The Patrick C. Walsh Hereditary Prostate Cancer Program

“For the first time, we have the potential to identify every gene involved in hereditary prostate cancer.”

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Our research is evolving. Today, we are curing urological cancers that were not curable even a few years ago, with better diagnosis, refined surgery and radiation, and newly discovered classes and combinations of drugs. Through the incredible generosity of our patients and friends, our world-class scientists are leading an all-out effort to track down the genes involved in hereditary prostate cancer. We’re also looking at the genes of men who are considering Active Surveillance, to make sure this is a safe option for them, and we are finding genetic and molecular markers that can tell us which men with the most aggressive prostate cancer can benefit from immunotherapy.

Our scientists at the Greenberg Bladder Cancer Institute continue to lead the field with pioneering molecular subtyping of cancer — finding specific groups of people with similar types of cancer, who will respond better to particular treatments — with new immunotherapy and chemotherapy approaches, and innovative mini-bladders, made from a patient’s own cells. In renal cancer, our strategy of highly patient-specific treatment has allowed hundreds of people to be safely monitored for small tumors, and our multidisciplinary “Go Team” is saving the lives of people who have tumors that are considered inoperable at other centers. Finally, with great sadness but also much joy, we honor the life of our beloved research director and friend, Donald S. Coffey, whose legacy continues in the generations of scientists he has trained.

Best wishes,

Alan W. Partin, M.D., Ph.D.

The Jakurski Family Director and Professor
The James Buchanan Brady Urological Institute
Urologist-in-Chief, Johns Hopkins Medicine
Cover Story: Dangerous Genes

“How many more BRCA2-like genes can predict aggressive disease risk and drug sensitivity? So far, the list of these genes is quite short.”

“Every year, worldwide, an estimated 1,111,700 men are diagnosed with prostate cancer and 307,500 men die from it,” says William Isaacs, Ph.D., the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology.

“The wide discrepancy between these two numbers shows that only a subset of these cancers progress to lethal disease.” This is good news for most men with prostate cancer – but men who have, or are at risk of getting, aggressive prostate cancer are desperately in need of smarter diagnosis and more specific treatment.

The key to more precise treatment for aggressive prostate cancer is in understanding the genes of that man’s specific cancer. Some drugs work much more effectively against particular mutated genes when cancer has escaped the prostate. Even when cancer is caught in the early stages, it’s critical to understand a man’s genetic risk – whether his cancer is aggressive or more benign.

A mutated version of the HOXB13 gene, discovered by Isaacs and his team, is the first verified prostate cancer susceptibility gene. Isaacs and colleagues at other centers have also discovered that more commonly mutated genes – defects that can cause several different types of cancer – are major factors in inherited prostate cancer risk, as well. For example, “work from our lab and others has shown that BRCA2 mutations increase the risk not only for prostate cancer, but for an aggressive form,” says Isaacs. In fact, “we now know that about one in 10 men who die from prostate cancer carry a damaged copy of BRCA2 or another gene involved in DNA repair, such as ATM.”

Finding one of these mutations in a man with prostate cancer has implications for his family, as well: “each child has a one-out-of-two chance of inheriting the risky gene. How many more BRCA2-like genes can predict aggressive disease risk and drug sensitivity?” Isaacs wonders. “So far, the list of these genes is quite short.”

As part of The Patrick C. Walsh Hereditary Prostate Cancer Program (see page 4), “in an effort to find additional genes that can predict prostate cancer risk, we have begun a large study, sequencing each of the over 20,000 inherited genes from different sets of prostate cancer patients: men with highly aggressive or lethal disease, men with more indolent or benign disease, and men with multiple affected family members.”

So far, Isaacs and his team have found a number of candidate susceptibility genes: mutated genes that are more common in men with aggressive disease than in men with low-risk disease, and are present in multiple members of prostate cancer families. “We are in the process of testing these candidates now,” says Isaacs. “So far, at least one gene has emerged that is worthy of further study: a gene called PPF1BP2, which also has been implicated in metastatic breast cancer. “They have found mutations in this gene more often in men with aggressive prostate cancer than in men either with less-aggressive disease, or men who don’t have prostate cancer. Also,”we have observed multiple families where each affected member carries the same mutation in this gene.”

Much more work is needed, Isaacs notes. One day, he hopes, the presence or absence of such genes “will guide our treatment decisions, so that every man is treated appropriately for his specific prostate cancer risk.”

Our cover story continues on the next page.

ON THE COVER So much to celebrate!
From left: William Isaacs, Patrick Walsh with philanthropist Bernard Schwartz (seated).
Schwartz has been a good friend to The Brady for many years: with his late wife, Irene, he established the Bernard L. Schwartz Distinguished Professorship in Urologic Oncology in 1996, once held by Alan Partin and currently held by H. Ballentine Carter. In 2000, Schwartz answered another call and established the Schwartz Research Fund to explore the role of dietary factors in the initiation and progression of prostate cancer, and when Walsh stepped down as Director of The Brady in 2004, Schwartz once again made a substantial gift to The Patrick C. Walsh Prostate Cancer Research Fund and became a member of our Founders’ Circle.

Congratulations

Bruce J. Trock, Ph.D., Professor of Urology, Epidemiology and Oncology, an internationally recognized leader in prostate cancer epidemiology, outcomes, and biomarker research, was installed as the Frank Hinman, Jr. Professor in Urology. This professorship is named after Dr. Hinman, a graduate of the Johns Hopkins School of Medicine and renowned surgeon, genitourinary educator, and illustrator.

From left – Beyhan Trock, Alan Partin, and Bruce Trock
On February 13, 2018, Patrick C. Walsh, M.D., University Distinguished Service Professor Emeritus, and Director of The Brady for three decades, turned 80. The Brady wished to honor this milestone, and asked Walsh for his suggestions. He recommended that we contact his former patients, asking for their help in completing the work he began in the 1980s with molecular biologist William Isaacs, Ph.D., the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology.

Walsh’s scientific passion is hereditary prostate cancer research. In fact, he and Isaacs were the first to identify and define hereditary prostate cancer, and to discover that prostate cancer is one of the most “heritable” cancers: inherited genetic factors play a role in about half of all men with prostate cancer, and inherited faulty genes account for at least 10 to 15 percent of deaths from this disease.

“In honor of his 80th birthday, we wanted to recognize Pat Walsh with a gift that would bring him great pleasure and fulfillment. Through the generosity of many of his friends and longtime patients, we have established The Patrick C. Walsh Hereditary Prostate Cancer Program, to determine the genetic causes of, and develop effective treatments for, hereditary prostate cancer,” says Alan W. Partin, M.D., Ph.D., The Jakurski Family Director and Professor.

The Brady is uniquely poised to carry out this mission, Partin adds: “Over the past 30 years, with Dr. Walsh’s leadership, we have built one of the world’s largest collections of hereditary prostate cancer samples, with more than 3,000 families and 8,000 individual patients, available for sequencing studies. With funding, we will use advanced DNA sequencing technologies to find the genes responsible for the strong hereditary predisposition to the disease.”

Already, with generous support from more than 125 donors from the U.S. and several other countries, this project is under way and sequencing has begun. The first major contribution came from Bernard Schwartz, a longtime supporter of The Brady and member of our Founder’s Circle.

There’s even more to come: The Brady plans to raise funds to start a Hereditary Prostate Cancer clinic, to be run by urologist Christian Pavlovich, M.D. This will include a comprehensive genetic testing and counseling program to test men for mutations in important genes related to prostate cancer: HOXB13, as well as DNA-repair genes such as BRCA1, BRCA2, ATM, and the others that we expect to discover as a result of the current sequencing efforts.

For the first time, we have the potential to identify every gene involved in hereditary prostate cancer. This history-making project will help thousands of men and their families to understand their family cancer risk, seek early detection and treatment, and save many lives.

**Cover Story: The Best Birthday Present Ever**

**THE PATRICK C. WALSH HEREDITARY PROSTATE CANCER PROGRAM**

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**Donations drive discovery!**

If you would like to support this effort, please use the contribution card included in this issue or contact Elissa Kohel in the Brady Development Office at ekohel1@jhmi.edu and 410-955-8351. We welcome your partnership.
Combination Immunotherapy Combats AR-V7+ Prostate Cancer

“Most of the benefit from ipilimumab plus nivolumab appeared to occur in patients who had one of these gene mutations, particularly in two men with BRCA2 mutations.”

Good news for some men with very aggressive prostate cancer: in a small study at Hopkins, a combination of two immunotherapy drugs has made a significant difference – shrinking tumors partially or completely – and two of 15 men have shown exceptional responses.

No one is suggesting that these drugs would produce the same promising results in all men with aggressive prostate cancer. Instead, this is an exciting example of precision oncology – finding the right drug (or combination of drugs) to work for the right patient and the right cancer.

The study, done by researchers at The Kimmel Cancer Center and The Brady Urological Institute and led by Emmanuel Antonarakis, investigated the use of combination checkpoint immunotherapy in the treatment of a lethal form of advanced prostate cancer. The findings were published in Oncotarget.

The 15 men in the study had AR-V7-positive prostate cancer; AR-V7 is an aggressive variant of the androgen receptor, first reported in a landmark paper by Jun Luo and Antonarakis (this can be diagnosed by a blood test). The men received a combination of immunotherapy drugs called “checkpoint inhibitors,” ipilimumab and nivolumab. This is the first clinical trial to target this specific form of prostate cancer, “which can lead to fatal disease in only six to nine months and has inadequate treatment options,” says Antonarakis. It is also the only published study of these combined immunotherapy drugs in prostate cancer.

Patients received treatment by IV infusion: 3 mg per kilogram of nivolumab plus 1 mg per kilogram of ipilimumab every three weeks for four doses, followed by a maintenance regimen of 3 mg per kilogram of nivolumab alone every two weeks thereafter. The patients were enrolled between December 2016 and October 2017.

Two of the 15 men (13 percent) experienced a significant drop in PSA – by at least 50 percent. “More encouragingly,” notes Antonarakis, “one-quarter of patients achieved an objective response, meaning that their tumors shrank partially or completely. These responses were durable and typically lasted more than nine to twelve months.”

But here’s the most exciting part: At least two of these patients were still alive more than 18 months later – which means that Antonarakis and Luo don’t even know how long the response will last, because it’s still happening.

