenia—meaning you have lower-than-normal bone density, but it is not severe enough to be labeled as osteoporosis.

To help keep an eye on your T-score, prostate cancer experts recommend a BMD assessment before beginning treatment with ADT. If your T-score is -1 or higher, you can wait two years before the next test. However, if your score is less than -1, you should have another BMD test in six to twelve months.

Experts also recommend the following treatment guidelines from the National Osteoporosis Foundation. According to these guidelines, doctors should consider drug treatment to halt bone loss if your T-score is -2.5 or lower or you have already had a hip or vertebral fracture. Also consider drug treatment if your T-score is between -1 and -2.5 and you meet one of the following two criteria:

- your 10-year probability of experiencing a hip fracture is 3 percent or more
- your 10-year probability of experiencing a major osteoporosis-related fracture is 20 percent or more.

To determine these probabilities, your doctor is likely to use a tool called FRAX, which assesses your risk of a fracture based not only on your BMD but also on a number of other factors such as your age, weight and alcohol intake. You can access the tool at www.shef.ac.uk/FRAX. Click on “Calculation Tool” and choose your country and race. If you are on ADT for prostate cancer, select yes for item number 10 (secondary osteoporosis).

**Drug Treatment Options**

When medication is required to halt bone loss in ADT users with prostate cancer, bisphosphonates are the first-choice. Selective estrogen receptor modulators (SERMs) offer a second-line option, and a recently approved monoclonal antibody called denosumab (Xgeva) also works well.

**Bisphosphonates.** These drugs work by slowing the rate of bone breakdown, helping to preserve existing bone mass. Studies in men taking ADT for prostate cancer show that these drugs can improve BMD in the spine and hip.

Zometa (zoledronic acid) does this very well, and also helps prevent bone pain and other bone complications of hormonal therapy. It is given intravenously every three months.

Side effects associated with bisphosphonates include flu-like symptoms (muscle aches and pains and fever), nausea, fatigue and kidney damage. Rare instances of osteonecrosis of the jaw (a
Serious bone disease that affects the jaw) have been reported, particularly after use of intravenously administered bisphosphonates. As a precaution, the American Dental Association and the American Association of Oral and Maxillofacial Surgeons recommend having major dental work performed at least two weeks before the initiation of treatment with a bisphosphonate.

**SERMs.** These medications mimic some of the actions of estrogen, a hormone that can help stimulate bone-building osteoblasts and shut down bone destroying osteoclasts. Studies show that the SERMs raloxifene (Evista) and toremifene (Fareston) can increase both spine and hip BMD in ADT users with prostate cancer.

A recent double-blind, placebo-controlled Phase III study evaluated the use of Fareston (80 mg daily) in 646 men receiving hormone deprivation therapy for prostate cancer versus placebo in 638 men. At the end of the two-year study, the incidence of new vertebral fractures was 2.5 percent in the Fareston group and 5 percent in the placebo group. Compared to patients in the placebo group, the patients taking Fareston had significantly increased levels of BMD in their hips and spine. However, 2.6 percent of patients (17) taking Fareston had a problem with blood clots as compared to 1 percent of patients (7) given placebos.

A major concern with SERMs is that they increase the risk of blood clots. If you already have an increased risk of blood clots (for example, if you are over age 80 or have had a previous blood clot, recent surgery, or a recent bone fracture, or if you are immobile), treatment with a SERM is not recommended.

**Xgeva: The latest bone-protecting drug.** Xgeva (denosumab) was approved by the FDA in 2010 to help prevent bone loss in people with metastases from prostate cancer. This drug has been shown to decrease bone loss and increase time to skeletal-related events such as fractures, bone pain and spinal cord compression.

This drug is the same osteoporosis treatment drug called Prolia, but it is used at a much higher dose. Xgeva is injected under the skin once a month. Zometa, another drug used for the bone complications of advanced prostate cancer, on the other hand, requires intravenous administration and this has proven to be an inconvenience for some patients. An FDA advisory committee recently voted against approving an additional usage for Xgeva as a drug that could prevent or delay prostate cancer spreading to the bone in men with castration-resistant prostate cancer, noting that the drug did not result in increased survival or higher quality of life.

**What Else Can You Do?**

If you have advanced prostate cancer, here are additional steps you can take to preserve your bone health:

**Exercise.** An exercise program that includes weight-bearing aerobic exercise, resistance training and balance exercises can help preserve your bone density.

