

IMMUNOTHERAPY.

HOW WE'RE TRAINING THE BODY TO FIGHT CANCER



2014 ANNUAL REPORT

UPMC CancerCenter
University of Pittsburgh Cancer Institute

INSIDE:

PLuSS/LUNG
CANCER
SCREENING

LEMIEUX
SCORES FOR
LYMPHOMA
CENTER

INTEGRATIVE
ONCOLOGY

BREAKTHROUGHS & BEGINNINGS



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LAST YEAR WAS A BUSY ONE AT UPMC CANCER CENTER AND THE UNIVERSITY OF PITTSBURGH CANCER INSTITUTE (UPCI).

We welcomed new physicians and researchers into the fold, and several of our members secured significant grants from the National Cancer Institute and other prestigious organizations. We celebrated our volunteers who contribute so much to our mission. We also established a partnership with colleagues in Kazakhstan to present the International Oncology Symposium and create the National Research Oncology Center, slated to open in 2017. In so many areas, our research is producing tangible achievements. This year, we look forward to even more new beginnings.

Our rich history of groundbreaking research has also put our ongoing work into the global spotlight. Two years ago, the journal *Science* declared cancer immunotherapy to be the “Breakthrough of 2013,” but our physicians and researchers have been at the forefront of immunotherapy research since the 1980s. UPMC CancerCenter and UPCI’s inaugural director, **Ronald Herberman, MD**, introduced the initiative in 1985, and with the generous support of the Hillman Foundation, Hillman Cancer Center opened in 2002. Today, Hillman remains our flagship site with scientists and clinicians collaborating to advance research studies into innovative treatments used across our network and around the globe.

This report features an overview of the work we’re doing in cancer immunotherapy.



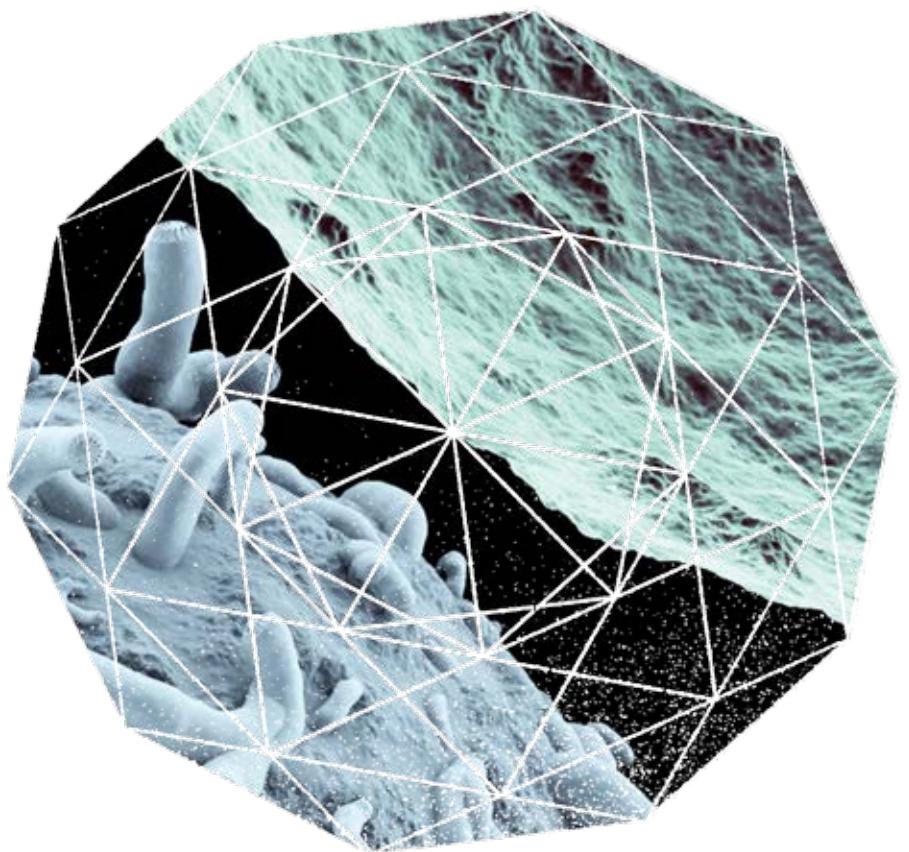
We encourage you to visit our online Annual Report at UPMCancerCenter.com/AnnualReport2014 for more information.

We’re continually expanding the research side of our work to create a robust pipeline of exciting new therapies for cancer treatment. Pittsburgh is already a leader—a vanguard—when it comes to cancer immunotherapy. We’ll carry on that research, and investigate other aspects of cancer prevention and treatment, in ways that will bring hope to our patients and to others around the world.

Nancy E. Davidson
NANCY E. DAVIDSON, MD

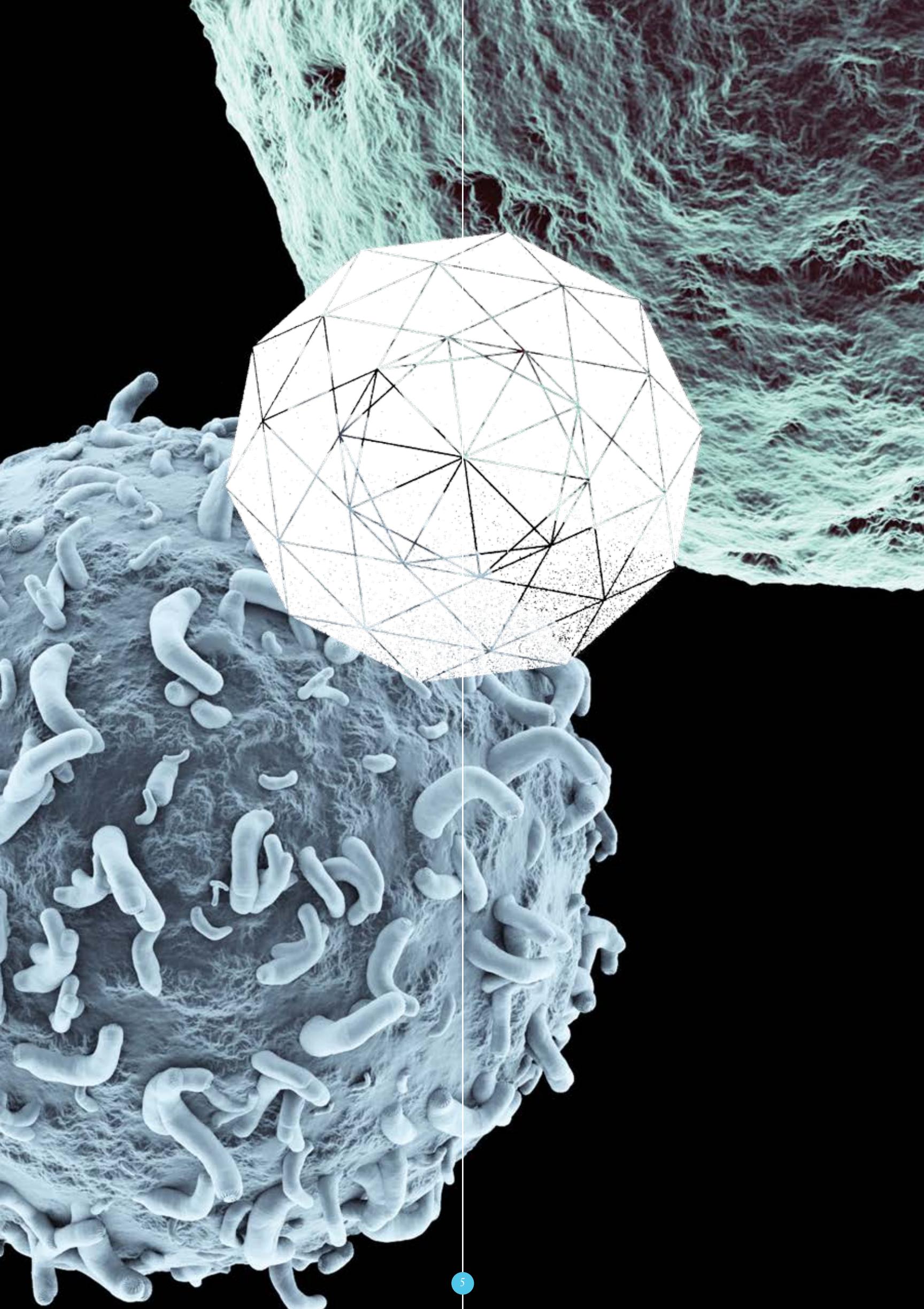
Director, University of Pittsburgh Cancer Institute and UPMC CancerCenter

Stanley Marks M.D.
STANLEY M. MARKS, MD
Chairman, UPMC CancerCenter



BOOSTING THE IMMUNE SYSTEM TO FIGHT CANCER

The application of immunology to the treatment of cancer is getting a lot of press lately, but this breakthrough has actually been years in the making. Immunology always has held the potential to revolutionize cancer treatment, and, for many patients, immunotherapy may be the “next big thing” that enables a gentler course of treatment with improved outcomes.



IMMUNOTHERAPY

"The problem with immunotherapy is that cancer is different. People are used to tapping the immune system to fight invaders, but when it comes to tumors, there is no foreign component. The cancer is part of the patient. This makes it hard to understand."

