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You’ll read a lot about precision in this issue of *Discovery*: Precision diagnosis, precision imaging, precision treatment of localized disease and precision oncology through gene-targeted therapy. Our cover story celebrates an exciting convergence of events: better-than-ever ability to see tiny sites of prostate cancer through PSMA PET, developed here at the Brady by Martin Pomper; breakthrough research that overturns what we all thought we knew about how prostate cancer spreads — and widens our window of curability considerably — and exciting new “spot welding” radiation therapy, being tested in a clinical trial by Phuoc Tran to see if men with oligometastasis can be cured. As always, this issue is packed with stories on the exciting research happening here at the Brady — and as always, I feel like we have barely tapped the surface. There is so much to tell you about, in prostate cancer, and in other cancers, as well. For example, results were so promising from an international study led by Noah Hahn that the FDA has approved a new immunotherapy drug for people with advanced bladder cancer. David McConkey, Director of our Greenberg Bladder Cancer Institute, and colleagues have identified five different molecular subtypes of bladder cancer — precision diagnosis that will lead to precision treatment. More precision diagnoses may be on the way with a “liquid biopsy” for bladder cancer. And in kidney cancer, the American Urological Association has changed its guidelines in large part due to the work of a Brady team led by Mohamad Allaf and Phillip Pierorazio. The new guidelines are based on personalized medicine. That’s our goal for every patient we see here at the Brady: to find the best treatment for that person’s specific disease.

Best wishes,

Alan W. Partin, M.D., Ph.D.
The Jakurski Family Director
Urologist-in-Chief
Professor of Urology
The James Buchanan Brady Urological Institute
Reassuring news for men treated for localized prostate cancer: New findings by Brady investigators prove that you are more likely to be cured than ever. Even better: on the slim chance that cancer recurs, it is much more likely to be in a nearby spot that – thanks to new imaging and treatment pioneered at the Brady – can be detected and treated successfully.

These findings, which have been submitted for publication and were presented at the national Prostate Cancer Foundation meeting in October, overturn a 2009 study from the University of Washington whose results have been widely accepted – and have proven needlessly worrisome for many men with localized prostate cancer. So, says Pienta, “we set out to revisit that,” in a research project with Brady resident Heather Chalfin, M.D. This work was made possible by support from philanthropists Carolyn and Bill Stutt, founding members of the Patrick C. Walsh Prostate Cancer Research Fund.

“DTCs are cancer cells that escape the primary cancer and enter a different organ, representing a first step toward detectable metastasis,” explains Chalfin, “and a common landing zone for prostate cancer cells is the bone marrow.”

But how common, exactly, is it for stray prostate cancer cells to find their way to the bone marrow in localized disease? Not very, and the Brady team discovered this by looking for prostate-specific evidence of cancer. In the 2009 study, the investigators used markers for epithelial cells (cells in the lining of tissue and organs), “which were not specific enough,” says Chalfin. “In fact, normal men – and women – have cells with epithelial markers in the bone marrow.”

Using prostate-specific markers, “we discovered that DTCs are only rarely found in localized prostate cancer. This changed our understanding of how prostate cancer metastasis occurs.” Basically, “everything we thought was true is wrong.”

What this means for patients is a revolution in treating cancer that has escaped the prostate. “Our evidence suggests that lymph nodes, instead of bone marrow, are the true reservoir of micrometastatic disease,” Chalfin says.

Perfect Timing

This discovery couldn’t have come at a more opportune time – because now we have the technology to see where that cancer is hiding.

Several years ago, Brady investigator Martin G. Pomper, M.D., Ph.D., Director of Nuclear Medicine and Molecular Imaging, solved a puzzle that had frustrated scientists for decades. In the past, scientists tried to engineer antibodies to recognize prostate-specific molecules, particularly PSMA (prostate-specific membrane antigen, which sits on the surface of prostate and prostate cancer cells), and then add an imaging agent that glows in the presence of those
What Pomper achieved, in short, is a way to see cancer that’s about the size of a BB wherever it may be hiding in the body, using a PSMA PET scan. This is cancer that no one was able to see before. And now we are finding new ways to treat it.

Continued from page 3 »

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What Marty did was to find a urea-based small molecule that actually binds to PSMA.” This tiny “grabber,” or “linker,” molecule sticks to PSMA like glue – but that alone wouldn’t be nearly as noteworthy if Pomper hadn’t also used innovative chemistry to glue F18, the radioactive fluorine that glows in a PET scan, to that small molecule.

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Previously, doctors could only track a rising PSA and wait until cancer grew big enough to cause symptoms or show up on a bone scan or MRI.

**Treating Oligometastatic Cancer**

Brady physicians and scientists are at the leading edge of a sea change in treating small bits of cancer that have made their way out of the prostate early, before they turn into full-blown metastasis. This is called oligometastasis, and it is treatable. “In men who have biochemical recurrence – say a PSA of 0.5 ng/ml after radical prostatectomy – the typical thing to do is go ahead and irradiate the whole pelvis,” says Pienta. “But if we can spot the cancer and it’s just in a single lymph node, we can actually try to just irradiate or remove that one lymph node – and ideally we can save that man from whole pelvis radiation and ADT,” androgen deprivation therapy, or hormonal therapy. If a spot of cancer does show up in the bone, it can be treated focally, as well, with stereotactic radiation. Radiation oncologist Phuoc Tran, M.D., Ph.D., is leading a clinical trial doing this, discussed on Page 6.

But what about men who have more than a few small bits of cancer? There’s new hope here, too, says Pienta. “There are new clinical trials available for men with lots of disease who light up with PSMA PET imaging, and we now know that we can attach a radioactive bomb to the PSMA molecule.”

This is Pomper’s chemistry, now being used for treatment as well as detection. Using an analog of Pomper’s grabber imaging molecule, physicians in Germany have been treating men with metastatic prostate cancer for several years. However, they have not performed clinical trials using this technology, and although some men have experienced remission of cancer, they have also had significant side effects, including the loss of their salivary glands. Another issue: several different radioactive molecules, called radioligands, can be used to kill the cancer, and it may be that the side effects are fewer with one type than with another. Pienta co-led a “think tank” meeting with scientists in September to establish clinical trials that will determine the safest and most effective way to use these radioligands.

Could these radioligands work even better in combination with immunotherapy? Pienta believes they might. The new class of immunotherapy drugs called checkpoint inhibitors is causing its own revolution – putting men and women with widely metastatic forms of cancer, including lung, breast, prostate, bladder, and melanoma – into long-term remission. These drugs don’t work for everybody, and scientists believe that’s because not everyone has the same checkpoint involved. Briefly, cancer has a diabolical way of putting the body’s great immune warrior cells, T cells, to sleep. It dupes checkpoints, which are molecules that control the T cells, into thinking all is well: think of security guards looking at a bank of video camera feeds, where nothing is happening on screen – because the crooks have hijacked the cameras and are showing the same uneventful scenes over and over again. There are different checkpoints, and new drugs that target them individually.

Pienta suspects that radioligands might galvanize the immune system – and make immunotherapy drugs work better – by “killing some of the cancer cells, releasing pieces of cancer,” called neoantigens, “not normally seen by the immune system. This would allow the immune system to recognize that cancer is present,” so it can start to attack these foreign invaders.

But that’s not the whole story with today’s immunotherapy breakthroughs. Cancer also dupes macrophages – immune cells that are like bouncers at a bar to keep out the riffraff – into letting in cancer cells, and keeping out the T cells. Pienta is a pioneer in the study of macrophages in cancer, and is investigating and designing new therapies to knock out these macrophages.

This work, and the work on DTCs, and Pomper’s PSMA-targeting small molecules, are generating huge momentum, and this is a very exciting time at the Brady, says Pienta. “We’re really defining new ways to understand prostate cancer. Thanks to Carolyn and Bill Stutt, we have a new window into how prostate cancer occurs, and when and where it spreads, and this leads us to new ways to treat it with fewer side effects.”

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**Donations drive discovery!**

*If you are interested in making a personal investment in critical research like this, 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.*
You’ve done it for so long, and thank goodness, it has always come back undetectable. Sometimes you wonder if maybe you could stop taking the yearly PSA test; but then again, you’ve read that cancer can come back many years after a prostatectomy. Is it ever safe to stop PSA testing?

Yes! Reassuring evidence from Brady studies provides some guidelines. Several years ago, urologist Stacy Loeb, M.D., now on the faculty at New York University, examined Hopkins prostatectomy patients who had an undetectable PSA at 10 years after surgery. With further follow-up, she reported that recurrence was very rare for men with low-grade (Gleason 3 + 3) disease, and not a single man developed metastatic disease after 10 years. She suggested that men with low-grade disease could reasonably stop testing if their PSA levels remained undetectable for 10 years.

But what about men with intermediate- or high-risk disease? There remains “no standard practice regarding when PSA testing can be stopped for these men who have an undetectable PSA level over longer periods of time,” says Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. Walsh was senior investigator in a new study that looked at long-term PSA levels of more than 700 Brady prostatectomy patients whose PSA levels have remained undetectable for 20 or more years of follow-up. The other investigators include Wesley Ludwig, M.D., biostatistician Zhaoyong Feng, Bruce Trock, Ph.D., and Elizabeth Humphreys.

“We suggest that PSA testing can be stopped at 20 years for men with an undetectable PSA and intermediate- or high-risk prostate cancer.”

Ludwig, Brady resident and the study’s lead author, notes that of the men with intermediate- and high-risk disease, a very small number (2.3 percent) developed prostate cancer recurrence, only a single patient developed metastatic disease, and none died of prostate cancer.

“We found that the majority of men who had detectable PSA developed it within two years of their radical prostatectomy, and the likelihood decreased every five years,” Ludwig reports. Previously, Brady investigators have shown that the likelihood of having PSA return after 15 years is only 1.5 percent.

