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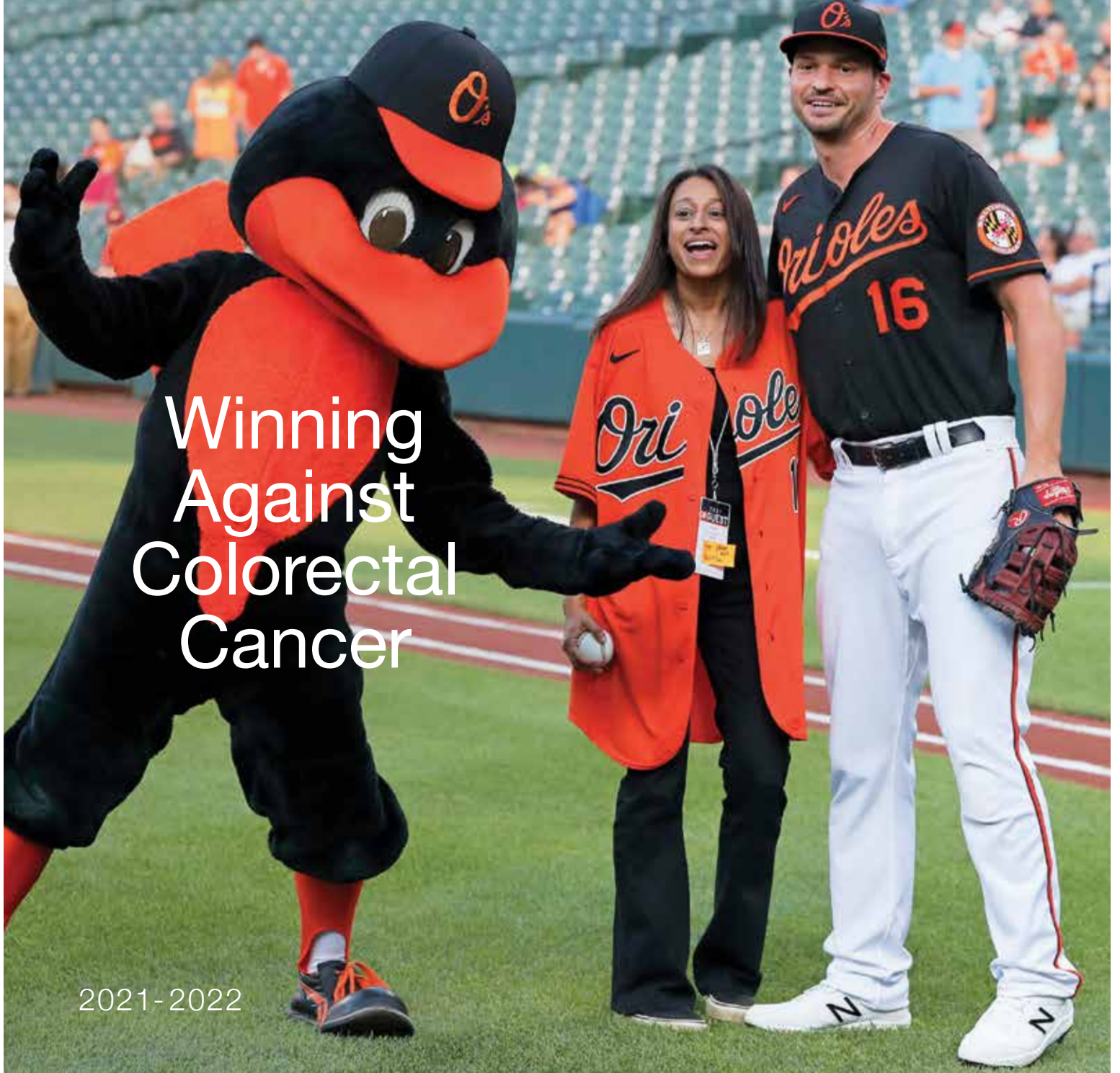
THE JOHNS HOPKINS KIMMEL CANCER CENTER

COLORECTAL CANCER MATTERS

THE NEWSMAGAZINE OF THE
COLORECTAL CANCER RESEARCH CENTER OF EXCELLENCE

Winning
Against
Colorectal
Cancer

2021-2022



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CLICK ON THE HEADLINE TO READ THE STORY



Making History

Discoveries That Paved the Way for Unprecedented Progress



Micromanaging Colon Cancer

The Microscopic Society Living Within Us



Discovery

Advancing New Therapies Through Clinical Trials



Earlier Screening Being Studied

Research of Screening for Colorectal Cancer Starting at Age 40



A Model for Progress

Building a GI Cancer Program in Greater Washington Area



Vaccine Approaches for Advanced Colorectal Cancer

Unique Vaccine Strategies to Help Patients



Beating Colon Cancer During a Pandemic

Jerold Looks Forward to Returning to His Hobbies



Noteworthy

- Kimmel in the Community Combatting Colon Cancer
- Expert Named to National Cancer Advisory Board
- Web Exclusives on our Cancer Matters Blog



Advances

- Colon and Rectal Cancer Surgery
- Shorter Course of Radiation Therapy – *The 5x5 Approach*



Inspirational and Transformational

Coming in the Next Issue



Unexpected Opponent

Baltimore Orioles' Trey Mancini Defeats Colon Cancer



Complex Care for Complex Cancers

A Young Woman's Journey with Advanced Colorectal Cancer



2021/2022

COLORECTAL Cancer Matters

The Sidney Kimmel
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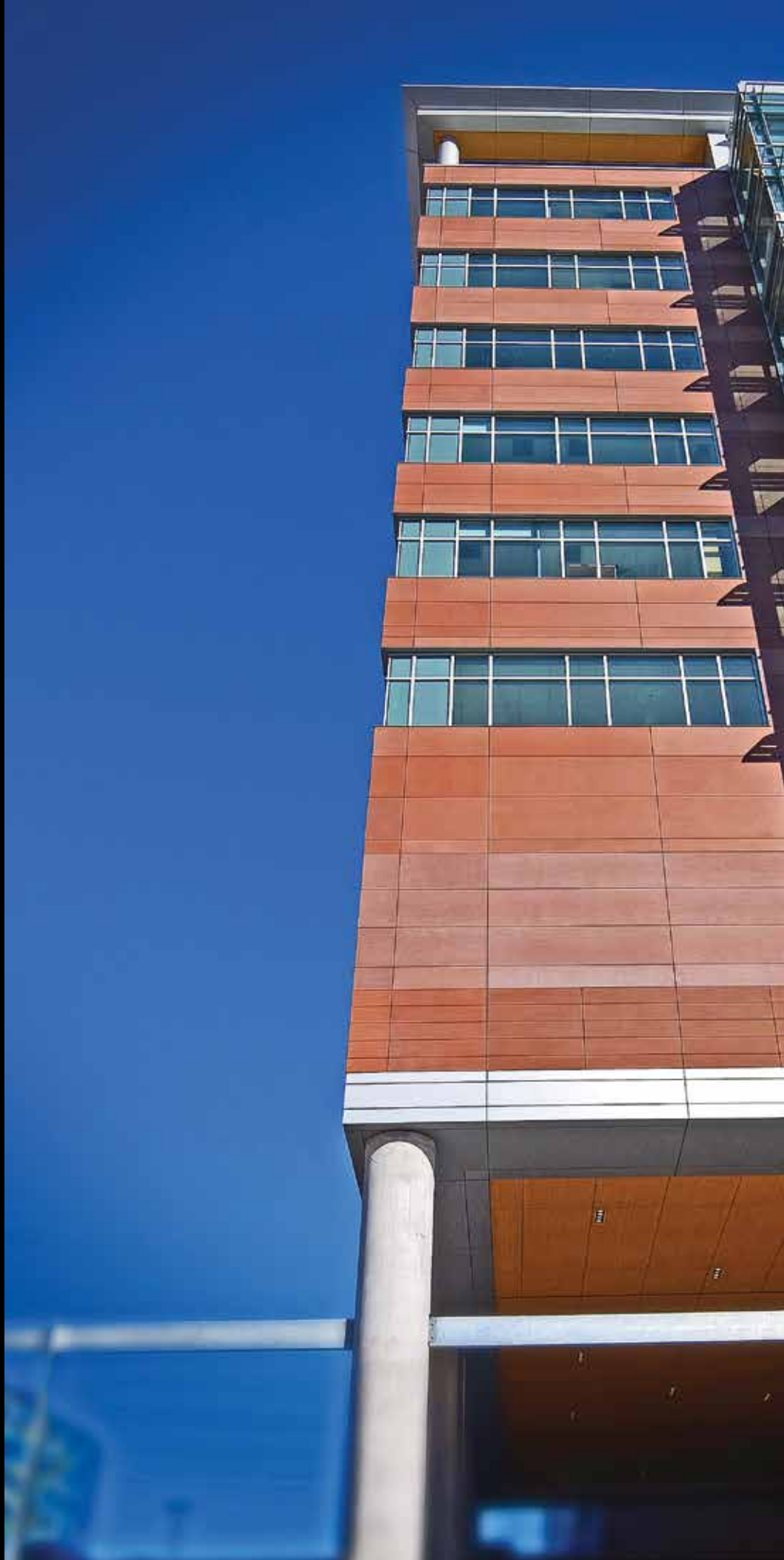
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ON THE COVER:
Nilofer Azad, M.D. with Trey Mancini. Dr. Azad threw out the
first pitch at Oriole Park at Camden Yards.