— Dario Vignali, PhD, vice-chair, Department of Immunology, University of Pittsburgh School of Medicine and co-leader, Cancer Immunology Program, University of Pittsburgh Cancer Institute

UPMC CancerCenter, in partnership with the University of Pittsburgh Cancer Institute (UPCI), has been working toward the application of immunotherapy for cancer since 1985. Our founder, Ronald Herberman, MD, was a prominent researcher in the field, and his work laid the foundation for one of the largest integrated clinical cancer care networks in the United States. He believed that we could harness the immune system and direct it toward the prevention and treatment of cancer—and he was right. Today, we have the benefit of years of research demonstrating its efficacy.

"A tumor is not a bag of cancer cells—it's growing and it's complex, it's a dynamic dance between cancer cells and stromal cells and immune cells. A delicate balance is what keeps the tumor alive and growing. How do the constituent parts of the microenvironment contribute to the life of a tumor? That's what we're finding out."

— Greg Delgoffe, PhD, assistant professor, Immunology, University of Pittsburgh School of Medicine

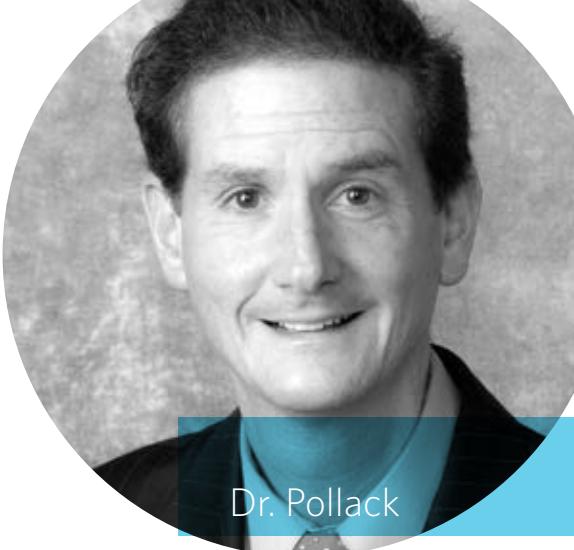
In 2014, our team saw promising progress in several areas of cancer immunology research and clinical application. Researchers and physicians have made great strides toward the discovery of novel approaches to cancer treatment that harness the power of the body's own built-in protection mechanism. We've accomplished a lot—but there's still so much more to do.

We're treating brain tumors with vaccines.

Ian Pollack, MD, is co-director, Neurosurgical Oncology and chief of Pediatric Neurosurgery at Children's Hospital of Pittsburgh of UPMC. In 2014, he continued his work as a principal investigator on studies funded by the National Institutes of Health investigating novel therapies for brain tumors and evaluating molecular markers of tumor prognosis.

Dr. Pollack's group has been conducting an immunotherapy trial for children with brain tumors. Children with diffuse brainstem gliomas (BSGs) and other high-grade gliomas (HGGs) typically do not fare well, even with current therapies.

The researchers identified a series of glioma-associated antigens (GAAs) that are commonly overexpressed in pediatric gliomas and developed a vaccine including GAA epitope peptides in children with newly diagnosed BSGs and HGGs. These proteins boost the natural immune response against the antigens expressed in the tumors. Initial results showed that more than half of the vaccinated children developed an effective immune response—and, in a significant number of subjects, the tumors shrank.



Dr. Pollack



Dr. Kirkwood



Dr. Butterfield

"The fact that we can shrink malignant brain tumors is exciting. Some patients' responses have been unprecedented in terms of degree."

— Ian Pollack, MD, co-director, Neurosurgical Oncology & chief, Pediatric Neurosurgery, Children's Hospital of Pittsburgh of UPMC

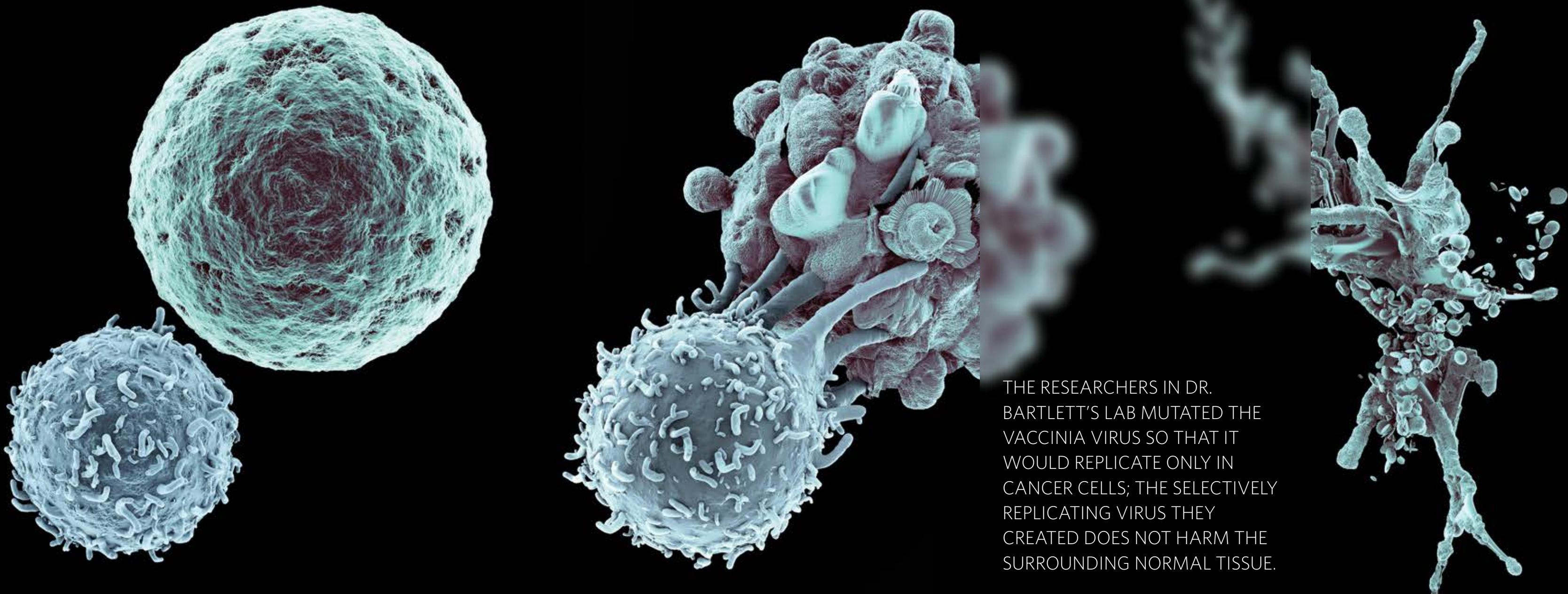
This trial is expanding to include 10 of the largest pediatric institutions in the United States. Dr. Pollack will continue to serve as the principal investigator as the study grows. If this work continues with the same degree of success, immunotherapy may become a new standard of care for some brain tumors.

We're developing a melanoma vaccine.

Lisa Butterfield, PhD, is the principal investigator leading a research group that is developing a vaccine against melanoma. **John Kirkwood, MD**, co-leader, of the UPCI Melanoma Program is the principal investigator leading the clinical trial of the vaccine. Their work focuses on inoculating dendritic cells to set the immune system in motion.

Dendritic cells act as guards, reacting to pathogens and initiating the immune response that causes T cells to differentiate and eliminate intruders. Researchers have been testing dendritic cells in immunotherapy clinical trials for 20 years. Dr. Butterfield's SPORE (Specialized Program of Research Excellence)-sponsored project is exploring the genetic engineering of adenovirus, an upper respiratory tract virus, to produce three antigens expressed by melanoma tumors. Infection of the patient's dendritic cells with the engineered virus provokes an immune response, which then fights the tumor.

So far, the researchers have seen a positive clinical response. Several subjects with Stage 3 disease have remained free from recurrence, and subjects with Stage 4 metastatic disease also are experiencing the benefits of immune response. In fact, one Stage 4 patient's tumor decreased by 50 percent. This partial response in total tumor volume is an encouraging sign that the melanoma vaccine project is on the right track.



THE RESEARCHERS IN DR. BARTLETT'S LAB MUTATED THE VACCINIA VIRUS SO THAT IT WOULD REPLICATE ONLY IN CANCER CELLS; THE SELECTIVELY REPLICATING VIRUS THEY CREATED DOES NOT HARM THE SURROUNDING NORMAL TISSUE.

"These early clinical responses are doing a good job of demonstrating the efficacy of immunotherapy for cancer. We now have scientific and clinical evidence that this approach is valid and full of possibility. It's a great time to be involved in this research."

— Lisa Butterfield, PhD, professor, Medicine, Surgery, and Immunology and director, UPCI Immunologic Monitoring and Cellular Products Laboratory

We're fighting BRAF inhibitor resistance in melanoma.

The BRAF gene produces a protein in the Raf kinase family of growth signal transduction protein kinases, which are related to retroviral oncogenes. Mutations of the BRAF gene are present in up to 50 percent of melanomas, making this gene primary as a jumping-off point for the development of a therapeutic strategy.

The eventual development of selective BRAF inhibitors that interrupt its downstream signaling gave rise to targeted therapy in melanoma. However, many patients whose tumors exhibit BRAF inhibitor resistance can develop disease at new sites, which means that drug-induced selection pressure is likely driving metastasis.