Genetic mutations affect response, too:
The men in this study were already different from many patients with advanced prostate cancer because of their AR-V7 variant. Were there other differences that might help predict which men will respond best to this double checkpoint inhibitor approach? Yes: the specific genetic mutations are very important.

“In these six men, we detected gene mutations of BRCA2 (3 men), ATM (2 men), and ERCC4 (one man).”

The job of DNA repair genes is to fix mistakes that occur in the DNA as cells divide – to keep a mistake from being repeated over and over again. “Remarkably,” notes Antonarakis, “most of the benefit from ipilimumab plus nivolumab appeared to occur in patients who had one of these gene mutations, particularly in two men with BRCA2 mutations. This finding is important, because BRCA2 is not a gene that was previously thought to sensitize patients to immune-checkpoint inhibitors.” If this proves true in larger studies, “it will have profound implications for other diseases such as breast and ovarian cancers, where these genes are more frequently mutated.” An estimated 20 percent of men with metastatic prostate cancer have mutations in BRCA2 or related DNA-repair genes. “This study suggests that these gene mutations may be even more common in men with the AR-V7+ form of prostate cancer, perhaps as high as 40 percent.”

Traditionally, immunotherapy has not been very successful in prostate cancer, and this is because compared to other forms of cancer, prostate cancer tumors have fewer mutations. This makes it easier for them to blend in with more normal-looking cells, “and camouflage themselves from immunological destruction.”

However: “While prostate cancer is generally regarded as a low–mutation-burden tumor, and immune-checkpoint inhibitors have resulted in only modest benefits when used alone, these results suggest that AR-V7+ prostate cancers may.

Continued on page six >
be associated with a greater number of DNA-repair gene mutations and a higher mutation load,” says Antonarakis. “This, in turn, could be further exploited by using combination immunotherapy. “If these findings are confirmed by others, this could offer hope to these patients with AR-V7+ disease who have few, if any, good treatment options.”

The study also showed that the combination of nivolumab plus ipilimumab was safe and tolerable in men with AR-V7+ advanced prostate cancer. “We did see some important side effects including colitis, pneumonitis and hepatitis – all caused by an over-activated immune system. These side effects were managed with prompt administration of steroids, which often resulted in reversal of these conditions.”

Encouraged by these preliminary findings, Antonarakis and his team are now expanding the study to include more patients. This larger study is currently open to enrollment (https://clinicaltrials.gov/ct2/show/NCT02601014?cond=NCT02601014&rank=1), and is actively seeking participants. If you are interested, please call Mrs. Rana Sullivan at 410-614-6337.

"Currently, there is no drug that can target AR-V7, but targeting HOXB13 may prove to be more feasible.”

Does this new finding mean that men who inherit the mutated HOXB13 gene are destined to develop advanced prostate cancer? Not at all, says Luo. “We did not especially look at the mutated form of HOXB13. While we confirmed the importance of HOXB13 in prostate cancer, the link between the mutated form and AR-V7 is not known, and it remains possible that the mutated HOXB13 may not have a role in disease progression.”

Could HOXB13 be a target for treatment to slow the growth of advanced prostate cancer?

Much more work is needed to understand exactly how these two miscreant molecules interact, Luo adds. “Nevertheless, preclinical work presented in the study showed that silencing HOXB13 significantly decreases CRPC tumor growth by suppressing AR-V7 function. These early results clearly identify HOXB13 as a pivotal upstream regulator of AR-V7—driven prostate cancer.”

HOXB13 and AR-V7: Genetic Partners in Crime

We thought AR-V7 and HOXB13 were bad enough on their own. Now, as two separate trails of exciting research have converged, Brady scientists have discovered that these molecules work together as a diabolical duo to drive castration-resistant prostate cancer (CRPC). This finding provides important new insight on how CRPC works, and may suggest new targets for treatment.

AR-V7, an aberrant androgen receptor that develops in advanced prostate cancer, was discovered by Jun Luo, Ph.D., Professor of Urology, in a seminal study published in 2009. Now, AR-V7 can be detected in a blood test, developed by Luo, which can help guide treatment decisions in men with CRPC.

HOXB13, a mutated gene that greatly raises a man’s risk of getting prostate cancer, was discovered in 2012 by William Isaacs, Ph.D., the William Thomas Gerrard, Mario Anthony Dahon and Jennifer and John Chalsty Professor of Urology, and colleagues in a seminal study published in the New England Journal of Medicine.

Separately, each of these mutations means trouble. But in a new study, led by Luo and published in Proceedings of the National Academy of Sciences, he and Isaacs unexpectedly discovered that AR-V7 and HOXB13 “were, in fact, partners in crime that, together, cause prostate cancer to progress,” says Luo.

In this new study, investigators from Hopkins and Duke University found that the HOXB13 protein is “universally required for AR-V7 binding to DNA, a process thought to drive castration resistance in prostate cancer,” Luo explains. The team discovered direct physical interaction between HOXB13 and AR-V7 – and this suggests a new target for treating CRPC:

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Encouraging work by Luo, left, and Antonarakis on AR-V7 and aggressive, advanced prostate cancer is leading to new strategies — and new potential targets — for treatment.
A Key Target in Aggressive Prostate Cancer May Lead to New Drug Development

Prostate cancer steals the kindling from the neighbor’s woodpile – and this may help explain why androgen deprivation therapy stops working: the cancer bypasses it, and makes its own supply of male hormones.

Scientist Marikki Laiho, M.D., Ph.D., is hoping to kill two birds with one stone, shutting down two critical pathways – one for growth, and one for fuel – in aggressive prostate cancer by blocking a single target.

That target, RNA polymerase I, “governs the production of cellular RNA, and is highly activated in cancer,” says Laiho, the Willard and Lillian Hackerman Professor in Radiation Oncology. In work that began with funding from The Patrick C. Walsh Prostate Cancer Research Fund, Laiho found that switching off RNA polymerase I “curbs cancer cell growth and shows therapeutic benefit in preclinical cancer models.” But this work also brought another gene into the spotlight: PTRF, associated with polymerase function, which also plays a critical role in lipid metabolism. “This gene may have high relevance in prostate cancer, because it seems to be shut down in the stromal (connective tissue) cells of the prostate tumors.”

With postdoctoral fellow Jin-Yih (Nick) Low, who is an expert on PTRF, Laiho is exploring the links between RNA synthesis and lipid metabolism. “The early observations are striking,” Laiho says. “They suggest that the loss of PTRF in the stromal cells is a driver event that promotes aggressive characteristics in prostate cancer cells.” Interestingly, this loss of PTRF changes the way fat is metabolized by the cancer. Laiho and Low have discovered “the loss of lipid uptake in the stromal cells and an increase in the lipid content of the prostate cancer cells. For the cancer cells, this is a substantial benefit – they gain more fuel for growth and building blocks for production of androgens.” Basically, prostate cancer steals the kindling from the neighbor’s woodpile – and this may help explain why androgen deprivation therapy stops working: the cancer bypasses it, and makes its own supply of male hormones.

In mice, Laiho and Low are deleting PTRF in the prostate to see how this affects the ability of advanced cancer to invade and spread to distant sites. Further, their new insight on the role of PTRF in lipid metabolism is leading to exciting new studies on how diet affects prostate cancer development and progression. If fat inflames the cancer, could a low-fat diet help slow it down?

Also collaborating on this work are Hopkins colleagues Nathan Brennen, Brian Simons, and Samuel Denmeade, and Elina Ikonen, at the University of Helsinki, Finland.

“Liquid Biopsy” for Advanced Prostate Cancer Spots Tiny Danger Signs Sooner

A blood test for key genetic mutations could help doctors get the jump on the most aggressive cancer sooner, with more aggressive or gene-specific treatment.

If only prostate cancer could talk. Then we might be able to get direct answers to questions, such as: Is it still responding to treatment? Or: Has something important changed? Getting frequent updates from a biopsy is not feasible; it’s hard on the patient, and also an expensive, impractical way to search for answers.

Last year in Discovery, we reported that Brady scientist Paula Hurley, Ph.D., and colleagues were getting close to finding the next best thing to cancer that talks: a simple blood test – a “liquid biopsy” for advanced prostate cancer. This highly sophisticated test finds traces of DNA left behind in the blood by cancer cells. Imagine following a trail of tiny, widely spaced crumbs: that’s the challenge here; there may not be that many in a sample of blood, so these remnants of cancer are not easy to find and difficult to extract (see story on page 14).

But expertise and persistence are paying off, and once deciphered, these clues have quite a lot to say. In recent work submitted for publication, Hurley and colleagues set out to understand how mutations in the androgen receptor and other genes can predict how well advanced prostate cancer will respond to different forms of treatment. In the study, the team studied the blood of 62 Hopkins patients with metastatic castration-resistant prostate cancer (CRPC) at various points in their treatment and as cancer progressed between 2014 and 2018. “We used a ‘liquid biopsy’ to detect tumor-specific mutations in these patients before they started enzalutamide, abiraterone, or a combination of both,” says Hurley. “We found that men with a high tumor burden detected in the blood were less likely to respond to enzalutamide and abiraterone.”

In addition, they found that men with certain mutations in the androgen receptor had a shorter response to therapy, and that the loss of key genetic pathways (TP53 or PTEN) was associated with more lethal cancer.

How could these findings help patients, and what comes next? Knowing what to look for and finding these danger signs as early as possible might provide a critical window – and help doctors get the jump on the most aggressive cancer sooner, with more aggressive or gene-specific treatment.
H. Ballentine Carter is the pioneer of active surveillance (AS) for men with low-risk prostate cancer. Over the last two decades, he has found that for most men in this situation, careful monitoring is perfectly safe. But some men are more likely to develop higher-risk cancer. “We know that some men who pursue this strategy will lose the opportunity for cure,” Carter says, “either because a more aggressive prostate cancer was lurking within the prostate and was missed on prostate biopsy, or because the low-grade cancer progressed to a more aggressive form.”

Is there any way to predict? Carter and colleagues at Hopkins and North Shore Health System in Chicago have turned to the genes for clues. There are two kinds of genetic mutations: germline mutations are ones we’re born with; somatic mutations just develop on their own. Of particular interest in prostate cancer are recent discoveries by Johns Hopkins scientist William Isaacs, Ph.D., and others that men who have germline mutations in DNA-repair genes such as BRCA1 and BRCA2 (better known for being linked to breast and ovarian cancer) are more likely to develop aggressive prostate cancer.

