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A REVOLUTION IN SURGERY

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"An Incredibly Hopeful Year"

This may be our most exciting issue yet. Our cover story takes you inside SLICE, our state-of-the-art Surgical Learning and Innovation Center of Excellence, with the Patrick C. Walsh Discovery and Learning Laboratory serving as a main feature. Ahmed Ghazi's patented, custom-designed surgical models are revolutionizing the practice and performance of complex cases, as well as the training of surgeons and residents. Then, on page 2, I highlight how our Brady surgeons are performing not just minimally invasive surgery, but noninvasive surgery. We are not just using scalpels, but ablation-guided interventions: zapping, freezing, and steaming cancerous tissue – even kidney tumors!

We have good news for patients at every stage of prostate cancer, from active surveillance (proof for the first time that diet can slow the growth of cancer; page 8) to radiation therapy (a new approach to protect the rectum; page 9) to metastatic cancer treatment (for some patients, gene-targeted drugs are killing the cancer without the need for hormonal therapy; page 5). We also celebrate the amazing career of world-renowned molecular geneticist William Isaacs (page 4), who is retiring after more than three decades at the Brady.

We are so proud of our Schaufeld Program for Prostate Cancer in Black Men (page 6) – particularly our Schaufeld Scholars. We're also proud of the fine scientists, such as Karen Sfanos (page 12), who have received seed money from the Patrick C. Walsh Prostate Cancer Research Fund, and gone on to produce field-changing research.

Finally, findings by Jeannie Hoffman-Censits and colleagues, in a study published in the *New England Journal of Medicine*, have led to FDA approval for a new treatment combination for bladder cancer. Doctors and scientists at our Greenberg Bladder Cancer Institute are offering new hope to patients at all stages of bladder cancer (page 17). As Dr. Hoffman-Censits puts it: For patients with locally advanced and metastatic urothelial cancer of the bladder and upper tracts, "2024 has been an uncommon and incredibly hopeful year."

Hope abounds at the Brady, and I am proud to show you some of the many things we are doing in this issue of *Discovery*.

Mohamad E. Allaf

Mohamad E. Allaf, M.D.
Jakurski Family Director
The James Buchanan Brady Urological Institute
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COVER STORY

A REVOLUTION IN SURGERY

A transformation in how surgeons learn, practice, develop and refine procedures is happening, and its epicenter is the Patrick C. Walsh Discovery and Learning Laboratory, part of the new Surgical Learning and Innovation Center of Excellence (SLICE).

"Patrick Walsh transformed a major operation in urology and revolutionized the treatment of prostate cancer," says *Jakurski Family Director* of the Brady, Mohamad "Mo" Allaf, M.D. "He worked tirelessly on discovery – finding ways to control dangerous bleeding, uncovering significant, previously unseen and unknown nerve structures that are critical for erection, and preserving the sphincter responsible for urinary control – and then refining his operation over the next decades. **This laboratory, named in Dr. Walsh's honor, is the new home of transformative surgical innovation and learning at the Brady.** Here, as part of SLICE, we will incubate future discovery, nurture urologic surgeons-in-training, and help experienced surgeons learn new procedures and techniques."

SLICE is the brainchild of Ahmed Ghazi, M.D., Director of Minimally Invasive and Robotic Surgery at the Brady. The seeds were planted years ago, during his surgical training in laparoscopy and robotic surgery. It struck him at the time that "there was no ideal way to train a surgeon. We were training on the go – basically, building the plane as we flew."

Wouldn't it be better, he thought, if new surgeons could develop proficiency in procedures *before* they performed them on patients? Ghazi explored this idea using a machine simulator; these are effective for student pilots, who spend many hours doing simulation flights. But surgery is tactile. There is blood, tissue, fat, muscle, fascia, and bone. A glorified video game, he realized – no matter how high-tech and realistic the experience – is just not the same.

ON THE COVER *SLICE offers unprecedented opportunities for surgeons and surgical residents to develop proficiency in procedures — before they perform them on patients.*

"There was no ideal way to train a surgeon. We were training on the go – basically, building the plane as we flew."

"SURGERY BLEEDS"

Then he tried making surgical training models using 3D printing. This, too, was not the solution. "Surgery bleeds. I knew from the beginning that whatever models we made, they needed to bleed." So, 3D printing could not make the organs – but it *could* be used to make molds for organs that did look and feel just like the real thing. The key turned out to be the use of hydrogel, a water-based, semi-solid polymer scaffold that can absorb fluids and maintain its shape.

Eventually, Ghazi had his first prototype, a small block of hydrogel with a vessel in the middle. The "blood" was not red: "It was actually black ink because we couldn't find anything else. But it looked very realistic." When he tested it, the replica tissue bled. **And it kept bleeding – so much that Ghazi had to close the fake wound. He couldn't walk away from it**. "I thought, 'This needs to stop'" – and this, he says, was an "aha!" moment. The hydrogel models were so life-like that they were compelling. Next, with a biomedical engineer, Ghazi developed and patented a detailed library of all the different textures that, layered together, make up a realistic human anatomy, and of different organs: kidney, liver, colon, prostate, bladder.

Then he got a master's degree in education. He has developed curricula for different sets of learners: medical students; surgical residents; practicing surgeons who want to learn a new technique or procedure; and practicing surgeons who want to plan and practice a specific operation for complicated cases, such as a large kidney tumor. The models can be generalized for training or made patient-specific, using the patient's own imaging and biopsy results.

WHAT MAKES THIS DIFFERENT?

"There are several surgical training and simulation centers across the U.S.," says Ghazi. "What makes ours different? The ability to combine an innovative and patented methodology to custom-build very realistic, bleeding models for training." To maintain consistency and quality, the surgical models are built in-house. "We custom-build the model to the learner's level, and we customize the learning platform based on who the learner is. Our educational approach is also essential: we innovate not only to design the models, but also to design the actual curriculum for training."

For example, learning at the Walsh Laboratory can happen over months. "That's really geared for people adopting a very new approach they've never done before," Ghazi explains. Or it can be done in a "master class" environment, "three or four days of hands-on training that enables an already proficient surgeon to adopt a new technique," and this, too, is customized. "Before anybody starts our programs, we evaluate them. We customize the training based on their starting level, and at the end we want them to get to the expert level."

What's an expert? Ghazi has determined that, as well. "We got 50 expert urologists to perform surgery using our models," and then by tracking the surgeons' eye movements, data on technique from the machine itself, and from sensors placed within the models, "we were able to quantify what it means to be an expert surgeon. To get surgeons to expert level, we use proficiency-based progression. **It's not like you do this ten times and then you're done, but you continue to do it until you reach a certain level."**

The Brady will be constructing a facility for SLICE on the Johns Hopkins Medicine campus that Ghazi is customizing for optimal surgical training. The space will enable operations to be transmitted in ultra high-definition 3D, as well as telesurgery and remote training using a secure 5G network."From here, I will be able to take control of a surgical robot or

Continued on the next page >

Ghazi: *"From here, I will be able to take control of a surgical robot or machine across the country and teach somebody based there."*

machine across the country on the West Coast, and teach somebody based there." SLICE has two Da Vinci surgical robots for training purposes, and "we are in negotiations to get more," Ghazi says. There will also be equipment and models for teaching endo-scopic surgery, laparoscopic surgery, and open surgery.

"Our major source of revenue is philanthropy," Ghazi notes, with additional funding through several societies, NIH grants, and industry-sponsored grants. Those who come to Hopkins for training or a master class pay a registration fee.

PLANNING FOR VERY DIFFICULT OPERATIONS

Word of mouth about SLICE is already spreading among patients as well as surgeons. One patient "has a very difficult tumor in her kidney," Ghazi explains. "She spoke with several urologists at other centers. The tumor is very deep in the kidney, surrounded by blood vessels." Several doctors told her the entire kidney needed to be removed. The patient, a scientist, "didn't think a tumor that small – about 3 cm – should require removal of the entire kidney." The patient contacted Ghazi and asked if he could save her kidney. His answer: "I don't know. What I need to do is make a model of your kidney (with a hydrogel tumor embedded in the precise location of the real one) and practice on it." Ghazi did, and he found a way to do a partial nephrectomy. "The patient is coming from New York and will watch as I perform a practice operation in virtual reality. We will meet in the metaverse, and we will virtually go inside the tumor. We'll be virtually standing in the kidney, and I will show her, 'that's your tumor, that's your blood vessel.'"

Ghazi has had similar sessions with other patients, and the response has been overwhelmingly positive: One patient said, "If you end up sacrificing the kidney, I am assured that you did everything in your means to save it.' Going to these lengths gives the patient extra peace of mind."

IMPROVING PROSTATECTOMY

With MRI images, Ghazi can create an exact replica of the prostate in all its complexity. "This is truly customizable surgery: there's no way this surgery will be the exact same for each patient," because each prostate is slightly different; the structures surrounding it may be different, and each tumor is unique. "We aim to perfect the surgery," he says. **"I believe that 10 years from now we will not be removing the entire prostate; we will remove part of the prostate."** If cancer is near the nerves, does this mean just cut as much tissue as possible? "What if we say, 'Let's practice and see?' That is the trajectory where we are going in prostate cancer."

PRESERVING ORGANS NEAR THE BLADDER

In patients who undergo surgery to remove the bladder, "we're teaching new techniques for organ preservation" – of the prostate in men, and the uterus in women. "These are more difficult procedures that require extra training, and that's why fewer people do them," says Ghazi. He is working with Brady urologist Armine Smith, M.D., with funding from a patient, to develop models to perfect these techniques.

Surgeons, says Ghazi, "can never get complacent. The technology is changing ever so rapidly." Everyone needs continuing education. "If our vision for SLICE is realized, Johns Hopkins will become a destination for urologists, cardiologists, interventional radiologists, gastroenterologists – we have models and courses for multiple specialties," and for entire surgical teams, as well. ■

A New Era of Surgery

"This is not just less invasive; it's noninvasive, with minimal side effects, and it's better for the patient."

First, there was open surgery. Then there was laparoscopy, surgery performed by inserting a long, thin tube with a high-resolution camera, light, and specialized instruments through a few small incisions. Then there was robotic surgery, also completed with few tiny incisions; and now, there is a single-port robot, a tool for surgeons to operate with just one tiny incision.

Meanwhile, in the realm of imaging: first there were x-rays, and then came CT scans. Then there was MRI, and now PSMA-PET. Once, pathologists only looked at cancer cells with microscopes. Now they can perform genomic analysis on individual biopsy samples – which means a surgeon might not need to remove the entire organ, but just the cancerous tissue within it. And this, for the patient, means preserving more function, having fewer side effects, and recovering more quickly.