The men most likely to have a delayed return of PSA were those who had an elevated PSA at the time of radical prostatectomy, higher clinical and pathologic stage, and positive surgical margins. The good news is that even with a return of PSA, these men have excellent chances of survival.

With the longer follow-up period in this study, the investigators were able to analyze risk from 20 to 30 years. Because the risk of recurrence is so low after 20 years of undetectable PSA, and because it takes an average of eight years after PSA reappears before metastasis to develop, “we suggest that PSA testing can be stopped at 20 years for men with an undetectable PSA and intermediate or high-risk prostate cancer,” Walsh says.
Pushing Back the Frontier of Curability

In oligometastasis, by treating “not only the primary disease in the prostate or the pelvis, but also the few metastatic lesions, perhaps men can actually live a long time without disease progression and even be cured.”

Not too long ago, the dividing line between prostate cancer that was considered curable and cancer that might not be was the prostate itself—and whether the cancer was confined to the prostate or had spread beyond it to a distant site. That’s not the case anymore, says radiation oncologist Phuoc Tran, M.D., Ph.D. The frontier of curability is being pushed back.

“Clinically speaking, we prescribe treatments for men with prostate cancer as though prostate cancer presents in clear clinical states,” he says. Think of a Venn diagram: in one circle are “men we believe to have purely localized disease, and they are curable by surgery or radiation.” In the other circle are men with metastatic disease, men who are considered “treatable but not curable with our current therapies. In general, this old treatment paradigm says that men with localized disease benefit mostly from local therapies like surgery and radiation and very little from systemic treatment like hormones and chemotherapy.”

But Tran and Brady colleagues are among scientists who believe these circles intersect. New evidence suggests that in men with oligometastasis—just a few spots of cancer outside the prostate—by treating “not only the primary disease in the prostate or the pelvis, but also the few metastatic lesions, perhaps men can actually live a long time without disease progression and even be cured.”

This is a dramatic and very exciting change in scientific thinking, and it’s happening because of advances in imaging (see story on Page 3) and radiation therapy—particularly the development of stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation (SABR). “SBRT and SABR are highly focused radiation given in an intense fashion,” says Tran. “I tell patients it’s like spot welding—focused on a small area, very intense, and theoretically ablative, meaning it kills all the cancer in that spot.”

The Baltimore ORIOLE Trial

Can this new SABR technology plus treatment of localized cancer help men with oligometastatic cancer? “We wanted to test our idea in a rigorous way,” says Tran. “Our Baltimore ORIOLE trial is a randomized clinical trial in patients with oligometastatic prostate cancer (defined as three or fewer metastases).” To be eligible, men must have received either surgery or radiation for the primary prostate disease, and have had no hormonal therapy for their metastatic disease. “They can have had hormonal therapy in conjunction with treatment for their primary disease,” such as a short course of androgen deprivation therapy (ADT) with external-beam radiation therapy, “but not for their metastatic disease.”

Men are randomly assigned either to receive SABR to up to three metastatic sites, or to a short observation period of three to six months—but this doesn’t mean that the men assigned to observation can’t get SABR, Tran states. “The randomization is two to one to SABR, versus a short–no longer than one- to six-month–observation period, after which they can cross over to the SABR treatment.” Other criteria for eligibility: small metastatic sites (less 250 cc) and a PSA doubling time of less than 15 months. “We chose less than 15 months because there are men who have biochemical failure or low-volume metastatic disease with long PSA doubling times, sometimes many years,” explains Tran. “These men probably don’t need any treatment immediately—or possibly, ever. A PSA doubling time of less than 15 months allows us to zero in on patients for whom SABR treatment may make a difference.”

Because of the possibility of long-term remission or even cure, the study has been filling up fast, Tran adds. “We have been enrolling quickly and have 35 men out of 54 total. Thus far, as expected, we have seen only minimal side effects from the SABR, and all men continue to work and are able to resume their normal activities during the short treatment,” which generally lasts less than three weeks. Early results “look promising. The trial also has a number of cutting-edge genetic, blood and imaging studies associated with it that men would not have access to otherwise.”
Channing Paller and Mark Markowski; urologists Ashley Ross and Michael Gorin; radiologists Steven Rowe and Martin Pomper; and statisticians Hao Wang from Johns Hopkins and Adam Dicker from Thomas Jefferson University. The study is funded by the Movember Foundation and the Prostate Cancer Foundation.

If you are eligible and are interested in joining this study, please contact Tran at 410-614-6477.

A New Target in Preventing Metastasis

How does cancer get out of the prostate and into someplace distant, like the liver? With lots of bending and stretching. To become extra flexible, prostate cancer cells re-activate a genetic process that was turned off in infancy. A Brady team, led by radiation oncologist Phuoc Tran, M.D., Ph.D., and Reem Malek, Ph.D., a postdoctoral fellow in Tran’s lab, has uncovered exactly how this works.

“TWIST1 is a cell plasticity factor that is used in embryonic development,” explains Tran. “Our group has found that it plays a critical role in promoting prostate cancer metastasis.” In previous studies, Brady scientist Paula Hurley, with Brian Simons, D.V.M., Ph.D., Ashley Ross, M.D., Ph.D., and Ted Schaeffer, M.D., Ph.D., found that TWIST1 turns on a gene called HOXA9.

This was surprising: HOXA9 “has long been associated with some forms of leukemia, but has never been implicated in prostate cancer,” Hurley says. “We discovered that TWIST1 and HOXA9 are silenced shortly after birth.” In collaboration with University of Washington scientists led by Colm Morrissey, “we showed that TWIST1 and HOXA9 co-expression was re-activated in mouse and human primary prostate tumors, and further enriched in human metastasis.”

Think about old books buried deep in the stacks of a library, says Tran: “The information is there, but you can’t get to it.” Through a series of events at the molecular level, instigated by TWIST1, the information in HOXA9 makes its way to the library’s reading room.

“But it may be possible to stop this,” says Malek. In the laboratory, the team found that “targeting HOXA9 was sufficient to prevent TWIST1-induced aggressive prostate cancer,” which means that this program is “therapeutically targetable.”

Hopkins investigators Steven An, Ph.D., and Ted DeWeese, M.D., Ph.D., also contributed to these findings. This work, published in Cancer Research, was funded by gifts from the Motta and Nesbitt families and grants from the Prostate Cancer Foundation, Movember Foundation, the National Institutes of Health and the Department of Defense.

High Blood Sugar and Prostate Cancer

If you have pre-diabetes or diabetes, here’s another reason to try to get your blood sugar under control: if you get prostate cancer, you are more likely to die from it.

“We found that men with high blood sugar and men with diabetes were more likely to die from prostate cancer.”

This is the finding of a new study led by Brady epidemiologists. “We knew from previous studies that men who have diabetes have a lower risk of developing prostate cancer, but that they may have a higher risk of dying from prostate cancer if they do develop it,” says Corinne Joshu, Ph.D., M.P.H., senior author of the study.

With colleagues Michael Marrone, M.P.H., and Elizabeth Platz, Sc.D., M.P.H., she aimed to understand more about the connections between blood sugar and prostate cancer.

In an analysis of data from more than 5,000 cancer-free men in the Atherosclerosis in Communities study, they studied three markers for blood sugar in men who did not have diagnosed diabetes: fasting glucose, hemoglobin A1c, and glycated albumin,” Joshu explains, and worked “to better classify low, normal, and high blood sugar.”

Men who were classified with high glycemia (blood sugar) on all three markers had “almost a five times greater risk of dying from prostate cancer,” compared to men who were normal on all three markers. Men with a diabetes diagnosis appeared to have a three-fold or greater risk of dying of prostate cancer – and so did men who did not have diabetes who had low blood sugar.

“These patterns were consistent in black men and white men,” notes Joshu. “The results reinforce the importance of efforts to prevent the onset of diabetes,” with weight loss, a healthy diet and exercise, “and to maintain good blood sugar control in men with diabetes – especially in black men, who suffer a disproportionate burden of prostate cancer, hyperglycemia, and diabetes in the U.S.”

Joshu: Controlling blood sugar can significantly lower the risk of dying from prostate cancer.
Among prostate cancer’s most effective weapons are immune checkpoints: natural compounds that cancer hijacks to trick the body into leaving it alone to grow and spread. Imagine a tiny version of the iron “boot” placed on a car with unpaid parking tickets. That’s a checkpoint, and in this case it’s on the T cells – the immune system’s mightiest soldiers, whose job is to attack foreign invaders. Cancer uses multiple checkpoints, each tethering part of a T cell, like the ropes the Lilliputians used to restrain the giant Gulliver.

Checkpoint inhibitors are new drugs that cut the ropes and wake up the sleeping T cells. In clinical trials, these drugs have achieved spectacular results – in some, but not many, people with metastatic cancer. Each checkpoint inhibitor works on a particular checkpoint, like a key in a specific lock. There is no master key to release all the shackles at once and unleash the T cells, no single checkpoint inhibitor that works equally well in everyone. This may be because some cancers have different checkpoints involved, or because the genetic profile of the cancer is somehow different.

How about combining these drugs? Are two checkpoint inhibitors better than one? That’s what Brady scientists Emmanuel Antonarakis, M.D., Jun Luo, Ph.D., Charles Drake, M.D., Ph.D., (now at Columbia University) and colleagues suspected, and they have been testing this hypothesis in a small clinical trial – with exciting results. The patients in their trial are men who have developed a mutated androgen receptor called the AR-V7 variant (discovered at Hopkins by Luo and Antonarakis, who also have developed a blood test for it). “Patients who have the AR-V7 variant respond poorly to the androgen receptor-targeting drugs, abiraterone and enzalutamide, and may also show poor responses to the chemotherapy drugs, docetaxel and cabazitaxel,” says Luo. “There is a great need for new drugs to help these men.”