Making History

Discoveries That Paved the Way for Unprecedented Progress

IF THE STRENGTH of a program can be measured by the foundation upon which it is built, the Kimmel Cancer Center's Colorectal Cancer Research Center of Excellence and its Multidisciplinary Clinic are titans.

The rich history of colon cancer discovery at the Johns Hopkins Kimmel Cancer Center began in the fields of genetics and epigenetics, has advanced into immunology, and now has harmonized to bring the concept of precision medicine into practice. The research has been occurring simultaneously in laboratories throughout the Johns Hopkins Kimmel Cancer Center but remarkably intersected to create promising new, first-of-their-kind therapies.

Genetics

In the 1980s, without the benefit of today's automated gene sequencing technology, colon cancer was at the center of paradigm-shifting research by cancer genetics pioneers **Bert Vogelstein, M.D.**, Clayton Professor of Oncology; **Kenneth Kinzler, Ph.D.**, Barry Family Professor of Oncology; and group. They revealed colon cancer as a genetic disease, caused by a building series of inherited and acquired gene alterations. As the genetic errors accumulate, cancers originate, grow



Vogelstein



Kinzler

and finally spread. It started with small clusters of abnormal cells in the lining of the colon, advancing to benign tumors known as polyps, then to a cancerous tumor in the colon and finally pushing the tumor to its most lethal form, as it spreads outside of the colon to other parts of the body.

Today, these discoveries have led this research team, and others across the country, to develop genetic tests, screening diagnostics and targeted therapies for colon and other cancers. Ushering in the age of molecular biology, Drs. Vogelstein, Kinzler and his co-collaborators were among the first to apply it to the study of a human disease, developing the knowledge and tools to look inside the submicroscopic molecules of the cell to reveal those rare, uncorrected errors in our DNA that put the cancer process in motion.

This science was a cornerstone for the colorectal cancer research program and its multispecialty clinic. It represented a critical turning point in cancer discovery and the opportunity to bring about unprecedented changes in how cancer treatment could be imagined and delivered. We now understood that colorectal cancer—and other cancers—centered on a delicate balance between cell growth accelerators known as oncogenes and the cancer-controlling genes called tumor suppressor genes that kept them in check. Alterations to these genes, either inherited or acquired throughout life, disrupted the delicate balance, giving an advantage to cell growth. More than providing

an understanding of the causes of the disease, it began to reveal targets for prevention and treatment.

Benjamin Baker, a Johns Hopkins internist, was intrigued by this revolutionary concept that cancer was caused by genes gone awry. He helped Kimmel Cancer Center investigators form the Bowel Tumor Working Group, which proved to be a turning point, bringing together seasoned clinicians and investigators with bright, young scientists to explore this visionary, gene-centered hypothesis in colorectal cancer.

One by one, they uncovered a series of genetic mistakes that revealed how colorectal cancer started and progressively became more and more dangerous as these genetic alterations accumulated. They identified the genes responsible for the major forms of inherited colorectal cancer as well as genes that initiated the more common noninherited form of the disease.

Having identified the gene alterations that caused inherited colon cancers, such as familial colon cancer and familial adenomatous polyposis (FAP), they developed tests to detect the alterations and radically changed how these patients were managed in the clinic. For the first time, clinicians could know which family members had inherited colorectal cancer-causing mutations so that those at risk could be monitored closely for cancer. As important, the tests also revealed family members who did not have the gene mutations so they could be spared unnecessary screening measures. It was the first example of precision, or individualized, genome-based medicine for patients with typical forms of cancers.

At the time, little was known about colon cancer other than it was an unstable disease that got worse with time. Dr. Vogelstein credits Dr. Baker and the formation of the collaborative working group for advancing the understanding of colon cancer. The seed money brought together through the Bowel Tumor Working Group proved to be a key turning point.

As colon cancer research was advancing, these discoveries also triggered other investigators at the Kimmel Cancer Center and around the country and the world to look for similar patterns in other cancers.

Researchers looked first to the rarest of colon cancers, inherited colon cancer syndromes, for the answers. Though they represented the smallest percentage of colon cancers, the Bowel Tumor Working Group team believed the same genetic underpinnings that led certain families to be plagued by an alarmingly high incidence of colon cancer—and typically at a much younger age—would shed light on colon cancers among the general population.

Each person inherits two copies of every gene—one from the father and one from the mother. In inherited colon cancer syndromes, family members are born with only one good copy of a gene, giving them a head start on the colon cancer process. As subsequent assaults from diet and other environmental carcinogens knock out the one good copy, the cascade of cellular errors that ultimately results in cancer is put in motion.

As they looked for genetic errors among inherited cancers, Drs. Vogelstein and Kinzler, and pathologist



Stanley Hamilton, M.D., identified a mutation of the APC gene in FAP, a rare inherited syndrome in which affected people get hundreds of benign tumors known as adenomas or polyps in their colons. Further studies showed the same mutation to be the one that jump-starts the cancer process in



the nearly 140,000 people within the general population who are diagnosed with colon cancer each year.

For gastroenterologist and Bowel Tumor Working Group team member **Francis Giardiello, M.D.**, the discoveries were monumental.

“Now that we knew the genes, we could figure out the pathways they work through and use them as targets for treatment,” says Dr. Giardiello.

He was already anticipating the need for combination therapies to overcome the complexity of the disease. He predicted that therapies that hit just one molecular pathway or cell activity wouldn’t work because the body has many systems in place that protect key functions. Like other normal cellular mechanisms, cancer has hijacked these protective properties to act as barriers to therapy.

“There are multiple pathways involved in colon cancer, so we have to target them all, and that means using multiple drugs,” says Dr. Giardiello. “Up until 2000, we used one or two drugs to treat colon cancer, with 5FU being the main one. It wasn’t that great, but nobody had a better drug. But, if we use it in combination with other drugs, it could hit more pathways and be more effective.”

At the same time, experts were discovering alterations that did their cancer-causing damage by altering the chemical environment of DNA. These were known as epigenetic alterations.

Epigenetics

Cancer genetic and epigenetic research have advanced dramatically in the last decade, and with the leading experts in both disciplines at the Kimmel Cancer Center, investigators have uncovered a convergence of the two fields. Many of the genes mutated in cancer are genes that regulate epigenetic processes, providing a link between genetic mutations and epigenetic abnormalities. Like a volume control, epigenetic alterations can amplify or dampen a series of genes, changing the global expression pattern and dramatically altering the behavior of cells.

These chemically mediated on and off switches alter the function of genes without mutating the DNA, usually by adding chemical groups to the signaling portion of genes or by tightening or relaxing how the DNA is packaged

within the cell.

Like Drs. Vogelstein and Kinzler in cancer genetics, Kimmel Cancer Center researcher **Stephen Baylin, M.D.**, was a pioneer in the field of



cancer epigenetics research.

He revealed that chromatin, a complex combination of proteins, mainly histones, is responsible for compressing the six feet of DNA to fit inside a cell. A loose chromatin, he found, resulted in normal gene expression, but add methylation to the mix, and histones hold the DNA together tightly and interfere with the gene expression.

This tightened chromatin, Dr. Baylin and team found, can keep genes, including tumor suppressor genes, in a constant state of non-expression. It can cause cancer cells to behave in a primitive, embryoniclike manner. Unlike normal embryonic cells, which receive and respond to signals that tell them to stop making new cells, epigenetically altered cancer cells seem to maintain their ability to replicate, renew and divide.

Scientists do not know what prompts the cancer-promoting changes in chromatin structure. They suspect it may be a repair mechanism engaged in response to cell injury, such as chronic inflammation. Although the cause is uncertain, Dr. Baylin's research revealed that combining a demethylating drug with a histone-blocking drug (HDAC inhibitor) loosens the chromatin and restores some gene expression.

The first clinical study of this epigenetic-targeted therapy included patients with advanced colon cancers.

Colorectal Cancer Research Center of Excellence Director **Nilofer Azad, M.D.**, helped lead these clinical studies. The ability of the epigenetic therapy to return suppressor gene function to a more normal state primes cancer cells to respond better to anticancer drugs and potentially immunotherapies, says

Dr. Azad. She worked with the Baylin team to identify epigenetic biomarkers that could predict sensitivity to certain chemotherapy drugs.

"Many drugs have been tested and looked inactive when they are given broadly to large groups of patients, but we are finding that there are subsets of patients who may benefit, and we can use epigenetic markers to identify these patients," says Dr. Azad. "Drug treatments are limited for colorectal cancer patients, and this is one approach that could help us significantly expand options for patients."