Surgery is becoming more minimally invasive than ever before. "We are in a new surgical era at the Brady," says Mohamed Allaf, M.D. "We are seeing miniaturization of surgery." Prostatectomy and some kidney surgical procedures are performed using only one tiny access point. "We're even using this single-port approach in reconstructive surgery. These are patients who have had either trauma, like a gunshot wound or car accident, or who have had previous surgery, sometimes with radiation. They have a lot of scar tissue. Just a few years ago, we had to make a big incision and remove the scar tissue just to make space – to fix a blocked ureter, for example. Now we can navigate and operate in small pockets in the body. We can sneak in, fix what needs to be fixed, and finish our work with the faintest trace."

SURGERY WITHOUT A SCALPEL

Brady surgeons are performing and perfecting more "ablation-guided interventions," as well. Instead of a scalpel, they are "zapping, freezing, or steaming" cancerous tissue,

says Allaf. "Dr. Arvin George has started a focal therapy program for select patients with prostate cancer using ablative energy: high-intensity focused ultrasound (HIFU), using ultrasound waves to kill tissue; microwave energy; or freezing it with cryotherapy. He's using water vapor (steam) on localized prostate cancer in the VAPOR2 trial (see story on page 11). This is not just less invasive; it's *noninvasive*, with minimal side effects, and it's better for the patient."

In carefully selected patients, Brady urologists use this same tissue-vaporizing technology, called aquablation, to destroy overgrown tissue and relieve urinary symptoms of benign prostatic hyperplasia (BPH). Another form of ablative energy – the laser (in the HoLEP procedure)—is "the gold standard" for removing excess tissue within the prostate, Allaf notes.

Ablating kidney tumors: Hopkins is one of a few centers using ablative energy to kill kidney tumors. "The alternative is surgery," says Allaf. One patient, who had been told by his doctors in Canada that he would need major surgery to remove his kidney, was evaluated by Brady urologists and considered a good candidate for ablation. "The procedure took an hour and a half. He walked out of the hospital, flew back to Canada after percutaneous ablation of his kidney tumor, needed no recovery time – and he kept his kidney."

This procedure is done in collaboration with interventional radiologists, and this is another big change that Allaf sees in urologic surgery. "The changing terrain for patients moves across disciplinary boundaries," he says. "No longer is the surgeon seeing a patient and making a unilateral decision. We're working with radiologists, pathologists, medical oncologists, radiation oncologists, and data scientists."

Analyzing information: Why are information scientists involved with patient care? Because this is the era of big data, says Allaf. Thousands of individual pieces of data – from imaging, PSA tests, genomic analysis of biopsies, pathology reports, and blood and urine biomarker test results – are now available for each patient. Brady urologists use computers to sift through that data to craft nuanced, individualized care plans. In prostate cancer, for instance, "There's a lot of quantitative information on an MRI," says Allaf. "A computer can look at all the pixels and tell us a little more about what we're seeing. When we take biopsies, we get a big genomic analysis from the pathologist. We can analyze this information and predict how best to get rid of the cancer in the least invasive way. We're minimizing surgery, but also quantifying it."

Using 3D models: "With Dr. Ghazi's models (see cover story), if we have a difficult case we can rehearse an intervention," says Allaf. "We can figure out the best approach for the individual. This is unique and exciting, and it's truly precision surgery: using the 3D models integrated with a quantitative approach, and then implementing the best technology for that patient's cancer."

These 3D models are also being used to improve surgery in very young children with bladder exstrophy – a rare condition requiring a complex reconstructive operation developed by Brady pediatric urologist Robert Jeffs, M.D., and refined by his successor, John Gearhart, M.D., and surgeons Chad Crigger, M.D., M.P.H., and Heather Di Carlo, M.D. To correct the congenital abnormality of the bladder and the pelvic bone structure, these surgeons are using intraoperative, 3D MRI-guided pelvic floor navigation and dissection.

Using tracers to see the invisible: Allaf has just completed and is analyzing data from a clinical trial of robotic prostatectomy using a PSMA tracer – the same type of tracer used in PSMA-PET imaging. It highlights prostate-specific membrane antigen (PSMA), a molecule that sits on prostate cancer cells. In the study, PSMA-containing cells show up on the screen as bright green. "The green we see is so dramatic," he says, "but sometimes there's just a greenish hue to the tissues. We can't discern if it's green enough." Allaf envisions routinely using computer vision to zoom in on a hazy area and quantify the amount of green. "If you don't see it, it doesn't mean it's not there. But even if the human eye can't see it, the computer can detect it. All of this is leading toward an approach to surgery that we're very excited about."

A similar tracer – blue, not green – is being used in bladder cancer surgery at the Brady. The technique is called blue light cystoscopy, and it's also done with computerized guidance. "The surgeon puts a dye into the bladder an hour before the cystoscopy," Allaf explains. "The dye is absorbed by the cancer cells, making it invisible to the naked eye. However, it emits a blue light, allowing us to view the cancer more effectively. Even just a few years ago – like all of these advances – this would not have been possible." ■

Allaf: *With the help of computers, surgeons can detect and remove tiny bits of cancer too small to be seen with the naked eye.*

Isaacs *wearing the Brady tie (designed by Peg Walsh).*

A Legendary Scientist is Retiring

William Isaacs will be greatly missed at the Brady.

It is no exaggeration to say that molecular geneticist, William B. "Billy" Isaacs, Ph.D., is a giant in his field, a research pioneer who has contributed greatly to our knowledge and understanding of the genetics of prostate cancer – a field he helped originate. **A Google scholars search shows that Isaacs has authored or co-authored 788 papers and numerous book chapters, and has been cited in other researchers' papers nearly 83,000 times**.

Isaacs, the *William Thomas Gerrard, Mario Anthony Duhon, and Jennifer and John Chalsty Professor of Urology*, is retiring after more than three and a half decades at the Brady. He will be greatly missed. His longtime colleague and collaborator, Jun Luo, Ph.D., the *Alan W. Partin, M.D., Ph.D. Professor in Urology*, will be taking over as head of the Patrick C. Walsh Hereditary Prostate Cancer Program – a program Isaacs has led for many years.

HEREDITARY PROSTATE CANCER RESEARCH BEGAN AT THE BRADY

Here are some highlights of this remarkable program: In the late 1980s, Walsh, Brady resident Gary Steinberg, and M.D./Ph.D. student Bob Carter defined and characterized hereditary prostate cancer. They established the clear link between family history and a man's likelihood of developing the disease, and laid the groundwork for the exciting research that would define Isaacs' career.

In 1992, Carter, Walsh, and geneticists Barton Childs and Terri Beaty published a landmark study in the *Proceedings of the National Academy of Science*. They established for the first time the genetic basis for prostate cancer and predicted that a rare, "high-penetrance" genetic mutation would be found in families with early age of diagnosis and multiple affected family members.

This launched the partnership between Walsh and Isaacs, who joined the Brady faculty after earning his Ph.D. in the lab of renowned Brady scientist Donald S. Coffey, Ph.D. **Over the last 34 years, their discoveries transformed the field.** Walsh was the clinician who identified the families (more than 3,000) to be studied, and Isaacs was the scientist analyzing their DNA (more than 8,000 samples), looking for the mutations that cause the disease to be transmitted from one generation to the next. This was a Herculean task, akin to looking for one misspelled word in 20 sets of the *Encyclopedia Britannica*! After two decades of painstaking work, Isaacs found the gene Walsh and colleagues had predicted: in 2012, in collaboration with Kathleen Cooney at the University of Michigan, Isaacs' research team identified *HOXB13* as the first major susceptibility gene for prostate cancer.

A mutated *HOXB13* gene was thought to be a risk only for men of Nordic European descent, but in 2021, Isaacs, Luo, and colleagues discovered a mutation on *HOXB13* called *X285K* that is linked to more aggressive cancer in Black men.

In 2008, Isaacs, along with longtime colleagues Henrik Grönberg in Sweden and Jianfeng Xu at Wake Forest University (later NorthShore University), published the first paper showing the ability of five common genetic variants (called single nucleotide polymorphisms or SNPs, pronounced "snips") to predict the risk of being diagnosed with prostate cancer. His group was also among the first to show that these SNPs contributed to the inherited risk for prostate cancer in high-risk men of African descent as well as in European men.

Building on this work, Isaacs and his team, in partnership with scientists at Howard University, began a first-in-field project to identify factors in the genome and immune system in Black men with aggressive, locally advanced, or metastatic prostate cancer.

Isaacs was part of an international study in 2020, published in *European Urology*, showing that men of African – but not European – descent have a particular SNP that raises the odds of developing prostate cancer. "This pretty much, hands down, is the most important genetic risk marker I've seen for Black men," Isaacs said.

In 2016, in another first-of-its-kind study, Isaacs and colleagues completed a detailed genetic analysis of 96 men who died of prostate cancer at age 65 or younger. "We sequenced all regions on each chromosome that code for proteins," Isaacs said. "Surprisingly, we found that **more than 20 percent** of these patients carry inherited mutations which inactivate a class of genes responsible for repairing damaged DNA." This study and other work by Isaacs' group and international research groups identified a short list of bad genes that appear in lethal prostate cancers. This work also changed how scientists thought about prostate cancer – because these mutated genes (most notably, *BRCA1, BRCA2, ATM,* and *PALB2*) – are also involved in the worst cancers of the breast, colon, ovaries, and pancreas. They can be inherited by men and women. For the first time, a connection was made between prostate cancer and other cancers that run in families.

Several years ago, when asked what was most important about his time at the Brady, Isaacs said: "The environment at the Brady is truly unique and astoundingly nurturing. I consider it an honor and a blessing to have had the privilege to spend my entire career in this mecca of American urology." ■

Brady Team Finds Another Prostate Cancer Gene

"In men who carry the defective code but have yet to develop the disease, early screening will detect prostate cancer at a time when a cure is possible."

In their tireless search for genes responsible for prostate cancers that run in families, William Isaacs, Ph.D., Jun Luo, Ph.D., and Jianfeng Xu, Ph.D., of NorthShore University, and their team have found another gene: *MMS22L*.

MMS22L is a protective gene: its job is to fix damage to the DNA that can lead to cancer.

When this gene, like *BRCA2* (see previous page), is knocked out of commission by a faulty genetic code, DNA damage can run amok. "When it's mutated," says Isaacs, "it not only increases the lifetime risk of developing aggressive prostate cancer, but has a 50-percent chance of being passed on to the next generation."

Fortunately, now that *MMS22L* has been identified, it can be tested for: "We have a simple saliva test that detects some of the defective genetic codes that shut down genes important in protecting our genome, such as *BRCA2*," says Luo. "*MMS22L* can be added to the saliva test."