Hussein Tawbi, MD, PhD, associate professor of Medicine, Clinical and Translational Science, UPCI, and his team discovered that the signaling of a protein-tyrosine kinase known as EPHA2 was an adaptation to BRAF inhibition therapy. The team's work produced solid evidence that BRAF inhibition promotes the adoption of a therapy-driven metastatic phenotype in melanoma. By targeting both EPHA2 signaling and BRAF, the development of therapy-resistant disease at new sites may be prevented.

We're fighting cancer with the vaccinia virus.

David Bartlett, MD, chief, Division of Surgical Oncology, UPMC CancerCenter, is developing tumor-selective oncolytic vaccinia viruses that preferentially infect and destroy cancer cells.

The vaccinia virus is a large, complex member of the poxvirus family, with a linear, double-stranded DNA genome encoding approximately 250 genes. It is best known as the active component of the smallpox vaccine. The researchers in Dr. Bartlett's lab mutated the vaccinia virus so that it would replicate only in cancer cells; the selectively replicating virus they created does not harm the surrounding normal tissue. They then used it as a vector to deliver gene therapy directly to tumor sites: genetically engineering the virus caused the immune system to regard the genes as foreign. The team's work demonstrated that intratumoral injection of oncolytic vaccinia virus resulted in selective-infection antitumor activity.

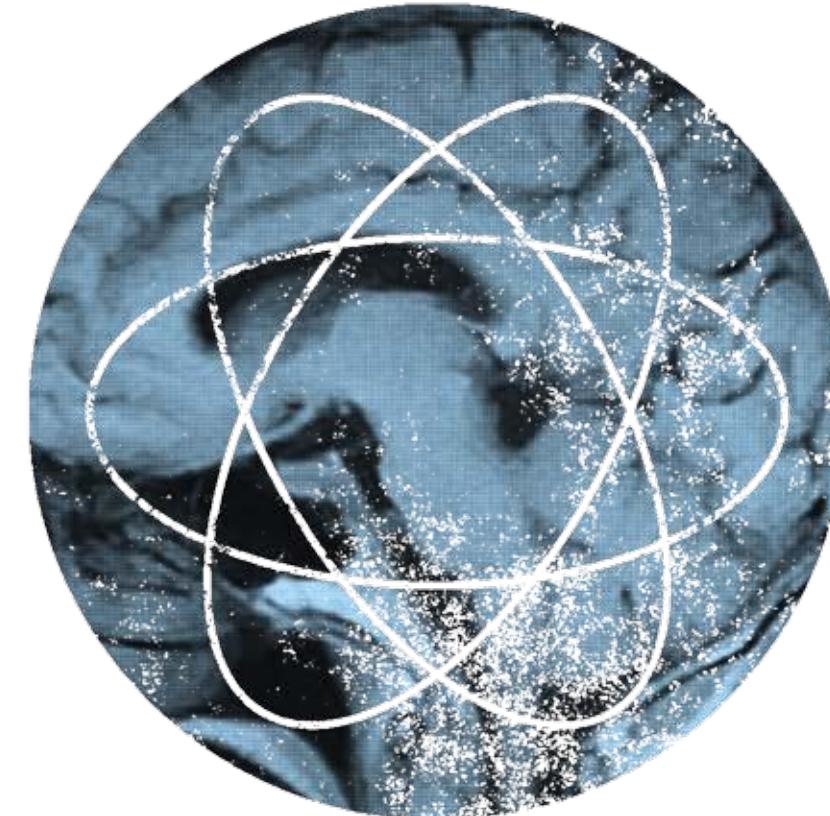
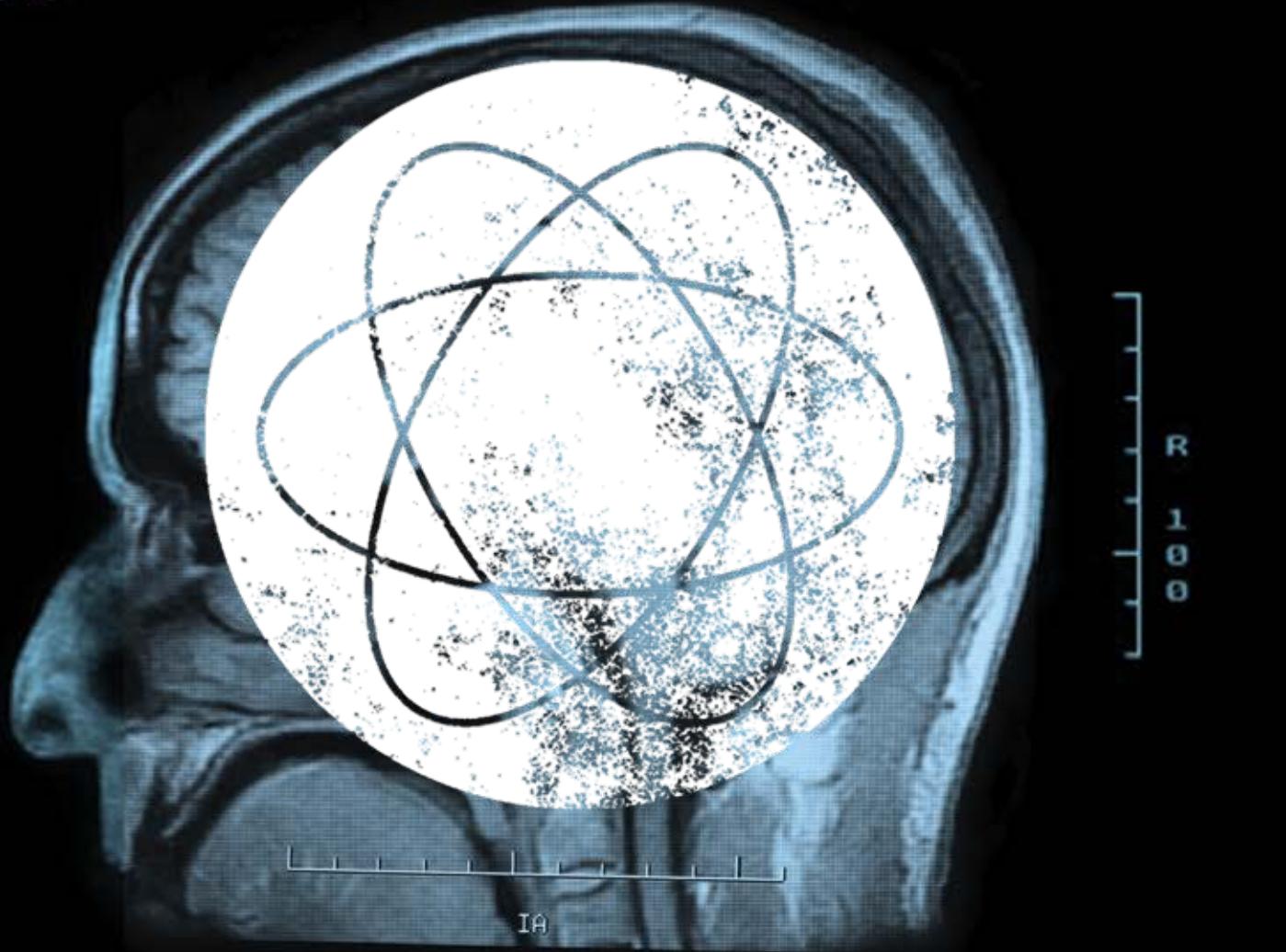
Ongoing research focuses on employing regional therapeutics, or the delivery of agents directly to the blood vessels that lead to a tumor, in the delivery of the vaccine. Using the circulatory system to deliver this mutated virus may allow doctors to take a broader aim at all of the tumors in the patient's body. Dr. Bartlett also is studying complement inhibitors that inactivate the virus when it reaches the blood, allowing it to travel to tumors in higher concentrations for more profound effect.

"Checkpoint inhibitors in combination with traditional vaccination can be powerful. If a virus can cause exposed cells to send danger signals to the immune system, then complement inhibitors will make the response even stronger."

— David Bartlett, MD, chief, Division of Surgical Oncology, UPMC CancerCenter, and the Dr. Bernard Fisher Professor of Surgery at the University of Pittsburgh School of Medicine



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WE'RE COMBINING STRATEGIES TO FIGHT MELANOMA BRAIN METASTASES

Melanoma research has served as a starting point for most immunotherapeutic drugs developed over the past three decades. Nearly all of the latest drugs that involve the immune system have roots in the treatment of melanoma; of these, nivolumab (an anti-PD-1 monoclonal antibody) is the most significant. But, until recently, all of this research and drug development has excluded patients with melanoma brain metastases.

Hussein Tawbi, MD, PhD, associate professor of medicine at UPCI, is leading several studies that indicate significant benefits from combining therapeutic approaches in patients with melanoma brain metastases. Clinical trials of nivolumab (Phases 2 and 3) and pembrolizumab (Phase 1) are demonstrating that immunotherapy is effective in metastatic melanoma. More research shows that simultaneously targeting the BRAF gene in patients with mutations thereof (present in up to 50 percent of melanomas) while administering immunotherapy can increase the response rates—and the durability of the response—in these patients while reducing toxicity.

Dr. Tawbi is also engaged in research regarding another combination therapy—that of dasatinib plus dendritic cell vaccination. Dasatinib inhibits

the BCR-ABL, SRC, c-KIT, PDGFR, and ephrin tyrosine kinases and enhances T-cell infiltration into the tumor microenvironment. Combining dasatinib with dendritic cell vaccination appears to provoke a durable immunotherapeutic response against melanoma.