Immunology

When it comes to cancer immunology, Kimmel Cancer Center researchers were once again positioned to make groundbreaking discoveries, including one that was centered on colorectal cancer.

At the Bloomberg-Kimmel



Institute for Cancer Immunotherapy, Director **Drew Pardoll, M.D., Ph.D.**, and team were studying the PD-1 immune checkpoint and a promising new

immunotherapy that inhibited the checkpoint, causing the immune system to attack a certain subset of cancers. Lung cancers and melanomas were the best responders in the first clinical studies. A single colon cancer patient responded to the treatment.

In an effort to solve the mystery of the single colon cancer responder, Dr. Pardoll sought the advice of the Vogelstein/Kinzler group, along with their clinical translation leader **Luis Diaz, M.D.**

Peeking his head around the door during a lab meeting, Dr. Pardoll asked the group, "Do you have any idea why this one colon cancer patient responded to anti-PD-1 immunotherapy when the others did not?"

Its conclusion had paradigm-shifting results for colon cancer and many

other cancers. It centered on a 1993 research discovery. The group asked, "What is the patient's mismatch repair status?"

Some 20 years earlier, Drs. Vogelstein, Kinzler and team identified a genetic alteration linked to Lynch syndrome, a hereditary form of colon cancer that is caused by mistakes in mismatch repair genes.

The job of mismatch repair is to correct copying errors that occur when DNA replicates and cells divide. People who inherit a defective copy of the gene experience high rates of mutations and are at increased risk of developing colon cancer. Colon cancers in patients with mismatch repair deficiency have more than 1,000 mutations, while those without typically have less than 100.

The signals sent out by the mutated genes were an announcement to the immune system that they don't belong. In this case, the cause of the cancer—the mismatch repair mutation—is also its Achilles' heel. The more mutations that exist in the cancer, the louder the signal and the more likely it is that the immune system will take notice.

In fact, the single colon cancer responder had Lynch syndrome. At the time the Vogelstein/Kinzler group discovered the mismatch repair mutation, it also developed a test for it so those affected could be screened and their colon cancers detected in an early



and curable stage.

Dr. Diaz, working with gastrointestinal cancer immunology expert **Dung Le, M.D.**, saw a clinical opportunity. The test was used to confirm the single responder had mismatch repair alterations, and Dr. Le used it to identify other colon cancer patients with the same genetic defect to begin a clinical study of the benefit of immunotherapy.

She led a three-year clinical trial, funded by **Swim Across America**, the **Lustgarten Foundation**, the **Skip**



Discovery Advancing New Therapies Through Clinical Trials

Extending the promise of new cancer drugs, and particularly immunotherapies, to more colorectal cancer patients is a focus of clinical trials at the Colorectal Cancer Research Center of Excellence, says Nilofer Azad, M.D., who directs the Developmental Therapeutics Program at the Kimmel Cancer Center.

“There are multiple clinical trials combining immunotherapy drugs for patients with metastatic colorectal cancer,” says Dr. Azad, who is exploring epigenetic drug and immunotherapy drug combinations. “Epigenetic drugs change the way cancer genes are expressed, and we can use that change to target the immune system.”

Laboratory researcher Franck Housseau, Ph.D., a colorectal cancer and immunotherapy expert, is collaborating with colon cancer clinical expert Dung Le, M.D., to identify new targets on the surface of colon cancer cells that could help make the immune system recognize and destroy colon cancer in more patients.

“We have a major effort to move new drugs into patients,” says Dr. Azad, who is also a principal investigator on the Stand Up To Cancer Colorectal Cancer Dream Team and leads its gastrointestinal cancer efforts.

She is also a member of the National Cancer Institute Molecular Analysis for Therapy Choice working group, the largest clinical trial in the United States to study precision medicine—individualized therapies based on the unique genetic characteristic of a patient’s cancer.

Viragh Foundation, the Banyan Gate Foundation, the Commonwealth Fund and the Sol Goldman Pancreatic Cancer Research Center. The trial included 86 patients with colorectal and 11 other kinds of cancer who had the mismatch repair genetic defect. Dr. Le found that half of the patients responded to an immunotherapy drug called pembrolizumab.

“Our study results led to a new standard of care that includes mismatch repair deficiency testing to help identify a wider group of patients who have failed other therapies but may benefit from immunotherapy drugs,” says Dr. Le. “For other treatments, including chemotherapy, the changing tumor biology due to accumulating mutations causes treatments to stop working, but it seems to make immune therapies work better.”

Her study helped set the stage for the historic 2017 U.S. Food and Drug Administration approval of the anti-PD-1 checkpoint blocker pembrolizumab for all cancers that have mismatch repair deficiency. It was the first-ever drug approval not tied to a specific cancer type. In 2020, a new FDA approval permitted first-line treatment of patients with inoperable, advanced colorectal cancer that has

spread to other places of the body and has mismatch repair deficiency. It marked the first immunotherapy approved for this patient population as a first-line treatment that can be given to patients without chemotherapy.

“It is rare to get a response in colon cancer patients who have not responded to other standard therapies, and most of them had just months to live,” says Dr. Le. “It has been a game changer in the treatment of this cancer.”

The Multidisciplinary Difference

The interaction among all research and clinical specialties that led to this breakthrough discovery is the hallmark of the Johns Hopkins Colorectal Cancer Research Center of Excellence’s Multidisciplinary Clinic.

The Multi-D Clinic—as it is referred to by care providers and patients alike—melds multiple specialties, precision treatments designed specifically for the unique characteristics of each patient’s cancer and the innovative research that revolutionized progress against colorectal cancer.

As rates of colorectal cancer increase, including among younger

adults, Dr. Azad looks for more and creative ways to attack this cancer. Colorectal cancer is the third most common form of cancer in the world and the second leading cancer killer in the United States. Incidence is increasing, and this multifaceted approach, harnessing the most advanced research and patient care, will save lives, she says.

She calls for a greater emphasis on education and prevention, accelerated biomedical research, and the exploration of new treatments, particularly combination therapies, epigenetic therapies immunotherapies, and an enhanced focus on quality of life and long-term survivorship.

“We never forget the science, and that puts us at the forefront of clinical breakthroughs,” she says. “We have leading genetics, epigenetics and immunology researchers working side by side with clinicians to bring these next advances to fruition.”

That edge cannot be overstated.

“I can’t think of another place like this, with this level of interaction” says Dr. Vogelstein. “You can’t manufacture that kind of environment. It has to be built from the ground up, and we’re very fortunate to have it here.”

Milestones That Matter

- Genomic discoveries revealed the genetic mutations that cause colorectal cancer initiation and progression.
- Epigenetic research and emerging therapies provide the promise of manipulating cancer cells so they are easier to treat and less able to evade treatment.
- Immunotherapies provide long-lasting control of specific colorectal cancers, including some advanced cancers.
- Better detection methods, including circulating tumor cell technology known as liquid biopsy, detect small clusters of cancer cells years before they are visible on CT or other scans.

- Advances in precision medicine, including identification of critical cancer signatures, allow providers to customize treatment for individual patients.

Advances On the Horizon

Expanding survivorship services for long-term care of patients.

- A colorectal cancer tissue bank linked to clinical outcomes will include tissue and blood samples of patients treated in the Colorectal Cancer Research Center of Excellence’s Multidisciplinary Clinic. Blood samples obtained over time will monitor effects of therapy and begin to link detailed clinical outcomes to specific genetic and epigenetic characteristics.

- Tumor samples of all stages of human colorectal cancer tumors implanted in mouse models, called xenografts, should provide a better understanding of how colorectal cancer develops and spreads. These models can also be used to test novel cancer therapies against individual patients’ tumors.
- Understanding the role of epigenetic therapy as primary therapies to prime the immune system and to reverse chemotherapy resistance.
- Sequencing the genome and epigenome of primary and metastatic colorectal tumors.
- Optimizing the sequencing of surgery, chemotherapy and radiation therapy to cure metastatic colorectal cancers.

A Model for Progress

Building a GI Cancer Program in the Greater Washington Area



GASTROINTESTINAL CANCER EXPERT Valerie Lee, M.D., is building a



colorectal, pancreatic and gastric cancers program at Sibley Memorial Hospital in Washington, D.C. Among her goals is expanding the number of clinical trials available to cancer patients. She is excited about collaborating with experts in the Johns Hopkins Proton Therapy Center, located at Sibley, to explore the role of proton therapy, particularly how it could be used to treat liver metastases—cancer that spreads from the colon, pancreas or other organ to the liver.

Dr. Lee is involved in a broad range of clinical research aimed at getting more patients to potentially curative surgery and at preventing cancer recurrence and spread. She is exploring treatment combinations, including immune checkpoint blockers, drugs that remove restraints

cancer cells place on the immune system; cancer vaccines, which draw cancer-fighting T cells to the cancer; and radiation therapy to go after cancer cells directly and help augment the immune response. She is also studying the benefits of immunotherapy and radiation therapy after surgery to prevent cancers from coming back.