Recently, Isaacs, the William Thomas Gerrard, Mario Anthony Duhon and Jennifer Chalsty Professor of Urology, with Jianfeng Xu and colleagues at North Shore, explored the relationship between mutations in three DNA-repair genes – BRCA1, BRCA2, and ATM – and lethal prostate cancer. They found that only 1 percent of men with localized, low-grade prostate cancer had germline mutations in these three genes, as compared to 6 percent of men with lethal prostate cancer. Further, men with one of these defective genes who developed aggressive prostate cancer tended to die from it sooner after diagnosis, and at a younger age.

“Our findings suggest that a man who carries one of these mutations may be better off with treatment rather than surveillance.”

How might this affect men in AS – or, as Carter puts it: “Might a germline mutation in a DNA-repair gene tip off the urologist that a man with a low-grade prostate cancer considering surveillance should think twice?” To find out, Carter, Isaacs and biostatistician Mufaddal Mamawala, with North Shore scientists Xu, Brian Helfand, and Charles Brendler, looked for germline mutations in 1,211 men with low-risk cancer enrolled in AS at Hopkins and North Shore. From blood samples,
they sequenced 54 DNA-repair genes, then looked for links between mutations and “grade reclassification,” the finding of higher-grade cancer on follow-up biopsies. Among men who inherited a mutation in BRCA1/2 or ATM, the rate of grade reclassification—the finding of higher-grade cancer—was 42 percent compared to 23 percent of other men, says Carter. Upon observation, significantly more men—55 percent—who carried the mutated BRCA2 gene alone were found to have higher-grade cancer (such as Gleason 3 + 4).

The 51 other DNA-repair genes evaluated were not so clearly linked to the risk of higher-grade cancer. “At this point, we are not suggesting that all men considering AS undergo gene sequencing to look for DNA-repair gene mutations,” and larger studies are needed to confirm these findings, he states. “However, men who have a family history of lethal prostate cancer or other cancers (such as breast, ovarian, or pancreatic), especially across multiple generations and affecting younger people (in their fifties or younger), should consider testing.” Although for the majority of men considering AS, the risk of such a mutation is low, “our findings suggest that a man who carries one of these mutations may be better off with treatment rather than surveillance.”

But it’s not that straightforward. As Epstein has also found for many years, when men undergo prostatectomy and a pathologist looks at the entire prostate specimen, some men are found to have a higher stage of cancer, and are “upgraded.” A few men are actually found to have more low-grade cancer and are downgraded. This brings us to AS. “Some experts have questioned whether there is a subset of men with Gleason 3 + 4 = 7 cancer with favorable characteristics, who have a minimum risk of adverse pathology at surgery, who could also have been candidates for active surveillance,” says Brady resident Hiten Patel, M.D., M.P.H. With colleagues Jeffrey Tosoian, M.D., M.P.H., Ballentine Carter, M.D., and Epstein, Patel recently investigated this issue.

In a large cohort study, they found that 25 percent of men diagnosed with low-volume, Gleason 3 + 4 disease on biopsy, turned out to have “adverse surgical pathology,” says Patel. “This is a four- to five-times higher risk than for men with low- and very low-risk prostate cancer.”

Could Some Intermediate-Risk Men Do Active Surveillance?

Gleason 7 disease is considered intermediate-risk prostate cancer. Is it safe for Active Surveillance (AS)? That’s a complicated question.

More than a decade ago, Jonathan Epstein, M.D., the Rose-Lee and Keith Reinhard Professor in Urologic Pathology and Director of Surgical Pathology, reported that Gleason 7 cancer behaves differently depending on whether there is more Gleason 3 or more Gleason 4; now, pathologists have two Gleason 7 categories: Gleason 3 + 4, and 4 + 3.

“It is a four- to five-times higher risk than for men with low- and very low-risk prostate cancer.”

Because of this significant risk, Epstein says, “these findings do not support the presence of a ‘favorable’ subgroup of Gleason 3 + 4 disease” at this time. He adds that some newer factors, including the percent of pattern 4 and the histology of the pattern 4, along with MRI findings and new molecular tests may one day identify a favorable subset of Gleason 3 + 4 men—men who could safely go on AS.

But for now, Epstein adds, “men with Gleason 3+4=7 prostate cancer who are otherwise eligible for curative intervention (surgery or radiation) should be fully informed as to the avoidable risk associated with use of AS.” Their findings were published in JAMA Oncology.

Patel and Epstein: 25 percent of men diagnosed with low-volume, Gleason 3 + 4 disease on biopsy turned out to have “adverse surgical pathology.”
If You Have Lymph Node Metastases After Radical Prostatectomy, What Should You Do?

Determining factors included seminal vesicle invasion, a Gleason score of 9 or greater, having three or more positive lymph nodes, and having positive surgical margins. Men with one or more of these findings would benefit from ADT plus radiation.

What should happen when a man is found to have lymph node metastases (LNM) after radical prostatectomy? Some doctors would advocate waiting; others would advise a course of androgen deprivation therapy (ADT), or external-beam radiation therapy – or both.

Which option is right? That’s a trick question: they all are, depending on whether or not the man has “adverse pathology.” A new analysis, published in the British Journal of Urology, provides much-needed guidance for men in this situation. In this Brady-led study using hospital records from the National Cancer Data Base, investigators looked at survival outcomes in 8,074 patients with LNM after prostatectomy between 2004 and 2013.

After surgery, 4,489 of these men were managed with observation; 2,065 were treated with adjuvant ADT; and 1,520 received adjuvant ADT together with external-beam radiation therapy. The average follow-up time for all patients was a little over four years.

“We found that the men who were managed with observation were older than those who received adjuvant ADT or ADT plus radiation,” says Brady urologist Mohit Gupta, M.D., the study’s lead author. “The patients treated with adjuvant ADT, or with ADT plus radiation had more aggressive pathology” – findings such as a higher pathological stage of cancer, a higher Gleason score, positive surgical margins, and a greater amount of cancer in the lymph nodes.

However, despite having more aggressive disease, the men managed with adjuvant ADT plus radiation did better than the man managed either with observation or with ADT alone, he adds. The predicted five- and 10-year overall survival rates were about 88 percent and 68 percent, respectively, for observation; about 88 percent and 68 percent for ADT, and about 91 percent and 74 percent for ADT plus EBRT.

The Brady investigators, including Hiten Patel, Zeyad Schwen, Phuoc Tran, and Alan Partin, also found that certain pathological findings raised the likelihood of having lethal disease, “and men who have one or more of these independent predictors would benefit from receiving adjuvant ADT plus radiation,” says Gupta. These included the presence of cancer in the seminal vesicles, a Gleason score of 9 or greater, having three or more positive lymph nodes, and having positive surgical margins. “Conversely, we found no benefit in survival rates between the treatment groups in men who lacked any of these adverse features.”

Based on this research, “we conclude that patients with adverse pathology who are found to have LNM benefit most from adjuvant ADT plus external-beam radiation therapy.” However, “patients without high-risk features may be managed with observation and forego the complications associated with extra treatment.”

Prostate Cancer Therapy and the Gut Microbiome

It may be that targeting the gut microbiome – in the form of prebiotics, probiotics, or even fecal transplant – may make ADT and other forms of treatment much more effective.

What does the microbiome (the millions of bacteria) in your gut have to do with the effectiveness of treatment for prostate cancer? Probably much more than we realize, says Brady scientist Karen Sfanos, Ph.D.

“The gut microbiome can influence cancer therapy by its ability to chemically modify drugs.” This relationship works both ways: “Cancer-fighting drugs can also alter the composition of the bacterial species that live in the gut – and this, in turn, may affect how well that treatment works.”

In a recent study, Sfanos and colleagues were the first to examine the relationship between the gut microbiome and types of androgen deprivation therapy (ADT) used to treat advanced prostate cancer.

“We found that there are measurable differences in the gut microbiome between men taking oral formulations of these medications and men who were not taking them,” she says. The gut bacteria may not only influence clinical responses to ADT; it also might modulate the anti-tumor effects of other drugs for advanced prostate cancer, including immunotherapy.

Further work is needed, but if additional studies prove that the gut bacteria can help determine how men respond to prostate cancer treatment, it may be that targeting the gut microbiome – in the form of prebiotics, probiotics, or even fecal transplant – may make ADT and other forms of treatment much more effective. This research was published in Prostate Cancer and Prostatic Diseases.

Gupta: “Despite having more aggressive disease, the men who received adjuvant ADT plus radiation did better.”
End-of-Radiation PSA and Intermediate-Risk Cancer

End of Radiation PSA (EOR-PSA) is an important predictor of the success of radiation therapy. How important? Radiation oncologists Phuoc Tran, M.D., Ph.D., Theodore DeWeese, M.D., and colleagues are still finding out. Previously, they showed that undetectable EOR-PSA can predict survival in prostate cancer. Now they’re looking at how prostate cancer risk comes into play: particularly, for men who have intermediate-risk prostate cancer.

“Men with intermediate-risk (IR) disease don’t all have the same outcomes with standard treatments,” says Tran, who is working to make this category of cancer more precise, and then to fine-tune treatment for men accordingly. “There are patients with favorable and unfavorable IR prostate cancer.” EOR-PSA may be able to help determine which men have a good chance of being cured after radiation therapy, and which men need extra treatment.

“There are patients with favorable and unfavorable intermediate-risk prostate cancer.”

Tran is senior author of a recent study of 302 men with IR prostate cancer who were treated at Johns Hopkins with radiation therapy between 1993 and 2006; the average period of follow-up was more than a decade. “We wanted to determine whether EOR-PSA could help us risk-stratify these men even further,” says Tran. Of these men, 178 had unfavorable IR, and 124 had favorable IR. “We found that EOR-PSA was helpful in predicting metastasis and prostate cancer death among patients with unfavorable IR. These findings suggest that we may be able to determine which IR men will require more intense treatment following radiation therapy,” with the hope that providing extra treatment “at a clinically meaningful time point” can make a critical difference for these men.

This work was published in the journal, Prostate. Co-investigators in the study were Jonathan Hayman, Ryan Phillips, Di Chen, Jamie Perin, Amol K. Narang, Janson Trieu, Noura Radwan, Stephen Greco, Curtiland DeVille, Todd McNutt, Daniel Y. Song, and Theodore L. DeWeese.

New Device Extracts CTCs From Blood

It’s a cellular version of “no man left behind.” Recovery of CTCs is 100 percent.