In their clinical trial, the investigators treated AR-V7-positive prostate cancer patients with a double-shot of two checkpoint inhibitors, ipilimumab and nivolumab, which have worked well individually. “Encouragingly,” says Antonarakis, “four of the 15 patients who received the combination immunotherapy achieved favorable tumor-killing responses, with PSA levels dropping and metastatic tumors shrinking.”

The investigators found that all four men who responded well happen to have a particular type of genetic mutation: a faulty DNA repair gene. DNA repair genes, such as BRCA1-2, are part of the body’s genetic maintenance crew; their job is to detect and fix mistakes before they can cause damage. “Based on these early promising results, we plan to expand our clinical trial to 15 additional patients,” says Antonarakis. If the results hold up, “we will begin to design larger trials to test the combination of ipilimumab plus nivolumab in men with AR-V7-positive prostate cancer.” This work was presented at the 2017 annual meeting of the American Society of Clinical Oncology (ASCO).

Meanwhile, Brady pathologist Tamara Lotan, M.D., Antonarakis, and colleagues at the University of Washington have been studying another checkpoint inhibitor’s success at treating advanced prostate cancer that involves faulty DNA repair genes.

“When one of these genes is defective,” explains Lotan, “it can cause many DNA mutations to accumulate within a tumor. In colon cancer, these mutations cause the expression of many abnormal proteins that actually catch the interest of the patient’s immune system.” The body’s response is foiled by the checkpoints: the T cells are kept from noticing – and killing – these weird-looking cancerous cells.

But another checkpoint inhibitor, called pembrolizumab, is achieving dramatic, long-term responses in some men with prostate cancer – men who have mutated DNA repair genes in their metastatic cancer. “Pembrolizumab can reactivate the immune response in these men,” says Lotan. Her group is among the first to characterize prostate tumors with deficiencies in the mismatch repair proteins. In collaboration with the University of Washington, “we found that tumors with mismatch repair defects comprise nearly 10 percent of very high-grade tumors. We also showed that these types of prostate tumors do have a higher number of immune cells,” which correlates with a higher number of mutations. They also demonstrated that only some tests that look for mismatch-repair mutations work well in the setting of prostate cancer. These results have exciting implications that “will help us identify the men with metastatic prostate cancer who are most likely to be greatly helped by checkpoint inhibitors.” This work was published in Clinical Cancer Research.

Lotan and Antonarakis: No single checkpoint inhibitor works equally well in everyone. But some checkpoint inhibitors work very well in some men with prostate cancer.
Haffner: Understanding this protein, called AIM1, might open up entirely new avenues for treating advanced cancer.

The Protein that Makes Metastasis Possible

Discovered: How cancer cells, Houdini-like, squeeze themselves out of their home environment and into new tissue and bone.

Like ghosts, cancer cells can move through walls. They do it by morphing into stretchy, flexible new shapes. Previously in Discovery, we reported on this important finding by scientists Michael Haffner, M.D., Ph.D., Srinivasan Yegnasubramanian, M.D., Ph.D., Steven An, Ph.D., and colleagues from the Brady, the Sidney Kimmel Comprehensive Cancer Center and the Bloomberg School of Public Health.

The mystery of metastasis – how cancer cells, Houdini-like, somehow squeeze themselves out of their home environment and into new tissue and bone – has long baffled scientists. With support from the Patrick C. Walsh Prostate Cancer Research Fund and the David H. Koch Foundation, Haffner, Yegnasubramanian, An and colleagues identified a protein that “controls cell migration, invasion and metastasis formation in prostate cancer,” says Haffner. This protein, called AIM1, also might open up entirely new avenues for treating advanced cancer. Their discovery was recently published in Nature Communications.

AIM1, “binds and modulates the major component of the cytoskeleton in normal prostate epithelial cells,” Yegnasubramanian adds. In invasive primary prostate cancer, they found, AIM1 seems to have an out-of-body experience, separating itself – think of a soft-shell crab, or a cicada shedding its skin – from the cancer cell’s cytoskeleton. “We also found that AIM1 was often deleted or reduced in expression in metastatic prostate cancer.” In laboratory models, when the scientists cut the expression of AIM1, cancer cells began to remodel themselves, and “this increased their invasive and migratory potential. Taken together, these findings implicate the loss of AIM1 function in conferring prostate cancer cells with the ability to invade and produce invasive cancer and metastases.”

If the team can crack the molecular code – the nuts and bolts mechanisms behind the shape-shifting – it may one day be possible to block them, and to prevent or halt prostate cancer metastases.

Preserving the Treasure Trove of Prostate Tissue

“The DNA and RNA in surgical specimens is a gold mine of new information, and at Hopkins, where we have over 20,000 of them and long-term follow-up on our patients, there is much to learn.”

For today’s sophisticated pathology studies, it turns out that prostate tissue, like revenge, is better served cold. That’s because top pathologists like Angelo De Marzo, M.D., Ph.D., aren’t just looking at the cells anymore. They’re looking at the DNA and RNA – of cancer cells, and even of bacteria. It’s like the Dr. Seuss book, Horton Hears a Who: they keep looking at smaller and smaller things, and finding whole new worlds to study. The problem is, to gain the most information from these kinds of studies, the tissue needs to preserved, preferably by freezing it – which is easier said than done.

If you have ever had prostate tissue removed, it has gone right from the operating table to the pathology lab, where it was “fixed” in formalin, and then put it into a hard wax block. Then the pathologist made a few ultra-thin slices of tissue, stained with dye to make the cells easier to see, and put them on a microscope slide. The Gleason grade of cancer is based on how the prostate cells look.

But that’s just the tip of the iceberg these days: new technology allows scientists to look for mutations and gene activity. “The DNA and RNA in surgical specimens is a gold mine of new information,” says Patrick Walsh, M.D., University Distinguished Professor Emeritus, “and at Hopkins, where we have over 20,000 of them and long-term follow-up on our patients, there is much to learn.”

All that leftover tissue that becomes part of the permanent tissue database has traditionally been stored at room temperature – but De Marzo and colleagues have shown that this causes RNA and DNA to degrade over time. The ideal freezers “are large, commercial, ultra-low temperature units that cost a lot of money and take up a lot of space,” says De Marzo.

Recently, Javier Baena, M.D., and Qizhi Zheng M.D. from De Marzo’s lab, along with Brady colleagues Karen Sfanos, Ph.D., and Bruce Trock, Ph.D., and Eva Corey M.D., and Colm Morrissey Ph.D., from the University of Washington, found that at room temperature, “most genes showed markedly diminished signals by five years, with significant degradation beginning at one year.” Fortunately, Baena, Zheng, and Sfanos found that if new slides are stored in an inexpensive household freezer, the RNA signals will be preserved, at least up to five years.

“Our findings strongly suggest that the standard method of room temperature storage should be called into question and changed,” says De Marzo. Clearly, pathology labs don’t have the money or space to store all prostate tissue specimens in freezers. But they could use smarter storage of the most critical blocks of tissue – probably only one or two for each patient.

This work was supported by The U.S. Department of Defense Prostate Cancer Biorepository Network (PCBN), and the National Cancer Institute. Other investigators who took part in the study are Helen Fedor B.S., and Jessica Hicks M.Sc., from Johns Hopkins, and Toby Cornish M.D., Ph D., from the University of Colorado.
Active Surveillance in Low-Risk Men

Is active surveillance right for you?
“For many men with low-risk prostate cancer, active surveillance (AS) is an ideal approach,” says Brady resident Jeffrey Tosoian, M.D. “However, it’s important to note that all low-risk cancers are not the same.”

Tosoian and a team of Brady investigators recently compared cancer characteristics of low-risk patients who enrolled in AS to those of men who underwent immediate radical prostatectomy. H. Ballentine Carter, M.D., the Bernard L. Schwartz Distinguished Professor of Urologic Oncology and the urologist who pioneered active surveillance at the Brady, led the study. Investigators also included Mufaddal Mamawala, Hiten Patel, Ridwan Alam, Jonathan Epstein, and Ashley Ross.

“Insufficient” cancer: Prostate cancer is considered pathologically “insignificant” if it is detected in fewer than three of 12 biopsy needle cores, and in less than half of all positive samples. “We found that the proportion of men meeting the ‘insignificant’ criteria was significantly higher – 73 percent vs. 18 percent – in men who chose AS than in men who were treated with surgery,” says Tosoian. “Furthermore, only 8 percent of AS patients had 4 or more positive biopsy samples, as compared to nearly half of the surgery group.”

“Low-risk men who have done well on AS at Hopkins have been “a distinct group of patients with a limited amount of cancer.”

The authors concluded that low-risk men who have done well on AS at Hopkins have been “a distinct group of patients with a limited amount of cancer. While many men with more extensive low risk cancers could do very well on AS, our experience has not yet tested this possibility.”

Active Surveillance and the Risk of Grade Reclassification

If you’re thinking about active surveillance (AS), it’s important to understand that for many men, AS doesn’t last forever. That’s why all those follow-up biopsies are so important: prostate cancer can change over time, and a low grade – grade group 1 or Gleason score 6 – may creep higher. “It is important for men considering surveillance to have a clear understanding of the risk of grade reclassification and the chance of cure if that should occur,” says H. Ballentine Carter, M.D., the Bernard L. Schwartz Distinguished Professor of Urologic Oncology and the urologist who pioneered AS.

Active surveillance is a great option for many men with low-grade prostate cancer. The important caveat: Your situation may change over time.

That said, AS is more popular than ever, and deservedly so, Carter adds. “The new American Urological Association guidelines for prostate cancer state that for men with low-grade prostate cancers (grade group 1 or Gleason score 6) discovered early, active surveillance is the best care option. In fact, it is likely that soon, more men in this group will choose AS than surgery or radiation therapy.” But again, there’s that caveat: your situation may change over time.