Radiation therapy, she says, “cleans up cancer cells that may be at the surgical borders and also is a creative way to release neoantigens to stimulate the immune system.” Neoantigens are signals given off by cancer cells that alert the immune system to their presence.

Dr. Lee is hopeful about the promise of immunotherapies, which have worked incredibly well for a subset of patients. “We just need to better understand how to turn on the switch to expand this benefit to more patients,” she says. Dr. Lee’s clinical research will reveal obstacles to the immune response, including what cells

in the environment of tumors, called the microenvironment, are interfering with the immune system’s ability to recognize and attack.



Ashwani Rajput, M.D., director of the Kimmel Cancer

Center for the national capital region, is leading a study looking at how immunosuppressive cells in the tumor microenvironment help tumor cells to escape the immune system.

“Due to the intricate nature of the tumor microenvironment and the interplay of immunity and tumor cells, our knowledge of how immunosuppression leads to cancer cells escaping detection by the immune system remains limited,” says Dr. Rajput. “Although some cells and signaling pathways indirectly promote the initiation and progression of tumors, others may act as immune activators to enhance immunity against tumor cells.” Better understanding the tumor microenvironment, he says, will provide useful information to understand immunosuppression in colorectal cancers and to help determine the most comprehensive, promising treatment plan.

“If we can understand the factors that lead to successful survival rates and the mechanisms of how these



tumors evade natural immune responses, we can achieve better outcomes and learn to further enhance the immune system to fight tumors,” he says.

Michael Pishvaian, M.D., Ph.D., director of gastrointestinal, developmental therapeutics and clinical research programs for the Johns Hopkins Kimmel Cancer Center in the national capital region, agrees. Over the past decade Johns Hopkins has led the way in the field of immunotherapy for different cancers, including colorectal, and continues to expand its knowledge of how the immune system

can be used to fight cancers.

“For colorectal cancer, there has always been a standard algorithm for treatment. Twenty percent have stage 4 cancer by the time it is discovered, and by then it has spread,” says Dr. Pishvaian. “We can help them live longer and hopefully be cured through new novel approaches to care, but to do this, we need to depend on experimental therapies.”

He says Johns Hopkins has one of the premier precision medicine programs in the country, with many clinical trials focused on patients and their unique biomarkers, so patients can be offered several therapy options tailored to their specific cancers.

“Patients can be hesitant about participating in a trial, but for some, it is their best hope for a cure,” he says. “Many of our patients are still doing well 10 years or more following a trial.” Dr. Pishvaian notes that 30 years ago, a patient diagnosed with colon cancer had months, not years, to live. “Now, we are able to turn this diagnosis into a chronic disease that can be manageable, giving patients so much hope.”

Despite the promise of new therapies, Dr. Lee says, screening, may be the best weapon against colorectal cancer. Catching precancerous polyps or tumors at their earliest stage will benefit patients in their care and outcomes. She explains that data have recently shown that colorectal cancer has gone down slightly in those over 50 but has risen in younger patients. Experts are evaluating the benefits of lowering the recommended screening age (see story on p.22). For example, the American Cancer Society now recommends colorectal cancer screening beginning at age 45 instead of age 50. Dr. Lee noted that recently, based on a small study looking back

at patients previously treated, genetic and molecular markers emerged that may be useful for assessing risk.

Hereditary risk factors, such as familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), play an important role, and people with these risk factors should be screened early. However, Dr. Lee says, there are other nonhereditary causes that must be explored.



Croog



Chung

“Colon cancer has been thought of as one disease that comes from polyps through the mutation mechanism, but that’s not always the case,” she says. Identifying the molecular profile of a tumor may help determine if a patient will respond to a particular therapy or would be a good candidate for a clinical trial.

Drs. Lee, Rajput and Pishvaian are joined by surgeons **Kelly Lafaro, M.D.**, and **Haniee Chung, M.D.**; **Martin Paul, M.D.**, regional director of minimally invasive surgery; radiation oncologist **Victoria Croog, M.D.**; nurse practitioner **Kaitlin Lockhart**; nurse navigators; social workers; interventional radiologists; gastroenterologists; pathologists; and palliative medicine experts in building services and bringing multispecialty therapy and patient-tailored precision medicine to the area.



Lockhart

“We have great collegiality among all of the specialties. We all work together. Every expert has a voice,” says Dr. Lee. “It is a model for progress, and there is a lot coming our way soon.”

Beating Colon Cancer During a Pandemic

JEROLD SAYS HE WAS feeling fine. Then, during a routine screening colonoscopy in early January 2020, his doctor found an abnormal polyp that turned out to be stage 3 colon cancer. Specialists at the Johns Hopkins Kimmel Cancer Center at Sibley Memorial Hospital in Washington, D.C., fast-tracked his case and managed his care mostly virtually during the COVID-19 pandemic. Now, he’s looking forward to ringing a bell at the hospital for patients who completed cancer treatment and returning to his favorite hobbies.

After the colonoscopy, Jerold’s doctor told him not to worry and referred him to Sibley, where he met with surgeon **Martin Paul, M.D.**

“I was pretty scared, but he explained to me what the process was,” says Jerold, 62, of Silver Spring, Maryland. “I had been totally in the dark. I’m the type of guy who basically stayed away from doctors and hospitals. I hate taking medicine, even aspirin.”

Dr. Paul ordered some preoperative tests and scheduled surgery for Jan. 23.

“They treated me really well. I mean, everyone from the general reception staff to the nurses to the anesthesiologist,” Jerold says. “I guess they all could tell I was anxious. They walked me through everything gradually.”

After surgery, Jerold saw medical oncologist **Valerie Lee, M.D.**, who discussed his options for chemotherapy. The two agreed to an aggressive chemotherapy regimen that combined infusions of an anticancer medication as well as pills. Jerold had a port installed and received his first infusion in late February 2020. Soon after, the COVID-19 pandemic caused a shutdown in the Washington metro area and most



Johns Hopkins has one of the premier precision medicine programs in the country, offering several therapy options tailored to specific cancers.

of the nation. “This is when it got really interesting,” he says.

Jerold also took medication for interstitial lung disease, which lowered his natural immunity, and because public health experts weren’t yet sure about how the coronavirus was spreading, Dr. Lee worried about him coming to the hospital infusion center for treatment. She talked to him about switching his chemotherapy to a regimen of all pills, and he started seeing her for follow-up appointments by telemedicine instead of in person. She also advised him to stay home except for occasional appointments at a lab for bloodwork.

Jerold, who was retired from his job in cybersecurity with the federal government, relied on the support of his wife and family during this time. He says he tried to keep active at home, either reading, watching TV, cooking or walking his dog. He also used his elliptical machine and took breaks outside on his porch for fresh air. Meanwhile, either Dr. Lee or **Kaitlin Lockhart**, a medical oncology nurse practitioner, called him periodically to check in. Jerold completed his cancer treatment in late August.

For now, Jerold’s bloodwork looks good, and he returns to Sibley periodically for CT scans to monitor. He looks forward to when he can ring a bell that marks the completion of cancer treatment.

Jerold says he is looking forward to returning to his favorite activities: fishing, hunting, riding his motorcycle, traveling with his wife and spending more time with his grandchildren.

“Everyone I dealt with at Sibley was really nice,” he says. “For what I went through, I think they did a great job, and I appreciate them for it.”

Even with the pandemic ongoing, it’s important for Americans as young as 45 to schedule their screening colonoscopies, Dr. Lee says.

“The procedure can be done very safely,” she says. “Check with your doctor about the precautions they have in place. We would much rather see people diagnosed with earlier cancers that can be cured.”

ADVANCES

Colon and Rectal Cancer Surgery



Efron

JONATHAN EFRON, M.D. is focused on new and more effective ways to treat rectal cancer. Treatment involves a multispecialty team, and the stage of the cancer at the time of diagnosis guides treatment recommendations, he says. Radiation and/or chemotherapy is usually the first step, followed by surgery.

“The course of treatment depends upon whether the cancer has spread outside of the rectum walls or is contained,” Dr. Efron, the Mark M. Ravitch, M.D. Endowed Professor of Surgery, explains. If surgery is recommended, he says, there are many minimally invasive options now available.

A laparoscopic approach uses a camera and instruments placed through small incisions to free cancer and remove the portion of colon and rectum that has cancer, he says. New technology allows surgeons to operate laparoscopically through the anus to remove early-stage cancers from the rectum. Robotic surgery is also an option, he says.

“We’re utilizing the robot now for almost all colorectal tumors, as long as it’s not a recurrence or a very complicated situation, where patients have had multiple surgeries in the past,” says **Bashar Safar, M.B.B.S.**, chief of colorectal surgery. “The advantages are our patients have equivalent outcomes with shorter recoveries and less pain.”