**Get enough calcium.** Calcium is a key mineral that strengthens bone, and a calcium deficiency can lead to osteoporosis and a risk of fracture. The NOF recommends that adults over age 50 get at least 1,200 mg of calcium a day.

**Get enough vitamin D.** Vitamin D contributes to bone health by helping the body to absorb calcium. The NOF recommends that people over age 50 get between 800 and 1,000 IU of vitamin D each day.

**Don’t smoke.** Smoking—and perhaps even exposure to secondhand smoke—is linked to an increased risk of osteoporosis and bone fracture. Quitting can reduce your risk of further bone loss and fracture. If you need help quitting, talk to your doctor. Counseling, nicotine replacement therapy and prescription medication can help.

**Limit alcohol consumption.** Chronic alcohol use can disrupt calcium and hormone levels in your body and can increase your risk of falls that could lead to a fracture. If you drink, it’s best to do so in moderation. The usual recommendation for men is no more than two drinks a day.
William B. Isaacs, Ph.D.

William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology
Professor of Oncology
Johns Hopkins University School of Medicine
William B. Isaacs, Ph.D.

Discovering the Gene for Inherited Prostate Cancer

As a researcher, I have spent my entire career trying to understand the genetic variants that may be responsible for increased risk of prostate cancer. We have been following certain patients and their families ever since the early 1990s, when Dr. Patrick Walsh first became interested in the question of hereditary prostate cancer.

After a 20-year quest to find a genetic driver for prostate cancer that runs in families and strikes men at younger ages, we have finally identified a rare, inherited mutation linked to a significantly higher risk of prostate cancer; it is called HOXB13, and men who inherit this mutation have a 10 to 20 times higher risk of developing prostate cancer.

We’ve known for a long time that prostate cancer can run in families, but finding its underlying genetic basis has always been the problem. Although this gene is responsible for only a small fraction of all prostate cancer cases, the discovery of HOXB13 may provide important clues about how prostate cancer develops. It may also help identify those men who might benefit from additional or earlier screening.

For this HOXB13 study, which was published in The New England Journal of Medicine, we collaborated with experts at the Translational Genomics Research Institute in Phoenix, Arizona, who used the latest technology to sequence the DNA of more than 200 genes in a human chromosome region known as 17q21-22. Our Johns Hopkins team, which worked with researchers from the University of Michigan, started with samples from the youngest patients in 94 families who had participated in studies at Hopkins and Michigan. Each of those families had multiple cases of the disease among close relatives, such as between fathers and sons or among brothers.

Members of four different families were found to have the same mutation in the HOXB13 gene. HOXB13 plays an important role in the development of the prostate during the fetal stage and later in life. We knew we were on to something when we discovered that the mutation was carried by all 18 men with prostate cancer in these four families.

Working with researchers at Wake Forest University, we also found the HOXB13 gene mutation among 5,100 men who had been treated for prostate cancer at either Johns Hopkins or the University of Michigan. The mutation was uncovered in 72—1.4 percent—of the men. It
turned out that those men were much more likely to have at least one first-degree relative—a father or brother—who also had been diagnosed. Looking for HOXB13 in a control group of 1,400 men who didn’t have prostate cancer, we found the mutation in only one man.

From our research, we determined that HOXB13 was much more common in men who had:
- a family history of prostate cancer
- an early cancer diagnosis compared with men diagnosed later
- no family history of prostate cancer and were older than 55

Using the HOXB13 gene gives us more confidence that we are getting closer to unlocking secrets to the genetic underpinnings of prostate cancer. We now believe that this genetic marker can account for at least a portion of the hereditary form of prostate cancer. With further study, it may be possible one day to have a genetic test for inherited prostate cancer in much the same way that tests are available to look for BRCA1 and BRCA2 mutations that greatly increase a woman’s chance of developing breast or ovarian cancer.

Our genetic findings in prostate cancer are in their early stages. We need to continue studying HOXB13 and look at larger groups of men. Our next step will be to develop a mouse model with this mutation to see if it causes prostate cancer. Future DNA sequencing may also identify additional rare variants that contribute to prostate cancer risk in families.

■ Whole Genome Sequencing and Its Effect on Future Prostate Cancer Research

It took researchers involved in the Human Genome Project 13 years and almost $3 billion to sequence, or identify, the human genome for the first time in 2003. This enabled scientists to finally determine the order of nucleotides—represented by the letters A, C, T and G—that make up DNA. It's the sequence of these letters that helps determine the traits of an organism, healthy or otherwise.