Carter and colleagues have closely followed men enrolled in the Hopkins AS program for more than 15 years. “We have shown that grade progression occurs in approximately one in three men, that 95 percent of those with grade progression have grade group 2 (Gleason score 3+4), and that only 5 percent of men will be found to have grade group 3-5 or Gleason scores 4+3 or higher. That means the long-term risk of progression to grade group 3 or higher is only 1.5 percent, and progression to grade group 2 is less than 29 percent.”

Who’s at higher risk? There are some predictive factors, including high PSA density and the number of cancerous cores, Carter says. His team’s latest research has found one more clue: age at diagnosis.

“Older men are more likely to harbor aggressive prostate cancer, and more likely to die of prostate cancer than younger men,” says Carter. Even older men diagnosed with low-grade cancer: in a recent study, urology resident Sasha Druskin, M.D., and Brady epidemiologist Bruce Trock, Ph.D., evaluated more than 1,600 men aged 41 to 81 in the Hopkins AS program. After accounting for factors including race, PSA density and the amount of cancer at diagnosis, older age remained a key risk factor for grade reclassification. “We found that men age 70 or older at diagnosis had more than a twofold greater risk than men younger than 60 of being reclassified to grade group 2,” says Carter. Men between age 60 and 69 had a 1.4-fold greater risk.” Further, the likelihood of having a higher grade – grade group 3 or above – was
The evidence suggests that ADT alone may no longer be the standard treatment for men with newly diagnosed metastatic prostate cancer.

If you have been diagnosed with metastatic prostate cancer and your doctor wants to start ADT (androgen deprivation therapy, which shuts off the supply of testosterone and other male hormones), ask about starting abiraterone (Zytiga), as well.

This is the message from the LATITUDE and STAMPEDE clinical trials, two major studies recently published in the New England Journal of Medicine: Giving abiraterone plus low-dose prednisone along with Lupron to “hormone-naïve” men (who are just starting ADT) increased survival significantly – by an average of 18 months, but about 25 percent of men showed an increased survival of four years, and a small percentage of those men have had no progression of cancer for even longer.

Timing may be an important part of the equation. Until this study, abiraterone has been used as a second-line drug, given if ADT stops working, instead of right up front when a man starts ADT. “The evidence suggests that ADT alone may no longer be the standard treatment for men with newly diagnosed metastatic prostate cancer,” says medical oncologist Mario Eisenberger, M.D., the R. Dale Hughes Professor of Oncology and Urology.

But there’s an important caveat, immediately noted by Eisenberger and medical oncologist Michael Carducci, M.D.: “While the survival improvement with the combined ADT and abiraterone approach on these two studies is a major accomplishment, the reports suggest that the vast majority of men on both studies assigned to the ADT-only arm never received abiraterone when their disease became resistant. This raises the question on whether initial ADT plus abiraterone simultaneously is actually superior to ADT followed by abiraterone;” the current standard of care. “We hope that follow-up information can provide more clarity on this important issue.”

The survival benefit shown in these studies combining ADT and abiraterone is very similar to the benefit for men on ADT who take docetaxel (Taxotere); in fact, Eisenberger’s pioneering work on docetaxel several years ago helped that drug become the standard of care for men with castrate-resistant prostate cancer. There are far fewer side effects with abiraterone plus low-dose prednisone than there are with docetaxel. (Prednisone is necessary with abiraterone to help the adrenal gland make sufficient amounts of cortisol.) But abiraterone is very expensive. It costs $9,000 a month; however, a generic form of the drug is expected to come on the market within the next two years.

“The CHAARTED study two years ago, which added chemotherapy (docetaxel) to ADT, and the LATITUDE and STAMPEDE studies strongly support that adding another approach to standard ADT may substantially improve outcomes,” says Carducci. These findings raise many new questions, including: What’s happening in these patients on both abiraterone and ADT? Does the combination delay cancer from mutating and becoming more resistant to treatment? Could some of these men do even better with a third drug – docetaxel – added to the mix? Could new biomarkers help tell which men will respond best?

Because the world of advanced prostate cancer is changing so rapidly, with exciting and complicated advances on so many fronts, “we believe that all men with advanced or metastatic prostate cancer should seek an opinion from a medical oncologist,” says Eisenberger.

Good News for Men with Advanced Prostate Cancer

“The evidence suggests that ADT alone may no longer be the standard treatment for men with newly diagnosed metastatic prostate cancer.”

If you have been diagnosed with metastatic prostate cancer and your doctor wants to start ADT (androgen deprivation therapy, which shuts off the supply of testosterone and other male hormones), ask about starting abiraterone (Zytiga), as well.

This is the message from the LATITUDE and STAMPEDE clinical trials, two major studies recently published in the
Could Bacteria Raise Your Risk of Developing Prostate Cancer?

The urinary tract is not sterile. In fact, it’s full of bacteria, and some of them are linked to the development of chronic inflammation in the prostate.

You’re full of bacteria cells: trillions of them make up your microbiome – distinct ecosystems in and on your body. Some of these bacteria are bad, and cause infections and disease. Other bacteria are good, and help keep us healthy. Until recently, clinicians and scientists believed that one area of the body was bacteria-free: the urinary tract, which they thought was sterile. It turns out, they were wrong. This discovery opens the door to new research into what may cause prostate cancer in some men, and may lead to new ways to prevent it.

Our microbiome changes all the time, depending on such environmental factors as what we eat – for example, the kind of gut bacteria that are supported by a diet of cheeseburgers, chips and sodas are not the same bacteria that thrive when you eat lean meat, fruits and vegetables. Indeed, says Brady scientist Karen Sfanos, Ph.D., “alterations to the healthy microbiome can lead to overgrowth of harmful, pathogenic types of bacteria.” This change is called dysbiosis, and it can lead to the development of chronic inflammation – which, in turn, “is linked to the development of many types of disease, including cancer.”

Even prostate cancer? Maybe so. Thanks to more sophisticated testing methods, scientists can see what they couldn’t see before: bacteria in the urine and urinary tract. “We now know,” says Sfanos, “that there’s a urinary microbiome with its own distinct bacteria” – different from, say, the bacteria that live on your skin or in your gut.

Sfanos and other Brady investigators including pathologist Angelo De Marzo, M.D., Ph.D., have been studying the possibility that chronic inflammation in the prostate sets the stage for the development of prostate cancer. What causes the inflammation? Maybe infection. What causes the infection? Bacteria. “The recent discovery of a urinary microbiome, coupled with the fact that the urinary tract runs through the prostate,” which means that bacteria in the urinary tract might find their way into prostate tissue, “led us to hypothesize that prostate infections that may lead to prostate cancer development may be caused by dysbiosis in the normal urinary microbiome.”

To test this idea, Sfanos and her lab have sequenced the genes of bacteria present in urine samples from a large collection developed by Alan Partin, M.D., Ph.D, the Jakarta Family Director of Urology. “We have profiled the bacterial communities in the urinary microbiome from 129 men” with or without prostate cancer. This is uncharted territory, and among their discoveries is that “the urinary microbiome in men is very different from that which has been previously reported in women.” For example, “we found that the urinary microbiome in men is often enriched with a type of bacteria called Actinobacteria. This is of particular interest because certain types of Actinobacteria have been linked to the development of chronic inflammation in the prostate.”

The team also found low levels of certain bacteria known to cause sexually transmitted infections (STIs) in these men. “This was surprising because the men in these studies did not have symptoms of STIs – indicating that men may carry low levels of these organisms in their urinary tract without knowing it,” says Sfanos.

Ultimately, Sfanos and her team hope to figure out which types of bacteria raise a man’s risk of developing prostate cancer. It may be that “men can be tested for this high-risk urinary microbiome, and then could be treated with specific antibiotics as a way of preventing prostate cancer from developing.” This study was recently published in the Journal of Urology. Other Hopkins investigators who contributed to the study include Eva Shrestha, Ibrahim Kulac, Onur Ertunc, Srinivasan Yegnasubramanian, and Leslie Mangold.

Putting Positive Surgical Margins into Perspective

The words, “positive surgical margins,” are scary to hear – but much of the fear that those words create is unnecessary, says Jonathan Epstein, M.D., the Reinhard Professor of Urologic Pathology.

After radical prostatectomy, when the removed prostate is sent to the pathologist for examination, “it is not uncommon for the margins to be positive – to have tumor at the cut edge, which potentially could indicate that some cancer has been left behind.” However, he adds, “only about half of prostate cancers with positive margins recur after surgery.” This also means that half of men who have positive margins never have a recurrence of cancer.
“The question is, can we help predict which tumors will come back – and which men will benefit from early post-operative radiation therapy – and which positive margins are less likely to cause trouble?” Because Epstein has looked at tens of thousands of prostate specimens in his distinguished career, he knows that the positive surgical margin itself is not as important as some other factors. “Prostates can have separate tumors with different Gleason grades, or there can even be different grades within the same tumor,” he explains. “In the same prostate, there may be a high-grade cancer not at a margin, and a separate low-grade tumor that does go to a margin. Currently, 85 percent of pathologists would report on the overall tumor, saying that it is high-grade and the overall margin status as positive – giving the false impression that there is high-grade tumor at the margin.”

“In the same prostate, there may be a high-grade cancer not at a margin, and a separate low-grade tumor that does go to a margin.” Many pathologists would report on the overall tumor, “giving the false impression that there is high-grade tumor at the margin.”

Based on several small studies that Epstein has led, Hopkins pathologists have long made note of such factors. Since 2010, “we have routinely documented the Gleason score at the margin and length of the positive surgical margin after prostatectomy.” In a current study of 4,082 consecutive patients undergoing radical prostatectomy between 2010 and 2014 at Johns Hopkins, Epstein and colleagues showed that men who had a lower Gleason score at the margin were less likely to have a return of PSA after surgery, and “we conclude that the Gleason score of the cancer at the positive margin site should routinely be documented. This might spare men who have lower-grade cancer at the margin from post-operative radiation therapy.” This work was published in the Journal of Urology.