MMS22L is probably not responsible for nearly as many cases of prostate cancer as *BRCA2*, notes Luo, but it is important for those who have this mutation to be aware. Luo likens the team's long hunt for rare prostate cancer genes to explorations in remote areas. **"We say many roads lead to Rome, and now that the major roads are mapped, what about the less-traveled paths?** We are essentially trying to map many of these less-traveled paths to Rome. We suspect there are more prostate cancer genes out there. The problem is, it is difficult to identify them because, fortunately, the defective codes are quite rare."

Isaacs explains: "We have in front of us a map of the human genome that has three billion codes. Our task has been, to a large extent, hunting down the culprits and pinpointing the precise location of the defective codes on the map." Every code found, he adds, "increases our ability to help patients and their families."

In the case of *MMS22L*, the team discovered a defective code in eight families participating in research within the Patrick C. Walsh Hereditary Prostate Cancer Program. The defective code shuts down this gene.

Knowledge is power, and "in men who carry the defective code but have yet to develop the disease, early screening will detect prostate cancer at a time when a cure is possible," says Luo. "In addition, there are promising drugs, such as PARP inhibitors, that may be used to target cancer with these specific types of defective genes." ■

Good News for Men with an Abnormal *BRCA2* Gene and Aggressive Prostate Cancer

Using genetic information to personalize treatment for some patients

Not all prostate cancer is alike – especially the aggressive kind. This is very important, because two men with the exact same stage and grade of cancer may have different cancer-related genes. Depending on the genetic makeup of the tumor, one man's cancer may respond to certain drugs, while another man's may not. In fact, these drugs may so specifically target the cancer that they are fully effective – *even without the addition of androgen deprivation therapy (ADT)*.

"A longstanding goal of clinical researchers at Johns Hopkins has been to develop effective systemic therapies to treat recurrent and metastatic prostate cancer without requiring hormonal deprivation," says Hopkins medical oncologist Catherine Marshall, M.D., M.P.H.

This year, three Hopkins investigators did just that in studies of drugs called PARP inhibitors. In previous studies, PARP inhibitors have shown success in treating patients with faulty DNA repair genes (such as *BRCA1/2, CHEK2, ATM*, and others) when combined with hormonal therapy. **But what if the hormone therapy was omitted? Could a PARP inhibitor stop the cancer on its own, simply by targeting a bad DNA repair gene?**

The first trial, recently published in *JAMA Oncology*, was led by Marshall and Emmanuel Antonarakis, M.D. (now at the University of Minnesota; he remains an Adjunct Professor of Oncology at Hopkins). In this trial, 51 men with a rising PSA after treatment for localized prostate cancer (previous prostatectomy and/or radiation therapy) were treated with the oral PARP inhibitor olaparib (Lynparza®). They did not receive ADT. "Remarkably," says Marshall, "of the 11 patients with germline (inherited) or somatic (acquired) *BRCA2* mutations, all achieved a remission, some of which lasted more than three years!"

However, as the investigators suspected, this treatment is highly specific and only works when there is a mutated DNA repair gene. "None of the men without DNA repair gene mutations benefited from the treatment."

According to Marshall: "This trial demonstrates that targeted therapy has efficacy in selected patients (those with *BRCA2* mutations) with PSA-recurrent prostate cancer, and may provide alternatives to hormonal therapy for some men in this setting."

The second study was led by Hopkins medical oncologist Mark Markowski, M.D., Ph.D., and Antonarakis, and published in *The Oncologist*. This trial, called TRIUMPH, went one step further to study 12 patients with metastatic prostate cancer who had an inherited DNA repair gene mutation. Here, patients were treated with a different oral PARP inhibitor, rucaparib (Rubraca®). Patients received no concurrent hormonal therapy or chemotherapy. "Among the seven patients with *BRCA1/2* mutations, all but one had significant remissions of their cancer," says Markowski. The average duration of remission was one year, but some lasted as long as three years. "Patients with other DNA repair gene mutations generally derived less benefit from rucaparib, although one patient with a germline *CHEK2* mutation achieved a remission lasting more than two years."

These results, Markowski continues, are "remarkable and go against the central dogma that hormone therapy is a required component of prostate cancer systemic therapy. We showed that even in the presence of metastatic prostate cancer, some patients can be treated with a non-hormonal therapy that is oral and has minimal side effects compared to ADT."

RULE BOOK? WHAT RULE BOOK?

And this is just the beginning, says Antonarakis: "These two studies represent a paradigm shift in the management of advanced or metastatic prostate cancer, and they break every rule in the rule book. Instead of treating all prostate cancer patients with a one-size-fits-all approach, we are using genetic information to personalize treatment for some patients who may be managed effectively with oral targeted agents and in whom castrating therapies can be avoided or delayed. We are grateful to all the patients who put their trust in us and took a risk to participate in a study that went against the grain of standard practice." ■

THE SCHAUFELD PROGRAM FOR PROSTATE CANCER IN BLACK MEN

Schaufeld Scholars Making a Difference

"Maybe part of the reason why Black men are more likely to die from prostate cancer is that they are reluctant to go to the urologist. One way to encourage this might be to support the training of more Black urologists and scientists."

Steve Silverman had prostate cancer, but it's gone now. With advice and treatment from Mohamad Allaf, M.D., and Patrick Walsh, M.D., his cancer was diagnosed early and removed successfully. "The surgery, the post-op, the recovery all went well," he says.

But he knows that many men are not as fortunate. In particular, men of African ancestry have the highest risk of developing aggressive and potentially fatal prostate cancer, due to genetic and environmental causes and also disparities in health care, including a lack of early detection.

Silverman and his wife, Elizabeth, have a long history of philanthropy and of generously giving back to make the world a better place. When they heard about the Schaufeld Program for Prostate Cancer in Black Men, they wanted to contribute. "Maybe part of the reason why Black men are more likely to die from prostate cancer is that they are reluctant to go to the urologist," Steve says, "and one way to encourage this might be to support the training of more Black urologists and scientists."

With this goal in mind, each year the Schaufeld Program funds Schaufeld Scholars: post-baccalaureate students interested in science, medicine, and health disparities who come to Hopkins for two to three years. The scholars are paired with a faculty mentor, and they conduct prostate cancer research and volunteer to lead health education in the community. They also prepare for graduate school and shadow Hopkins faculty and trainees.

Now, through the generosity of the Silvermans, there is an additional endowed Schaufeld Scholar position: the *Silverman Family Fellow*.

"POTENTIAL TO DIVERSIFY THE BIOMEDICAL WORKFORCE"

So far, three Schaufeld Scholars have graduated from the program. "Two are in medical school, and the third is working in a lab at Stanford and applying to Ph.D. programs," says Tamara Lotan, M.D., the *Rose-Lee and Keith Reinhard Professor in Urologic Pathology*, who with Allaf co-directs the Schaufeld Program. "One of our scholars was first author in a study published in *Cancer Research Communications*, and was co-first author in a paper published in *European Urology Oncology*."

This year, Hopkins scientist Karen Sfanos, Ph.D., received a Department of Defense (DOD) Prostate Cancer Research Program Health Disparity Award to study the immune microenvironment and the microbiome on prostate cancer immunotherapy response in Black men. The grant reviewers cited the Schaufeld Program as a strength of Sfanos's application, noting that the program is "enabling a statistically significant number of Black men to be included" in the clinical trial, and noted the Schaufeld Scholars Program "has the potential to diversify the biomedical workforce in the long term."

Working in Sfanos's lab is Schaufeld Scholar Shango Rich, a graduate of Norfolk State College who majored in biology and chemistry. Like all the program's Scholars, he spent time in different labs and then picked a lab to join.

Rich is excited by what he's investigating: "We're looking at race and prostate cancer progression, and how the microbiome may affect it," he explains, "how bacteria can affect different bodily processes, and how that, in turn, can affect prostate cancer progression. Particularly, how racial identity affects how the body responds to food and hormones. How the prostate relates to this is different in every person, but in the Black population, it seems to respond a lot more aggressively."

MENTORING AND SHADOWING

Rich plans on taking the MCAT (medical school admissions exam) in 2025, and Lotan and Allaf will make sure that he and the other Scholars are poised for success. "We fund an MCAT prep course, which lasts several months," says Lotan. "We also provide mentoring. That's one of the things I'm most proud of: we have a series of mentoring workshops and shadowing opportunities for the students. It can be a little bit isolating for someone to come fresh from college into a lab at a big university," she continues, "to get plunked in amid mostly graduate students and residents. We tie them in with a network of people from underrepresented groups – junior faculty, residents, fellows, graduate students – who have an interest in helping our Scholars." Twice a month, Scholars meet a "near-peer mentor, someone just a few years older. They can pick their brain about that person's life story, medical school application, their career pathway."

Lotan brings in people from many walks of medicine to talk to the Scholars about their jobs. "We've had people from the medical school come in," with advice on navigating the admissions process. "We've also brought in financial aid people to talk about how to pay for medical school. That's a very big piece of the puzzle."

"THAT MAKES IT WORTH IT"

Recently, Rich and other Scholars participated in interactive surgical demonstrations at the Minimally Invasive Surgical Training and Innovation Center (MISTIC) Lab and in the operating room. "I really enjoyed shadowing Dr. Allaf. He was determined to make this a great learning experience even for someone with little experience in surgery. He constantly explained every move he made to his team and residents, but also well enough for me and my fellow scholars to understand. He is an exceptional surgeon, and he really shines as a mentor and teacher."

"There is nothing more fun than watching people grow and be successful and accomplish their dreams."

Lotan says co-directing the Schaufeld Program is "one of the proudest accomplishments in my recent career. There is nothing more fun than watching people grow and be successful and accomplish their dreams."

Adds Rich: "This work that we're doing is very important. Sometimes it feels to me, at least, that what I can contribute is very small. But everything we know about medicine started from the small achievements of people like me contributing to something larger. That makes it worth it. It's intellectually stimulating, but it also helps people. It's actually going to mean something in the end." ■

Lotan and Rich: *So far, two Schaufeld graduates have gone on to medical school, and the third is working in a lab at Stanford and applying to Ph.D. programs. Rich, right, plans on taking the MCAT in 2025.*

After Surgery or Radiation for Prostate Cancer: Are There Disparities in Treating Complications?

"Urinary incontinence and erectile dysfunction (ED) are known complication risks after radical prostatectomy and radiation therapy for localized prostate cancer, and some reports have suggested disparities in their occurrences among Black men and men of lower income groups," says Arthur Burnett, M.D., M.B.A., the *Patrick C. Walsh Professor of Urology*.

Is it possible that similar disparities exist in the *treatment* of these complications? To find out more, a research team led by Burnett looked at the timing and care of thousands of prostatectomy and radiation patients who experienced urinary incontinence and/or ED after treatment between 2015 and 2021.

They found that Black men were statistically *more* likely to receive surgical care for ED, but less likely to receive urinary incontinence surgical care than White men, in all cohorts except for radiation therapy-induced urinary incontinence. Surgical care was highest among patients in the lowest income quartile in all cohorts – except, again, urinary incontinence after radiation therapy.