The optics with the robot are better for rectal cancers, says Dr. Safar, allowing surgeons to see the area in greater detail.

“Technology is advancing at a very rapid pace, and equipment gets better, making it easier to do these procedures with smaller and smaller incisions,” says Dr. Efron. These smaller incisions can translate to a more rapid recovery, but he points out that they don’t reduce the complexity or difficulty of operation. Despite being minimally invasive, these surgeries are technically demanding and best performed by experts in specialty centers like the Colorectal Cancer Research Center of Excellence.



Safar

When done correctly by a well-trained surgeon, they have similar outcomes, including preventing recurrence, to open surgeries, Dr. Efron says.

In fact, a recent study by Drs.

Efron and Safar, and **Ashwani Rajput, M.D.**, director of the Johns Hopkins Kimmel Cancer Center for the national capital region, found that patients with intermediate—stages 2 and 3—rectal cancers who receive all of their treatments



Rajput

in one facility may have better five-year survival rates than patients whose care is divided among different facilities.

The work suggests that enhanced treatment coordination is protective in patients undergoing multimodal therapy for rectal cancer, Dr. Rajput says.

At Johns Hopkins, surgeons develop and train on new technologies at its Minimally Invasive Surgical Training and Innovation Center. There, surgeons have access to the most advanced robotic training capabilities. For example, a new robotic system called SP places three instruments together in one tube, allowing surgeons to perform minimally invasive robotic procedures through a single port instead of the four to five currently used. SP is approved by the Food and Drug Administration for urology procedures but is expected to soon expand to colorectal operations, says Dr. Safar.

We do a lot of surgeries and offer advanced expertise, and Dr. Safar says we are always considering the individual needs of each patient. Close interaction with basic scientists and other specialists also means patients can get matched quickly to other innovative modes of therapy and clinical trials.

New advances in the treatment of recurrent rectal cancer is one

example. “We now have better techniques of operating so we can do bigger procedures,” says Dr. Efron. “If the cancer hasn’t spread to other places, we can still do large surgical resections within the pelvis and maintain quality of life and good outcomes.”

He says sometimes they will include intraoperative radiation therapy in these cases. “We have that capability to deliver radiation to the patient during the operation when the abdomen is open, minimizing toxic effects of radiation to surrounding tissue and organs,” says Dr. Efron. “The way we do reconstruction of the rectum and colon improves the chances of removing all of the recurrent cancer, survival and quality of life after surgery.”

Shorter Course of Radiation Therapy

The 5x5 Approach

ONE OF THE NEWEST approaches in colorectal cancer treatment is called 5x5, developed by radiation oncologist and colorectal cancer specialist **Jeffrey Meyer, M.D.** It involves abbreviating a typical five-week course of radiation therapy to five days. After a two-week rest, patients begin two months of chemotherapy. The regimen is easier for patients, with far less interruptions to patients’ normal

Technology is advancing at a very rapid pace, and equipment gets better, making it easier to do these procedures with smaller and smaller incisions.

routines. To date, more than 40 patients have received the 5x5 therapy.

“Patients obtain better responses by giving radiation and chemotherapy up front before surgery,” explains Dr. Meyer. In some cases, Dr. Meyer and surgeon

Jonathan Efron, M.D., report that tumors completely disappear, leaving behind only a scar, and surgery is not needed. Instead, patients are monitored closely for



Meyer

any signs of the cancer returning. Other times, the tumors get significantly smaller, and a difficult surgery is made easier, reducing the risk of complications.

“It’s a new approach, so we are still studying it, but long-term outcomes appear to be as good as the traditional, longer courses of radiation therapy and chemotherapy,” says Dr. Meyer.



Unexpected Opponent

Baltimore Orioles' **Trey Mancini**
Defeats Colon Cancer

PROFESSIONAL BASEBALL PLAYER

TREY MANCINI innately has a winning attitude, and he hopes his recent fight against colon cancer will provide encouragement to others battling the disease.

Trey was just 27 in spring 2020, returning to Sarasota, Florida, to begin spring training and his fourth season with the Baltimore Orioles.

Remarkably, aside from some fatigue, Trey had no symptoms to warn him that he would soon be facing the most difficult opponent of his career. When the routine physical all players receive upon reporting for spring training revealed he was extremely anemic, the head trainer suspected Trey was bleeding internally. The Orioles training staff moved quickly, and on March 6, a colonoscopy—among the tests ordered to identify the source of the suspected bleed—revealed something completely unexpected: Trey had colon cancer.

Learning of the news, Trey's parents rushed to Sarasota to be with their son and his girlfriend, Sara, as they made decisions about the next steps. The family was sadly all too familiar with colon cancer, as Trey's dad overcame stage 2 colon cancer at age 58.

With this family history, Trey planned to begin screening for the cancer at age 40, as guidelines recommend. At just 27, and with no inherited genetic predisposition that would have pointed to an early onset of cancer, there were no warning signs to suggest a need for earlier screening.

"Colon cancer incidence is increasing in people under age 50," says **Nilofer Azad, M.D.**, director of the Colorectal Cancer Research Center of Excellence, who recently conducted a study supporting the cost-effectiveness of colon cancer screening beginning at age 40 instead of 50 (see story on p. 22). The growing number of colon cancer diagnoses in younger patients is more than a statistical trend to Dr. Azad. She sees it firsthand in her clinic, making it a pressing area of research. "We don't know why we are seeing

more colon cancer diagnoses in younger patients, but we are working to find out,” she says. Researchers are studying a wide array of potential contributors, including antibiotics, dietary factors, the bacteria colonizing the gut and more.

As Trey, his girlfriend and parents discussed where he should go for treatment, they all agreed on Johns Hopkins. “It was clear-cut that we were going to Hopkins,” Trey recalls. “The place needs no introduction. Everyone knows how good it is. The team is based in Baltimore, so I spend the majority of my year there. It all seemed to fit.”



Trey and Sara

Despite the many years of dedication and hard work that led to Trey reaching the pinnacle of sports, earning a spot on the roster of a professional baseball team and realizing the dream of players from Little League through college, baseball was no longer the immediate priority.

He was moved to the injured list for the 2020 season. “That was a weird feeling,” he says, “but I had bigger fish to fry. I wasn’t thinking about baseball. I hoped to be able to play again, but if I couldn’t, I’d figure it out.”

On March 12, 2020, Trey began treatment for colon cancer, and surgeon **Jonathan Efron, M.D.**, a gastrointestinal cancer expert, removed the tumor in his colon.

“It was a strange day,” recalls Trey, who describes, not surprisingly, feeling very nervous. As a professional athlete, he was accustomed to steeling his nerves for competition, but this

was different. He could prepare for baseball—training to keep his body in shape, studying film and practicing—but there is no preparing for cancer.

This was Trey’s first surgery. Despite playing baseball since he was 4 years old, he had never had a serious injury. Now, within a span of five days, he had gone from learning something was wrong to finding out he had cancer.

He awoke from surgery surrounded by family and learned that Dr. Efron was able to remove the entire tumor in his colon. A few days later, however, on his 28th birthday, the pathology

results revealed the cancer had begun to spread to a few nearby lymph nodes. This meant Trey would need chemotherapy to prevent the cancer from spreading and forming new tumors in other parts of his body.

“It was the worst birthday. I was hoping after surgery to be done with it,” says Trey. When he met with Dr. Azad, he understood why it was important. “I like to know the science behind things, and she explained everything. I felt like I was in good hands,” says Trey..”

All of this was happening as the COVID-19 shutdowns were beginning. “I felt like I went to sleep and woke up to a completely different world,” says Trey. Spring training had been shut down, and worse, he had to go to his chemotherapy appointments alone. To protect patients from the risk of COVID-19 infection, no visitors were allowed.

“The infusions took about four hours,” he says. “The nurses and other staff were incredible and so caring. They made a difficult time much easier.”

It was also hard for Trey’s girlfriend, Sara, who was by his side from the beginning. Now, with the shutdown, she couldn’t go with him to treatments and was his sole care provider at home. His close-knit family had to stay in touch with the two of them from a distance because of COVID-19.

Trey finished chemotherapy in September 2020. Dr. Azad continues to monitor him with scans every three months to ensure the cancer has not returned.

“I can’t say enough about Dr. Efron, Dr. Azad, my nurses, everyone. The care I received provided constant reassurance that I was in the right place. I felt fortunate to have my treatment at Johns Hopkins,” says Trey. He also credits his girlfriend and family for his recovery. “I wouldn’t have gotten through the last year without them,” says Trey.

As he recovered from his cancer and prepared to return to baseball, Trey worked out as often as he could to regain his strength. He needed to be fit to return to baseball, but he also was aware that an active lifestyle was shown to reduce the risk of cancer recurrence.

A cancer diagnosis and treatment, along with the COVID-19 pandemic, made for a tough year for Trey, but in March 2021, he returned to spring training. He recognizes that the experience has changed him. “I appreciate every day,” he says.