Helping the Immune System Fight Prostate Cancer

Imagine you’re trying to get across a field, but it’s full of Stonehenge-sized boulders. That’s what’s happening to the body’s frustrated immune soldiers in metastatic prostate cancer.

Prostate cancer makes it tough for the body’s immune system to fight it. One tactic it uses is to put T cells, the body’s enemy-fighting soldiers, to sleep (see story on page 8). Another is to set up barricades to keep these and other immune cells off the battleground.

“A major reason why the body doesn’t do a more successful job of fighting off prostate cancer, especially metastatic castration-resistant prostate cancer, is poor infiltration of immune cells,” says Brady scientist John Isaacs, Ph.D. “This is also a key reason why immunotherapy is not more successful in prostate cancer. We desperately need to find a way to remove this barrier and let the immune cells in.”

Isaacs, with Nathaniel Brennen and Samuel Denmeade, may have found a way to breach this roadblock. First, they identified the culprits here: mesenchymal stem cells (MSCs), immune-suppressing cells made in the bone marrow. “We discovered that prostate cancer recruits these MSCs,” says Isaacs, “which then infiltrate the sites of metastatic cancer and block the activity of many types of immune cells.”

Imagine you’re trying to get across a field, but it’s full of Stonehenge-sized boulders. That’s what’s happening to the body’s frustrated immune soldiers. But Isaacs, Brennen and Denmeade have come up with a cellular “boulder-buster.” They have designed and synthesized a new prodrug that “selectively depletes these immune-suppressive, tumor-infiltrating MSCs.” Based on their preclinical studies, published in Oncotarget, they propose that reducing the sheer number of MSCs “will restore the immune system’s ability to infiltrate sites of prostate cancer and kill cancer cells.”

Even more promising: “We expect the prodrug will have even greater anti-tumor effects when used in combination with other forms of immunotherapy, such as immune checkpoint inhibitors that will wake up the sleeping T cells,” says Isaacs.

The team’s findings may lead to development of a biomarker test, as well: One day, the presence or absence of MSCs “may help distinguish which men need immediate local treatment and which men do not.”

Isaacs, Denmeade, and Brennen: New prodrug is a cellular “boulder-buster” that paves the way for immune cells to reach the tumor. This prodrug may work even better when combined with other forms of immunotherapy.
The Great Promise of PSMA-Targeting Agents

When linked to a radioactive dye, it can show on a PET scan where small bits of cancer are hiding, and when paired with a radiopharmaceutical agent, it can kill those pockets of cancer and potentially even stop metastatic disease.

It’s a tiny version of a heat-seaking missile – except the target locked onto by this particular missile is PSMA (prostate-specific membrane antigen), which sits on the surface of prostate cancer cells. The weapon itself is a small molecule, originally designed as a PSMA-based imaging agent by a team led by Martin Pomper, M.D., Ph.D., and scientists are still discovering what it can do. When linked to a radioactive dye, it can show on a PET scan where small bits of cancer are hiding, and when paired with a radiopharmaceutical agent, it can kill those pockets of cancer and potentially even stop metastatic disease.

“We started working on PSMA-based imaging agents back in the late 1990s,” says Pomper, the Henry N. Wagner, Jr., Professor and Director of the Division of Nuclear Medicine and Molecular Imaging. Pomper’s team was not the first to try to harness PSMA as a way to get to prostate cancer; in 1996, scientists linked an antibody to PSMA and used SPECT imaging to see hidden prostate cancer cells. But success was limited. Antibodies are cumbersome; it takes several days from the time they are administered until they clear the bloodstream and reach the target cells. “We prefer not to use antibodies,” Pomper explains. “We want to be able to scan within an hour or so after injection. We prefer the small molecules for therapy, too, and this is where the field seems to be moving.”

Pomper should know; his versatile small molecule has galvanized the field of nuclear medicine. This molecule and its derivatives have generated huge interest worldwide – especially in Europe, where scientists have linked the small molecule to alpha- and beta-emitting particles and are reporting long-term remissions in some men with metastatic prostate cancer. Think of molecular LEGOS: “You just switch what’s attached to the small molecule, and you can go from imaging to irradiating the cancer – cancer you can’t even see, potentially. This would be impossible using external-beam radiation.”

German scientists, who were able to move right into using PSMA-targeted radiotherapy without the painstaking clinical trials required in the U.S., have even reported cures in a few men – but also some side effects, including the loss of the salivary gland, where some PSMA-bearing cells also live. That’s because, although scientists called it “prostate-specific,” PSMA is not solely confined to prostate cancer. “PSMA is present in the normal prostate, present in the brain, the kidney and the intestines,” Pomper notes, “but it’s really expressed much higher in malignant prostate tissue. It’s also expressed in the neovasculature – the vessels tumors need in order to grow in place or metastasize.”

PSMA is present in many different cancers, too. “Renal cell carcinoma, glioblastoma, pancreas cancer and other cancers have PSMA in the blood vessels around them – not in the tumor itself,” and this is an exciting potential avenue for future research: finding a way to target and kill PSMA-bearing areas around some terrible cancers that desperately need effective treatment.

Pomper keeps tinkering with the molecule and agents that link to it. Recent work with colleagues in Radiology and Radiation Oncology has led to the first published small-molecule alpha-particle emitting agent to treat prostate cancer. “Alpha particles are emitted from certain molecules as a consequence of radioactive decay,” he explains. “They are useful for treating cancer because they provide a lethal punch to the DNA of malignant cells – more so than other forms of radiation. The key is to enable the alpha emitter to reach the cancer cells selectively, leaving normal tissues unharmed.”

A team led by radiation oncologist Ana Kiess, M.D., Ph.D., linked an alpha-particle emitter to Pomper’s small molecule. “Using this agent, we were able to prolong the lives of immunocompromised mice bearing human prostate tumors,” says Pomper. This study lays the groundwork for future clinical trials in men with prostate cancer, and for the design of even safer, next-generation alpha particle agents. Also, it “represents a pivot by our group from developing imaging agents to finding better agents for therapy.” In a few months, the group will be leading a phase I clinical trial for beta particle-emitting agents it has developed.

This work was published in the Journal of Nuclear Medicine and won the Editor’s Choice Award. In recognition of his research on PSMA-targeting agents, Pomper also has received the Paul C. Aebersold Award for 2017 from the Society of Nuclear Medicine for “outstanding achievement in basic science applied to nuclear medicine.”
A “Liquid Biopsy” for Advanced Prostate Cancer

“How do bloodhounds follow a trail through the woods? Their noses are particularly good at picking up molecules of scent in the air. Something similar happens with cancer cells in the blood.

Wouldn’t it be nice to know what’s happening in the prostate, or in a metastatic tumor, without having to do a biopsy? It may be that everything doctors need to know is already in the bloodstream. Brady scientist Paula Hurley, Ph.D., and colleagues are working hard to learn how to decipher the clues: minuscule pieces of DNA, left behind in the blood by cancer cells.

How do bloodhounds follow a trail through the woods? Their noses are particularly good at picking up molecules of scent in the air. Something similar happens with cancer cells. “All cells, including cancer cells, shed tiny pieces of DNA in the blood,” explains Hurley. These small pieces of DNA, called cell-free DNA, can be traced and deciphered. One immediate benefit from this glimpse at a man’s cancer would be to guide his treatment – and avoid treatment that isn’t going to work. In advanced cancer, for example, mutations in the androgen receptor can tell doctors that a man may have developed resistance to the drugs abiraterone and enzalutamide, and that a different form of treatment might be more successful. Another benefit: “Compared to a traditional biopsy of the cancer, a ‘liquid biopsy’ that detects cancer-specific mutations in the blood is less invasive, easier to perform, and much kinder to the patient for follow-up monitoring,” Hurley notes. “It is also much better at capturing differences in cancer cells between cancer sites.”

With support from the Patrick C. Walsh Prostate Cancer Research Fund and the Department of Defense, Hurley and colleagues are working on improving the sensitivity and specificity of detecting cancer-specific mutations in the blood. Their latest findings were published in Oncotarget.

“You’re Not Going to Die From This.”

Chad Odom knew he was at a higher risk for prostate cancer because his dad had it at age 60. But he never expected to be diagnosed with it at age 46. In fact, he put off getting a biopsy.

Odom got his first PSA at age 45, and it was 4.4 – much higher than it should be. (Brady researchers have established that a PSA for a man in his forties should be 0.6.) His urologist said, ‘Yep, we need to do a biopsy right now,’” Odom recalls. “It was not what I wanted to hear, of course. So I went to another urologist” in his hometown of Greenville, S.C. “He did a percent-free PSA test and said, ‘You’ve only got between a 5- and 10-percent chance of having prostate cancer. Let’s wait two or three months and do another test.’ I said, ‘Yeah, let’s wait.’ Then we did a biopsy and I had cancer – but luckily, it was caught very early.

“As soon as I found out I had it, I called Dr. Walsh, because my dad read Dr. Walsh’s book 14 years ago,” when he was diagnosed with prostate cancer.

“As soon as I found out I had it, I called Dr. Walsh, because my dad read Dr. Walsh’s book 14 years ago,” when he was diagnosed with prostate cancer.

Odom, an entrepreneur whose company, Encore Container, produces, refurbishes and recycles plastic containers for industrial use and is one of South Carolina’s fastest-growing companies, wanted to give back. Three months after his surgery, Odom made a generous donation to the Prostate Cancer Discovery Fund, which supports many research projects and areas of need related to prostate cancer across the Brady. “The care from beginning to end at Johns Hopkins really was incredible,” for which he is grateful.