Are men who experience urinary incontinence after radiation therapy somehow less likely to seek help for it? "We don't have a definitive explanation," says Burnett, "although factors related to culture and access to alternative treatments besides surgery may be related. Further prospective studies investigating the basis of these results would be helpful." This study was published in *BJUI Compass*. ■

Personalized Prostate Biopsy

The novel biopsy plan sharpens the diagnosis of prostate cancer.

For several years now, a Brady team led by Dan Stoianovici, Ph.D., Director of the Urology Robotics Program, and urologist Misop Han, M.D., the *David Hall McConnell Professor of Urology and Oncology*, has been working to refine prostate biopsy so that it is less likely to "miss" cancer.

They have developed a novel, personalized approach, which the team just published in *Prostate Cancer and Prostatic Diseases*. "We can generate a personalized biopsy plan for every patient," says Stoianovici, "based on an individual's unique prostate anatomy and MRI findings."

Their findings have exciting implications for many men: "In our study, we found that a personalized systemic biopsy likely achieves adequate detection and sampling of areas of interest identified on MRI in men with small prostate glands" – an important outcome, because not all patients have access to an MRI fusion biopsy, where the MRI image is combined with transrectal ultrasound to create a more detailed picture. However, the team recommends that men with large prostate glands should get MRI fusion-targeted biopsies.

This study was supported by grants from the National Cancer Institute and the Patrick C. Walsh Prostate Cancer Research Fund. ■

Active Surveillance and Artificial Intelligence

If you are considering active surveillance (AS) for slow-growing prostate cancer, you really want to make sure that this is what you have: low-grade cancer cells with no aggressive features. The pathologist's evaluation of your prostate biopsy tissue plays a critical role in determining your best course of action.

But not all pathologists are equal, says Hopkins pathologist Tamara Lotan, M.D. "The evaluation is often subjective, and there is significant variability among pathologists. Also, not much has changed in the way we have done this evaluation over the last 60 years."

In a recent study, Lotan and her research team, along with Brady urologist Christian Pavlovich, M.D., and former Brady urologic oncology fellow Claire de la Calle, M.D., wondered whether artificial intelligence (AI) algorithms could improve the overall accuracy and consistency of prostate biopsy evaluations. The study was published in the *Journal of the National Cancer Institute*.

"We looked at how well these AI algorithms evaluated biopsy tissue of patients who are undergoing AS," says Lotan. Their findings were impressive: "We found that in two separate AS cohorts," men diagnosed with Grade Group 1 prostate cancer by the pathologist, "the AI algorithm sometimes assigned a higher grade to the tumor sampled in the initial diagnostic biopsy." Then, the patients whose samples were "upgraded" by the AI algorithm "were more likely to be upgraded to Grade Group 2 or higher when their tumors were later re-biopsied than patients whose initial biopsy samples were not upgraded by AI.

"Thus, AI was better than the human eye at predicting which patients might subsequently require definitive therapy for their prostate tumors," says Lotan. "Ultimately, such algorithms will give all AS patients access to expert pathology opinions, even if they do not get treated at large centers like Hopkins." ■

For Men on Active Surveillance, Diet Really Does Make a Difference

Good news for men on active surveillance (AS) for prostate cancer: Instead of just hoping for the best – that your cancer won't progress and that you can delay or avoid treatment – you can take action to help lower your risk. Choosing a healthy diet can make a big difference.

***Pavlovich, Trock, and Su**: What's good for the heart is good for the prostate — "A heart-healthy diet, or a Mediterranean diet, is a prostate-healthy diet." Eating anti-inflammatory, nutrient-rich foods can help slow the growth of prostate cancer.*

This is the striking result of a new study, published in *JAMA Oncology* by a team of Brady investigators including epidemiologist Bruce J. Trock, Ph.D., the *Frank Hinman Jr. Professor of Urology*, urologist Christian P. Pavlovich, M.D., the *Bernard L. Schwartz Distinguished Professor in Urologic Oncology*, and Brady resident Zhuo Tony Su, M.D.

"Diet is one of the most important factors that a man can modify to reduce his risk of prostate cancer," says Trock. "What you eat affects multiple pathways directly related to cancer risk, including inflammation, DNA repair, and metabolic changes."

What you eat — and don't eat — can either give you cancer-fighting nutrients and antioxidants (from a diet rich in fruits and vegetables and lean meats), or junk (from additives such as food coloring, chemicals, fillers, sugars, and fats). In addition, food can be either soothing or inflammatory to your body. Chronic inflammation plays a role in many health conditions, including heart disease, diabetes, autoimmune disease, and cancer. Similarly, what you drink and don't drink – particularly, alcohol, sugary drinks, and even diet drinks with various sweeteners – is important, too.

"Men managed with AS often ask whether changing their diet can reduce their risk of developing more aggressive disease," says Pavlovich, Director of the Prostate Cancer AS Program. Until now, Pavlovich did not have hard evidence to back up what he and many investigators believed to be true: that diet can help slow the growth of prostate cancer. "Previous studies have looked at diet in men undergoing AS, but have not found a statistically significant association with disease progression," Pavlovich says. "Most studies have evaluated specific foods or nutrients, rather than capturing the characteristics of a man's overall diet."

In this study, Trock, Pavlovich, and Su analyzed self-reported diet information from all the men in the AS Program, looking to correlate overall diet quality and dietary inflammatory potential with prostate cancer grade reclassification (when higher-grade cancer is found on a follow-up biopsy).

"From 2005 to 2017, 886 men with Grade Group (GG) 1 prostate cancer enrolled in the AS program," says Trock. "They completed detailed questionnaires describing their usual dietary patterns," from which the investigators calculated a Healthy Eating Index (HEI) score. "The HEI is a measure of overall diet quality," Trock explains. "We also calculated each man's Dietary Inflammatory Index (DII), a way to measure the inflammatory potential of his diet. Then we looked at whether either the HEI or DII influenced risk of grade reclassification (or upgrading) to GG2 and to GG3 (extreme grade reclassification – a condition that warrants definitive treatment) on a surveillance biopsy."

After an average follow-up of 6.5 years, 187 men had grade reclassification to GG2 cancer, and 55 had extreme grade reclassification to GG3 or higher. But as they added diet to the equation, the investigators found something remarkable: "For each 25-point increase in the HEI, the risk of grade reclassification to GG2 decreased by 28 percent," says Su, "and the risk of GG3 cancer decreased by 48 percent!" The investigators found no significant association with the DII.

This study is the first to demonstrate that a healthy diet is associated with a lower risk of grade reclassification, particularly for GG3 disease. Pavlovich advises his patients that what's good for the heart is also good for the prostate. "A heart-healthy diet, or a Mediterranean diet, is a prostate-healthy diet." ■

A Major Advance in Understanding How Prostate Cancer Begins

"The activated MYC *gene could be orchestrating a series of changes that transform the normally harmonious cellular city into a dystopia."*

If normal cells are law-abiding citizens, then cancers are outlaws, says scientist Vasan Yegnasubramanian, M.D., Ph.D., the Director of inHealth Precision Medicine at Johns Hopkins. "They're like rogue citizens who break the rules, corrupt or coerce other citizens to behave in ways that can support the cancer and cause the city to enter into chaos. When we observe that chaos, it appears that every cancer is very different, and seems way too complex to understand and figure out ways to treat it. This is what happens in prostate cancer."

But Yegnasubramanian and a team of researchers had an idea: what if, despite all the differences among prostate cancers, they share a similar origin story – **a molecular reason why they went rogue?** A recent study with scientists from across the Johns Hopkins School of Medicine has shown that activation of a powerful gene called *MYC* is a chaos-producing event that most prostate cancers have in common.

"To understand how *MYC* activation could lead to the complex spectrum of alterations we see in prostate cancer and surrounding cells, we couldn't just observe human tissues," Yegnasubramanian explains. "We needed to watch the process unfold over time, by studying mouse models that mimic human prostate cancer."

In a groundbreaking study using cutting-edge single-cell sequencing and molecular pathology technologies, they showed that activation of *MYC* in the cancer cells generated signals "that started to give them capabilities such as higher metabolism to fuel their growth." Then, "to our surprise, we saw that this initial activation of *MYC* also set off an alarm system in the cells," a flurry of activity: "Genes were expressed that signaled to immune cells, the body's police force, that something was wrong. But strikingly, the *MYC*-activated cancer cells eventually figured out ways to shut off these alarm bells! They even figured out how to corrupt some of the immune cells and other nearby cells to help them evade the policing immune cells. Switching off those alarm bells and evading the immune surveillance paved the way for the *MYC*-activated cells to become invasive, and to completely disrupt the surrounding cells."

These findings, published in the journal *Nature Communications*, represent a major advance in understanding the complex nature of prostate cancer and its environment. "They suggest that the activated *MYC* gene could be orchestrating a series of changes that transform the normally harmonious cellular city into a dystopia taken over by invading cancer cells." Now, armed with this new understanding, scientists can look for ways to deactivate or shut down *MYC*, and perhaps prevent or even reverse the damage caused by prostate cancer. ■

When Prostate Cancer is Low-Grade but Invasive

"Grade group (GG) 1 prostate cancer is considered low-risk based on its non-aggressive clinical course for the majority of patients," says urologist Nirmish Singla, M.D. "However, there is an uncommon subset of these low-grade tumors that is capable of invading through the capsule of the prostate."

What happens when these low-risk tumors poke outside the prostate (this is called extraprostatic extension, or EPE)? In a recent study, published in the *Journal of Urology*, former Brady urologic oncology fellow Michael Rezaee, M.D., and colleagues looked at the data on patients who underwent radical prostatectomy at the Brady between 2005 and 2022. "We found that among patients undergoing radical prostatectomy for GG1 prostate cancer, there were no differences in biochemical recurrence by the presence or absence of EPE," says Singla, the study's senior author. However, for patients with GG2 disease who had EPE, biochemical recurrence (the return of PSA) was more likely.

"Our findings are reassuring," says Singla, "affirming that GG1 prostate cancer is a low-risk disease – even when tumors invade beyond the prostate. However, future research is needed to understand how EPE may influence the natural history of GG1 tumors on active surveillance." ■

Protecting the Rectum During Prostate Radiation Therapy: A Spacer Balloon

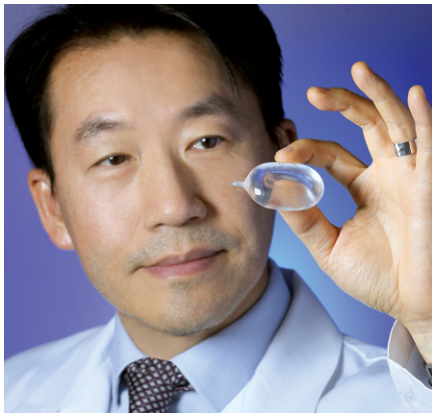
The prostate's next-door neighbor is the rectum, and even with the high accuracy of external-beam radiation therapy for prostate cancer, there is a risk of rectal proctitis (inflammation), with side effects including diarrhea, cramps, bleeding, and pain. Gel spacers – cushions of an injectable gel, which move the rectum farther from the prostate – have been shown to reduce these side effects. But there is room for improvement, says Hopkins radiation oncologist Daniel Song, M.D., Professor and Director of Genitourinary Radiotherapy. Song and colleagues have been looking for a more precise and reproducible approach. Promising results of a recent trial suggest they have found one: a biodegradable balloon.