On March 1, he returned to the field for the first time since his cancer diagnosis. “It felt surreal,” he says. During his first at-bat, his teammates, opposing team players and fans marked the occasion with a standing ovation. Trey’s mom, dad and girlfriend were there clapping as tearful and joyful witnesses to the national headline-making tribute honoring Trey’s triumph over cancer.

“It was an amazing moment,” says Trey.



Complex Care for Complex Cancers

A Young Woman's Journey with Advanced Colorectal Cancer

WHEN MAGGIE BEGAN experiencing mild symptoms—a small amount of rectal bleeding and occasional constipation—her primary care doctor referred her to a gastroenterologist, who didn't think it was anything serious, probably a hemorrhoid. After a few weeks, the bleeding subsided, and her other symptoms seemed to be improving a bit.

Maggie was just 29, and because of her young age, her doctors may not have considered colon cancer a likely culprit. They did not pursue additional tests.

From 2016 to 2017, her gastrointestinal symptoms gradually worsened and now included intermittent bloating, constipation, diarrhea and abdominal pain. Her doctor at the time attributed the cause of her ongoing and increasing symptoms to irritable bowel syndrome (IBS), a catchall of sorts for gastrointestinal complaints that cannot be explained by other diagnoses. At the doctor's recommendation, she tried adding more fiber to her diet and following a FODMAP diet. FODMAP stands for fermentable, oligosaccharides, disaccharides, monosaccharides and polyols, and the diet, which suggests eliminating foods high in these carbohydrates, like fructose and lactose, may improve IBS symptoms.

It didn't work for Maggie. Her symptoms continued to escalate, and by spring 2019, they became unmanageable, she says. Now, they were interfering with her activities, with her fluctuating between

constipation and a sudden urgency to go, accompanied by considerable abdominal pain. In addition to the gastrointestinal problems, Maggie also began experiencing significant premenstrual symptoms and difficulty with urination.

"I was miserable," she says.

At the time, Maggie, now an assistant professor of psychiatry and behavioral sciences, was studying attitudes about death and reading a related book, *The Unwinding of the Miracle: A Memoir of Life, Death, and Everything That Comes After* by Julie Yip-Williams. The book chronicles the author's diagnosis, treatment and death from colon cancer at age 42. Although Maggie was reading the book for its relationship to her professional work, she couldn't help but notice some similarities between the author's experiences and her own, as both were diagnosed with IBS.

"I didn't really believe I had cancer," Maggie recalls, "but the book prompted me to push for more aggressive care. I sent my primary care doctors a message and asked them to put in an order for a colonoscopy."

The results were shocking, Maggie says. The colonoscopy revealed a large mass the size of a grapefruit. More tests found the tumor had invaded nearby lymph nodes and reproductive organs.

"I'm only 32. I was an active person. I didn't have any of the common risk factors, like smoking or obesity. Colorectal cancer was a very

shocking diagnosis," she says.

Maggie wasn't completely unfamiliar with the disease. Two grandparents died of colorectal cancer in their 80s, but there was no familial cancer syndrome to predict such an early onset of colon cancer. Maggie's mother had breast cancer. That was the cancer on Maggie's radar.

"I knew something was wrong, but I didn't think it was cancer," says Maggie. Although there was some relief knowing the source of her symptoms, the size and extent of the tumor were alarming.

"I knew colon cancer was an illness that killed a lot of people, including my grandmother and grandfather. I knew it was serious, but I was still hopeful," she says.

Her hope, Maggie says, largely stemmed from the response and care of the team of experts at the Kimmel Cancer Center's multidisciplinary Colorectal Cancer Research Center of Excellence.

There were many difficult times leading up to her diagnosis, but the decision to seek treatment at the Kimmel Cancer Center, she says, was easy. As a school of medicine faculty member, she called it a natural choice.

"I had high expectations for Johns Hopkins," Maggie says. "I knew that my departmental colleagues were at the cutting edge of their field, so I expected the same from the oncology faculty. I couldn't imagine going anywhere else for cancer treatment."

Her expectations were realized



Maggie

from the first appointment, she says. “My doctors were optimistic, and they treated my case with urgency,” Maggie says. “I knew it was serious, and there was real reason for concern, but they always treated me like I was curable. That was important to me.”

Medical oncologist and colorectal cancer expert **Nilofer Azad, M.D.**, director of the Colorectal Cancer Research Center of Excellence—the team’s quarterback—coordinated Maggie’s care.

It was a dynamic and complex case that involved special considerations, such as fertility preservation because of Maggie’s age.

“Everything became easier from my first appointment with the Multidisciplinary Clinic,” says Maggie. “They took care of all of the components and appointments. I didn’t have to ask for a fertility consultation—they already had a reproductive endocrinologist ready for referral. Everyone communicated and put my needs at the forefront. They helped to schedule all of my appointments and scans. When you talk about multidisciplinary care, you realize how difficult it is to

coordinate all of these experts, but they made it look easy and seamless. They did all of the work. I didn’t have to do anything.”

Beyond the nuts and bolts of the medical care, Maggie was just as impressed by the compassion of the colorectal cancer team.

“This was a very emotional time for me, but they listened patiently to all of my questions and concerns. They considered all of my needs, and they took the time to discuss all of the options before we jumped into treatment,” she says.

Maggie met with a reproductive endocrinologist before she began chemotherapy to discuss ways to preserve her fertility. The size of the mass made it too difficult to do a procedure called an egg retrieval at that time.

Maggie’s treatment plan began with two of months of a standard chemotherapy combination—the drugs 5-fluorouracil, or 5-FU, and oxaliplatin—commonly used to treat advanced colorectal cancer. But the treatment had no effect on her tumor or her symptoms. Maggie was in severe pain and unable to eat most foods, subsisting on only baby food and nutritional supplement drinks.

“I was in a bad place,” says Maggie. “That was the lowest point for me.”

The Hope of Immunotherapy

During her darkest time, however, came a light of hope.

A few years earlier, Kimmel Cancer Center genetics and immunology researchers revealed a connection between a genetic mutation to a spellchecklike feature of genes and response to immunotherapy. It was called mismatch repair deficiency. The genetic alteration that may have contributed to the development of her cancer was also, ironically, the

feature that made her a candidate for a new cancer therapy called immunotherapy, which engages the body’s own immune system to fight cancer.

Mismatch repair deficiency prevents cells from repairing mistakes in the DNA, leading to many mutations in important cancer-suppressing genes. The cancer-causing mistakes make the cancer cells look different enough to attract the attention of the immune system, causing it to deploy cancer-killing immune T cells to the tumor. Unfortunately, that’s not enough to kill the cancer.

Cancer cells have a way of interfering with immune on/off switches, called checkpoints. They are vital to regulating the immune response—helping to ignite an immune response to an injury or unwelcome invader, like bacteria or viruses—and they shut the immune response down when the job is done. In cancer, malignant cells corrupt this process and send signals to turn the checkpoint switch to off before the immune system has done its job against the cancer cells.

Drugs, called checkpoint blockers or inhibitors, turn the immune switch from “off” to “on,” unleashing an immune cell attack against tumor cells.

Maggie was in the right place at the right time. A homegrown Kimmel Cancer Center discovery was about to become the key to her survival.

The research that uncovered mutations in mismatch repair genes in colon cancer occurred nearly two decades earlier in a Kimmel Cancer Center cancer biology laboratory. In 2014, those researchers collaborated with Bloomberg-Kimmel Institute for Cancer Immunotherapy researchers to connect mismatch

“This was a very emotional time for me, but they listened patiently to all of my questions and concerns.”

repair alterations to response to immunotherapy with checkpoint blocker drugs.

Maggie's tumor was tested and retested, confirming it had this genetic characteristic, and in September 2019, Dr. Azad started Maggie on her first course of immunotherapy. She received two checkpoint blocking drugs—one called ipilimumab, or anti-CTLA-4, and another called nivolumab, or anti-PD-1—which target specific immune checkpoints, reengaging the immune response against the cancer.

Dr. Azad shared results of a study of the drug combination with Maggie that showed colorectal cancer patients whose tumors have this genetic alteration responded well to the treatment.

Maggie received the immunotherapy combination intravenously every three weeks for four doses and then nivolumab alone every two weeks. Within a couple of weeks of beginning immunotherapy, she began to feel better.

"The pain and constipation went away. I could eat again," says Maggie.

Then, on Oct. 31, 2019, Dr. Azad called Maggie with the news that every cancer patient yearns to hear. The treatment was working. Maggie's CEA blood test, which is often elevated in patients with colon cancer, was normal, and her CT scan showed a dramatic reduction in the size of the tumor.

Maggie's pain had been managed with opioids and over-the-counter pain relievers. Within weeks of beginning the immunotherapy, she no longer needed the opioids and eventually didn't require the over-the-counter pain relievers either.

The plan was to continue the nivolumab until her tumor stopped responding to it, what Dr. Azad referred to as "achieving maximum response."