But he is also thinking of the future: he wants to help find a cure. Odom has two children, a daughter and a son. The family history worries him. His son is at a higher risk to have prostate cancer, and because William Isaacs, Ph.D., the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology, and other Brady scientists have shown that the prostate cancer risk can be passed from either the mother or father, his daughter’s sons may be at higher risk, as well. In December 2016, Odom made a generous five-year pledge to the Brady to support the research of Isaacs and Ken Pienta, M.D., the Donald S. Coffey Professor of Urology. (Pienta’s work is featured in our cover story.)

Back home in South Carolina, Odom is trying to raise awareness about prostate cancer. “I tell everybody I know,” he says. “Have you had your PSA checked? Have a physical. Get that blood work done. It’s worth it.”
Read About the Research You have Helped Make Possible.

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

We are funding the cure. Since its inception in 2005, the Patrick C. Walsh Prostate Cancer Research Fund has awarded millions of dollars to Johns Hopkins scientists in every discipline with good ideas worth pursuing that can help us understand more about prostate cancer — to help us save lives, to find better ways to treat it at every stage, and even to help prevent it. Applications are reviewed by a Scientific Advisory Board composed of noted Hopkins scientists and lay members. These awards wouldn’t have been possible without the tremendous and amazing generosity of our patients and friends. On these pages you’ll find some of the exciting work this year’s award winners are doing to make life better for men with prostate cancer and their families.

2017 Awardees

Angelo De Marzo, M.D., Ph.D.
The Carolyn and Bill Stutt Scholar
Departments of Pathology, Urology, and Oncology

Michael Gorin, M.D.
The R. Christian B. Evensen Scholar
Departments of Urology, Oncology, and Radiology

Michael H. Johnson, M.D.
The Virginia and Warren Schwerin Scholar,
Departments of Urology and Oncology

Peter Searson, Ph.D.
The Irene and Bernard L. Schwartz Scholar,
The Johns Hopkins Whiting School of Engineering, and the
Department of Oncology

Dan Stoianovici, Ph.D.
The Dr. and Mrs. Peter S. Bing Scholar
Departments of Urology, Mechanical Engineering, Neurosurgery, and Oncology

Sharon Gerecht, Ph.D.
The Beth W. and A. Ross Myers Scholar
Department of Chemical and Biomolecular Engineering

Paula J. Hurley, Ph.D.
The Phyllis and Brian L. Harvey Scholar
Department of Urology, Mechanical Engineering, Neurosurgery, and Oncology

Jun Luo, Ph.D.
The Nancy and Jim O’Neal Scholar
Department of Urology

Daniel Y. Song, M.D.
The Thomas C. Quirt and Jack W. Shay Scholar,
Departments of Urology, Oncology, Radiation Oncology and
Molecular Radiation Sciences

Using Robotics to Improve Prostate Biopsy

“We believe that the use of the robot can potentially improve the accuracy of prostate biopsies and detect prostate cancer better than a freehand biopsy.”

In the U.S. alone, about one million prostate biopsies are performed every year. If each biopsy takes at least a dozen cores of tissue, that’s an awful lot of needle sticks – especially for men who are getting a repeat biopsy.

Most of those biopsies are done freehand with transrectal ultrasound (TRUS) guidance – and there is room for improvement.

Previously, in an effort to make prostate biopsy more accurate, the Brady’s own master mechanical engineer, Dan Stoianovici, Ph.D., director of the Urology Robotics Program, designed and developed a novel robot to hold and move the ultrasound probe accurately and to track the exact location of the ultrasound target. Misop Han, M.D., the David Hall McConnell Professor in Urology, collaborated with Stoianovici to test the device during prostate biopsy in five men.

“We found that the TRUS Robot could handle the ultrasound probe well, with no complications,” says Han. With newly developed software, they were able to reconstruct the 3-D image of the prostate and the biopsy cores within it.

“We proved that 3-D, image-guided robotic biopsy is both feasible and safe,” Han adds. “We believe that the use of the TRUS Robot can potentially improve the accuracy of prostate biopsies and detect prostate cancer better than a freehand biopsy.”

Now, with funding from the Patrick C. Walsh Prostate Cancer Research Fund, Stoianovici is building on this success. He has developed a novel ultrasound probe for imaging the prostate and guiding needle biopsies. “The probe combines imaging and robotic components,” says Stoianovici. “It is an entirely novel concept that offers fundamentally accurate ultrasound-guided needle targeting independent of the physician’s skill.”

The versatile device’s potential applications include “transrectal or transperineal access, systematic or fusion biopsy, and needle-based focal ablations.”

The pair will be bringing the probe to its first clinical trial for safety and feasibility.


Precision Treatment in Men with CRPC

Precision detection would “focus on a patient’s individual variant androgen receptor burden.”

Previously in Discovery, we reported an important breakthrough in understanding why two second-line hormonal therapy drugs for metastatic castration-resistant prostate cancer (CRPC) don’t help some men. The drugs, enzalutamide (Xtandi) and abiraterone (Zytiga) are very expensive, and if they are not going to work, men can save thousands of dollars a month – and better yet, try something different that may prove more successful. Both drugs target the androgen receptor, but like a key trying to fit the wrong lock, the drugs fail to work in men who develop a mutated androgen receptor. Brady scientists Jun Luo, Ph.D., and Emmanuel Antonarakis, M.D., not only discovered this variant receptor, called AR-V7; they developed a blood test for it.

Now, they would like to refine their test even further to offer “precision detection,” says Luo, “to focus on a patient’s individual variant androgen receptor burden.” To do this, in tissue studies conducted by Brady pathologist Angelo De Marzo, M.D., Ph.D., they are using a novel RNA in situ hybridization (RISH) method they developed “to visualize AR-V7, achieving a resolution of a single splice junction.” Basically, this means that they can look for variant receptors on the molecular level – one molecule at a time – “to determine a patient’s overall variant androgen receptor burden beyond AR-V7.” A study using their new technology was recently published in European Urology. Postdoctoral fellow Yezi Zhu, Ph.D., is a co-investigator on this project.

Long-Distance Cancer Care

All men with prostate cancer don’t have access to good medical care. In fact, men in rural areas and in remote parts of the world don’t have ready access to medical care at all. But just about everybody has a cell phone, and most of us have access to a computer and the internet. Is there a way to tap into the technology we have to provide the care some of us don’t have?

Urologist Michael Johnson, M.D., believes the answer is yes – and that remote clinical care can provide Hopkins medicine to men who aren’t able to come to Baltimore. “For many men with prostate cancer, where you live determines your cancer care. My goal is to find a way for digital and internet-based technologies to overcome this barrier and allow men worldwide to have access to the expertise at Hopkins.”

Just about everybody has a cell phone, and most of us have access to a computer and the internet. Is there a way to tap into the technology we have to provide the care some of us don’t have?

To do this, Johnson is using telemedicine to provide “remote clinical visits.” He is also designing an app for smart phones that will allow men to track their progress after radical prostatectomy “and make sure they are recovering as expected.”

Why Do Some Men Do Better With Immunotherapy?

Some men with widely metastatic prostate cancer have had spectacular results on immunotherapy drugs like pembrolizumab. Other men – whose scans show very similar metastases, whose Gleason and PSA numbers are the same – aren’t helped much at all.

Why is it that some men’s immune systems can be whipped up into a frenzy and can attack metastatic cancer, causing it to melt away? The secret doesn’t lie in what pathologists can see in prostate tissue or a lab test. It’s much smaller than that: it’s in the genes. Specifically, it’s on the number of mutations a cancer has, or its “mutational burden.”

Why is it that some men’s immune systems can be whipped up into a frenzy and can attack metastatic cancer, causing it to melt away?

This means, basically, that the cancer has so much baggage – think of a whale, with barnacles all over it – that it looks different enough to cause the immune system to take notice. All the immune system needs, in this case, is a little kick-start – the immunotherapy drug – and it’s ready for battle. “Hypermutation is thought to be caused by inactivation of DNA mismatch repair genes – genes like MSH2,” explains Brady scientist Paula Hurley, Ph.D. “It’s the normal job of these genes to fix damaged DNA.”

“We hypothesize that some men with metastatic castration resistant prostate cancer (CRPC) have resistance to anti-androgen drugs – enzalutamide and abiraterone – because they have many mutations,” says Hurley. Now she wants to prove it. With co-investigator Brian Simons, D.V.M., Ph.D., she will be looking at the genes of men with metastatic CRPC before they start on androgen receptor drugs and later, if their cancer stops responding to these drugs.

“These studies will provide critical information on how mutational burden leads to resistance to androgen receptor drugs, and will help determine who might respond well to immunotherapy.”

Prostate Cancer Research Fund
Can PSMA PET Help Determine Which Men Have Significant Prostate Cancer that Needs to be Treated?

Earlier in this issue (see Pages 3 and 14), we’ve talked about Martin Pomper’s PSMA-targeting small molecule, and how well it can show otherwise hidden metastatic cancer on a PET scan. Can it be used even earlier – at the time of diagnosis – to help determine which men have clinically significant, high-grade tumors?

There is a critical need for such discernment, says urologist Michael Gorin, M.D., because PSA is often not that helpful. “A major shortcoming of the PSA test is that it is not specific for detecting clinically significant, high-grade tumors, leading to overdiagnosis of low-grade or indolent prostate cancer that probably doesn’t even need to be treated.”

It would be nice to have more insight before prostate biopsy – so men who probably have indolent cancer wouldn’t have to have needles stuck in their prostate. “PSMA is expressed by prostate cancer cells, and the degree of expression directly correlates with prostate cancer grade and stage.” To this end, Gorin is testing how well PSMA-targeted PET/CT scanning works before biopsy in men who are being screened for prostate cancer.

A Better Model for Aggressive Prostate Cancer

This project is dedicated to the nearly 30,000 American men who die each year of prostate cancer. “While great progress has been made, there is a pressing need to develop better treatment,” explains pathologist Angelo De Marzo, M.D., Ph.D. “Sadly, about 95 percent of new cancer drugs fail in clinical trials – sometimes after investments of more than a billion dollars.” A major contributing factor to this high failure rate is “a lack of animal models in which new drugs and drug combinations can be tested.”