"Combination therapy is the next frontier in the control of metastatic melanoma, and we are leading the way in this area."

— Hussein Tawbi, MD, PhD, assistant professor of Medicine, Clinical & Translational science, UPCI Melanoma and Skin Cancer Program, co-director, UPCI Sarcoma Program, & director, UPCI-CTRC

2014 BRINGS A FRESH APPROACH TO LUNG AND THORACIC CANCERS

THE UPCI LUNG CANCER PROGRAM IS LEADING TRANSLATIONAL RESEARCH INVESTIGATING THE MOLECULAR PATHWAYS THAT LEAD TO LUNG CANCER.

The program's goal is to improve early detection, prevention, and treatment of this disease, which is projected to kill an estimated 158,040 Americans in 2015. In 2014, researchers and physicians in the program saw their work—and ranks—expand to fulfill the promise of new opportunities.

We're committed to promoting early detection.

Although lung cancer causes more deaths than breast, prostate, and colorectal cancer combined, screening for its early detection is not typically recommended. This means that many patients with lung cancer are not receiving the early intervention that may lead to better outcomes. Lung cancers that are diagnosed early are associated with lower mortality than cases diagnosed at more advanced stages. Continued improvement of lung cancer-related outcomes will require regular screenings and early intervention.

PLuSS update: Predicting risk with computed tomography

To meet this challenge head-on, the Pittsburgh Lung Screening Study (PLuSS) is working to improve risk prediction. PLuSS is part of the larger Specialized Program of Research Excellence (SPORE) in Lung Cancer, a prestigious National Cancer Institute research grant project now in its third five-year funding cycle. One of the goals of the SPORE program is improved risk prediction, aimed at helping basic, translational, and clinical scientists to determine which of their patients are most in danger of developing lung cancer.

As part of our risk prediction studies, we have examined the efficacy of computed tomography (CT) scanning for early-stage lung cancer, the use of which is slowly becoming more widespread. Volumetric analyses, including doubling times of CT-detected lung nodules and lung cancers, have proven useful in follow-up and management of adenocarcinoma, in particular. We expect that the results of our research will influence the management of indeterminate lung nodules detected on screening CT scans, and we believe that low-radiation CT scanning can contribute to a 20 percent decrease in mortality.

"Any test that reduces the probability of death from lung cancer is good news. This is an exciting time for lung cancer screening and early detection."

— David Wilson, MD, MPH, associate professor of Medicine, University of Pittsburgh School of Medicine and associate director, Lung Cancer Center, UPMC CancerCenter

Because of this research, Medicare and commercial insurers alike have now approved the use of CT scans for early detection of lung cancer in smokers and former smokers. We are confident that the increase in scanning for early-stage lung cancer will contribute to improved outcomes for patients with tobacco exposure. PLuSS will be enrolling more patients in the near future.

WE'VE RECRUITED THE FIELD'S TOP TALENT.

The Lung Cancer Program also added two prominent physicians in 2014.

Already home to oncology leaders including **Mark A. Socinski, MD**, and **James Luketich, MD**, as well as **Steven D. Shapiro, MD**, who contributed to the 2014 Surgeon General's report examining and updating the medical community's progress in battling the effects of tobacco use, the Lung Cancer Program also added two prominent physicians in 2014:



Dr. Herman



Dr. Sarkaria



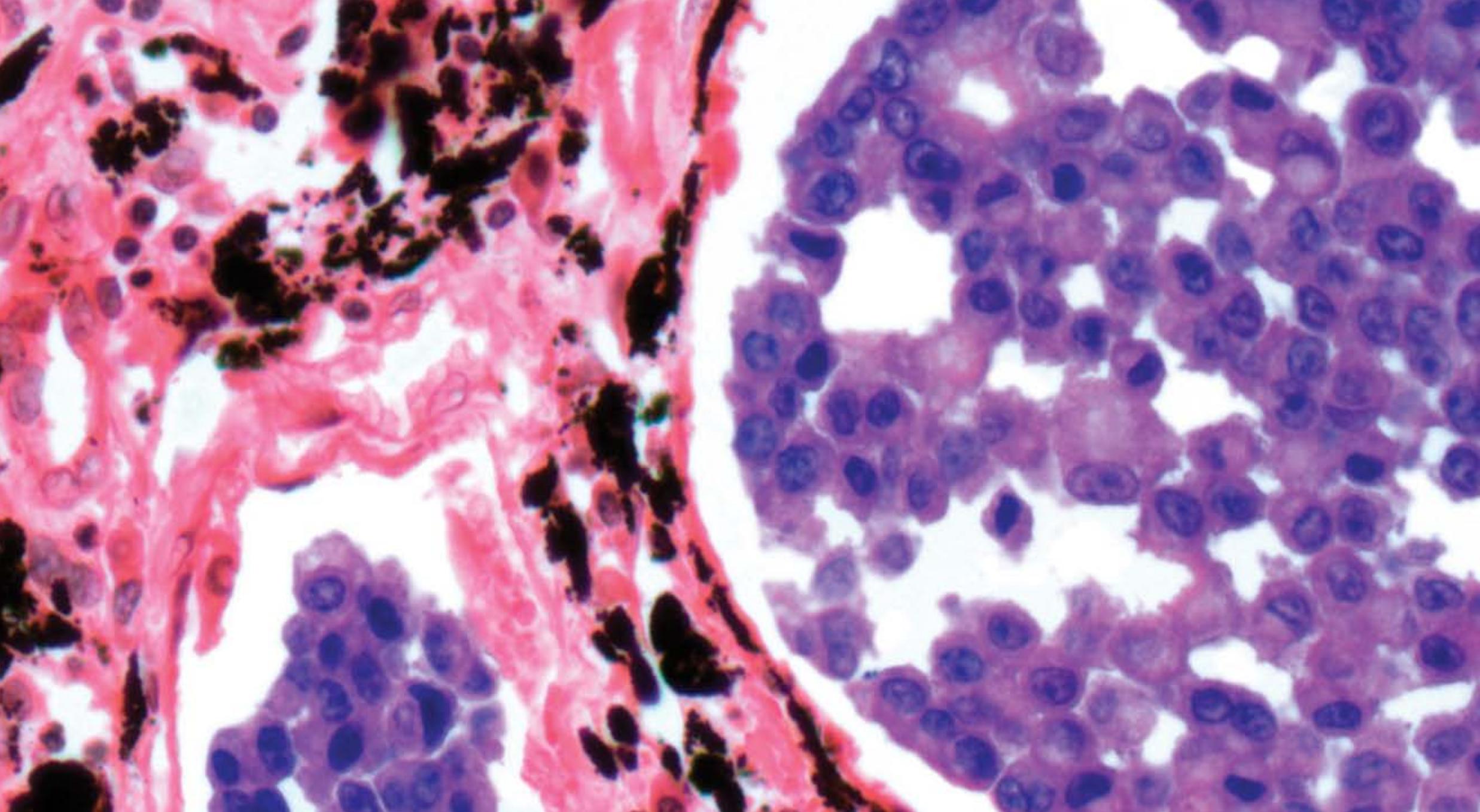
Dr. Wilson

James G. Herman, MD, joined UPCI as co-leader of the Lung Cancer Program and SPORE Principal Investigator. A practicing medical oncologist, Dr. Herman is known internationally for his work in epigenetics, particularly for the development of the methylation-specific PCR assay (MSP), which is widely used to characterize DNA methylation patterns. He has published more than 250 papers and served on the editorial boards of *Clinical Cancer Research* and the *Journal of Clinical Oncology*, among others.

Inderpal Sarkaria, MD, joined the Department of Cardiothoracic Surgery at UPMC as director of Thoracic Robotic Surgery, vice chairman for Clinical Affairs, and co-director of the Esophageal Surgery Institute. Dr. Sarkaria specializes in malignant and benign diseases of the chest including the lungs, pleura, esophagus, and mediastinum and is highly experienced in Video Assisted Thoracic Surgical (VATS) approaches including VATS lobectomy. He has lectured extensively at meetings of national and international thoracic surgical societies. Adding a thoracic surgeon of his caliber will allow the Lung Cancer Program to offer the full complement of the most advanced approaches to lung cancer treatment.



We encourage you to visit our online Annual Report at UPMCancerCenter.com/AnnualReport2014 for more information.



WE'RE TARGETING LUNG CANCER CHECKPOINTS

MARK SOCINSKI, MD, CO-LEADER OF THE UPCI LUNG CANCER PROGRAM, HAS BEEN WORKING WITH RESEARCHERS ALL OVER THE WORLD TO BRING IMMUNOTHERAPY FOR LUNG CANCER INTO THE MAINSTREAM, AND EARLY IN 2015, THAT WORK PAID OFF.