There are 3 billion chemical base pairs that make up the DNA double helix at the center of every cell. Intermingled through the DNA are 20,000 to 25,000 genes. The complete set is known as the genome and this incredible “recipe book” tells the body how to make proteins, heart cells, brain matter, muscle and bone. An erroneous letter hidden deep inside a gene can boost the risk of developing prostate cancer, for example, or it can start the cellular destruction in the brain that eventually leads to Parkinson’s disease much later in life.

The best way to get to the root cause of a serious illness like prostate cancer is to sequence a person’s genome. The Human Genome Project has helped me and my fellow researchers find the genetic errors that trigger disease. It has also fostered the creation of newer, faster and less expensive methods of gene sequencing. The machines used in the Human Genome Project read 25,000 bases a week in 1990 and 5 million a week in 2000. The next-generation gene
sequencers being used today can read 250 billion bases in a week, which makes it possible to conduct experiments once considered too expensive or simply impossible.

Our goal as genetic researchers is to discover new gene variants that can influence a person’s tendency to develop prostate cancer and other diseases. Our progress is directly linked to technology advances, and these technological breakthroughs are going to revolutionize human genetics. You can’t underestimate the importance of this.

A day will come soon when everyone’s genome will be sequenced and included as a routine part of their medical records. Next-generation sequencing machines can help achieve this goal in the near future with the wider dissemination of faster and affordable sequencing machines capable of reading 10 million letters of genetic code in just two hours. For the first time, every scientific laboratory will be able to afford one.

Using powerful sequencers that are now available, a human genome can be read in eight days at a cost of $10,000. It’s expected that sometime in 2012, the next-generation sequencing machines will be able to map a human genome in 15 minutes, all for $1,000 or less. Not only is this increase in speed and cost reduction in the next-generation gene sequencers turning biology upside down, it is also getting us much closer to finally discovering the molecular makeup of diseases affecting individual patients. This will eventually allow us to define prostate cancer by its underlying molecular causes, which will greatly aid in the development of highly specialized pharmacogenomic treatments for prostate cancer.
Charles L. Sawyers, M.D.

Chair, Human Oncology and Pathogenesis Program
Memorial Sloan-Kettering Cancer Center
Castration-resistant prostate cancer is the most advanced form of the disease. When I was at UCLA in the 1990s, we were interested in understanding why patients failed to respond to hormonal therapy. Activation of the androgen receptor drives tumor growth. One type of hormone therapy includes drugs that lower androgen levels; another type binds to the androgen receptor and blocks androgen binding. While hormone therapy is effective in almost everyone for a period of time, it eventually stops working; the patient now has castration-resistant prostate cancer. The tumor cells become hormone refractory and proliferate, which ultimately leads to death of the patient.

When we first started our work, castration-resistant prostate cancer was called “androgen-independent” prostate cancer. Because tumor cells continued to grow despite the significant reduction in testosterone levels achieved through drug therapy, these cells, by definition, were no longer dependent on androgens in order to survive.

In a paper published in 2004 in the journal *Nature Medicine*, our group reported that increased expression of the androgen receptor was driving castration resistance; the cancer was not androgen independent. We showed that this excess level of androgen receptor allowed tumor cells to utilize limited amounts of testosterone. This work also showed that castration-resistant tumor cells were still dependent on the androgen receptor. Our data suggested that inhibitors that are more potent, or are blockers of the androgen receptor, may be effective in castration-resistant prostate cancer.

Despite our findings, there was little interest from drug companies in pursuing new antiandrogen drugs. Therefore, our academic research team decided to search for compounds that would shut down androgen receptor signaling in prostate cells that expressed high levels of the androgen receptor, similar to the levels found in castration-resistant tumors.

We teamed up with Dr. Michael Jung, a chemist at UCLA, and he soon came upon something that had been described in an old patent filed by a French company: It was a compound that bound to the androgen receptor 100 times tighter than bicalutamide, or Casodex—the most

**Charles L. Sawyers, M.D.**

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**The Discovery and Development of MDV3100 for Castration-Resistant Prostate Cancer**

MDV3100 will initially be used for men who have failed chemotherapy for their prostate cancer, but there are now ongoing trials with the drug in men with advanced cancer who have not started chemotherapy.
commonly used antiandrogen drug used for reducing hormone levels in men with advanced prostate cancer.