About 95 percent of new cancer drugs fail in clinical trials – sometimes after investments of more than a billion dollars. A major reason why is a lack of good animal models.

With Charles Bieberich, Ph.D., of the University of Maryland–Baltimore County, whose lab has expertise in genetic engineering of mice, De Marzo is developing a better animal model. “Human cancers arise due to the accumulation of mutations in DNA, and we can now easily make the same mutations happen in the DNA of mice,” says De Marzo. “This has allowed Dr. Bieberich’s laboratory to engineer a state-of-the-art mouse model of human prostate cancer – giving us, for the first time, a powerful platform to test new drugs.” However, there’s more to do: “We are learning that mice often don’t metabolize drugs the same way that humans do.” Another drawback to mice is that they are really small, which “makes it difficult to test new ways of imaging growing prostate cancers.”

With this Patrick C. Walsh award, De Marzo and Bieberich will “leverage our experience with mice to develop a state-of-the-art rat model of human prostate cancer.” Rats tend to metabolize drugs in much the same way that humans do, and their prostates are nearly ten times bigger than those of mice. “When this work is completed, we will have developed a powerful new tool in the fight against prostate cancer: a next-generation animal model in which the safety and effectiveness of new drugs and imaging methods can be carefully tested.”
Helping Men Recover After Radical Prostatectomy

Brady surgeons know that for many of their radical prostatectomy patients, recovery can take weeks to months. They also know that some things, such as exercising and maintaining a healthy lifestyle, can help men recover faster and do better. But after the men leave the hospital, they don’t always report back in a regular or detailed way. Here’s where Peter Searson, Ph.D., an engineer with the Johns Hopkins Whiting School of Engineering, may be able to use technology to help make life better for these men and their partners.

“Exercise is known to improve the health and well-being of prostate cancer patients,” Searson explains. With funding from the Patrick C. Walsh Prostate Cancer Research Fund, he aims to use remote monitoring technologies to track the physical activity and weight of men after radical prostatectomy. He also wants to find out “whether men who receive personalized feedback of their physical activity levels and weight are more likely to stick to exercise and dietary programs, and whether they have improved quality of life.”

Making Radiation More Effective: Breaking Cancer’s DNA

For men with localized but aggressive prostate cancer, combining radiation and androgen deprivation therapy (ADT) has been shown to make a big improvement in survival. This treatment is effective,” explains radiation oncologist Daniel Song, M.D., because of a double-whammy effect: “radiation breaks the cancer cell’s DNA, which can kill it, while hormones starve the cancer of its need for testosterone.”

Breaking the DNA strand makes the whole tumor more sensitive to radiation.

Another benefit of breaking the DNA strand: it makes the whole tumor more sensitive to radiation. “We have found that flutamide, a well-established drug that treats prostate cancer, can also produce DNA strand breaks,” Song continues. With co-principal investigators Srinivasan Vegnasubramanian, M.D., Ph.D., and Theodore DeWeese, M.D., Ph.D., “our strategy is to confirm these findings in men who have chosen to receive testosterone suppression and prostate brachytherapy, or seed implant. In this project, men will be given a dose of flutamide before the procedure, and while they are already anesthetized for brachytherapy, they will undergo a prostate biopsy. “We will examine the biopsies to check for DNA strand breaks induced by flutamide, and if they are positive, we will move this work into a clinical trial for men with localized, aggressive prostate cancer.” Co-investigators are pathologists Angelo De Marzo, M.D., Ph.D., and Michael Haffner, M.D., and Jonathan Coulter, Ph.D., from the Department of Radiation Oncology.

A New Way to Study Prostate Cancer Cells in Real Time

It turns out that prostate cancer cells don’t need much oxygen; in fact, they thrive in a low-oxygen environment. Scientists have much to learn about what goes on in this weird environment of hypoxia, because it’s hard to study. Now, thanks to Sharon Gerecht, Ph.D., from the Johns Hopkins Department of Chemical and Biomolecular Engineering, scientists can study oxygen-starved tumor cells in real time.

“Rapid growth and proliferation of tumor cells depletes nearby oxygen concentrations,” Gerecht explains. “This hypoxia, in turn, alters cancer cells’ behavior,” making them move faster, more likely to invade other tissue – and also less sensitive to drugs. “In fact, many studies indicate that hypoxia is a major driver of metastasis – which suggests that drugs to target metastasis must be developed in the context of hypoxia.”

Gerecht developed “novel, hypoxia-inducible hydrogels,” which allow scientists to watch how prostate cancer cells respond in an oxygen-starved environment. Using these hydrogels, “we will measure characteristics of prostate cancer motility and invasion and response to therapeutics.” They will watch how these cancer cells interact with immune cells – which may lead to better ways to make immunotherapy more effective. “We will also use an inhibitor of metastasis, identified by our group in sarcoma, in combination with current prostate cancer therapies to block metastasis in hypoxia. We hope our work will contribute to the understanding of prostate cancer biology and potentially identify new strategies for treatment.”
Immunotherapy in Bladder Cancer: Encouraging Results Prompt FDA Approval

The study didn’t just show the drug was safe; it significantly shrunk the tumors in some patients – particularly, in those with high PD-L1-expressing tumors.

Results from a Brady-led study, just published in *JAMA Oncology*, offer new hope to people with advanced bladder cancer. The results of this international phase 1 clinical study were so promising, in fact, that they prompted the FDA to approve the drug, called durvalumab.

Durvalumab is a “checkpoint inhibitor.” Checkpoints are tiny molecules that affect T cells, the immune system’s mighty soldiers. These checkpoints act as blindfolds that prevent the T cells from recognizing and attacking cancer cells. Checkpoint inhibitors are a new class of immunotherapy drugs that remove the blindfold and unleash the T cells. As we’ve discussed elsewhere in *Discovery*, immunotherapy doesn’t help everyone with advanced cancer – but when it works, it can achieve spectacular results.

There are several different checkpoints. One of them is called PD-1, and it binds to a second molecule, called PD-L1, to make sure the T cell is well and truly restrained – handcuffs to go along with the blindfold.

“Our goal was to establish the clinical benefit of durvalumab as a second-line therapy for locally advanced or metastatic urothelial carcinoma,” the most common type of bladder cancer, says Noah Hahn, M.D., director of the Brady’s Medical Oncology Bladder Cancer Program and the study’s senior author. But the study didn’t just show the drug was safe; it significantly shrunk the tumors in some patients – particularly, in those with high PD-L1-expressing tumors. In other words, these patients just happened to have the right target for this particular drug.

Other drugs that attack different checkpoints are under development; each may help a different subset of patients. “This is precision medicine,” says Hahn. Instead of a cookie-cutter approach, where all patients get chemotherapy and some of them are helped, “our goal is to get the right drug to the right patients, in whom it has a very high chance of success.”

There were 191 patients from nine countries in the study. Most were men, and the average age was 67. All but one had undergone previous chemotherapy with platinum drugs, without success. The objective response rate – the proportion of patients whose cancer shrank with the drug – was 18 percent among all patients, and 28 percent in those patients with the high PD-L1-expressing tumors.

But the news is even more exciting: “Among the subset of patients who responded to therapy, 77 percent had an ongoing response at the time the data was analyzed,” says Hahn. Side effects were rare, and only 2 percent had to discontinue treatment. “The average overall survival of more than 18 months among all patients represents the longest overall survival result among PD-1 or PD-L1-targeting immunotherapies tested so far in metastatic bladder cancer patients,” says Hahn. Based on these encouraging initial results, durvalumab received FDA approval in May 2017.

“Results of this and other PD-1/PD-L1 immunotherapy studies have solidified immunotherapy as a standard of care for advanced bladder cancer patients,” says Hahn. Building on this success, Hahn, urologist Trinity Bivalacqua, M.D., Ph.D., and other Hopkins investigators are leading studies examining the potential benefit of PD-1/PD-L1 immunotherapies given much earlier: as neoadjuvant therapy before surgery in muscle-invasive bladder cancer patients, and given in combination with radiation or intravesical BCG in patients with BCG-relapsing non-muscle invasive bladder cancer.
Bladder Cancer: Precision Diagnosis is Critical

Why the “one size fits all” approach to treating advanced disease doesn’t work: at the genetic level, each person’s cancer is different.

There probably won’t ever be just one wonder drug to help every person with advanced bladder cancer. That’s because – even if they have the same symptoms, same stage of cancer, and even the same course of disease – at the genetic level, they’re different. So if you have advanced bladder cancer and you’re sitting in a waiting room with several other people in the same boat, the drug that helps you might not help the guy sitting right beside you. But it probably will help some with your same subtype of cancer.

How do you know your subtype? From a tissue biopsy, ideally of metastatic cancer, which may have acquired different gene mutations from those seen in the primary tumor.

Scientists now know that there are 28 different genetic forms of prostate cancer, 11 different genetic forms of breast cancer, and at least five different genetic forms of bladder cancer. This is why, as we’ve discussed elsewhere in Discovery, the “one size fits all” approach to treating advanced cancer doesn’t work. It’s why scientists David McConkey, Ph.D., Director of the Johns Hopkins Greenberg Bladder Cancer Institute, and Woonyoung Choi, Ph.D., are working so hard toward precision diagnosis and treatment – starting with identifying the molecular subtypes of bladder cancer. They recently published their findings in European Urology.

“Because they are highly heterogeneous, bladder cancers are associated with unpredictable patterns of spread and responses to treatment,” McConkey explains, “but with next-generation DNA and RNA sequencing technology, we can actually see this heterogeneity at high resolution.” McConkey, Choi and others previously reported that bladder cancers can be grouped into RNA-based molecular subtypes that are “surprisingly similar” to the subtypes found in breast cancer. “What we did not know was whether the subtypes of bladder cancer were also associated with specific DNA mutation patterns – which could explain and predict someone’s sensitivity to conventional treatment, as well as gene-targeted drugs or immunotherapy.”