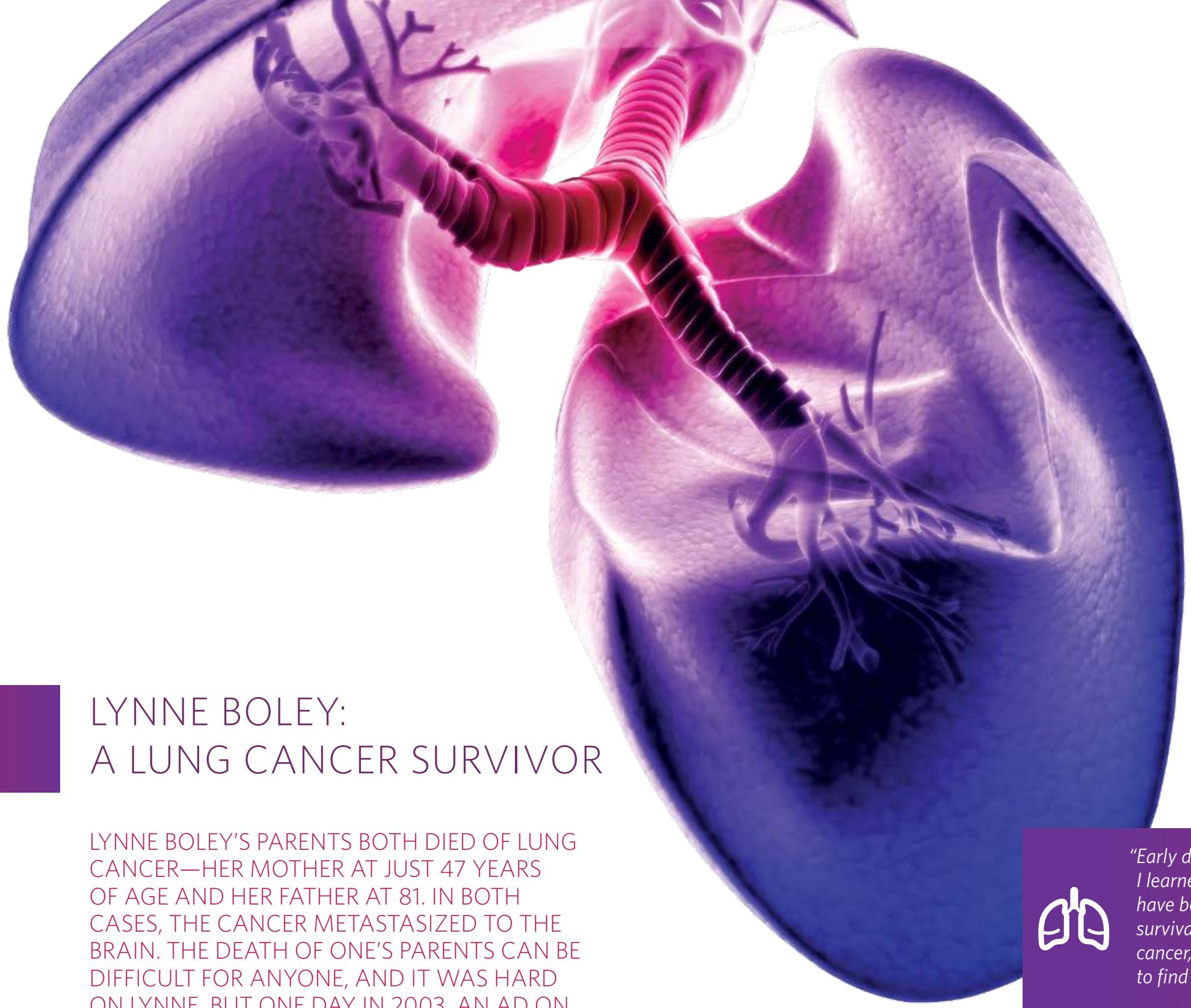
"WE'RE DEVELOPING THE FUTURE STANDARD OF TREATMENT FOR LUNG CANCER WITH OUR ONGOING RESEARCH INTO COMBINATION REGIMENS, WHERE CHEMOTHERAPY AND IMMUNOTHERAPY COME TOGETHER."

— Mark Socinski, MD, director, Lung Cancer Section, Division of Hematology Oncology at UPMC CancerCenter & co-director, UPMC Lung Cancer Center of Excellence

One focus of Dr. Socinski's research has been the treatment of metastatic squamous non-small cell lung cancer (NSCLC), which affects seven of eight people with lung cancer. Immunotherapeutic agents hold great promise in this area—in fact, the result of a recent Phase 3 trial of one of these agents has led to its approval by the FDA for the treatment of squamous NSCLC.

The immunotherapeutic agent that is now approved is nivolumab, which targets the PD-1 (programmed death 1) immune checkpoint receptor expressed on activated T-cells. Normally, the PD-1 pathway reduces the effect of immune-mediated destruction of healthy tissue, but cancer cells can exploit this pathway to protect themselves from tumor-specific T-cells. Nivolumab is an antibody that targets the PD-1 checkpoint molecule by binding PD-1 to its ligand, PD-L1, thereby suppressing the immune response.

In the trial, researchers found that patients treated with nivolumab lived a little more than three months longer than patients who received standard chemotherapy—a 40 percent reduced risk of death.



LYNNE BOLEY: A LUNG CANCER SURVIVOR

LYNNE BOLEY'S PARENTS BOTH DIED OF LUNG CANCER—HER MOTHER AT JUST 47 YEARS OF AGE AND HER FATHER AT 81. IN BOTH CASES, THE CANCER METASTASIZED TO THE BRAIN. THE DEATH OF ONE'S PARENTS CAN BE DIFFICULT FOR ANYONE, AND IT WAS HARD ON LYNNE. BUT ONE DAY IN 2003, AN AD ON THE TELEVISION INSPIRED HER TO USE HER OWN EXPERIENCES TO HELP OTHERS.

Lynne is not a person with a lot of spare time. "I worked for about 35 years as a senior administrator at a large school for children with psychological and behavioral challenges, and I also had kids of my own. Then I married a man who had kids too, and we made a sort of 'Brady Bunch' family," she says.

Lynne is also not prone to weakness. It's not easy to run a big school for troubled kids while bringing up a blended family and grieving the deaths of parents, but she did it. And, when she saw an ad asking for smokers to join a UPMC study on early cancer detection, she jumped at the chance. When her father was dying, she felt that many people along the way had judged him for being a smoker.

"Nobody blames the patient for getting breast cancer, but for smokers, there's not a lot of sympathy," she says. "Also, you don't see a lot of fundraising activities for lung cancer research. It's invisible."

She decided that one way to honor her parents and contribute to the cause of lung cancer research would be to participate in the study.

The study was PLuSS—the Pittsburgh Lung Screening Study, part of UPCI's larger Specialized Program of Research Excellence (SPORE) in Lung Cancer that is sponsored by the National Cancer Institute. The study's goal is to improve early detection.

Lynne's participation required quite a bit of her limited time. Every six months, she reported to UPMC for pulmonary function tests, sputum sampling, stress tests, CT scans, and other testing. She had to use some of her vacation days in order to keep up with the schedule, but she knew it was worth it. She also invested her own time in researching and writing outreach articles to raise awareness of lung cancer. Her work with PLuSS went on for 11 years—and then she got a phone call that nobody wants to get.

David Wilson, MD, MPH, associate professor of Medicine, University of Pittsburgh School of Medicine; associate director, Lung Cancer Center, UPMC CancerCenter, and the director, PLuSS study, called Lynne. The team had detected something suspicious on one of her scans—a tiny abnormality in her upper right lobe. As scary as that moment was, it awakened in Lynne another feeling as well. "I was amazed," she says. "Eleven years and 22 scans, and they put these scans side by side because somebody thought they saw something." The finding was too small to biopsy, so the team resected it. It turned out to be malignant, and she was out of the PLuSS study. Lynne felt she had no reason to believe she'd live.