Trust Dan Stoianovici, Ph.D., Director of the Urology Robotics Program, to come up with a brilliant mechanical solution to a perplexing liquid conundrum: how to extract circulating tumor cells (CTCs) from the blood. “We have gotten very interested in being able to measure CTCs as diagnostic, prognostic, and predictive biomarkers in many types of cancer, including prostate,” says Ken Pienta, M.D., The Donald S. Coffey Professor of Urology. “But this has long been easier said than done. Previous methods to isolate and analyze CTCs require multiple steps, and many of these rare cells get lost in the process; recovery rates are usually less than 80 percent.”

Then Stoianovici – who has created many novel devices and is the reason why the Brady’s Urology Robotics Program is world-renowned – decided to take a crack at it. With funding from The Patrick C. Walsh Prostate Cancer Research Fund, and with colleagues Gonzalo Torga, Doru Petrisor, Michael Gorin, and Pienta, he developed a novel device with “computer-controlled magnetophoretic CTC-antibody binding and direct extraction.” Basically, using specially engineered antibodies that magnetically bind to the CTCs, Stoianovici figured out how to get them to stick to a glass slide, which a pathologist can then study under the microscope. Even better: “the CTC recovery is total.” With this technique, it’s a cellular version of “no man left behind.” Recovery is 100 percent.

In early experiments using different cell concentrations, the device performed like a champ. The scientists say that more testing is needed before this can be adapted for wider use.

What’s the Best Way to Treat Localized, Gleason 9-10 Prostate Cancer?

The most aggressive localized prostate cancer has a Gleason score of 9-10. What’s the best way to treat it? Radiation oncologist Phuoc Tran, M.D., Ph.D., and colleagues recently took part in a multi-institutional study to find out. Their results were published in the Journal of the American Medical Association (JAMA).

Investigators at 12 hospitals in the United States and Norway compared the clinical outcomes of 1,809 men with Gleason score 9-10 prostate cancer after they had either radical prostatectomy, external-beam radiation therapy (EBRT) with androgen deprivation therapy (ADT), or EBRT plus a brachytherapy “boost” with ADT; the men were treated between 2000 and 2013. Of these men, 639 underwent radical prostatectomy, 734 had EBRT and ADT, and 436 had EBRT plus brachytherapy, along with ADT.

“ERBT plus brachytherapy and ADT appeared to afford the best outcomes.”

“We found that treatment with either EBRT and ADT or radical prostatectomy appeared to be equivalent – but EBRT plus brachytherapy and ADT appeared to afford the best outcomes of the three.”

This work was published with Hopkins co-investigators Ashley Ross, Jeff Tosoian, Stephen Greco, Curtiland DeVille, Todd McNutt, Daniel Y. Song, and Theodore L. DeWeese.
A Genetic Target to Help the Immune System Fight Cancer

Often in the microenvironment of prostate cancer are immune system cells, just sitting nearby and not doing anything. These cells need to wake up.

The body’s immune system is supposed to recognize enemy invaders and kill them. This doesn’t happen – or doesn’t happen nearly enough – in cancer, because cancer has a sneaky playbook of tactics to distract, stupefy, or dupe the immune system’s army. And yet: often in the microenvironment of prostate cancer are immune system cells, just sitting nearby and not doing anything. These cells need to wake up. Pediatric oncologist Alan Friedman, M.D., is looking at particular body defenders called macrophages: white blood cells that get co-opted by prostate cancer into helping it grow. These are called tumor-associated macrophages (TAMs), and they become traitors to their own kind: they actually suppress the immune system’s ability to fight off prostate cancer.

“Interestingly, TAMs are present in greater numbers in prostate cancers that are more aggressive,” says Friedman, “including cancers that have become resistant to androgen deprivation therapy (ADT).” But what if these TAMs could be turned back to the good side? This is what Friedman is trying to do. “We are looking for ways to alter prostate cancer TAMs – so that instead of helping the cancer grow, they will help the immune system fight the cancer,” he says. TAMs come in two varieties: M1 and M2. M2 TAMs are bad: they help cancer; but M1 TAMs are good: they fight it.

“Like all cells, TAMs contain genes within their DNA that govern their function.” Genes can be targeted. Recently, Friedman and colleagues reported that prostate cancer grows slower in mice that lack a certain gene (KLF4) in their TAMs. With this gene missing, the TAMs in these tumors had more M1 (good) and less M2 (bad) tendencies, “and these changes stimulated the immune system to attack the tumor cells, leading to slower tumor growth. Our results are exciting: they suggest that targeting KLF4 in TAMs may change the macrophages that help cancer grow into macrophages that help the immune system fight back.”

This work was published in *PLoS One*, and was funded in part by The Patrick C. Walsh Prostate Cancer Research Fund. In addition to Friedman, David Barakat, Rahul Suresh, Theresa Barberi, Ken Pienta, and Brian Simons contributed to this work.

Breaking Prostate Cancer’s Control Over the Immune System

Among the many changes that happen when prostate cancer becomes metastatic is a weird kind of freeze-tag, played at the protein level between cancer cells and cells of the immune system. It’s highly specific and tends to happen much more often in metastatic cancer than in cancer that is confined to the prostate.

The key players here are PD-1, a protein expressed on immune cells, and PD-L1, its doppelganger, found on some cancer cells. When these two “partner-proteins” meet, PD-L1 takes over and “The anti-cancer immune response is turned off; PD-L1 puts the brakes on the immune system,” says pathologist Michael Haffner, M.D., Ph.D. “Cancer cells are using PD-L1 to dampen the immune response.”

Is it possible to break this hypnotic spell – to snap the immune cells out of their stupor, so they can start fighting cancer again? Yes: “By blocking the interface between PD-1 and PD-L1,” which is already happening with some new immunotherapy drugs called checkpoint inhibitors, “the immune system can be unleashed to eliminate cancer cells,” explains pathologist Angelo M. De Marzo, M.D., Ph.D., Associate Director of Cancer Research Pathology. But in order to target this mechanism effectively, it’s important to know just what we’re dealing with, says Haffner: “How often is PD-L1 being used as a defense mechanism by prostate cancer to fight the immune attack?”

From left: Friedman, De Marzo, and Haffner: Prostate cancer has many ways to trick the body, so it can grow unhindered. Figuring out how to undo those tricks and unleash the body’s powerful immune system could make a huge difference in even the most aggressive cancers.

Those reddish-brown blobs you see are PD-L1, being expressed by cancer cells to fight off an attack from the immune system. Haffner and De Marzo are working on ways to shut down this response.
Is it possible to break this hypnotic spell – to snap the immune cells out of their stupor, so they can start fighting cancer again?

To address this question, Haffner and De Marzio worked with a team of Hopkins investigators including Gunes Guner, William Nelson, Srinivasan Yegnasubramanian, Tamara Lotan, Jun Luo and Emmanuel Antonarakis, and colleagues from the University of Michigan and Columbia University. Together, in a study published in the American Journal of Pathology, they analyzed nearly 600 primary and advanced metastatic prostate cancers. “We found that PD-L1 expression is present in only a small subset of primary tumors,” notes Haffner. However, PD-L1 was present in one-third of advanced metastatic prostate cancers. The findings from this study provide new insight into what the immune system is doing – and not doing – in prostate cancer, and will help guide development of drugs that can get the immune system back to fighting cancer.

Liver Fibrosis and PSA

“Given the higher prevalence of hepatitis C virus in Baby Boomers and rising prevalence of non-alcoholic fatty liver disease, our work has implications for prostate cancer screening.”

If you have liver problems, your PSA may not be as low as you think it is.

That’s the message from a new Hopkins study led by master’s student Anqi Wang and her advisor, epidemiologist Elizabeth Platz, Sc.D., M.P.H., with Mariana Lazo, M.D., Ph.D., Sc.D., H. Ballentine Carter, M.D., John Groopman, Ph.D., and William G. Nelson, M.D., Ph.D.

Previous studies had observed that men who have liver cirrhosis also have lower PSA levels, notes Platz. Could other liver conditions influence PSA as well? To find out, Wang, Platz and colleagues looked at PSA levels in nearly 7,000 men age 40 and older, and determined who likely had and did not have liver fibrosis – scar tissue in the liver, which develops as the liver attempts to fix cells damaged by disease. They used data from the National Health and Nutrition Examination Survey (NHANES). “We took into account age, race, ethnicity, body mass index, diabetes status, alcohol drinking, and smoking.”

In all the men, the investigators found, the presence of liver fibrosis was associated with lower PSA than in men without liver fibrosis – the more severe the fibrosis, the lower the PSA. “Men with an abnormal fibrosis score had a substantially lower odds of having a PSA over 4 ng/ml compared to men without fibrosis,” says Wang, and this was consistent despite race or ethnicity.

“Given the higher prevalence of hepatitis C virus in Baby Boomers and rising prevalence of non-alcoholic fatty liver disease, both of which can lead to liver fibrosis, our work has implications for prostate cancer screening,” Wang continues. “Men with higher liver fibrosis scores (more likely to have more severe liver fibrosis) had lower PSAs, and men with abnormal fibrosis scores had a lower odds of having an elevated PSA.”

The study raises the concern that men with these liver conditions may be less likely to have prostate cancer detected. “The risk and benefits of prostate cancer screening for men with liver fibrosis and liver disease should be considered in decision-making,” says Platz. Her advice for men in this situation: “Talk to your doctor if you have a liver disease about how it might affect the PSA test. And, if you are a Baby Boomer (born 1945-1965), consider a one-time check for hepatitis C virus infection.”

Custom-Tailored Prostate Biopsy

If every man’s prostate – like a fingerprint – is different, then why are all prostate biopsies the same?

This is an important question. Picture the map of the U.S., and imagine the shape of Michigan compared to the shape of Maryland. Prostate aren’t that different in size and shape, but every biopsy is done, in effect, as if they were all shaped like Wyoming – with the same basic plan, or template.

“Every man has a prostate of a different size and shape.”

“Every man has a prostate of a different size and shape,” says Misop Han, M.D., David Hall McConnell Professor in Urology. “Also, there is a significant movement of the ultrasound probe during the freehand sampling between biopsy cores that can potentially increase discomfort, and also cause inaccurate sampling.”