To address this question, McConkey and Choi led a collaborative project to characterize the DNA mutations and other DNA-based alterations in a large public data set. “Investigators from the University of North Carolina and Lund, Sweden, worked with us to assign the tumors to intrinsic molecular subtypes,” and then Choi characterized the DNA mutation patterns within them. The results confirmed that specific DNA mutation patterns indeed were associated with each subtype, and that these patterns could be used to increase the number of significant molecular subtypes beyond what was visible using RNA expression patterns alone.

“These results have immediate implications for using the molecular subtypes to guide our bladder cancer patients to precision treatment options,” says McConkey. “They also provide a new starting point for future laboratory studies aimed at identifying the specific genetic defects associated with these cancers.”

A “Liquid Biopsy” for Bladder Cancer

“These findings have the potential to help identify patients with clinically hidden disease who may benefit from additional therapy, and to help avoid overtreating those with no evidence of residual disease.”

Bladder cancer desperately needs its own version of the PSA test – a test that could answer questions like, “How aggressive is my cancer?” and “Is my treatment working?” or “Which treatment is right for me?”

Urology resident Heather Chalfin, M.D., believes the answer may lie in smarter reading of circulating tumor cells (CTCs), cancer cells that have made their way to the bloodstream. She has made important discoveries about CTCs in prostate cancer, as well (see story on Page 3) – insights that may be practice-changing. In both diseases, she has found that scientists could be looking at the wrong things.

“Bladder cancer circulating tumor cells (CTCs) have largely been studied with methods that rely on the epithelial marker, EpCAM, such as the CellSearch test,” she explains. Epithelial cells are in the membranous lining of tissue. “There have been many conflicting reports.”

But there are different CTCs, called EpCAM-negative, or epithelial-marker-negative CTCs, and “they have not been studied,” Chalfin continues, and these might prove to be much more helpful to scientists hoping to understand the state of someone’s bladder cancer.

Looking at these EpCAM-negative CTCs in blood samples from Hopkins bladder cancer patients with a novel detection assay called RareCyte, “we were able to show that CTCs are present at all bladder cancer stage groups,” says Chalfin. Better yet, “they exhibit phenotypic diversity for cell size and epithelial marker expression.” Which means that these cells could provide a window – the long-sought “liquid biopsy” – into bladder cancer.

With the old CTC test, “no CTCs would have been detected in non-muscle invasive patients in our study. But with the novel method, we found EpCAM-negative CTCs. These findings have the potential to help identify patients with clinically hidden disease who may benefit from additional therapy, and to help avoid overtreating those with no evidence of residual disease.”

Even better: “We have the capability to pick out and isolate individual stained CTCs and will be performing copy number
variation analysis and single-cell sequencing on these CTCs,” which means that they can look for mutated genes that might be targets for precision drugs.

“Also, in ongoing collaboration with the Greenberg Bladder Cancer Institute, we will be comparing CTC count with several other ‘liquid biopsy’ tests such as plasma-free tumor DNA as well as the MD Anderson molecular subtype, in an effort to identify the best options to personalize therapy for our patients.”

DISCOVERY IN KIDNEY CANCER

Brady Urologists Shape National Guidelines for Kidney Cancer

The new guidelines reflect the personalized approach to localized kidney cancer pioneered at the Brady.

The American Urological Association (AUA)’s guidelines for how to treat localized kidney cancer have changed – in large part due to the work of two Brady faculty members, Mohamad Allaf, M.D., and Phillip Pierorazio, M.D.

Last year, Allaf and Pierorazio led an eight-person team of Hopkins investigators, including Michael Johnson, M.D., and Hiten Patel, M.D., M.P.H., to create recommendations for the treatment of this disease, based on the existing literature and data – including important findings from the DISSRM study (see story on this page). This report served as the bedrock for the AUA’s new guidelines, “Renal Mass and Localized Renal Cancer.”

The AUA Guidelines are available online (www.auanet.org/guidelines/renal-mass-and-localized-renal-cancer-new-(2017)) and are summarized in the Journal of Urology.

“I am extremely proud of the role the Brady played in the development of these guidelines,” Allaf continues. “Not only do they reflect rigorous, evidence-based practices that are useful for patients and any practicing urologist; they reflect how we approach the management of renal masses at the Brady. We treat all of our patients as individuals and work with them to make the best choices together.”

Hopkins-Led Study Proves Active Surveillance is Safe for Small Kidney Tumors

Since 2009, Brady urologist Phillip Pierorazio, M.D., has run the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry, following patients with small, localized kidney tumors (stage T1a, 4 cm or smaller), who choose either active surveillance or immediate surgery. DISSRM is one of the world’s largest active surveillance programs for patients with solid, small renal masses. The registry follows the outcomes of 350 patients on active surveillance and 300 patients who have received treatment.

“Most tumors on active surveillance grow slowly, about 1mm per year, and no patient in active surveillance has had a kidney cancer spread or has died of kidney cancer.”

Kidney cancer can be fatal if it escapes the kidney, but surgical cure rates for kidney-confined tumors are excellent – about 95 percent. And yet, says Pierorazio, “More than 30 percent of small kidney tumors are benign lesions, not cancer. Of the 70 percent left, most are low-grade, indolent tumors that aren’t ever going to cause a problem. That only leaves about 5 percent that are potentially aggressive.”

Many people, then, who have small renal masses can safely avoid surgery, and the DISSRM results are bearing this out.

“Our data are finally starting to mature,” says Pierorazio. The study is designed to be fully mature when patients have been followed for five years.
So far, one quarter of patients have been followed for five years and the average follow-up is approaching three years. At a recent American Society for Clinical Oncology meeting, medical student Ridwan Alam presented the most up-to-date outcomes from DISSRM. “Most tumors on active surveillance grow slowly,” states Alam, “about 1mm per year, and no patient in active surveillance has had a kidney cancer spread or has died of kidney cancer.”

Additional findings presented at the American Urological Association (AUA)’s Annual Meeting in Boston indicated that overall tumor size, and not necessarily growth rate, may be the best indicator that a patient should discontinue active surveillance and undergo treatment.

“Because of this program,” says Mohamad Allaf, M.D., Director of Kidney Cancer at the Brady, “active surveillance is gaining recognition around the world. This is reflected in the updated AUA Guidelines (see story on Page 22) and the expanded role for active surveillance in the management of small renal masses – much of which can be attributed directly to data from DISSRM.”

Many Small Kidney Tumors Don’t Need to be Treated

Brady researchers found that each year, between 17,935 and 24,821 Americans with low-risk tumors undergo kidney surgery that they probably don’t need.

Forty years ago, about 30,000 Americans were diagnosed every year with kidney cancer. Today, that number is 60,000. Is it an epidemic? No, it’s the increasing use of CT scans for other problems.

“More and more kidney masses are discovered by chance,” notes Alice Semerjian, M.D., the Warburton-Jewett Urologic Oncology Fellow. “Most of these are localized and considered to be small renal masses, measuring less than 4 centimeters.” The standard management of kidney masses is surgical removal, but in recent years – in a shift led by Brady researchers – many people with small renal masses are choosing active surveillance instead.

Which tumors can safely be followed? In a study led by Semerjian, Brady investigators systematically reviewed the kidney cancer literature, identified six high-quality studies that described tumor pathology by size and combined these studies with data from the Johns Hopkins Renal Mass Database. “Low-risk tumors were defined as benign or low-grade cancers confined to the kidney,” Semerjian explains, “tumors that are believed not to grow or metastasize during a patient’s lifetime.”

The study showed that the vast majority – greater than 90 percent of tumors 2cm or smaller, and 80 percent of tumors smaller than 4 cm – of small renal masses are low-risk. Using U.S. population-based data, Semerjian and colleagues estimated between 17,935 and 24,821 patients each year undergo kidney surgery for a low-risk tumor – surgery that they probably don’t need. These findings were presented at the American Urological Association’s Annual Meeting in Boston.

“We know that most small renal masses are not dangerous,” says the study’s senior author, Phillip Pierorazio, M.D. “This study certainly puts into perspective the number of patients undergoing potentially unnecessary surgery and highlights the role of active surveillance in the initial management of many patients with small renal masses.”

But not all small tumors are safe, Pierorazio adds: “Some small renal masses can be dangerous, and this study highlights the need for better diagnostics – including blood, urine and imaging tests – to inform patients and providers about the risks associated with their mass.”

DISCOVERY IN PENILE CANCER

A Molecular Marker for Aggressive Penile Cancer

“It is possible that new drugs could be developed targeting this molecular marker that improve the treatment and survival outcomes in these patients.”

Penile cancer is a very challenging disease to treat and cure,” notes neurourologist Arthur Burnett, M.D., the Patrick C. Walsh Professor in Urology, “especially when it is not diagnosed early.” Making treatment even more challenging is uncertainty: not knowing “which clinical presentation carries the threat to progress, even when aggressive treatment is provided.”

Burnett, with Mark Ball, M.D., one of the Brady’s graduating chief residents in 2016, and pathologist George Netto, M.D., has been working to change this, by searching for novel molecular markers that could help guide treatment and predict the course of the disease.

The team investigated insulin-like growth factor-1 receptor expression in penile cancer, and “found that it is expressed in nearly two-thirds of men with penile cancer,” says Burnett. The presence of this receptor also correlates with lethal disease. This work, published in Urology, involved an analysis of tissue specimens collected in the pathology registry at Hopkins from 1985 to 2013.

“Our findings suggest the possible usefulness of identifying this molecular marker in men with penile cancer for counseling them about their risks of disease progression,” says Burnett. “In addition, it is possible that new drugs could be developed targeting this molecular marker that improve the treatment and survival outcomes in these patients.”
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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.

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