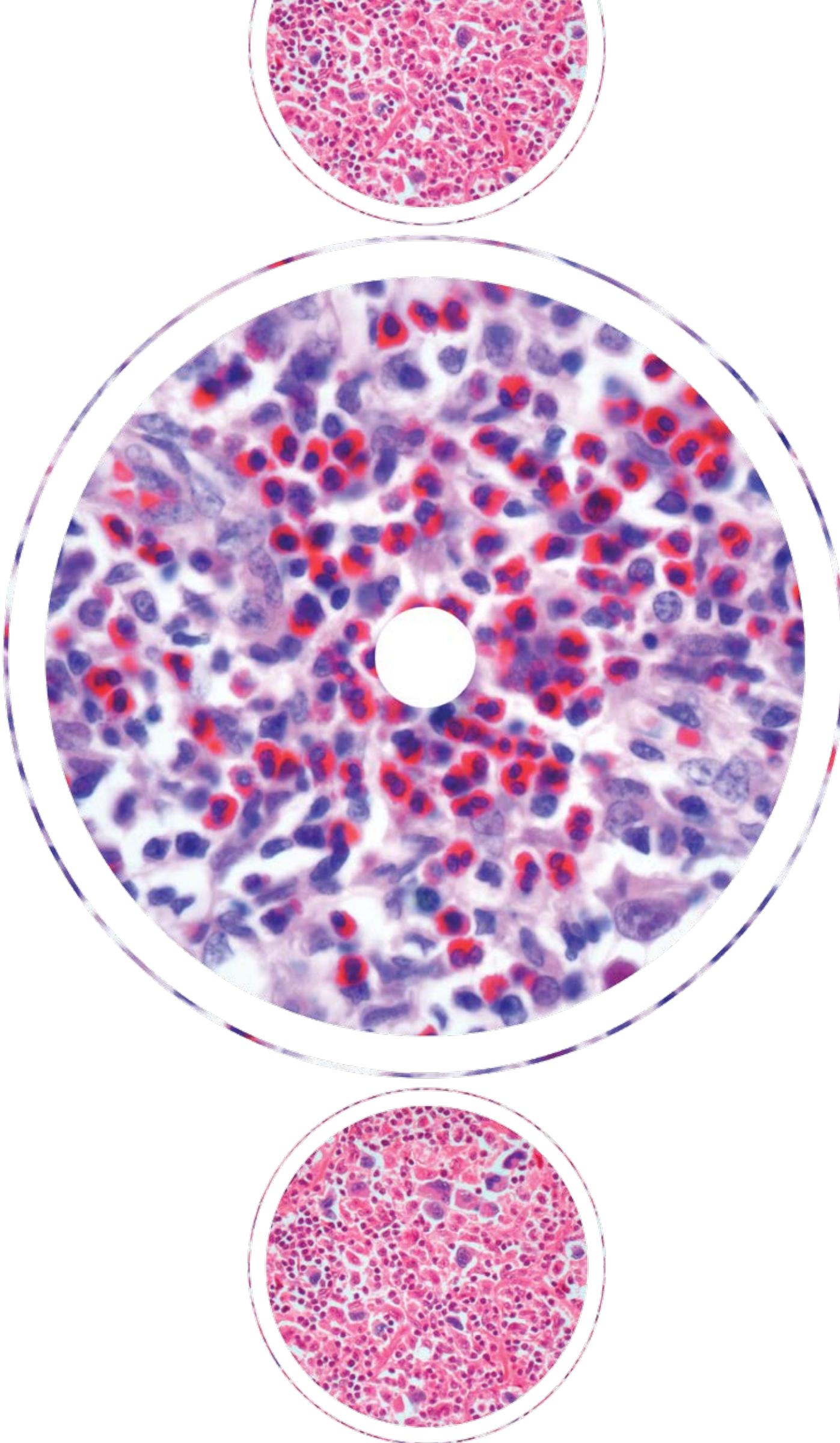


"Early detection is what saved my life," Lynne says. *"One of the more incredible things I learned was that, without early detection, my chance of surviving for five years would have been right around three to five percent. Because they caught it early, my five-year survival chance is more like 38 percent. There really is a way to find out you have lung cancer, and early detection is the key to survival. I am so amazed that UPMC was able to find my cancer and help me fight it so early."*

After three years of treatment, Lynne learned at a checkup that the cancer had metastasized to her lymph nodes. What followed was a grueling cancer journey that included chemotherapy and radiation (but, surprisingly, no hair loss). And then, two weeks before her final chemotherapy session, Lynne's house burned down. Two weeks after that, she lost her hair.

By this point, many of us would have given up—but not Lynne Boley. She felt unwell, but she found an apartment, kept up with her treatments, grew out her hair, and worked hard to understand the challenges she was facing. Lynne says she is doing well now—her cancer is in remission, she goes for yearly checkups, and she continues to read, write, and advocate for early screening for lung cancer. She also volunteers for PLuSS as a patient advocate at the group's monthly meetings and is working on creating a national fundraising activity to honor her dad.

THE MARIO LEMIEUX LYMPHOMA CENTER FOR CHILDREN AND YOUNG ADULTS



Pittsburghers love their sports icons, and it seems at least one sports icon loves us back. In June 2014, the Mario Lemieux Foundation contributed \$2.5 million to Children's Hospital to establish a new treatment center for kids and young adults with rare and challenging lymphomas. UPMC is contributing matching funds to establish this new center, known as the Mario Lemieux Lymphoma Center for Children and Young Adults at Children's Hospital of Pittsburgh of UPMC.

Because Children's is a destination care center, this gift will benefit kids from all over the world as well as right here in Pittsburgh.

Linda McAllister-Lucas, MD, PhD, chief, Division of Pediatric Hematology/Oncology, Children's Hospital, leads the new center, which delivers patient care and oversees laboratory and clinical research projects.

Mario Lemieux himself was present at the announcement of the foundation's gift, to the delight of some young sports fans receiving treatment at Children's. The hockey legend and philanthropist was diagnosed in 1993 with Hodgkin's lymphoma and underwent a course of radiation therapy—and when it was over, he went right back to leading the Pittsburgh Penguins.

"I WAS FORTUNATE TO HAVE A TYPE OF LYMPHOMA THAT HAS PROVEN TREATMENTS WITH GOOD OUTCOMES. I WANT TO CREATE A PLACE OF HOPE FOR KIDS AND YOUNG ADULTS AND THEIR FAMILIES WHO ARE DIAGNOSED WITH LYMPHOMAS THAT HAVE NO KNOWN CURES."

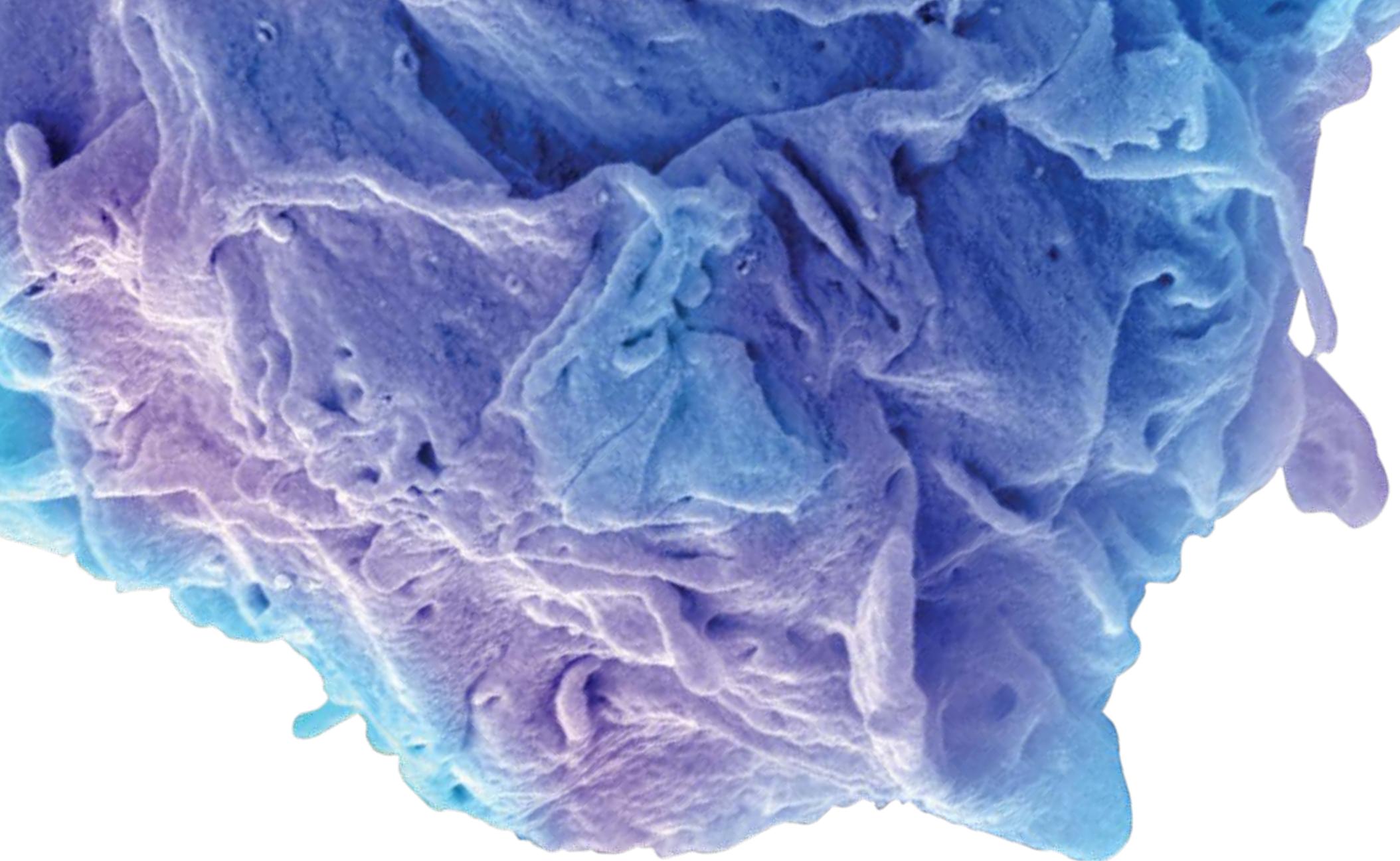
—MARIO LEMIEUX

More than 1,500 children in the United States are diagnosed with lymphoma every year, making it the third most common type of pediatric cancer. For 80 percent of these cases, standardized treatment protocols generally result in good outcomes, but for the remaining 20 percent, no effective treatment exists. The team at the Mario Lemieux Lymphoma Center for Children and Young Adults intends to remedy that situation.

With the new center up and running, complementing the hospital's established bone marrow transplant program and ongoing research, the future looks bright for the many children and families who visit Children's Hospital.



Read about the experience of one of our young lymphoma patients at Children's Hospital in our online ANNUAL REPORT at UPMCCancerCenter.com/AnnualReport2014.