"We evaluated the efficacy and safety of a novel spacer balloon that goes between the prostate and rectum, which allows the potential for controlled, adaptable deployment," says Song, who was first author of the study, published in the *International Journal of Radiation Oncology, Biology, Physics*.

The study involved 222 participants from 16 centers who had T1-T3 prostate cancer and no MRI evidence that their cancer had extended beyond the prostate. Patients were randomly assigned either to a balloon or control group, and then they received intensity-modulated radiation therapy. The balloon was placed with a needle inserted through the perineum (the area between the scrotum and rectum) using transrectal ultrasound guidance.

The trial showed that the balloon was effective at shielding the rectum for the duration of radiation treatment, says Song: "98 percent of men received significantly lower doses of radiation to the rectum – and, as a result, had fewer side effects in this area." In follow-up visits, the investigators found that the balloon material dissolved within six months after treatment in more than 98 percent of patients.

"These results are exciting," Song continues. The next step is to measure long-term differences in patients' side effects, since radiation proctitis can manifest 18 or 24 months after treatment in some patients. We believe the balloon will continue to pay even greater dividends over the long run." ■



***Song**: 98 percent of men received significantly lower doses of radiation to the rectum, and had fewer side effects in this area.*

Homecoming for Brady alumni: *"It was wonderful to reconnect with alumni and friends and honor Dr. Walsh's unparalleled contributions to the field.".*

Celebrating Walsh's 50 Years at Hopkins

Walsh's passion for discovery, commitment to students, and enduring care for patients continue to fuel surgical innovation and excellence at the Brady.

Fifty years ago, Patrick C. Walsh, M.D., came to the Brady as its third Professor and Urologist-in-Chief and Director of the Institute. This topic was our cover story for last year's *Discovery*: how he revolutionized the treatment of prostate cancer with his development of the nerve-sparing radical prostatectomy; developed a world-class team of scientists and surgeon-scientists studying urological disease; and recruited great faculty. Because thousands of patients with prostate cancer came to the Brady for treatment, and urologic surgeons from around the world came here to learn his procedure, Walsh and his wife, Peg, a brilliant interior designer, also transformed the Brady into the state-of-the-art facility it is today. **His career has been exceptional. Walsh is the most cited urologist in the world and the recipient of every major national and international honor and award in his field. He is truly a luminary in urology.**

Of the many Brady residents Walsh selected and trained as Chief of Urology, 87 percent entered academic careers. Many – including Mohamad Allaf, M.D., now the *Jakurski Family Director* of the Brady – went on to become leaders in academic medicine. In June, Brady alumni, along with patients, donors, and friends of the Brady, gathered to honor Dr. and Mrs. Walsh and to celebrate this remarkable milestone with a research symposium and celebratory dinner. "It was wonderful to reconnect with alumni and friends and honor Dr. Walsh's unparalleled contributions to the field," says Allaf. **"His legacy and impact on our community are profound."**

At the research symposium, Walsh gave a powerful, 50-minute summary of his 50-year journey at the Brady: *"If You Do Not Know Where You Are Going, How Will You Ever Get There?"* https://youtu.be/2lCx5VpmKJk.

Walsh made anatomical discoveries, first in the anatomy laboratory, with retired Dutch urologist Pieter Donker, and then in the operating room, where he ultimately pioneered new surgical techniques to craft a safer, far better operation to remove prostate cancer and preserve continence and potency. This procedure remains a gold standard of care today.

In his honor and spirit, the Brady organized a fundraising campaign called *Discovering Tomorrow*. The campaign has enabled the creation of the Patrick C. Walsh Discovery and Learning Laboratory within SLICE (see story on page 1), the new home of transformative surgical discovery and education in urology. This first-of-its-kind laboratory is off to a robust start, thanks to the generosity of our Pioneering Partners, donors who have made commitments of $100,000 or more, as well as gifts from Brady alumni. ■

Read more about Dr. Walsh and his exceptional career: https://www.hopkinsmedicine.org/news/articles/2023/12/50-years-patrick-and-margaret-walsh-came-to-brady

To learn more about the *Discovering Tomorrow* campaign celebrating Dr. Walsh, please visit: https://www.hopkinsmedicine.org/brady-urology-institute/ways-to-give/discoveringtomorrow

Caring For the Patient

"The secret in the care of the patient is in caring for the patient."
- Francis Peabody (1881-1927), Professor Emeritus, Harvard Medical School

Anyone who has spent time around Patrick Walsh has likely heard this quote from Francis Peabody. These are words Walsh lives by, and it is a message he has taught throughout his 50 years at the Brady.

At the Research Symposium in honor of Walsh, Brady urologist Jacek Mostwin, M.D., Ph.D., gave a memorable talk on this topic. He began with the story of a life-changing encounter.

The year was 1982, and Mostwin had been asked to drive Hugh Judge Jewett, M.D., to the Mid-Atlantic meeting of the American Urological Association. "Dr. Jewett was one of the most distinguished urologists of the 20th century," he says. "His entire professional life was dedicated to the Brady and the treatment of prostate and bladder cancer. He was the first to show evidence that radical prostatectomy could cure early prostate cancer. Now he was approaching 80 and knew that he had prostate cancer."

Mostwin and Jewett arrived a day early for the conference and ate together that evening. "It was a quiet dinner," Mostwin recalls, "mostly filled with Dr. Jewett's reminiscences, at the end of which he said, 'It's been a good life, after all.'" Over the next few days, Jewett began to develop bone pain from metastases from prostate cancer. "I searched around the local pharmacies to find a synthetic opiate to ease his pain, and also obtained a supply of the recently released ketoconazole, which would immediately reduce his testosterone levels to provide rapid relief of the pain caused by the expanding tumor in his spine," says Mostwin. "The following day, we drove back to Baltimore in relative silence. As we neared his apartment, he said to me, **'All my life I've treated this disease, but I never understood it until now.'"**

This idea of "understanding it now" stayed with Mostwin, and he is working to help students and practitioners develop a deeper understanding of illness. He teaches a seminar course to Johns Hopkins undergraduates. The students read and discuss books written by patients and by doctors, and study films looking at medicine from both the patient's and the doctor's perspectives.

In addition, he is collecting and studying first-hand accounts of illness and its treatment. "Our library consists of 16,000 book titles from 1990-2020, and it is growing," he says. Some of these works are being used to teach undergraduate premedical students, "who respond with enthusiasm and gratitude for opening their eyes to the human side of medicine," Mostwin continues. "We foresee a library and a project that can be enlarged, studied, and curated using advanced computer methods, creating new educational resources and programs for medical education and a broader public literacy. We are combining the skills and lessons learned from a lifetime of clinical work such as that of Dr. Jewett and today's Brady family with the understanding that he found through his personal experience."

The idea of understanding it now, he explains, "has shown us a way to work toward a practice of medicine that will be more truly human."

For access to Mostwin's talk and more information about the course (including a book list!), please visit: https://www.hopkinsmedicine.org/-/media/brady-urology-institute/documents/books-publications/Brady-symposium-lives-in-medicine-june-2024.pdf. ■

A New Tactic for Focal Therapy of Prostate Cancer: Water Vapor?

Focal therapy is not for every man with prostate cancer – but it is being used more often for certain patients with very limited, lower-risk cancer that is confined to the prostate.

The benefits of treating cancer within the prostate itself, rather than removing the entire gland surgically or destroying it with radiation, include fewer side effects: particularly, much lower risks of urinary incontinence or erectile dysfunction. Conversely, the risk is that focal therapy might not kill all the cancer – which is why, says Arvin George, M.D., Director of the Prostate Cancer Program at the Brady, rigorous follow-up is essential for patients who choose this option.

George performs laparoscopic and robotic radical prostatectomy on many patients, and he also performs focal therapy – which is still being studied – on a carefully selected cohort. He is heading several national clinical studies of various types of focal therapy, including cryotherapy, high-intensity focused ultrasound, nanoparticle-directed laser ablation, laser interstitial thermal therapy, and bipolar radiofrequency ablation. In a new study, he is investigating a novel tool: water vapor.

The study, "Vanquish® Water Vapor Ablation for PrOstateCancerR" (VAPOR2; NCT05683691), uses transurethral (through the urethra) water vapor – steam – to kill prostate cancer. "This trial is to examine the effectiveness of vapor ablation to prevent progression of disease risk," says George. Specifically, investigators are looking for effectiveness – to see if, three years after treatment, patients remain free from cancer; from cancer that is Gleason Grade Group level 2 or greater; and without need for salvage therapy.

"The primary safety endpoint is defined as freedom from incontinence at 12 months." Men eligible for this study are age 50 or older with a prostate volume of 20-80 cc; a PSA of 15 or lower; cancer stage T2c or lower, with Grade Group 2 disease as confirmed by MRI fusion biopsy. Participants will undergo follow-up MRI and biopsy at six, 24, and 36 months, and will be followed for five years. The study is currently enrolling patients. For more information, please visit: https://clinicaltrials.gov/study/NCT05683691 ■

A Pioneer in Understanding the Microbiome

With help from the Walsh Fund, Karen Sfanos has Contributed Field-Changing Research

Sfanos: *"It's amazing that the reviewers were willing to fund such a novel idea."*

Many of the scientists featured in *Discovery* jump-started their independent research careers with an award from the Patrick C. Walsh Prostate Cancer Research Fund. In fact, some major urologic discoveries have been nurtured and made possible by this seed money.

Since its inception in 2005, this remarkable Fund – which owes its existence entirely to patients and friends of the Brady – has awarded millions of dollars to Johns Hopkins scientists with good ideas worth pursuing. Their research has produced better ways to detect, treat, and prevent prostate cancer. Applications are reviewed by a Scientific Advisory Board comprised of noted Hopkins scientists and lay members.

Scientist Karen Sfanos, Ph.D., has received three awards from this fund. All three have generated important, field-changing research. Her major area of expertise is the microbiome – the millions of bacteria that live in the gut, and also the urinary tract – and their influence on prostate cancer development, progression, and response to therapy.