This compound did not inhibit the androgen receptor; instead, it activated it—an effect that was the opposite of what we were looking for. Using this compound as a starting point, we then made alterations to its chemical structure, and that converted the drug to an inhibitor. Additional changes allowed the compound to be absorbed into the blood when given by mouth to a mouse. Finally, we had MDV3100, an oral drug that was licensed to Medivation, Inc.

MDV3100 was first tested in a 140-patient clinical trial that began in 2007. Based on the success of MDV3100 in this first trial, a phase 3 randomized trial called AFFIRM was launched in 2009. In early February of this year, Dr. Howard Scher, chief of the Genitourinary Oncology Service at Memorial Sloan-Kettering, announced positive results with MDV3100 at the American Society of Clinical Oncology Genitourinary Cancers Symposium in San Francisco. Dr. Scher reported that the AFFIRM trial proved that MDV3100 was a promising option for men with prostate cancer who had already received prior hormones and chemotherapy. The trial included 800 patients from around the world with advanced cancer who received MDV3100. Of particular note:

- Men taking MDV3100 lived for an average of 18.4 months, compared with 13.6 months for men taking placebo.
- MDV3100 met all secondary endpoints, including radiographic progression-free survival (8.3 versus 2.9 months).
- PSA declines of 50 percent or greater were more common in the MDV3100 group than in the placebo group (54 percent versus 1.5 percent).
- MDV3100 was well tolerated. Common side effects included fatigue, diarrhea and hot flushes.

**WHY YOU SHOULD CONSIDER JOINING A CLINICAL TRIAL**

Even though there are now several therapeutic options for advanced and castration-resistant prostate cancer, with each new addition come questions about the best management strategies. For example, which of the drugs should be used at which point in the disease progression? And in what order?

Currently, there are no good scientific data to guide treatment decisions. You may want to consider participating in a clinical trial that could help provide answers and potentially lead to the development of new, more effective therapies for metastatic castration-resistant prostate cancer.

Clinical trials are sponsored by government agencies, medical institutions, pharmaceutical companies, foundations and other organizations. Most are listed at ClinicalTrials.gov, a searchable internet database maintained by the National Institutes of Health.
Approval of MDV3100 is anticipated sometime in 2012. The fact that this approval could occur just five years after the drug’s first use in humans points to our better understanding of the biology of prostate cancer and the role of the androgen receptor in particular. MDV3100 will initially be used for men who have failed chemotherapy for their prostate cancer, but there are ongoing trials with the drug in men with advanced cancer who have not started chemotherapy.

• ARN-509. ARN-509 is another androgen receptor antagonist, licensed to Aragon Pharmaceuticals of San Diego. A phase 1 clinical trial of ARN509 conducted at Memorial Sloan-Kettering is nearly completed; phase II testing has begun and has expanded to other clinical sites throughout the United States.

• Circulating tumor cell technology for monitoring drug therapy for advanced prostate cancer. Circulating tumor cells (CTCs) are cancer cells that have detached from an existing tumor and have moved into the bloodstream. In theory, measuring CTCs in a sample of blood can facilitate early detection of recurrent cancer in patients who are known to have the disease. By measuring CTCs in the blood, researchers can evaluate response to investigational drug therapies much sooner.

When it comes to using CTC tests as a standard diagnostic for advanced prostate cancer, the tremendous hope is that the tests will be useful. CTCs were included in both abiraterone and MDV3100 clinical trials. If CTCs could one day become a surrogate marker for response to experimental drugs, and if the FDA would accept that, the pace of drug development in prostate cancer would pick up dramatically. It would be a real game changer because the time lines for drug development will shrink tremendously.

• Possibility of newer drugs turning advanced prostate cancer into a chronic disease managed by medication. I do think that is possible but we will have to use the newer drugs earlier in the disease process, much earlier than we now use them. It’s the golden rule of almost any drug: If it is active in late disease, it will be even more active in earlier stages of the disease.
Oncotype DX Test for Prostate Cancer

Genomic Health has developed commercially available diagnostic tests for breast and colon cancer patients that have become the standard of care for hundreds of thousands of men and women at the time of initial diagnosis. By working with leading prostate cancer researchers, our next goal is to have a test to be used at the time of prostate biopsy that adds value beyond the Gleason score to help identify which are the aggressive tumors that need to be treated with surgery or radiation, and which are the ones that are clinically insignificant. The information provided by our Oncotype DX prostate cancer test will also help doctors and patients decide whether active surveillance is an appropriate course of action to pursue because the cancer is low risk.