TACKLING CANCER HEAD-ON: #88 VS. HODGKIN'S LYMPHOMA

RYAN HARKLEROAD IS BIG. AT SIX FEET, FOUR INCHES TALL AND 235 POUNDS—AND ABLE TO BENCH MORE THAN HIS OWN WEIGHT—HE'S WELL SUITED TO HIS POSITION AS A STARTING TIGHT END ON THE UPPER ST. CLAIR HIGH SCHOOL'S VARSITY FOOTBALL TEAM. BUT EVEN BIG, HARDY KIDS CAN RUN INTO HEALTH PROBLEMS.

In May of 2014, Ryan was working out in the weight room at school when his coach noticed a bump on his left elbow. Some people may have ignored such a small thing, but this coach somehow knew the bump was important. He told Ryan to put football on hold until he visited the doctor. So, Ryan did.

Ryan may look like an adult, but, as his mom says, "He's still only 16." Mary Beth Harkleroad and her husband, Norm, were presented with a few different options for Ryan's treatment because of his size, but since he is a teenager, she says, "We felt that he needed a doctor who knew how to

handle cancer in adolescents. We're so happy that we were referred to Children's." It turned out that Ryan had Stage 2 Hodgkin's lymphoma, indicating involvement of two or more groups of lymph nodes on the same side of the diaphragm.

The Harkleroads went to see Peter Shaw, MD, the clinical director of Oncology and head of the Adolescent and Young Adult Oncology Program at Children's Hospital of Pittsburgh of UPMC. The program proved to be the perfect fit for Ryan.

People between the ages of 15 and 21 need specialized care—not quite pediatric, not quite adult. Kids in this age group are growing fast, and they're also experiencing other changes that can require emotional and psychological attention. The Adolescent and Young Adult Oncology Program provides a comprehensive, collaborative approach to care that pairs pediatric oncologists with adult oncologists to care for each patient.

"He turned out to have the same diagnosis as Mario Lemieux, but at a different stage," says Ryan's mom, Mary Beth. "Hodgkin's lymphoma—it's a diagnosis no mother wants to hear." She reports that Ryan was stunned as well. But Ryan is a kid who doesn't let anything get him down.


"He decided right away that he was going to keep playing football," says Mary Beth. Even with six weeks of chemotherapy on his calendar (including three, six-hour sessions every week), Ryan kept pushing himself to keep up, practicing with the team and playing in games. Another series of treatments followed the initial course. Mary Beth was worried that that this hard physical work would be detrimental to his health, but the team at Children's Hospital gave Ryan's determination the green light—with some precautions.



Dr. Shaw and his team kept careful track of Ryan's blood counts, checking his blood work every week at his chemotherapy sessions. As long as the numbers were good, he was OK to play. "They told me that this was actually going to help, by helping Ryan keep a positive outlook," Mary Beth notes. "As long as he was physically able, he could play football."

Ryan did slow down a bit toward the end of the season; his mother reports that chemotherapy and radiation "wiped him out somewhat" but that he's doing very well. Everything looked good at his first three-month check-up, in February, and the Harkleroads are confident that this positive trend will continue at subsequent appointments.

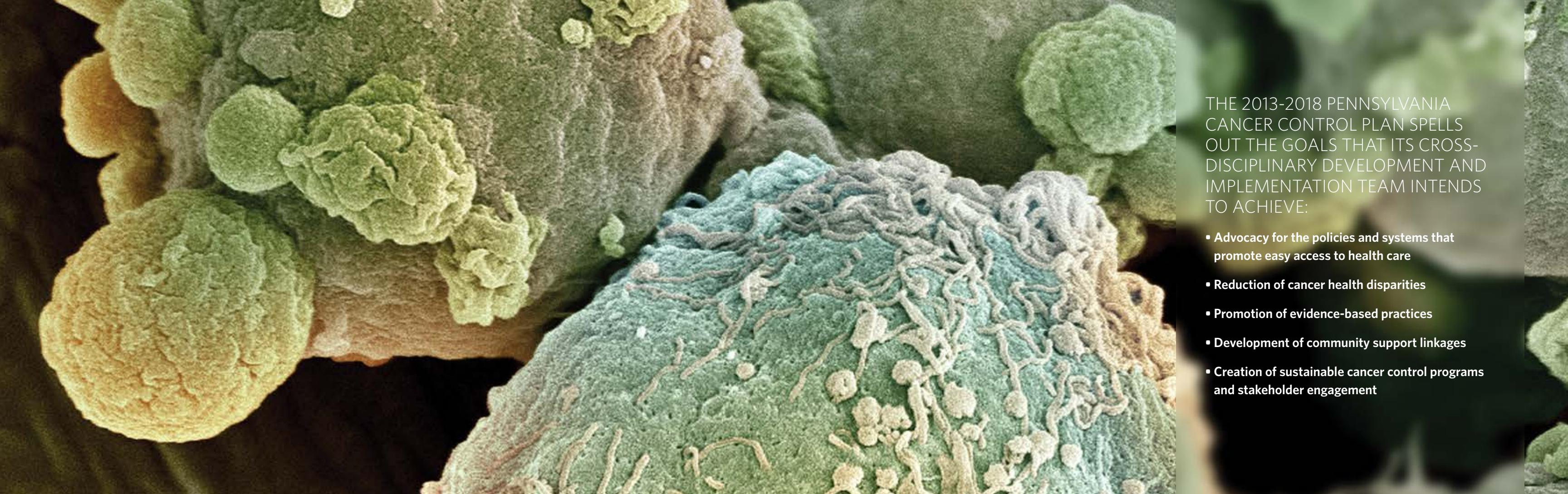
Dr. Shaw will keep Ryan under his care for the next 10 years to monitor for late relapse. Meanwhile, Ryan is checking out Division 1 schools and planning to study business finance after he graduates from high school next year.

"Even though it wasn't easy, the entire experience at Children's was nothing short of spectacular," says Mary Beth. "We are so grateful for the help that Ryan received there."



NEIGHBORS HELPING NEIGHBORS... TO MAKE OUR COMMUNITIES CANCER FREE

UPMC CancerCenter has always had a strong commitment to the communities we serve. Smoking cessation programs, educational partnerships, clinical trials, and a strong network of volunteers are a few of the ways we reach out to our neighbors—those at risk for cancer, those in recovery, and everyone in between. To us, our neighborhood extends beyond Pittsburgh. UPMC facilities throughout the region, along with individual practitioners in our network, help us to strive toward meeting our goal of serving patients quickly and conveniently.



THE 2013-2018 PENNSYLVANIA CANCER CONTROL PLAN SPELLED OUT THE GOALS THAT ITS CROSS-DISCIPLINARY DEVELOPMENT AND IMPLEMENTATION TEAM INTENDS TO ACHIEVE:

- Advocacy for the policies and systems that promote easy access to health care
- Reduction of cancer health disparities
- Promotion of evidence-based practices
- Development of community support linkages
- Creation of sustainable cancer control programs and stakeholder engagement

"Our organization's hub-and-spoke model is the reason we can serve patients and families so close to home."

— Dwight Heron, MD, director of Radiation Services, UPMC CancerCenter and chairman, Department of Radiation Oncology, UPMC Shadyside

Hillman Cancer Center is the hub, offering advanced treatment, clinical trial participation, adjuvant and complementary therapies, counseling, and more. Our network facilities and providers throughout the region are the spokes—and, thanks to the Pathways program, they offer the same high level of quality care as we do at Hillman. There are populations within our region, however, that are underserved by traditional health care delivery.

The elimination of racial and socioeconomic disparity, with an emphasis on reaching underserved patient populations, defined much of our formal outreach effort in 2014. Urban and minority patients, rural patients, the Amish, and others who tend to fly under the radar are often at increased risk for cancer. We posited that defining and locating these populations and designing programs to increase screening, promote smoking cessation, and offer education would enable us to achieve dramatic improvements in outcomes.

With a grant from the Pennsylvania Department of Health's CURE (Commonwealth Universal Research Enhancement) program, we found that eliminating barriers to seeking care and enabling earlier detection significantly improved upon pre-intervention baseline outcomes (especially in breast and lung cancer). Engaging with our patients and potential patients through tailored outreach throughout 2014 has allowed us to reduce the burden of cancer in a meaningful way. We intend to expand upon what we've built so that we can continue to serve all of our patients to the best of our ability in the years to come.

The Pennsylvania Cancer Control Plan

The Centers for Disease Control requires every state to develop a five-year plan to reduce cancer. The 2013-2018 Pennsylvania Cancer Control Plan spells out the goals that its cross-disciplinary development and implementation team intends to achieve:

- Advocacy for the policies and systems that promote easy access to health care
- Reduction of cancer health disparities
- Promotion of evidence-based practices

- Development of community support linkages
- Creation of sustainable cancer control programs and stakeholder engagement

Lyn Robertson, DrPH, RN, MSN, associate director of Health Equity, Education, and Advocacy at UPCI, served as a member of the statewide committee to create this plan, and she is now part of the stakeholder leadership team. Quarterly meetings and weekly conference calls keep the plan on track, and subcommittees work toward the achievement of specific goals—for instance, the team has involved the Pennsylvania Department of Transportation in efforts to develop pilot programs to provide transportation for patients who need it.

"Our vision is to eliminate the burden of cancer for Pennsylvania, and we are doing that by treating this plan as a living thing. We are always adjusting it to ensure that the data we collect is helping us to fine-tune the practices and policies that will deliver real results. I love everything I do, because it all comes together."