Her first Walsh Fund award was in 2013 when she was just starting her career. "I was very young," she says. "That award was to study mouse models of chronic inflammation and bacterial infections in the prostate, and it was the beginning of the part of my lab that is *still* looking at infections as a risk factor for prostate cancer."

That research led to a key finding related to other Brady research on a cancer-causing substance called PhIP, found in charred meat: Sfanos and colleagues found that in mice that developed prostate cancer due to PhIP, "if you add a bacterial infection to the prostate, the combination of PhIP and infection accelerates the rate not only of prostate cancer, but other PhIP-related cancers," she says.

At that time, the systemic effect of inflammation was a very new concept, Sfanos explains. This is what the seed money in the Walsh awards is designed to do: allow scientists to develop and test new ideas, and then, once vetted, leverage that research into larger, National Institutes of Health (NIH)-supported projects. "All of my Walsh Fund awards have been high-risk, high-reward."

The next award came in 2016, for a project that, Sfanos says, also seemed quite unorthodox. Her interest in the role of infection in prostate cancer led her to wonder where that infection might be coming from. She suspected that bacteria were escaping into the prostate from the urinary tract – but at that time, no one thought this could be a possibility. "The whole concept of a urinary microbiome was completely controversial," she says.

With this award, Sfanos provided further proof that urine is, in fact, *not* sterile. "Any part of the body that is exposed to air is colonized by microbes, and that absolutely is the case in the urinary tract," she says. "Part of that Walsh Fund award used the very large sample sets from the biobank created by (the Brady's late Director) Alan Partin M.D., Ph.D." Working with Partin and the research team, Sfanos obtained urine samples from more than 100 prostate cancer patients treated at the Brady. "This was the very first urinary microbiome study of prostate cancer," and it was published in the *Journal of Urology*. "That paper was a bit controversial," Sfanos recalls. "Reviewers weren't thrilled with the concept. But it catalyzed an entire field of study. It's amazing that the Walsh Fund reviewers were willing to fund such a novel idea. I don't think I could have funded that study through other sources." Her results were so strong that soon she received a prestigious V Scholar Award.

Her third Walsh Fund award is a study involving the gut microbiome. "Again, it's an out-of-the-box question, a finding we stumbled on in the lab." The study is based on a metabolite called equol, which is only made when soy products from the diet are converted by specific intestinal bacteria. "In the U.S., only about 30 percent of people make equol, but in Asian countries, where they eat a lot more soy, equol is much more commonly produced." Equol has anti-androgen effects on prostate cells. "In *in vitro* models, this molecule can target the androgen receptor."

Sfanos got interested in equol when she was conducting microbial profiling as part of the ORIOLE trial, led by former Hopkins radiation oncologist Phuoc Tran, M.D., Ph.D., which involved treating oligometastasis (only a few small areas of metastasis in prostate cancer) using SBRT radiation. "We found that patients harboring equol-producing bacteria had a lower risk of disease progression." The scientists speculate that equol makes the cancer more susceptible to radiation.

"With our current award, we are studying this in a mouse model," Sfanos says, looking at mice with prostate cancer who receive radiation alone, or radiation plus equol. "We are seeing greater tumor regression in mice that have the combination. Is there some influence on the immune system, as well?" She hopes to find out. "Aren't gut bacteria amazing?" ■

Male Hormones Made By... Bacteria?

"These bacterial androgens can interfere with ADT."

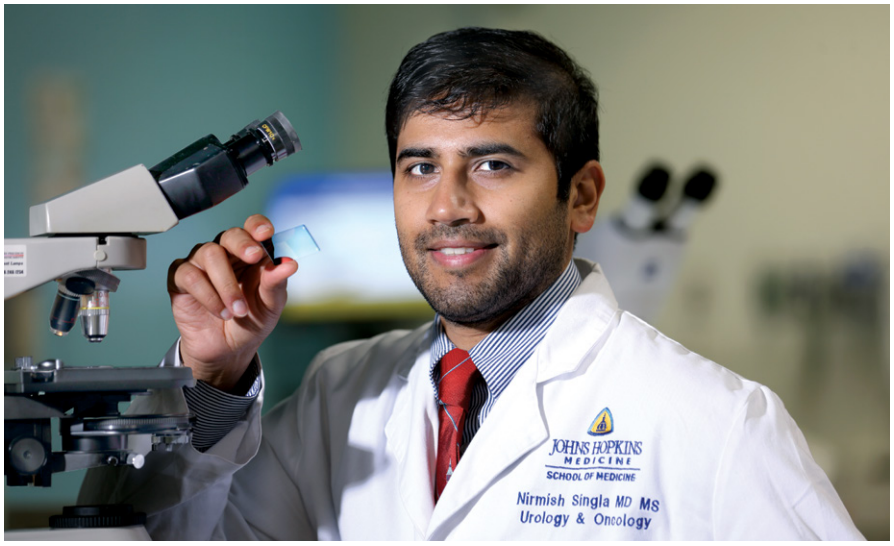
Men on androgen deprivation therapy (ADT) for prostate cancer may face an unexpected wrinkle: a new source of testosterone. **Where is it coming from? Bacteria!** But how can this be?

It turns out, Sfanos says, that "the bacteria that live in areas of the human body, such as the gut, are capable of converting substances found in the gut into hormones, including androgens (male hormones). These bacterial androgens can then interfere with ADT."

In a recent study of men with advanced prostate cancer, Sfanos teamed up with colleagues from the University of Illinois Urbana-Champaign. Her role was to look for bacterial androgen-producing genes in the gut and urinary tract and to determine the prevalence of these genes in relation to treatment response to the prostate cancer drug abiraterone acetate (Zytiga®).

Her colleagues identified two new bacterial genes that are capable of converting androgen precursors into androgens such as testosterone. "These bacterial genes were present in fecal samples and were elevated in a subset of men who were not responding to treatment. We also found that in addition to the gut, bacteria that produce androgens are also present in the urinary tract!"

The significance of androgen-producing bacteria in the urinary tract is not yet clear, Sfanos says. "However, it is possible that these bacteria may contribute to the early development of the disease. Overall, the study moves us one step closer to identifying bacterial genes that require targeted therapies, so that prostate cancer drugs can be more effective." ■



Singla: *"In patients with locally advanced RCC who are treated with surgery, there is a growing interest in neoadjuvant and adjuvant strategies to reduce the risk of recurrence and death."*

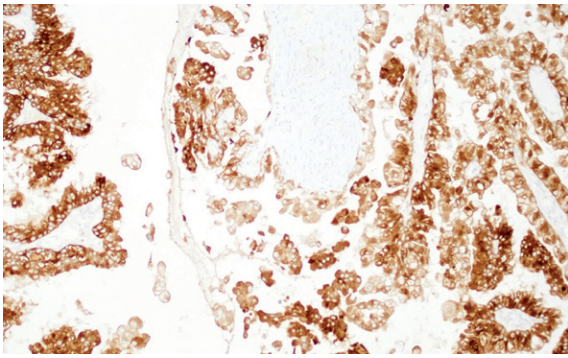
DISCOVERY IN KIDNEY CANCER

Rethinking "pT3a" Stage in Kidney Cancer

Stage pT3a kidney cancer is a catch-all title, says urologist Nirmish Singla, M.D., Director of the Kidney Cancer Program, and not all cancers in this group are equal. "By definition, stage pT3a kidney cancers are locally advanced and invasive," he explains. "However, some pT3a tumors invade the perinephric fat (fat around the kidney), some reach into the fat in the renal sinus (a space within the kidney), and some invade the renal vein or its branches. There can also be any combination of these features." Because the pT3a category is so broad, "simply defining a pT3a tumor by its pathologic stage may not adequately reflect its aggressiveness."

In a recent analysis of the SEER registry, a comprehensive database of case statistics maintained by the National Cancer Institute, former Brady urologic oncology fellow Michael Rezaee, M.D., M.P.H., and colleagues examined the different pT3a subtypes of more than 10,000 patients diagnosed with renal cell carcinoma (RCC). They found that patients who had a combination of two or more invasive subtypes were more likely to die of their cancer than those with just one subtype. "This discrepancy in survival was most pronounced in patients with stage pT3a papillary RCC," says Singla, senior author of the study, which was published in *Urologic Oncology: Seminars and Original Investigations*. "Invasion of the renal vein or its branches portended the worst prognosis, followed by renal sinus fat invasion, followed by perinephric fat invasion."

This study has important ramifications for delivering patient-specific treatment, Singla continues. "In patients with locally advanced RCC who are treated with surgery, there is a growing interest in perioperative (neoadjuvant and/or adjuvant) therapeutic strategies to reduce the risk of recurrence and death." At the same time, *the goal is to not overtreat patients*. "Our work highlights the need to refine pT3a staging criteria to help guide individualized, multimodal strategies to treat locally advanced kidney cancers." ■



The brown cells show a newly recognized subtype of kidney cancer, called renal cell carcinoma with fibromyomatous stroma. This tumor is characterized by molecular alterations in two main molecular pathways, TSC1/2/mTOR and TCEB1/ELOC. In a recent study, Hopkins pathologists Huili Li, M.D., and Andres Matoso, M.D., showed that an immunohistochemical stain called GPNMB is expressed only in the subset of tumors with genetic changes in these pathways. "This advancement provides a quick and inexpensive test to achieve subclassification of these tumors without the long wait and high cost of molecular testing," says Li. The study was published in the *American Journal of Surgical Pathology*.

When to Operate? A Guide for Patients with Metastatic Kidney Cancer

Does the patient need surgery? Should it be before or after systemic treatment, or not at all?

Cytoreductive nephrectomy (CN) is the surgical procedure to remove the primary tumor in patients with metastatic kidney cancer.

"The role and timing for CN—whether or not to offer it, in whom to offer it, and when to offer it—have been a moving target over the past couple decades as therapies have evolved," explains urologist Nirmish Singla, M.D.

"Multiple retrospective studies, including those done in collaboration with Brady investigators, have demonstrated benefits to CN in select patients," Singla continues. **"The key here is patient selection,"** but this is not always clear. "A combination of patient factors and tumor factors are important to consider in determining whether it would be beneficial to offer CN upfront," *before* systemic treatment; *after* a durable response to systemic therapy (this is "deferred" CN), or not at all. "This decision often involves a nuanced and complex multidisciplinary discussion tailored to each individual patient."

Singla and medical oncologist Yasser Ged, M.D., who co-lead the Kidney Cancer Program and established the Kidney Cancer Multidisciplinary Clinic at Johns Hopkins, recently proposed a treatment algorithm to help physicians and patients make this decision. It is based on several factors including the type of kidney cancer, degree and location of metastases, and whether the patient has other medical conditions. Their comprehensive review was published in *Current Opinion in Urology*, with postdoctoral fellow Stephan Brönimann, M.D. as first author. ■

Novel Treatment Approaches for a Rare Form of Kidney Cancer

"Targeting these receptors via a combination of novel and repurposed FDA-approved agents represents a new paradigm for treatment."