Releasing restraints on the immune system does not come without side effects. The drugs

can cause autoimmune effects in which they begin to attack normal tissue. Kimmel Cancer Center and Bloomberg-Kimmel Institute experts have also led the way in recognizing and managing these side effects.

Six months into treatment, Maggie's gastrointestinal symptoms remained at bay, but when she noticed joint pain, Dr. Azad recognized it was immunotherapy-related arthritis. She brought in rheumatologist **Laura Cappelli,**

M.D., who was able to bring it under control with the rheumatoid arthritis drug meloxicam.

"The Multidisciplinary Clinic was ready to address every need," says Maggie. "No matter what came up, they had a doctor for it. It was handled so efficiently."

By March 2020, Maggie remained hopeful. Her tumor was responding well to immunotherapy, and she was feeling great. She could never have anticipated a global pandemic, but



Maggie and husband

now Maggie and her care team were managing her colorectal cancer amid the threat of COVID-19.

Maggie's treatments were intravenous and required her to go to the Kimmel Cancer Center's Skip Viragh Outpatient Cancer Building for therapy. To help minimize Maggie's risk of exposure to COVID-19, Dr. Azad reduced her immunotherapy treatments to once per month.

Here again, Maggie was inspired by the response of her care team.

"I always felt safe," says Maggie. "The treatment rooms are private. The doctors and nurses wore personal protective equipment. Dr. Azad and my nurse practitioner, **Rachel Klein**, used telemedicine whenever possible to help minimize risk. I never felt at risk."

At last, in July 2020, Maggie received her last immunotherapy treatment. Scans showed the grapefruit-sized mass was now holding steady at the size of a grape. Radiation therapy to take care of any microscopic cancer cells that may be remaining in her pelvis and reduce the risk of her cancer coming back, and surgery to remove the tumor were the next steps in her treatment plan.

As the tumor regressed, however, she and her doctors could now vividly see its path of destruction. It left a hole in the wall of her vagina, requiring repair and also putting her at risk of recurrence of the cancer in her uterus and ovaries.

At the time of the surgery, Dr. Azad and colorectal cancer surgeon **Susan Gearhart, M.D.**, added gynecologic oncology surgeon **Rebecca Stone, M.D.**, to the team to perform a hysterectomy and vaginal reconstruction. Maggie was once again thrust into the emotional and

deeply personal reality of her battle against cancer.

"I knew from the beginning this was a likely outcome," says Maggie. "Still, it was upsetting."

Drs. Azad, Gearhart and Stone explained that surgery would be beneficial to her long-term survival.

"They were sad with me," says Maggie. "They made preserving my fertility a priority, and they respected my decisions. I never felt pressured or judged." The success of the immunotherapy made egg retrieval now possible, but with the hysterectomy, Maggie would not be able to become pregnant.

After considering all of the options, she knew their recommendation for a hysterectomy offered the best chance of keeping the cancer from coming back and spreading.

"I am very grateful for these doctors.

They see people in their most difficult moments and treat them with such grace and understanding," she says.

Fortunately, Maggie already had a therapist helping her through this difficult journey. However, this kind of support is also a service the multidisciplinary Colorectal Cancer Research Center offers. Patients can request consultations with a range of experts, including mental health providers, nutritionists, dieticians, palliative medicine providers and more.

In January 2021, Maggie underwent a complex, 10.5-hour surgery to take out the remaining tumor. The complicated surgery involved removing her rectum and parts of her sigmoid colon, and reconstructing her vagina. The surgery included a temporary ileostomy that connects part of the small intestine to an opening in the abdominal that can be reversed

after her remaining colon has an opportunity to heal. Using a piece of small bowel, Dr. Gearhart constructed a vagina, a procedure she has been performing and perfecting since 2002.

The extent and complexity of her colorectal cancer required the highest level of knowledge and skill. The journey was long and emotional, with many unexpected twists and turns—such as the COVID-19 pandemic—but the experts at the Colorectal Cancer Research Center of Excellence were prepared for each one, providing solutions.

"I've had the best possible outcome—a complete response with no visible cancer remaining," says Maggie. "It's the outcome that the entire team of experts made me always believe was possible. I had a very large mass, and it was very serious. I understood that, but they always treated me like I was curable."

Her physical recovery is happening quickly, and she is confident she will be able to return to her active life. The mental recovery will take longer, Maggie says, but she has a new perspective. She is excited to have more time to spend with her husband and family, who Maggie says were incredibly supportive.

"I do the things I want to do now. I don't wait," she says. Most recently, this includes beginning the French lessons she been thinking about for many years, moving into a new home and adding a dachshund puppy to the family.

She is also grateful because she knows the specialized care she received was built on decades of research. She believes the advances in immunotherapy that only unfolded in the last five years were also key to her surviving this cancer.

"I've had the best possible outcome—a complete response with no visible cancer remaining," says Maggie.



**“We have a major effort
to move new drugs into patients.”**

— Nilofer Azad, M.D.
*Director of the Colorectal Cancer
Research Center of Excellence*



Micromanaging Colon Cancer

There is a microscopic society living within us. Our bodies are home to more than 100 trillion microorganisms, more than 10 times the number of human cells in the body. Many of them reside in our gut. Most of the time, this microcommunity—which includes hundreds of species of bacteria—and its human host coexist harmoniously. The “bugs” we live with aid in digestion, metabolism and immunity.

HOWEVER, WITH SUCH an overwhelming numbers advantage, it may only take the activity of a single organism to shift this harmonious relationship in a way that can promote cancer, says infectious disease expert and Bloomberg-Kimmel Institute for Cancer Immunotherapy investigator **Cynthia Sears, M.D.**

Of the trillions of possibilities, Dr. Sears has zeroed in on a population that appears to be related to colon cancer development.

Biofilms

The entire colon is lined with a thick, protective layer of mucus and, under normal conditions, bacteria are excluded. In some colon cancers,

however, Dr. Sears and team have found biofilms made up of a subset of bacteria that has managed to invade the mucus. “They invade the layer of mucus that protects the epithelial cells lining the colon and upend the whole biology of the system,” says Dr. Sears.

With so many different forms of bacteria colonized within the human body, it is a difficult task to differentiate those that keep us



healthy from those that contribute to disease. In this case, the association seems clear. In preclinical research, the bacteria present

in some biofilms induce colon tumors. Amazingly, at least 50% of human colon cancers are covered in biofilms.

Dr. Sears doesn't yet know how these biofilms develop, but she has a hunch about their link to cancer. She speculates that they cause inflammation in the colon, which

spurs genetic mutations that lead to cancer. “When we look at people who undergo screening colonoscopy, we find a subset of people who have biofilms. What happens in that tissue and cells right under the biofilm are the same processes we see in cancer,” she says.

Another mystery was related to the location of the biofilms. In her team’s study of 178 surgery or colonoscopy patients treated at either The Johns Hopkins Hospital or the University of Malaya Medical Centre in Malaysia, the vast majority of biofilms were located in the right colon. “It’s virtually a universal



feature of tumors that appear in that section of the colon, although we don’t understand why,” says Dr. Sears.

She is working with cancer prevention

and control expert **Elizabeth Platz, Sc.D.**; cancer immunology expert **Drew Pardoll, M.D., Ph.D.**; and gastroenterologist **Francis Giardiello, M.D.**, on a large multicenter colonoscopy study—with 2,100 patients already enrolled—to define the natural history of biofilms and their association to changes in tissue. “When we detect biofilms, where are they? How long do they last, and what do they do? This is what we want to figure out,” says Dr. Sears.

The study will also establish a large bank of biofilm samples to integrate complex microbial and immune analyses. “We want to understand how the immune system responds to biofilms as well as the gene expression of these bacterial communities and how they interact with other bacteria inside of the biofilm,” she says.

Biofilms are a new discovery, and

Dr. Sears and team are the first to systematically explore them in colon cancer.

Patients with an inherited form of colon cancer, known as familial adenomatous polyposis (FAP), may provide some early answers. The disease is characterized by large numbers of polyps in the colon. Dr. Sears says FAP sufferers also often develop biofilms, but instead of being made up of many types of microorganisms, they primarily consist of two types of bacteria. “This is the best evidence so far that particular organisms may be relevant, and it may help us zero in on the bacteria that could be pushing this process,” says Dr. Sears.

Among her long-term goals, Dr. Sears hopes to use her findings to develop a noninvasive test to detect biofilms and predict a person’s risk of developing cancer. “Most colon cancers are known to develop slowly over time,” she says. “It’s a disease that’s curable if diagnosed early, and maybe biofilms are an early warning sign.”

Microbiome

Colorectal cancer is caused and influenced by a complexity of features, including genetics, immunology, inflammation and microorganisms. In one study, funded in part by **Swim Across America** and **Bloomberg Philanthropies**, Dr. Sears and collaborators showed that the interaction between a single gut bacterium—enterotoxigenic *Bacteroides fragilis* (ETBF)—and specific mutations directly influenced the biology of a tumor

Biofilms are a new discovery, and Dr. Sears and team are the first to systematically explore them in colon cancer.

and its response to immunotherapy.