How can we make biopsies smarter? This is where Dan Stoianovici, Ph.D., Director of the Urology Robotics Program, comes in: As we reported last year in Discovery, Stoianovici designed a novel robotic device, the TRUS Robot, that works through transrectal ultrasound (the imaging used to perform a prostate biopsy). Together, Stoianovici and Han have been working to refine the use of this robot.

They have created a new method to quantify the detection of clinically significant prostate cancer “based on a patient’s own prostate gland size and shape,” Han says. “We believe the TRUS Robot and the new algorithm will improve our ability to detect clinically significant prostate cancer, while decreasing the discomfort for our patients, allowing us to perform a personalized, systematic prostate biopsy.”
Pain Control after Radical Prostatectomy

Radical prostatectomy patients needed less than a quarter of the pain medications they were prescribed.

Here’s some good news about pain after radical prostatectomy: for most men, it’s not that bad! This is the result of a recent study by Brady resident Hiten Patel, M.D., with urologist Amin Herati, M.D., and Misop Han, M.D.

In an effort to decrease the overprescription and potential misuse of opioid-containing painkillers, the investigators studied more than 200 men who underwent radical prostatectomy – either the open or robotic procedure – at Hopkins in the past year.

“We found that there was no difference in opioid use by surgical approach,” says Patel. “However, men in both groups used less than a quarter – 23 percent – of the opioid medications that were prescribed.”

They also found that 84 percent of patients used less than half of their prescribed painkillers – which indicates that most radical prostatectomy patients are leaving the hospital with medicine they don’t need and probably don’t know what to do with: “Only 9 percent of men appropriately disposed of the leftover opioid medication at home,” Patel adds.

“Based on these results, we plan to decrease the opioid prescription after radical prostatectomy,” says Han, “so that we can provide adequate pain control without giving excess medications.” The team also plans to provide better instruction on proper disposal of unused opioid medications.

Thinking About Cancer in New Ways

Maybe we’re in a rut in the way we think about cancer, says Ken Pienta, M.D., The Donald S. Coffey Professor of Urology. This is why, “inspired by the way Dr. Coffey approached science,” (see Page 15), he has long sought out expert opinion from scientists in fields that have nothing to do with medicine.

What can experts from other fields show us about how cancer works?

Along with Bob Axelrod, an expert on social and economic game theory from the University of Michigan, Pienta recently discussed unconventional approaches to cancer in the journal, Molecular Cancer Research. When viewed from the lens of game theory, “cancer can be seen as a rebellion,” sparked by a few cells, and “a tumor is like a criminal gang that ceases to cooperate with the society as a whole, for its own selfish interests.” This may seem like “an anthropomorphism of cancer,” but it’s not, Pienta says. Instead, it’s a model of how a community interacts with its own members and with its neighbors.

“We have also taken this social science view and partnered with an expert in evolutionary ecology, Joel Brown from the University of Illinois, to understand what drives cancer cells to metastasize to other organs,” Pienta says. But theory is not enough: “We have to create models and ways to test new therapies. To do this, we have partnered with Bob Austin, a Professor of Physics at Princeton, to build special microenvironments that resemble what goes on inside a patient to test and develop new treatments for prostate cancer.”

Way back in 1962, a radiologist named David Smothers pointed out that “cancer is no more of a disease of cells than a traffic jam is a disease of cars. A lifetime of study of the internal combustion engine would not help anyone to understand our traffic problems.” Similarly, Pienta believes that scientists focus too much on “trying to understand the fine structure of the internal combustion engine – of DNA, RNA, and proteins – without understanding the context in which these molecules exist.”

PSMA-PET Data System

You know you’re doing something right when you have to develop a widespread system to support your work. Martin G. Pomper, M.D., Ph.D., Director of Nuclear Medicine and Molecular Imaging, and Steven P. Rowe, M.D., Ph.D., have just come up with the solution.

Pomper has developed small molecules that target PSMA, an enzyme that sits on the surface of prostate cancer cells. His small molecule can be attached to radioactive atoms to become radio tracers. The worldwide use of PSMA-targeted PET imaging in prostate cancer has skyrocketed.

But “as with any imaging test, there is a need to convey findings adequately from the interpreting radiologist” to the doctors who ordered the test, says Rowe. “We developed the PSMA reporting and data system (PSMA-RADS version 1.0), to tell referring clinicians of the likelihood that findings represent sites of prostate cancer, and guide the further work-up of indeterminate findings.”

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Donald S. Coffey: 1932-2017

He was “the father of modern science in prostate disease.” More than this, he was a great man.

The Brady lost a good friend last year, and the international world of prostate cancer research lost one of its brightest stars, a brilliant scientist, scholar, thinker, mentor and teacher.

For more than half a century, Donald S. Coffey, Ph.D., made The Brady a better place just by being here; for 30 of those years, he was our Director of Research – a scientific legend who trained and inspired generations of fellows and students and was a powerful driving force in the careers of dozens of scientists who were trying to understand prostate cancer. A gifted storyteller, he not only ignited the imagination and creativity of his students and colleagues; he genuinely cared about them. He was remarkable for his quick mind and gift for cutting through even the most intimidating scientific challenges to find the simple questions at the heart of them.

“Don was a genius,” says longtime friend and colleague, Patrick C. Walsh, M.D., Distinguished Service Professor Emeritus. He credits Coffey’s “brilliant ability to simplify” as the key factor in one of Coffey’s most important discoveries, the nuclear matrix of cells, the scaffolding that provides the structure of a cell’s nucleus, and helps organize its DNA. In cancer cells, Coffey discovered, the nucleus looks different. “As a non-pathologist,” explains Walsh, “he was able to simplify the pathology of cancer down to one rule: The nucleus is irregular. He then set out to find what makes a nucleus round, and in the process, discovered the nuclear matrix.”

But of all of Coffey’s achievements, the most important is that he has attracted, inspired, and trained the leaders in the field. “He is truly the father of modern science in prostate disease because of the many scientists he has personally trained, and the hundreds of others he has influenced,” says Walsh. “Today, when one looks at the leaders in urological research, every one of them has the imprint of Don Coffey, one way or another.”

Alan W. Partin, M.D., Ph.D., didn’t know he wanted to be a urologist until he spent four years working in Coffey’s lab as a graduate student; before that, he had wanted to be a pediatrician. “Don Coffey had the most unique grasp of human nature I have ever witnessed,” says Partin. “He touched the lives of countless individuals both within urology and oncology, and pressed them always to ask the question, if this is true, what does it mean?”

Coffey’s approach to teaching was simple. “Tell me the smartest people, and I don’t care what they do, I’m helping them.” A partial list of his former graduate students includes some of the top scientists in urology and oncology: Alan Partin, William Nelson, Ken Pienta, Ballentine Carter, Drew Pardoll, Arthur Burnett, Bert Vogelstein, John Isaacs, Herb Lepor, Angelo De Marzo, Shawn Lupold, William Isaacs, Andrew Fineberg, Alan Meeker, Lelund Chung, Warren Heston, and Jonathan Simons. “All these great people,” said Coffey. “It’s not that I teach them anything. It’s that, if you’re the best, I’ll give you an opportunity to do your thing, and we’re on our way.”

Among many other honors and awards, Don Coffey served as President of the American Association for Cancer Research, the largest cancer research society, with 35,000 members from 110 countries. He was President of the Society for Basic Urologic Research, and served on several major editorial boards. For 19 years, he served as a member of the National Prostatic Cancer Program of the National Cancer Institute, and as National Chairman of this board for four years. He published more than 250 research papers. Coffey received the Robert Edwards Award from the Tenovus Institute, both the Fuller Award and the Lifetime Achievement Award from the American Urological Association, the First Society of International Urology-Yamanouchi Research Award, that society’s highest research award, and the Distinguished Service Award from the American Cancer Society.

In 2015, Coffey received the American Association for Cancer Research’s highest honor, the Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research. He was the recipient of two Merit Awards from the National Institutes of Health.

Said Coffey about his work: “I’ve dedicated my life; I hope to die doing this. I don’t need any more honors, I’m paid more than I’m worth, I probably should get out of the way, but I still have questions.”

In honor of Don Coffey’s great ability to inspire and encourage so many young scientists, The Brady has set up the Dr. Donald S. Coffey Memorial Fund for Research, to support mentoring of future generations of urologic researchers. If you would like more information or are interested in supporting this fund, please contact Sushmitha Kosuri in the Brady Development Office at 410-955-8434.
A New Target to Keep Lethal Cancer Cells from Leaving Home

**Men who have higher levels of this gene tend to do better.**

Before it can leave the prostate and invade other sites, aggressive cancer needs to be able to take that first step: it needs the ability to move. “Cancers derive from epithelial cells,” says Sarah R. Amend, Ph.D., *The Donald E. Graham Scholar*. “These are highly proliferative cells,” but normally they don’t move around very much. In metastatic cells, however, a critical event occurs: “a population of cells gains movement ability,” a feature of a different type of cell called mesenchymal cells. “This little bit of cancer evolution is called the epithelial-to-mesenchymal transition (EMT).”

What drives EMT? In looking for specific culprits, Amend and colleagues found an unnamed gene, called *C1orf116*. Much about this gene is a mystery: “It remains largely uncharacterized, and its biological and molecular functions remain unknown,” says Amend. But her preliminary data suggests that *C1orf116* keeps prostate cancer from spreading. Men who have higher levels of *C1orf116* tend to do better; in lab studies, this gene seems to restrict movement of prostate cancer cells.

In research funded by The Patrick C. Walsh Prostate Cancer Research Fund, Amend and colleagues will work to clarify the function of this mystery gene in restricting metastasis.

**Chemoreceptors and Prostate Cancer**

What if lethal prostate cancer has a lot more going on than we ever knew? What if it has, in its own tiny, molecular way, senses like we all have – sight, smell, taste, sound, and touch? In new research funded by The Patrick C. Walsh Prostate Cancer Research Fund, Steven An, Ph.D., *The Frank E. Rath Spang & Company Charitable Trust Scholar*, is envisioning “an entirely new mechanistic framework for lethal prostate cancer.”

An and colleagues are exploring the idea that metastatic prostate cancer “is disseminated in time and space through a discriminatory repertoire of chemoreceptors” linked to a particular protein, called specialized G protein-coupled receptors (GPCRs). This new repertoire involves visual, taste, and smell perceptions.