Translocation renal cell carcinoma (tRCC) is rare – making up less than 5 percent of all cases of kidney cancer – and is more common in children than in adults. In children, it usually grows slowly, but in adults, this cancer can be aggressive.

Promising news: Johns Hopkins pathologist Kaushal Asrani, Ph.D., has identified potential new targets for treating tRCC: two receptors that sit on the surface of these cancer cells. The receptors, *EGFR* and *HER2*, are "commonly overexpressed and successfully targeted in numerous cancers," says Asrani, "including breast cancer."

In mouse models of tRCC, Asrani found *EGFR* and *HER2* in abundance – promising findings that earned him the Kidney Cancer Association's Translocation RCC Focus Award to investigate the therapeutic potential of targeting *EGFR/HER2* in tRCC.

In new research, along with Hopkins scientist Ravi Anchoori, Ph.D., and the biotech firm Anchoori founded (Up Therapeutics LLC), Asrani will explore the feasibility of targeting *EGFR/HER2*. They will use a combination of agents that are already FDA-approved and available – kinase inhibitors and antibody-drug conjugates – as well as some novel agents called lysosome-targeting chimeras (*LYTAC*s), which disrupt the cancer cells' ability to get rid of waste products. These agents have shown success in blocking other cancers, but have not been tested in preclinical models of tRCC.

"Targeting these receptors via a combination of novel and repurposed FDA-approved agents represents a new paradigm for treatment of tRCC," says Asrani. Further, "it may reveal new potential therapeutic targets in this deadly disease." ■

Why is Testicular Cancer on the Upswing in Hispanic Patients?

"We still have a lot of work to do to understand and combat this alarming trend."

Nearly 10,000 American males – the vast majority of them under age 50 – are diagnosed with testicular cancer each year.

"The incidence of testicular cancer has been steadily rising," says urologist Nirmish Singla, M.D., "and the rate of increase has been highest among the Hispanic population."

Recently, former Brady urologic oncology fellow Michael Rezaee, M.D., M.P.H., and Hopkins medical oncologist Roy Elias, M.D., co-led a clinical and molecular study using data from the National Cancer Institute's SEER Registry and the American Association for Cancer Research's database, GENIE.

Among nearly 44,000 patients diagnosed with testicular cancer between 2000 and 2020, they found the proportion of Hispanic patients steadily rose. "Compared to non-Hispanic White patients, Hispanic patients were more likely to be diagnosed at a *younger* age but more likely to harbor *more advanced disease* including metastases at diagnosis and more aggressive pathologic features," says Singla, senior author of the study, which was published in *Urologic Oncology: Seminars and Original Investigations*. "They also were more likely to die of their cancer."

What accounts for this rise in incidence among Hispanic males? It is likely complicated: instead of one or a few telltale bad genes, it is probably a combination of genetic, social, and environmental factors, Singla continues. "We still have a lot of work to do to understand and combat this alarming trend. Access to care, cultural barriers, quality of care, and biology may all influence outcomes in Hispanic patients diagnosed with testicular cancer." Increasing public awareness, so the disease can be diagnosed sooner, is essential, he notes, "and more adequately representing minority groups in future studies is paramount to improving outcomes. When caught early, this is a highly curable form of cancer." ■

DISCOVERY IN BLADDER CANCER

New Hope for a Rare, Aggressive Form of Bladder Cancer

Thanks to the team's results, SBC is no longer considered a chemotherapy-resistant form of bladder cancer.

Sarcomatoid bladder cancer (SBC) is rare – affecting fewer than five percent of patients with bladder cancer – but aggressive. It had been considered resistant to chemotherapy – until several years ago, when medical oncologist Noah Hahn, M.D., Deputy Director of the GBCI, tried something new in collaboration with Brady urologists.

"A sarcomatoid bladder cancer patient with bulky, unresectable (inoperable) disease was referred to the GBCI Multidisciplinary Bladder Cancer Clinic," says Hahn. He gave the patient a triple-drug combination of cisplatin, gemcitabine, and docetaxel (CGD), and the result was a shocker: "Surprisingly, the patient's tumor shrank dramatically, making cystectomy (removal of the bladder) possible. Once removed and examined under the microscope, **the bladder tissue showed a pathologic complete response – no evidence of tumor – at the time of surgery!"** says Hahn's colleague and mentee, medical oncologist Burles "Rusty" Johnson III, M.D., Ph.D.

Encouraged, over the next eight years, Hahn and other GBCI investigators gave CGD to 16 more patients with muscle-invasive SBC before cystectomy. "We found that 38 percent of these patients had a complete response – again, no tumor found – when surgery was performed to remove the bladder."

Their findings were published in *Bladder Cancer* in June 2024, and due to their results and the work of others, SBC is *no longer considered a chemotherapy-resistant form of bladder cancer*. "These results dispelled the longstanding dogma that chemotherapy does not work in this disease," says Johnson. "While our cohort is small, this study represents the first data generated in SBC patients who were treated with a uniform and consistent treatment regimen. This has provided the bladder cancer community with valuable insights," and may lead to larger studies and new therapeutic approaches.

But wait, there's more! Johnson and Hahn went deeper to learn about SBC, and the drugs that might kill it, on a molecular level. "Our team investigated the gene expression patterns of SBC tumor tissue by performing whole transcriptome RNA sequencing on patient samples before treatment," says Johnson.

And once again, they obtained results they didn't expect: "We found that SBC is heterogeneous, and thus does not represent a disease completely distinct from traditional muscle-invasive bladder cancer," says Johnson. They also discovered that immunotherapy drugs might work here: "It turns out that SBC tumors have high expression of multiple immune-related genes, such as PD-L1, whose expression in tumor samples often correlates with benefit to immune checkpoint inhibitors. We are planning clinical and laboratory-based studies to investigate this possibility." ■

The Microbiome and Bladder Cancer

How important is the microbiome – the population of millions of bacteria that live in a certain place, like the gut, the skin, or the urine – in bladder cancer? This is a fairly new question, and it's being asked by investigators Armine Smith, M.D., the *Mary and Armeane Choksi Scholar, Jean Hoffman-Censits, M.D.*, and David McConkey, Ph.D., Director of the Johns Hopkins Greenberg Bladder Cancer Institute and the *Erwin and Stephanie Greenberg Professor of Urology*.

"We're particularly interested in how the microbiome affects the course of bladder cancer and the response to treatments like Bacillus Calmette-Guerin (BCG) immunotherapy," says Smith. "The influence of microbiome composition on the effectiveness of BCG is largely unexplored."

Scientists have noticed that the urine of people with bladder cancer contains some species of bacteria that aren't seen in the urine of healthy people. For example, bladder cancer patients are more likely to have *Pseudomonas, Fusobacterium, Acinetobacter,* and *Anaerococcus.* People who don't have bladder cancer have entirely different species, including *Lactobacillus, Corynebacterium*, and *Veillonella*. And then there's *Streptococcus spp* – which may, or may not, correlate positively with bladder cancer.

Is this a chicken-and-the-egg situation? Which came first – the different bacteria, or the cancer? Nobody knows. Could changing the bacterial landscape of the urine affect response to treatment or slow down the disease? Again, this is all new territory.

And there are so many questions: "Women are less likely to get urothelial cancer than men – but they tend to be diagnosed at more advanced stages and to have poorer survival," says Smith. "What accounts for this gender-based disparity?" Among patients with urothelial cancer, is the microbiome somehow different between women and men?

To learn more, the investigators are collecting specimens from patients newly diagnosed with bladder cancer and from those undergoing intravesical immunotherapy and chemotherapy. "By analyzing their microbial composition, we aim to uncover critical relationships among the microbiome, clinical outcomes, and treatment success."

In a related study, the team will examine how treatments affect immune cells called cytokines, which "are crucial in BCG's effect against bladder cancer," says Smith. Cytokines, known to influence mood, may also play a role in the anxiety and depression experienced by many cancer patients. "To enhance our research, we have incorporated liquid biopsies" – sophisticated tests that detect and analyze cancer cells and tumor DNA found in the blood. "These cutting-edge diagnostics allow us to monitor the success of treatments more effectively," without the need for an invasive and painful surgical biopsy. ■

Neoadjuvant Chemotherapy in UTUC

For patients with high-risk upper tract urothelial carcinoma (UTUC), a course of neoadjuvant chemotherapy before surgery can be very helpful: In fact, two recent clinical trials, including one led by medical oncologist Jean Hoffman-Censits, M.D., have shown that as many as 19 percent of patients achieve a pathologic complete response (no cancer found by the pathologist after surgery) in the primary tumor. However, more than 60 percent of patients do have some residual disease after neoadjuvant chemotherapy.

Story continues on the next page >

What are the implications of residual disease after neoadjuvant chemotherapy? Brady resident Sean Fletcher, M.D., recently led a study to find out. In an analysis of nearly 2,000 patients who underwent radical nephroureterectomy for high-grade UTUC, those who had residual invasive ("non-responding") disease after chemotherapy were found to have relatively poor survival outcomes.

"The extent of residual disease after chemotherapy is linked to how patients will fare," notes urologist Nirmish Singla, M.D., senior author of the study, which was published in *European Urology Oncology*. "We need better ways of predicting who will respond to cisplatin-based chemotherapy so we can selectively offer it to those who will benefit from it. We also need to expand our clinical trial offerings to those who are less likely to respond to cisplatin."

Immunotherapy may help: Looking for a better approach for patients who don't respond to neoadjuvant chemotherapy, Hoffman-Censits is leading a multicenter, phase III clinical trial. Patients with high-risk, localized UTUC will be randomly assigned either to receive neoadjuvant chemotherapy alone or neoadjuvant chemotherapy combined with immunotherapy before surgery. Hoffman-Censits and Singla co-direct the UTUC Program and multidisciplinary clinic at Johns Hopkins. ■

A Better Treatment for NMIBC?

For treatment of non-muscle invasive bladder cancer (NMIBC), the "go-to" therapy for decades has been Bacillus Calmette-Guerin (BCG), says Max Kates, M.D., Director of Urologic Oncology. But BCG is not perfect, he adds. "There have been problematic shortages as worldwide demand has increased," resulting in rationing of the drug, "and for certain patients, adverse complications," including a host of possible side effects including flulike symptoms, fatigue, and urinary tract infection.

Is there a better way to go? Kates believes there is: a combination of two chemotherapy drugs, gemcitabine and docetaxel (GEMDOCE). He is Principal Investigator of the BRIDGE trial (NCT05538663), a national phase III clinical trial he designed to compare both approaches in newly diagnosed, high-risk patients. In intravesical treatment, both drugs have been well-tolerated with few side effects – which include nausea and bladder spasms.