ETBF is a cause of diarrheal disease and is associated with inflammatory bowel disease and colon cancer.

Dr. Sears and team used an enterotoxigenic *Bacteroides fragilis* (ETBF)-induced colon

cancer mouse model genetically engineered with a common colon cancer-related APC and BRAF mutation. They found that this combination of features was conducive to response to a type of immunotherapy drug, called anti-PD-L1. Anti-PD-L1 is a type of immune checkpoint inhibitor drug that helps boost the immune response to cancers that express the PD-L1 protein on their cell surface.

The APC gene is mutated in about 80% of sporadic colon cancers. The BRAFV600E mutation used in the study comprises approximately 90% of all BRAF mutations in human colorectal cancer, Dr. Sears says.

The researchers found that when the ETBF microbe infected the mice with the combined APC and BRAF gene mutations, the tumors had a marked change in microscopic tissue structure, immune response and epigenetic response. Epigenetics are nonmutational alterations to the DNA that affect gene expression and are caused by chemical changes to specific regions of genes or the way DNA is packaged inside the nucleus of the cell. The mice with both APC and BRAF mutations responded better to checkpoint inhibitor therapy. The findings support a building body of published research suggesting that the microbiome can influence the outcome of checkpoint inhibitor therapy.

“The bottom-line message is that the membership of the microbiome is extremely important to cancer biology,” she says.

“The opportunities to help patients are limitless, like catching lightning in a bottle.”

Earlier Screening Being Studied

Research led by **Nilofer Azad, M.D.**, director of the Colorectal Cancer Research Center of Excellence, finds beginning screening for colorectal cancer starting at age 40 instead of the typical age of 50 may be cost-effective.

The medical literature indicates that the incidence of colorectal cancer is increasing among patients under age 50, says Dr. Azad. She points to a 2017 study in *Journal of the National Cancer Institute* reporting that 30% of rectal cancers in the U.S. are now diagnosed in patients under age 55 and says oncologists are observing the same trend in their clinics.

In response, Dr. Azad and colleagues developed a computerized model to assess the cost-effectiveness of screening average-risk 40-year-olds using colonoscopy to explore the entire large intestine, flexible sigmoidoscopy to examine the rectum and lower colon, and three types of stool tests: a fecal occult blood test that detects microscopic amounts of blood in the stool, a fecal immunochemical test (FIT) that finds hidden blood in the stool coming from the lower intestines where the colon is and fecal immunochemical DNA testing that detects colon cancer cell DNA shed into the stool. They weighed factors, such as cost for screening and quality of life years added.

They found colorectal cancer screening at age 40 to be cost-effective using each of these modalities when compared to the standard of care of no screening until age 50. Flexible sigmoidoscopy provided the most favorable monetary benefit. Earlier screening suggested a potential savings of 2.1 million quality of life years and \$21 billion over the lifetime of the age group.

“Our study does not definitively say that people age 40 and up should be screened, but it does suggest that organizations that set national screening guidelines should be exploring our model and other models to determine whether age 40 is a better target,” Dr. Azad says. The American Cancer Society last year lowered its age for baseline colorectal cancer screening from 50 to 45. The U.S. Preventive Services Task Force recently did the same.

Like Dr. Azad, colorectal cancer expert **Valerie Lee, M.D.**, notes an increase in younger patients at the Kimmel Cancer Center’s Sibley Memorial Hospital site.



Lee

“We are seeing patients diagnosed in their 20s and 30s, and too often, they are diagnosed late because general doctors are not looking for this cancer in young patients,” says Dr. Lee.

In addition to earlier screening, the causes of the earlier onset of colorectal cancer are being explored. Investigators are studying a number of factors—from overuse of antibiotics and their effect on the collection of bacteria that live in the intestines to increased consumption of fast food—for their contribution. However, Dr. Azad cautions that for now, the earlier onset of colorectal cancer remains a mystery, and early detection is the best defense. “Doctors need to be aware of this change in demographics and consider colorectal cancer as a possible cause when younger patients present with symptoms,” she says.

Vaccine Approaches for Advanced Colorectal Cancer

Colorectal cancer expert **Neha Zaidi, M.D.**, is studying unique vaccine strategies to help patients with advanced stages of the cancer.

One of the approaches is a

vaccine that targets six altered KRAS proteins. KRAS is a common gene mutation in colorectal cancer, occurring in nearly 40% of colorectal cancer patients, she says. The vaccine will be studied in a clinical trial for patients with advanced colorectal cancer whose cancer did not respond to standard treatment and contains one of the six alterations to the KRAS gene the vaccine targets. She is hopeful the vaccine could help expand the benefit of immunotherapy to more patients with colorectal cancer.

A subset of colon cancers contain a genetic alteration to a mismatch repair gene, and these cancers often respond to treatment with anti-PD-1 and anti-PD-L1 immune checkpoint inhibitor drugs. Patients who do not have the mismatch repair gene alteration require more to stimulate an immune response. Dr. Zaidi says the vaccine should provide that stimulation, drawing cancer-killing immune cells to the tumor. It is given in combination with anti-PD-1 and anti-CTLA-4 drugs to help further boost the immune response. Immune checkpoints can serve as a brake on the immune response, and checkpoint inhibitors release these brakes, allowing the immune T cells to go to work against the cancer.



Zaidi

Another study in planning uses a vaccine created to specifically target the proteins unique to each patient’s cancer. Dr. Zaidi hopes the vaccine will be an option for patients with colorectal cancer who are newly diagnosed at an advanced stage and have not yet received treatment. Patients will have a biopsy to obtain a sample of their tumor. The sample will be analyzed for the specific proteins expressed in the tumor and the vaccine individualized to target those proteins. The vaccine will be given in combination with anti-PD-1 inhibitors.

NOTEWORTHY

Kimmel in the Community Combatting Colon Cancer

AFRICAN AMERICANS DIE disproportionately from colon cancer. When a higher death rate among African American men living along the I-95 corridor from Prince Georges County to Baltimore was identified through Cigarette Restitution Fund-supported research, the **DontDelay. Today** campaign was established. The collaboration was led by Kimmel Cancer Center Community Outreach and Engagement Associate Director **Otis Brawley, M.D.**, Bloomberg Distinguished Professor, in conjunction with the Maryland Department of Health Center for Cancer Prevention and Control, and **Radio One**, and initiated cancer prevention and early detection outreach to African Americans. Information on the importance of colon cancer screening, connection to



Brawley

no-cost screening and information on healthy diet, habits and exercise was provided.

Colon Cancer Expert Named to National Cancer Advisory Board

Nilofer Azad, M.D., M.D., Co-director of the Cancer Genetics and Epigenetics Program and Director of the Colorectal Cancer Research Center of Excellence, was appointed by President Joe Biden to serve as a member of the National Cancer Advisory Board.

Cancer remains a leading cause of death worldwide despite progress in prevention, early detection, and treatment. The National Cancer Advisory Board advises and assists the director of the National Cancer Institute at the National Institutes of Health on the activities of the national cancer program. Individuals are selected from among leading representatives in health and science, along with leaders in public policy, law, health policy, economics, management, and the environment. Among its activities, the National Cancer Advisory Board reviews grant applications for research, training, health care information, and programs for cancer patients and their families.

“It is such an honor to be named to the National Cancer Advisory Board, in particular by President

Biden, who has a true commitment to the cause of eradicating cancer,” Dr. Azad said. “This is a real opportunity to move the needle meaningfully to improve outcomes for our cancer patients, and I feel very fortunate to be asked to serve.”

Kimmel Cancer Center researcher **Ashani Weeraratna, Ph.D.**, Co-Director of the Cancer Invasion and Metastasis Program, the E.V. McCollum Chair of Biochemistry



Azad



Weeraratna

and Molecular Biology at the Johns Hopkins Bloomberg School of Public Health and a Bloomberg Distinguished Professor, was also named to the advisory board.

Web Exclusives on our Cancer Matters Blog

Baltimore Orioles’ Trey Mancini, Dr. Nilofer Azad and Dr. Bill Nelson discuss Trey’s treatment and return to baseball following his colon cancer diagnosis. Listen at <https://bit.ly/3mSQ7Vg>

Drs. Bill Nelson and Nilofer Azad discuss the importance of colon cancer screening and advances made in treating colon cancer. Listen at <http://bit.ly/2Dj8TiC>

Coming in the Next Issue:

Inspirational and Transformational

Roger Leventer, who established the Lynda Leventer Fund, in memory of his wife, and chairs the campaign to raise the funds that launched the Colorectal Cancer Research Center of Excellence, shares his personal journey and vision of how philanthropy can propel transformative advances in colorectal cancer discovery and treatment.



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Each contribution to the Johns Hopkins Kimmel Cancer Center makes a difference in the lives of cancer patients here at Johns Hopkins and around the world.

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