**Understanding how this “sensory” class of cell surface receptors works might lead to new markers to identify men at risk of developing lethal prostate cancer.**

Just imagine,” he continues, “that there are ‘eyes’, ‘nose’, and ‘taste buds’ on individual prostate cancer cells. What would they ‘see’, ‘smell’, and ‘taste’? Understanding how this “sensory” class of cell surface receptors works might lead to new markers to identify men at risk of developing lethal prostate cancer, An continues. Furthermore, “what if
‘sensory’ perceptions or photo/chemo-
sensory transductions are hard-wired to
cellular motions? Are there pathways by
which the forces of light might interfere
with cellular motions?” Could something
that smells bad or tastes bitter to these
chemoreceptors be used to stop cancer
from spreading?

An plans to find out. He hopes to create
a functional map of the “sensory” GPCR
landscape in prostate cancer and then to
correlate the “photo/chemo-mechanical
gene signature” he finds to the progres-
sion of metastatic disease.

DNA Repair Mutations and PARP Inhibitors

“PARP inhibitors may be able to
replace or postpone the need for
androgen deprivation therapy.”

Emmanuel S. Antonarakis, M.D., The
George and Mary Nell Berry Scholar, sees
great promise in PARP inhibitors. This
new class of oral drugs has helped some
men with advanced prostate cancer –
particularly those who have mutations
in certain “DNA repair” genes, such as
BRCA1, BRCA2 and ATM.

In some men, he believes, “PARP inhibitors
may be able to replace or postpone the
need for androgen deprivation therapy
(ADT).” These drugs seem to work best
in patients who either were born with
an inherited inability to fix DNA damage,
or those who acquired a mutation in a
DNA-repairing gene over time, as prostate
cancer grew and advanced.

However, it’s not always clear who will
benefit, and who will not. “While many
patients with inherited or acquired
mutations in these genes show a favor-
able response to treatment with a PARP
inhibitor, some do not benefit at all,” he
explains, “while others may benefit even
without having one of these mutations.

With funding from The Patrick C. Walsh
Prostate Cancer Research Fund,
Antonarakis is working to find a new test
to detect DNA damage in the cancer cells
themselves – using tumor biopsies from
patients with localized or metastatic
prostate cancer. He hopes this test, which
uses standard biopsy materials called
formalin-fixed paraffin-embedded
specimens, will be “a better predictor of
sensitivity or resistance to PARP inhibitor
therapy compared to DNA testing.”

The first step is to validate the new test,
called the In situ DNA Damage Response
Assay, in the laboratory. Next, “we will use
this method to test biopsies from patients
undergoing therapy with PARP inhibitors,
either olaparib (Lynparza) or rucaparib
(Rubraca) on one of two clinical trials,”
to determine if the assay is accurate in
predicting the success of these drugs in
prostate cancer.

What Happens at the Beginning
of Metastasis?

Robert H. Austin, Ph.D., The Luciana
and Joe Vittoria Scholar, is a professor of
Biophysics at Princeton and a Visiting
Scientist at The Brady. In a joint project
between The Brady and Princeton,
Austin and a team of investigators have
developed a way to study metastatic
prostate cancer on a very small scale, at
the level of microfluids.

We know a lot about what
happens next, after cancer
escapes from the prostate.
But what happens at the
very beginning?

“The critical early events in the
metastatic process remain largely
unknown,” Austin says. This prison
break, scientists suspect, is launched
by just a few particularly bad cells.
“We hypothesize that the harsh, low-
oxxygen, acidic, and low-nutrient
conditions generated by the rapidly
growing, organ-confined tumor exert the
necessary pressure that causes the lethal
disseminating tumor cells to emerge,”
and that this is “the critical early step
in prostate cancer metastasis.”

The Brady and Princeton team has
developed a microfluidic device that
can not only mimic these harsh
conditions in laboratory studies; it can
“simultaneously monitor the complex
dynamics in response to this stress”
in a heterogeneous cell population,
reproducing these early metastatic-
causing events.

“The overarching goal of our project is
to identify and characterize these lethal
disseminating tumor cells,” Austin
says. “Understanding the early steps of
metastasis will lead to new therapies to
disrupt and revert this process.”
Read About the Research You Have Helped Make Possible.

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

Can Droplets of RNA in Blood or Urine Predict Aggressive Cancer?

In this new project, the team will isolate these RNA biomarkers from the blood or urine of radical prostatectomy patients.

Extracellular vesicles (EVs) are little, membrane-wrapped droplets shed by prostate tumors into blood and urine. Small as they are, they’re packed with information—particularly, with molecules of RNA that can say a lot about the tumor they came from.

Shawn Lupold, Ph.D., The Jean and Ian MacKechnie Scholar, and Brady investigator Liang Dong, M.D., hope to use these RNA molecules as windows that will show the nature of localized prostate cancer. “Our goal is to identify RNA biomarkers capable of distinguishing men with more aggressive prostate cancer from men with less aggressive cancer,” says Lupold. “Tumors produce high levels of EVs,” and the membrane serves as a kind of bubble-wrap that “shields the RNA cargo from harsh conditions in the blood and urine.”

With funding from The Patrick C. Walsh Prostate Cancer Research Fund, Lupold and Dong will focus on two types of RNA molecule: microRNAs and alternatively polyadenylated (APA’d) mRNAs. Both are familiar to these investigators: “Our laboratory has previously identified specific microRNAs and APA’d mRNAs that are associated with high Gleason Grade prostate cancer,” says Lupold. In this new project, the team will isolate these RNA biomarkers from the blood or urine of radical prostatectomy patients, and then will compare them with the pathological results after surgery to see which men turn out to have higher Gleason Grade or more extensive disease.

Can PSMA-PET Predict the Risk of Metastasis?

After radical prostatectomy, the PSA level should be undetectable. If PSA comes back, this does not always require immediate treatment, or treatment at all—but sometimes, it does. “Certain men are at high risk of developing metastatic disease,” cancer that can be detected on a CT or bone scans, “and may benefit from early treatment,” says Mark C. Markowski, M.D., Ph.D., The Virginia and Warren Schwerin Scholar.

“Certain men are at high risk of developing metastatic disease and may benefit from early treatment.”

With support from The Patrick C. Walsh Prostate Cancer Research Fund, he hopes to clarify which men need extra help by using PSMA-targeted PET scans, “which can detect prostate cancer at low levels before it can be seen on conventional imaging. We will obtain PSMA-targeted PET scans in patients with biochemically recurrent prostate cancer,” and then follow them to see if they develop metastatic cancer as detected on CT or bone scans.

“Our goal is to use the findings on the PSMA-PET scan to predict the imminent development of metastatic disease,” with the hope of identifying which men will benefit from starting further treatment sooner.

A Molecular Urine Test for Aggressive Prostate Cancer

Wouldn’t it be nice if a simple urinary test could tell whether localized prostate cancer has aggressive potential? This goal may be achieved soon, with a molecular urine test developed by three Brady scientists, says Christian Pavlovich, M.D., The Irene and Bernard L. Schwartz Scholar. With co-investigators Jun Luo, Ph.D., and William Isaacs, Ph.D., and support from The Patrick C. Walsh Prostate Cancer Research Fund, “we will validate and refine this test in 300 men with cancers of varying aggressiveness, who will be undergoing radical prostatectomy.”

Wouldn’t it be nice if a simple urine test could tell whether localized prostate cancer has aggressive potential?

In this study, the investigators will compare results of the urinary test, taken before surgery, with pathologic findings after surgery. “We hope to determine how accurate the test is in finding aggressive prostate cancer,” and will seek to optimize it for greater accuracy.

This test uses specific RNA probes to identify prostate cancer cells in urine samples collected after digital rectal examination. “It is more often positive in men who have aggressive forms of prostate cancer,” says Pavlovich. The investigators hope the test will prove particularly helpful in men who are considering Active Surveillance, “to tease out which of these men actually harbor more aggressive cancers that were missed on prostate biopsy.”

Alpha-Particle Radiotherapy: Targeting Every Cancer Cell

If we can see it, how can we kill it?

With PSMA-targeting molecules, scientists can find metastatic sites of prostate cancer that may be too resistant to kill. If we can see it, how can we kill it? Stavroula Sofou, Ph.D., The R. Christian B. Evensen Scholar, believes the answer is synergy. “Alpha-particle radiopharmaceutical therapy has been shown to be impervious
to most of cancer’s resistance mechanisms, if it’s optimally delivered,” she says. A mixed approach seems to be even more effective: “We recently observed that combining two types of carriers (a radiolabeled nanoparticle and radiolabeled-antibody) of the same alpha-particle emitter results in a greater delay of tumor growth compared to that of the same dose when delivered by each of the carriers alone.”

Sofou suspects that this approach exposes a greater population of cancer cells to more drug, and for longer periods of time, as two forms of the same drug attack the cancer. In work supported by The Patrick C. Walsh Prostate Cancer Research Fund, she and colleagues will extend their initial observations to animal models.

Making PARP Inhibitors Safer for Normal Tissue

Can we make PARP inhibitors more cancer-specific, and more likely to leave normal cells alone?

PARP inhibitors are new drugs that have great promise in treating several forms of cancer. They block poly(ADP-ribose) polymerase (PARP) proteins, and seem to work best in patients with certain genetic mutations. But they can have “off-target” effects, says Fengyi Wan, Ph.D., The Charlton C. and F. Patrick Hughes Scholar.

The current PARP inhibitors, including Olaparib, all work in such a way that “therapeutic targeting of PARPI using these inhibitors could negatively impact numerous key procedures in normal cells,” Wan explains. “There is an urgent clinical need for improving the specificity and lowering the off-target effects of PARPI inhibitors.”

Wan’s laboratory recently discovered a crucial protein that also stimulates DNA damage-induced PARPI activation. In work supported by The Patrick C. Walsh Prostate Cancer Research Fund, he plans to target this protein’s effect as a novel strategy to develop a new category of PARPI inhibitors – agents that might be kinder to normal cells and processes. “Our specific aims during this project are to screen and validate potent drugs” that specifically inhibit this protein’s activation of PARPI, “and to assess their effect on the survival of advanced prostate cancer cells.”

Better Treatment for Urethral Structures After Prostate Cancer Treatment

Urethral stricture – the formation of scar tissue, with narrowing at the bladder neck and urethra – “can be a devastating side effect of prostate cancer therapy, leading to infection, bladder dysfunction and urinary retention,” says E. James Wright, M.D., The Carolyn and Bill Stutt Scholar. There are two basic ways to treat such a stricture and expand the narrowed area: a minimally invasive approach, with an incision into the scar to break its hold on the urethra, or a more complex procedure, open surgical graft repair.