Both BCG and GEMDOCE are *intravesical* treatments, administered directly into the bladder. But they work in very different ways. BCG is a form of immunotherapy made from live bacteria – in fact, the same strain of bacteria used to create the tuberculosis vaccine. BCG stimulates the immune system to attack the cancer cells lining the bladder – as it would fight off a common cold. In contrast, gemcitabine acts against cancer cells by blocking them from making DNA, and its partner in GEMDOCE, docetaxel, stops cancer cells from growing and dividing. Both treatments can shrink NMIBC and prevent it from recurring.

This trial, the first of its kind in more than 30 years, has the capacity to change the way early bladder cancer is managed," says Kates. "GEMDOCE offers a clear alternative that may be just as good as BCG."

So far, more than 500 patients have been enrolled in the BRIDGE trial from more than 60 centers. "As part of this effort, we are also collecting urine, blood, and tissue samples," says Kates. "Our goal is not only to demonstrate that intravesical GEMDOCE is equivalent to BCG, but also to develop genomic biomarkers that can predict which patients will respond best to which therapy."

Locally Advanced and Metastatic Urothelial Cancer: Encouraging Results from a Practice-Changing Study

For patients with locally advanced and metastatic urothelial cancer of the bladder and upper tracts (ureters and renal pelvis), 2024 has been an uncommon and incredibly hopeful year," says medical oncologist Jean Hoffman-Censits, M.D., co-director of the Upper Tract Urothelial Cancer Multidisciplinary Clinic. "In fact, for the first time ever, the standard of care for this disease has changed!"

Advanced urothelial cancer is the most common form of bladder cancer, and for many years the treatment has been a combination of two drugs: cisplatin and gemcitabine (CG). Now we know that a combination of the anticancer drugs, enfortumab vedotin, plus pembrolizumab (EVP), works much better – thanks to a landmark study, led by Hoffman-Censits and the EV-302 Trial Investigators, published in the *New England Journal of Medicine* in March 2024.

In this large trial involving nearly 900 patients, scientists from the Greenberg Bladder Cancer Institute, along with colleagues from 185 centers across 25 countries, compared the traditional CG treatment to the EVP combination. **"We found that patients treated with EVP lived almost twice as long compared to those treated with CG.** The time to cancer progression was significantly longer in the EVP treated group, as well."

More good news: the investigators found that EVP is "better tolerated by more patients than CG," says Hoffman-Censits.

The EVP drugs are less toxic because they are highly specific: "Enfortumab vedotin (EV) is in a new class of drug called an antibody-drug conjugate (see below), in which an anticancer drug is attached to a monoclonal antibody that seeks out cancer cells," Hoffman-Censits explains. "When it finds cancer cells, it binds to a protein on the surface of the cells and directs the cancer-killing drug inside, sparing nearby tissue." Pembrolizumab is an immunotherapy drug known as a "checkpoint inhibitor." It unleashes specific immune cells to help the body fight cancer.

Based on the study's strong results, the FDA has approved EVP for the treatment of urothelial cancers.

In related work: Hoffman-Censits and colleagues in Johns Hopkins Rheumatology are learning more about how EV works. "Antibody-drug conjugates are like smart bombs," she says. A very small payload – traditional cell-killing chemotherapy wrapped in a protective envelope – is attached at the molecular level to an antibody, an immune system weapon with a tiny target: in this case, a molecule called Nectin-4 that sits on the surface of urothelial cancer cells.

Because the target is so individualized, EV delivers the chemotherapy directly to the cancer cell. "This leads to profound cancer shrinkage in many patients, while generally sparing normal tissues," says Hoffman-Censits.

However, Nectin-4 is also found in the skin. Thus, skin reactions, sometimes severe, are common in nearly half of all patients treated with EV. "EV was FDA-approved (by itself, not in combination with pembrolizumab) for advanced urothelial cancer in 2019, and our

team was involved in the early studies leading to this approval. We noted, and were the first to report in the literature, that EV-related skin toxicity seems to correlate with out-comes including response and cancer-related survival." These results were published in *Frontiers in Oncology*. "Collection and analysis of these data were possible through efforts of talented postdoctoral fellow Elina Vlachou, M.D., who joins our team from Greece." ■

New Hope in Bladder Cancer Treatment

Good news for patients with bladder cancer: "Breakthroughs in drug development and in our understanding of cancer biology have allowed us to safely preserve more bladders and to de-escalate care," says Max Kates, M.D., the *R. Christian B. Evensen Professor in Urology* and Director of the Bladder Cancer Program

This "slow and steady de-escalation" is happening in the care of both muscle-invasive and non-muscle-invasive bladder cancer (MIBC and NMIBC), Kates adds. "Our hope is that our therapies will prevent the cancer from progressing and prevent the need for a cystectomy (bladder removal). But at the very least, we are often able to preserve bladders, sometimes for years."

Bladder cancer treatment has achieved synergy: **powerful new drugs are showing such remarkable results that patients who weren't considered candidates for surgery now have cancer that is now considered operable.** "It's been amazing," says Kates. "Probably the most important development that's occurred in the last half-century happened this past year with the approval of a combination of drugs called EV Pembrolizumab (EVP; see page 16) for metastatic bladder cancer."

When the results of clinical trials for EVP were presented at a national meeting of medical oncologists, the drug "got a standing ovation – which has never happened!" Kates notes. "We used to say that once you had metastatic bladder cancer, you had a four-percent chance of survival. Now that number is rapidly growing; I don't even know if we have an estimate. There are huge implications for all stages of the disease."

Before this drug, patients diagnosed with metastatic bladder cancer typically saw a medical oncologist. "Now we are seeing such profound responses from this disease that we're doing surgery to help consolidate some of these amazing responses from the systemic therapy." It used to be that bladder cancer was not a multidisciplinary field, he adds. "Now that systemic therapies have improved, medical oncologists are involved at the early stages, and surgeons are treating disease they never used to treat. That shows you how the field is completely changing in terms of how we're thinking about it. We are seeing complete responses!"

Kates and medical oncologist Noah Hahn, M.D., recently started a multidisciplinary clinic for NMIBC at Johns Hopkins. "Together, we see some of the most complicated cases of NMIBC in the region, and we develop a tailored treatment plan for each patient."

Doctors have known since the late 1970s that bladder cancer is "incredibly sensitive" to immunotherapy, Kates continues: "BCG is one of the oldest cancer drugs in the world, and one of the earliest forms of immunotherapy." EVP is next-generation immunotherapy.

The Johns Hopkins Greenberg Bladder Cancer Institute is one of the few centers devoted to research and treatment of bladder cancer in the world. "We see more than 50 new bladder cancer patients a month," says Kates, "and we have made an effort to have a clinical trial available to every patient in every disease space within bladder cancer – from the earliest stages to late-stage metastatic disease." Many of those trials involve combinations of therapy: immunotherapy and antibody-drug conjugates, as well as traditional chemotherapy and targeted therapy.

Some of these are "unique options that we may be the only center in the country able to provide" notes Kates.

This is what Kates wants patients and their families to know: "It does not need to feel like the end of your life if you receive a diagnosis of bladder cancer. The reason to come to a major center of excellence like Johns Hopkins is because we meld the art and science of medicine. The science is these new breakthroughs and the clinical trials. But at the end of the day, medicine is individual, and customizing the science to each patient, and their needs, and their family's needs, is what makes a difference." ■

BIG PLANS FOR THE FUTURE

Ron Singer and Penny Miller are partners, both inspiring examples of resilience, courage, and the power of a positive outlook.

Ron was diagnosed with bladder cancer in 2018, the year his wife passed away after a long battle with pancreatic cancer. Penny lost her first husband after 38 years of marriage; he died of stomach and esophageal cancer. She married again, and her second husband died of a heart attack 14 years into their marriage.

In 2020, Ron and Penny found each other. They have big plans for the future, starting with a cruise in a few weeks. "There's a lot more to do in life," says Ron. "Both of my parents lived to very old age. Penny's mom died at 99, and her dad was 101. God willing, we have a couple of decades left!"

Ron's bladder cancer was diagnosed early, when traces of blood showed up in his urine at a routine physical. "I practically lived at Johns Hopkins between 2015 and 2018, when my wife passed away," he says. He began seeing urologist Max Kates, M.D., and medical oncologist Noah Hahn, M.D. "They took care of me," he says. "We decided at that time to do a bladder preservation scenario, which involved radiation, chemotherapy, and some other treatments." The treatment was effective and allowed Ron to keep his bladder for six more years.

This year, however, "Dr. Kates and Dr. Hahn said, 'We think it's time to take the bladder out.'" Kates removed Ron's bladder and prostate. "So here I am now," says Ron, "roughly five months after the surgery, back in Florida," trying to get used to the "new normal" – living without his bladder, but cancer-free, no longer in pain, and sleeping better at night. Although he is "not 100 percent" accustomed to the ostomy bag, "I have a better quality of life."

Ron has committed $100,000 over the next five years to support the newly established Non-Muscle-Invasive Bladder Cancer Multidisciplinary Clinic (NMIBC MDC) at Johns Hopkins – the first of its kind in the country – which Kates and Hahn co-direct. "We've been donating towards their research for years," he says, "but we thought it would be a good idea to put those donations towards this MDC, and we will continue to support that clinic as long as they need it, so we can help other patients who are going through this."

Over the years, even before the MDC was stablished, "I have basically been in a multidisciplinary clinic – because every time I came to Hopkins, Drs. Kates and Hahn took care of me together. The two of them are terrific physicians. It was worth flying up from Florida and staying the two to three days each time." Ron also has a local urologist in Florida who coordinates with Kates and Hahn.

Ron's strong family support – his two sons meet him at the hospital whenever he comes to Hopkins, and Penny has accompanied him on every visit over the last four years – encourages him, and the care provided by Kates and Hahn bolsters Penny, too. "I have been so impressed," she says, "with how wonderful, compassionate, supportive, and capable they are." ■

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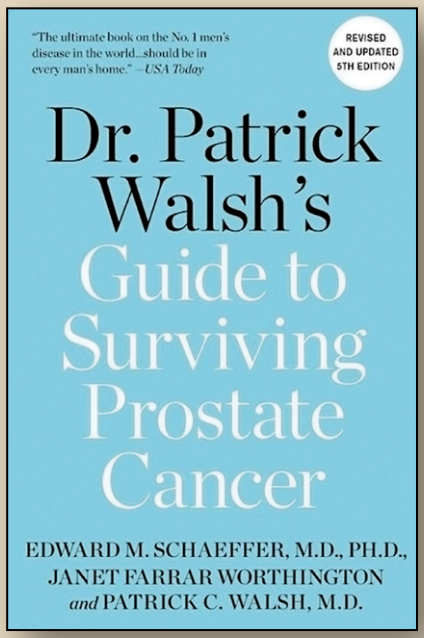

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