Following a prostate biopsy, small amounts of tissue taken during the biopsy will be sent to our laboratory in Redwood City, California for analysis. Here we will utilize our proprietary process to determine the aggressiveness of the cancer. Whether the test results indicate “good news” or “bad news,” the information will undeniably be helpful. Test results indicating that the underlying biology is not clinically significant will give greater confidence to the physician and patient that they can pursue active surveillance and monitor the cancer regularly. When our prostate test shows a more aggressive underlying biology, it will indicate—even if other factors look favorable—that more aggressive treatment should be initiated.

We need to understand prostate cancer on a molecular level and then diagnose and treat it based on a person’s underlying biology. Genomic Health is a company that has pioneered and worked with leading cancer researchers to advance personalized medicine so it can be tailored to an individual’s unique genetic profile. Because prostate cancers diagnosed today, in the PSA era, are often low risk, we expect a greater proportion of men would find our Oncotype DX prostate cancer test confirming that they have less aggressive disease while a smaller proportion of men will find that they have more aggressive disease.

Today, only a very small percentage of men diagnosed with prostate cancer pursue active surveillance, often out of fear that they have a cancer that could harm them. Our test will change that by allowing more men and their doctors to feel confident that active surveillance is right—and safe—for them.
We have just initiated the prostate cancer validation study for Oncotype DX prostate cancer assay and expect to get the results in 2012. If they are positive, we will make our test commercially available in 2013.

Our interest in prostate cancer is not short term, and not related only to the Oncotype DX test. We have the tools, the will and the resources to do the molecular studies to help characterize and individualize treatments for prostate cancer. As more treatments for advanced prostate cancer become available, we look forward to doing additional research in identifying the best drugs for the right person based on the biology of his prostate tumor.
Rely on Expert Health Advice From Johns Hopkins

*Ranked America’s #1 Hospital by U.S. News & World Report*

**The Johns Hopkins Prostate Disorders Bulletin**

Written by Dr. Jacek L. Mostwin and his esteemed colleagues at the world-renowned James Buchanan Brady Urological Institute, the *Johns Hopkins Prostate Disorders Bulletin* is an indispensable quarterly journal for men with prostate cancer. It also covers other prostate health concerns, including benign prostatic hyperplasia (BPH) and prostatitis, and related concerns such as overactive bladder and erectile dysfunction. In in-depth reports from leading experts and summaries of critical research findings, the *Bulletin* goes far beyond the basics to inform you about the latest therapeutic treatments, advanced news of clinical trials, and new medications, plus detailed answers to subscribers’ concerns about all aspects of your prostate health. A subscription includes 5 FREE special reports.

**Advanced Prostate Cancer Treatments—Know Your Options When Your Cancer Comes Back**

This 113-page guide features discussions with leading experts at Johns Hopkins on specific options for treating advanced prostate cancer. You will learn about current therapies as well as new approaches being developed here at Johns Hopkins and other important medical centers. These treatments include gene therapy to stop the advance of the disease, monoclonal antibodies that zap cancer cells throughout the body, and a variety of chemotherapy agents such as Taxotere and angiogenesis inhibitors (drugs that choke off the blood supply to tumors).

**Restoring Sexual Intimacy After Prostate Cancer Treatment**

Responding to a major concern shared by men facing surgery for prostate cancer, two leading experts at the James Buchanan Brady Urological Institute at Johns Hopkins provide the latest thinking on erection rehabilitation after radical prostatectomy. This in-depth report explores the full range of erectile dysfunction treatment options—effective oral medications, injection therapy, penile implants, and more. The report includes answers to dozens of real questions from patients on sexuality and prostate cancer.

**The Best Treatment Strategies for BPH**

Top specialists at Johns Hopkins’ renowned James Buchanan Brady Urological Institute present the latest thinking on managing benign prostatic hyperplasia (BPH), or enlarged prostate. This essential guide answers dozens of questions from patients searching for practical, no-nonsense advice on living with BPH. It covers current pharmacological therapies—and provides a thorough discussion of all the surgical options when medication no longer works, weighing the pros and cons of TUNA, TUMT, and TURP. Armed with the information in this guide, you’ll be able to meet with your own physician and make the right decisions in your quest for the best possible outcome.

For more information, or to order, go to:
www.johnshopkinshealthalerts.com/prostateoutlookbookstore
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