Neither procedure is perfect, says Wright: “The minimally invasive approach is simpler to perform, but it has a high failure rate; meanwhile, the complex repair procedure is technically challenging.” A third procedure, combining both internal incision and grafting, “is a viable option with development of a suitable temporary implant to expand the urethra and hold a graft in place.”

Graft healing requires two things, says Wright: “adequate blood flow to the urethra and accurate assessment after expansion, to ensure successful grafting without urethral injury.” In work funded by The Patrick C. Walsh Prostate Cancer Research Fund, Wright will use laser Doppler flowmetry to measure blood flow changes in the expanded urethra in men undergoing radical cystoprostatectomy (surgery to remove the bladder, prostate, and seminal vesicles). He hopes the study’s results will help guide development of a novel device and more effective treatment for these strictures.

Immune Profiling of High-Risk Prostate Cancer

Why doesn’t immunotherapy work as well in prostate cancer as it does in other forms of cancer?

It may have something to do with what’s happening with immune cells – which, if they were doing their job, would be attacking the enemy – in and near the cancer, in the cancer’s microenvironment. For example, one kind of immune cell, called CD8+ T cell, is a mighty warrior in other settings. But in prostate cancer, it is only present in low numbers, says Jelani Zarif, Ph.D., The Keith L. Bremer Scholar. “At the same time, prostate cancer tumors are infiltrated with immunosuppressive cells,” called M2-macrophages, which can reduce T cell function and prevent them from getting to prostate tumors and attacking them.

But that’s not the only problem: When compared to other cancers, prostate cancers have far fewer genetic mutations. Each mutation makes the cancer cell look slightly different. To the immune system, a cancer cell with many mutations sticks out like the proverbial sore thumb; it’s much more likely to recognize such a cell as something that doesn’t belong, and to attack it. But prostate cancer cells, with fewer mutations, don’t stand out so clearly.

These are two good reasons why “we hypothesize that anti-tumor T cell responses are not generated in advanced prostate cancer,” says Zarif, “and why checkpoint-inhibiting drugs aren’t as effective for many patients.” In work funded by The Patrick C. Walsh Prostate Cancer Research Fund, Zarif is conducting a comprehensive analysis of the anti-tumor T cell response in prostate cancer tissue samples.
Mini-Bladders for Study, Made From a Patient’s Own Cells
Making a mini-organ using the patient’s own tissue can spare time, money, and disappointment by predicting drug sensitivity and resistance – avoiding weeks or months of trial and error.

Until recently, scientists who wanted to study the bladder had to settle for studying just some of it – established cell lines, grown in a dish. Trinity Bivalacqua, M.D., Ph.D., the R. Christian B. Evensen Professor in Urology, Max Kates, M.D., and colleagues have come up with something much better: a miniature, 3-D version of an organ, grown from the bladder tumors of his patients.

In the setting of bladder cancer, making a mini-organ using the patient’s own tissue can spare time, money, and disappointment by predicting drug sensitivity and resistance – avoiding weeks or months of trial and error. Bivalacqua’s laboratory has shown that PDOs can be used to identify the molecular subtype of a patient’s tumor and the genetic pathways involved, which could make an important difference in treatment. “With PDOs, we can test common intravesical agents like BCG and chemotherapy, to determine their effectiveness ahead of time.”

Because these PDOs are so new, we have barely begun to tap their usefulness, adds David McConkey, Ph.D., Director of The Greenberg Bladder Cancer Institute. “Organoids have an excellent potential to help us find the vulnerabilities in cancer – so before we start treatment, we can find the option most likely to be successful.”

In Bladder Cancer, the Subtype Matters
The way we think about bladder cancer has been transformed. The revolution in thought, led by Greenberg Bladder Cancer Institute scientists David McConkey, Ph.D., and Woonyoung Choi, M.S., Ph.D., Director of Genomics, is this: there are different molecular subtypes of bladder cancer – each with distinct biological and clinical characteristics. Not only may they behave in significantly different ways; they may respond better to different forms of treatment.

In research with investigators at a number of institutions, Choi and McConkey have found similarities between these molecular subtypes and the basal-like and luminal subtypes of breast cancer. “These studies have dramatically transformed our understanding of bladder cancer,” says McConkey. As part of The Cancer Genome Atlas (TCGA) Bladder Cancer (BLCA) Analysis Working Group, McConkey published an updated description of these molecular subtypes based on data generated from more than 400 bladder tumors.

“One of particular interest,” he says, “was our identification of a new neuronal/neuroendocrine subset of the basal-like cancers. This particular form of cancer proved to be extremely aggressive in patients who were treated with conventional chemotherapy.” Clearly, a more specific approach is needed.

“A major objective for ongoing research is to develop tests to subtype bladder cancers in the clinic,” says McConkey. With TCGA investigators including Seth Lerner, Jaegil Kim, David Kwiatkowski and Joshua Meeks, McConkey is actively working to develop such a test. In a recent trial, patients with the neuroendocrine subtype responded to Genentech’s new immune checkpoint inhibitor, atezolizumab, with very encouraging results: “The group of patients who had the worst survival outcomes with conventional therapies had the best outcomes with atezolizumab. This observation strongly supports the aggressive further evaluation of immune checkpoint inhibitors in patients with small cell/neuroendocrine tumors.”
In international meetings, McConkey and Choi have helped come up with a “robust” group of five subtypes of bladder cancer; this is expected to be published soon. “This project has also inspired a collaboration among investigators at the GBCI, the Pasteur team, and Eva Comperat (Tenon Hospital, Paris) to use sequencing to deeply characterize larger numbers of small-cell and neuroendocrine tumors,” McConkey notes.

These five subtypes may be just the beginning, he adds: “It also appears that analyses of larger numbers of tumors will reveal additional layers of complexity.”

Recently, Choi, working with Seungchan Kim of Prairie View A&M University, discovered that “there are two distinct subsets of basal tumors that are associated with dramatically different biological and clinical properties. Specifically, these two subsets showed the opposite chemotherapy responses. One basal subset received the most benefit from cisplatin-based chemotherapy, whereas the other basal subset was resistant to it.” Some of this work by McConkey and Choi was published in Cell.

**Neoadjuvant Chemo-therapy And Upper Tract Urothelial Cancer**

“Patients who received neoadjuvant chemotherapy were more likely to have non-invasive disease at surgery – meaning their invasive disease had been eradicated.

Upper tract urothelial carcinoma (UTUC) can be nasty. “This relatively rare form of cancer – similar to urothelial bladder cancer – develops in the lining of the kidney or ureter,” explains urologist Phillip Pierorazio, M.D. High-grade UTUC can be lethal; in fact, “about half of all patients who have this aggressive form of UTUC die within five years of diagnosis.”

Traditionally, UTUC is treated with radical nephroureterectomy, surgery to remove both the kidney and ureter. Even though the surgical technique has improved, survival for patients who are treated with surgery alone “has not significantly improved over the last three decades.”

But people who have this same kind of tumor in the bladder do better. The key difference may not be in the tumors themselves, but in the way they are treated: Urothelial bladder cancer patients get neoadjuvant chemotherapy before surgery. Could this make a difference in UTUC? Yes! say Pierorazio and medical oncologist Jean Hoffman-Censits, M.D. Their results are very encouraging: “We have been using neoadjuvant chemotherapy before surgery for UTUC to shrink or downstage the tumor,” Pierorazio reports.

“The chemotherapy helps control for microscopic spread and optimizes renal function,” which, in turn, helps the chemotherapy do its job better.

Collaborators within The Brady and Greenberg Bladder Cancer Institute recently reported in the Journal of Urology on 32 patients who received neoadjuvant chemotherapy before surgery compared to more than 200 who received surgery alone. “Patients who received neoadjuvant chemotherapy were more likely to have non-invasive disease at surgery – meaning their invasive disease had been eradicated,” says Pierorazio, the paper’s senior author. Even more exciting: “About 10 percent of patients had no cancer found in the surgical specimen after it was removed. This indicates chemotherapy is really working – shrinking if not destroying entire tumors. The hope is that if the cancer is killed within the kidney, it will translate into better and longer survival for our patients.”

Hoffman-Censits recently presented exciting data on the use of neoadjuvant chemotherapy in a Phase 2 clinical trial at the American Urological Association’s Annual Meeting in San Francisco. The prospective clinical trial demonstrated a 14-percent eradication of disease with few serious side effects. These findings, she says, are “incredibly promising for our patients with high-grade UTUC.”

**“Liquid Biopsy”and Personalized Treatment for Bladder Cancer**

“These new tests are so sensitive, they can detect just one single cancer cell!”

Last year in Discovery, we reported on the exciting work of Heather Chalfin now one of the Brady’s Chief Residents, and David McConkey, Ph.D., in detecting circulating tumor cells (CTCs) in the blood.

Since then, Chalfin and McConkey have come even further in their quest for a test to detect these hard-to-find cells early and to learn, from analyzing them, about the cancer: is it aggressive? Is it slow-growing?

The reason why this is so important is that it lets doctors peek through a window that appears much earlier in the course of cancer: “Up until recently,” Chalfin explains, “cancers have been detected and monitored with CT or MRI scans. Yet these scans can only detect cancer cells that have multiplied enough times to form a cluster containing millions of cancer cells.”

The difference is akin to finding and interrogating a lone scout or advance party of an enemy – instead of waiting for the whole army to show up. How much better would it be to identify and track cancer “simply with a blood draw?” Much better, says Chalfin. “These new tests are so sensitive, they can detect just one single cancer cell that is invisible to a scan!” But it’s not just a matter of detection: “The ideal cancer blood test, or liquid biopsy, will help individualize patient care by suggesting which treatments are most beneficial to that patient, and will tell us who can safely avoid aggressive treatments.”

In search of the best test, Chalfin and McConkey have successfully used two types of liquid biopsies to detect and study bladder cancer in the blood. The first type discusses what we talked about last year: “it detects cancer cells themselves as they float through the bloodstream.” The second type of test looks at something even smaller than an individual cell: it looks at the DNA of a CTC; this is called circulating tumor DNA, or ctDNA.
DISCOVERY IN KIDNEY CANCER

In Active Surveillance, Some Small Kidney Tumors Just Go Away

“We don’t know if these are benign lesions that just disappear on their own, or if they are small cancers that the body fights off.”

Now you see them, now you don’t? In our pioneering active surveillance program for small kidney tumors (Delayed Intervention and Surveillance for Small Renal Masses, or DISSRM Registry), Brady researchers are documenting something no one knew existed: very small renal masses that just seem to go away. Then, some of them come back – but some of them don’t.

“In our growing experience with active surveillance, we have encountered this unique phenomenon in about 5 percent of patients,” says Arnav Srivastava, M.D., lead author of a study recently published in the journal, *Clinical Genitourinary Cancer*. With co-investigators Alexa Meyer, Phillip Pierorazio, Steven Rowe, Mohamad Allaf, and Michael Gorin, he documented this “spontaneous clinical regression,” or disappearance.

“These patients have at least one surveillance image showing no small mass in the kidney,” says Srivastava. In about half of these patients, the tumor shows up again on the next imaging test. This might be explained by “limitations of our current imaging technology,” he continues. However: “the other half of patients had their small renal masses remain undetectable for extended periods of time, or even permanently.”

Good news for the patients whose tumor – usually smaller than 1 cm – reappeared: none of these masses grew rapidly, “and all these patients were alive after five years.”

What about the ones that stayed gone for good? Good news there, too, says the study’s senior author, Pierorazio, Director of the DISSRM Registry. “Small renal masses that permanently disappear remain an area of great interest for the Kidney Cancer Team. “We don’t know if these are benign lesions that just disappear on their own, or if they are small cancers that the body fights off.”

The DISSRM: Nearly a Decade of Patient-Specific Treatment

“The risk of death from cancer is incredibly low in these patients, and choosing the right management strategy is highly patient-specific.”

When it comes to kidney cancers, size matters. Small renal masses (SRM) are tumors less than 4 cm in diameter. “Although most of these SRM are cancers, the majority are low-grade, indolent tumors – tumors that behave in a benign fashion,” says Mohamad Allaf, M.D., Director of the Kidney Cancer Program at The Brady, “and most patients with SRM die from other causes.”

More than 700 patients at three institutions have enrolled in the DISSRM (Delayed Intervention and Surveillance for Small Renal Masses) Registry since it opened in 2009. These patients are treated either with radical nephrectomy (removal of their entire kidney), partial nephrectomy (removal of their tumor and sparing of the kidney), thermal ablation (freezing or burning the tumor), or active surveillance.

In a study recently published in the *British Journal of Urology International*, DISSRM researchers demonstrated “very few deaths from cancer among all patients in the study,” says principal investigator Phillip Pierorazio, M.D., “The largest decreases in kidney function appeared in patients who had an entire kidney removed, and mental health scores were similar among all treatment groups. The risk of death from cancer is incredibly low in patients with SRM, and choosing the right management strategy is highly patient-specific.”

A Powerful Immunotherapy Mix for Bladder Cancer

The ADAPT-BLADDER trial will combine immune checkpoint-inhibitor therapy, BCG, and radiation therapy.

A complicated cancer needs a comprehensive approach. This is the thinking behind the ADAPT-BLADDER trial for non-muscle-invasive bladder cancer (NMIBC), for patients with recurrence after standard BCG therapy.

“This study brings together – for the first time – urologists, medical oncologists and radiation oncologists in planning and administering a combination of approaches,” says Noah Hahn, M.D., Associate Professor in Oncology and Urology and an internationally recognized authority on clinical trials and translational investigations in bladder cancer. He is the principal investigator of this study, which will combine “intravenously administered immune checkpoint-inhibitor therapy (durvalumab, an anti-PD-L1 antibody approved for metastatic bladder cancer), intravesically administered immunotherapy (BCG), and externally administered radiation therapy.”

The ADAPT-BLADDER trial is the first NMIBC study to look at immunotherapy (durvalumab) combined with radiation therapy, which started at The Brady and will expand to include 25 sites, Hahn adds.

“IT detects genetic material that is normally housed in the nucleus of a cell but can also be shed into the blood stream as cancer cells invade,” explains Chalfin.

“The ctDNA test allowed us to identify a unique mutation signature of genes, and the CTC test allows us to study the shape and appearance of individual cancer cells.” It’s kind of like using both fingerprints and facial recognition from cameras at a crime scene. “We hope that both of these tests will help us minimize overtreatment, and will help patients select the best treatment for their individual cancer,” says Chalfin.

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“We’ve Got a Team.”

They call themselves the Go Team.” As in, “when you get the phone call, you go!”

Discovery is full of stories about remarkable doctors and scientists working hard to save lives and improve quality of life from urologic cancer. The remarkable person in this story is a patient, Kevin Kiernan.

Just before Labor Day in 2015, Kevin was at the movies with his wife, Trish. He felt pretty good; in fact, he had just had a physical and gotten a clean bill of health. Then everything changed: he developed pain in his side, went to the urgent care center in his hometown of Telluride, Colorado, and got a late-night CT scan for a probable kidney stone.

The pain got a lot worse, and all of a sudden, so did his diagnosis. “The doctor said, ‘There’s a huge tumor on your kidney and all kinds of questionable activity in your circulatory system. You’re susceptible to a clot or a stroke,’” says Kevin. “That was a shocker. It just came out of nowhere.” Trish went home, packed a suitcase, and told their kids what was happening. Kevin went by ambulance to the hospital in Grand Junction. Early the next morning, he received the grim news that his cancer had traveled up from his kidney to his vena cava and had reached his heart. And then: “Get your affairs in order. You probably don’t have long to live.”

At this point, Kevin says, “We were just in shock. The urologist said, ‘I’ve read about this, but never seen it. We don’t have a clue as to what to do.’ I said, ‘Where do I go?’ He said, ‘I’ll start researching. You start researching. Get on the phone and call everybody you know.’”

One of Kevin’s first calls was to his friend, Missy, whose husband had been successfully treated for prostate cancer at The Brady by urologist Ted Schaeffer (now Chief of Urology at Northwestern). Missy texted Schaeffer on Labor Day. Within an hour, Kevin got a text from Schaeffer. In it was a link to The Brady’s webpage, where not only was Kevin’s very rare condition, “Kidney Cancer with Vascular Invasion,” discussed (http://urology.jhu.edu/kidney_cancer/kidney_cancer_Vascular_Invasion.php); there were video clips of the operation to treat it.

The message from Schaeffer, Kevin recalls, was: “We’ve got a team.” Within a day, Brady urologic surgeon Phil Pierorazio called and said, “How quickly can you get here?” Kevin made plans to fly to Baltimore immediately. “About an hour later, I got an email from Pierorazio, copied to all the different surgeons,” says Kevin. The multidisciplinary team of surgeons, an interventional radiologist and a specialized anesthesiologist, was very familiar with every aspect of this difficult operation and ready to perform it on short notice: “They call themselves the Go Team,” says Kevin. As in, “when you get the phone call, you go! My cancer was as advanced as it gets, but Phil Pierorazio said they probably see 10 or 12 patients a year as advanced as I was.”

The surgery, on Monday – just a week after Labor Day – took 11 hours and involved full cardiac bypass. In a well-orchestrated procedure, the team removed Kevin’s kidney, cooled his body temperature, temporarily stopped his heart, took the tumor out, reconstructed his heart and his vena cava, then warmed him back up and brought him to the ICU.

Kevin’s surgical margins were negative. “My experience here at Hopkins saved my life and allowed me to see my son get married, and hopefully will allow me to see my other kids get married and have kids,” he says, “and that’s an amazing gift.”

After the operation, Kevin and Pierorazio started talking. Kevin asked whether there had been any risk factors or early warning signs that he should have seen. “He said: ‘That’s the problem with kidney cancer, why the fatality rate is so high. There aren’t any symptoms, because you have another kidney that masks it. There’s no way you could have known.’ I said, ‘How could that be? Can people just start getting preemptive scans?’” Pierorazio told Kevin that it was not feasible to scan everyone – but that he and urologist Mohamad Allaf were working on a way to detect a diseased kidney in urine. Kevin asked what he could do to help, and he and Trish committed a million dollars to get this urine test developed.

Kevin and Trish have also joined the Brady Advisory Board. “I was fortunate enough to have great care, and now I’m also fortunate enough to be involved in helping save lives from kidney cancer. Trish and I are very blessed. We had been wondering what we could do to make a difference: this is it.”

In April 2018, Kevin’s cancer came back. “But in the two and a half years they bought me with the surgery, immunotherapy is now out of trial, and they are treating me with these tools that weren’t available then to extend my life,” he says, adding: “What Hopkins gives you is the peace of mind that you’ve made every right choice. Most people wonder: Should we get a second opinion? Are we doing everything we can? That just eats you alive. But the day I walked in that door, I knew there wasn’t anything else we needed to do; that now it’s just up to fate, and that’s huge.”

Kevin is very encouraged by the success of immunotherapy in treating cancer, and by the recent momentum seen worldwide in testing these newest drugs. “If Pierorazio and I, with the urine test, can get the original diagnosis before cancer grows, and surgery and immune therapy can knock it out, then maybe we’ve found a curative treatment for kidney cancer. That’s what I’m excited about.”
Every Man Needs This Book.

Each year, more than 160,000 American men are diagnosed with prostate cancer. The good news is that more men are being cured of this disease than ever before.

Now in a revised fourth edition, this lifesaving guide – Amazon’s #1 Bestseller in Men’s Health for 24 years – by renowned expert Dr. Patrick Walsh and acclaimed science writer Janet Farrar Worthington offers a message of hope to every man facing this illness.

Prostate cancer is a different disease in every man—which means that the right treatment varies for each man. Giving you a second opinion from the world’s top experts in surgery, pathology, urology, and radiation and medical oncology, this book helps you determine the best plan for you. Learn:

- What causes prostate cancer: your risk factors, including heredity, diet, and environment
- Why African American men are more vulnerable, and what they need to know
- Which simple changes in your diet and lifestyle can help prevent or delay the disease
- Why the digital rectal exam and PSA test can save your life—and how newer blood tests and imaging make the diagnosis more accurate
- New treatment guidelines that enable many men to safely undergo active surveillance and delay treatment
- Advances in radiation and surgery that save lives and reduce side effects
- Breakthroughs in the treatment of advanced cancers such as gene-targeted therapy and immunotherapy that are prolonging life and offering new hope

FOURTH EDITION

What you need to know about prostate cancer: Revised and updated with the latest advances in surgery, radiation, and precision oncology.