— Lyn Robertson, DrPH, RN, MSN, associate director of Health Equity, Education, and Advocacy at UPCI

Pennsylvania is one of the first states asked to develop a cancer plan based upon the chronic disease model, which considers epidemiology, environmental approaches, health system interventions, and community clinical linkages in the effort to manage and reduce disease. Limited resources necessitate data-driven recommendations; careful aggregation and analysis allow the committee to direct efforts efficiently toward the reduction of cancer cases, death rates, and co-morbidities through institutional efforts and community outreach. The result is a dynamic pattern of protocols and policies that promote healthful behaviors in schools and communities while keeping a sharp focus on eliminating disparities in access to treatment.

Because UPMC CancerCenter and UPCI serve both urban and rural populations, delivering clinical treatment and conducting groundbreaking research, our representation on this team ensures that the resulting plan incorporates the many perspectives that are critical to making its implementation a success.

INTEGRATIVE ONCOLOGY: POWERFUL HELP THAT GOES BEYOND TRADITIONAL MEDICINE



Dr. Francis



LANIE FRANCIS, MD, HEMATOLOGIST AND MEDICAL ONCOLOGIST, UPMC CANCERCENTER'S HILLMAN CANCER CENTER, HAS ALWAYS HAD A STRONG COMMITMENT TO TREATING THE WHOLE PATIENT.

Emotional and psychological issues can produce tremendous stress, and stress can exacerbate physical symptoms that are directly or indirectly related to the disease process. Holistic practices, including yoga, meditation, massage, nutritional support, and music therapy, can significantly improve patients' moods and lower their stress, contributing to their overall well-being and potentially improving outcomes.

Dr. Francis noticed that while she was addressing medical issues with her patients, they often really wanted help with managing their lives. Stress, nausea, stiffness, fatigue, and other symptoms respond well to yoga, so she started recommending it to her patients. As they began to report positive responses to non-medical approaches, she realized it was time to organize a formal system of providing integrative support.

"These are elements of living well. Lifestyle changes can really improve the cancer journey in a meaningful way."

—Lanie Francis, MD, hematologist & medical oncologist, UPMC CancerCenter

In 2013, Dr. Francis organized the first Integrative Oncology Wellness Fair at UPMC CancerCenter to provide patients, caregivers, and physicians with information and resources that can help them fight cancer from a different perspective. Last year, the second Wellness Fair brought even more qualified non-medical support providers into the fold in a systematic way. Providers are extensively interviewed and required to comply with the UPMC code of ethics before they are accepted into a preferred-provider database, which cross-references providers and their specialties with the symptoms they can help to alleviate. Referring physicians and the community providers work closely together to monitor the patient's progress and make adjustments as needed.

Based on positive feedback from participants and providers alike, Dr. Francis's holistic wellness program is likely to continue helping an increasing number of patients for many years to come.

CLINICAL PATHWAYS: PAVING THE WAY TO EXCELLENCE IN 17 STATES...AND COUNTING

Customized and standardized.

UPMC CancerCenter is a pioneer in the development and use of cancer treatment pathways—evidence-based decision-support tools that enable physicians to deliver the best quality care to their individual patients in specified situations.

Via Oncology, a subsidiary of UPMC, rolled out Via Oncology Pathways at UPMC CancerCenter in 2005 with the goal of ensuring the highest quality, consistent patient care within the network. Today, oncologists around the country and throughout the UPMC CancerCenter network use Pathways. Embedded protocols are mandated in every UPMC CancerCenter facility, whether it be Hillman Cancer Center or at another center in the network, making the same high standard of detailed, personalized care available to all patients regardless of geography.

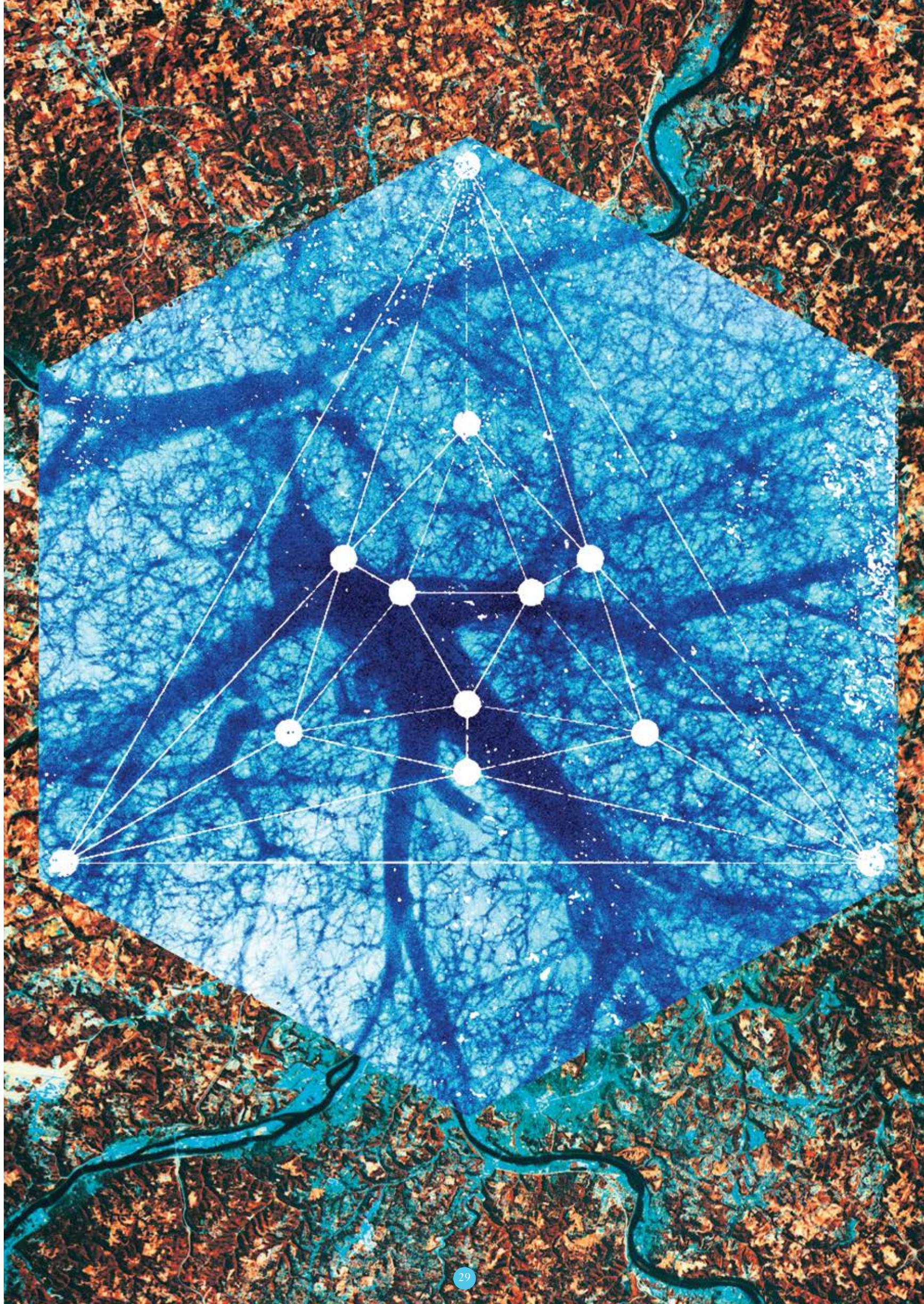
Pathways are assimilations of the best practices and protocols associated with the many different types and presentations of cancer, based on clinical evidence and backed up by multidisciplinary expertise. Each Pathway leads the physician through ordered evaluation and treatment strategies that combine maximum efficacy with lowest toxicity to provide the best care in a cost-effective manner. The tools also record patient information, deliver statistics on the patient population to our researchers, and alert physicians to clinical trial opportunities for patients based on their individual data.

Our Pathways program is setting the standard nationally for optimized cancer care.

In 2014, 97 percent of our patients were enrolled in the UPMC CancerCenter Pathways database, making this powerful tool a driving force in our provision of quality care throughout the network. The program has also branched out beyond our own health system to bring standardized care to other sites. Indiana University Health Cancer Centers and Space Coast Cancer Center are just two of the more than 900 oncology providers in 17 states now offering the specialized tools developed by our team.

"UPMC CancerCenter Pathways is a way we can ensure we are providing the best care to all of our patients. This is not 'cookbook' medicine—it's evidence-based and reflects the best of what science has to offer."

—Peter Ellis, MD, deputy director, Clinical Services, UPMC CancerCenter



BATTLING BREAST CANCER IN KAZAKHSTAN

HOW UPMC IS BRINGING HIGH-TECH COMPREHENSIVE CARE TO AN UNDERSERVED POPULATION



In the United States, breast cancer screening and treatment are ubiquitous. The pink ribbons, fundraising activities, and mammogram reminders are hard to miss. But in Kazakhstan, reminders and reliable results have been hard to come by until very recently. The mortality rate from breast cancer in Kazakhstan is roughly equivalent to the U.S. rate (around 21 deaths per 100,000), and screening and treatment practices have not kept up with what many practitioners would consider optimal.

Margarita Zuley, MD, vice chair, Quality and Strategic Development, chief of Breast Imaging in the Department of Radiology, and associate professor of Radiology at the University of Pittsburgh, became aware of this disparity when physicians from Kazakhstan came to Pittsburgh to observe the UPMC program in action. These visits lasted only a month or two—hardly long enough to share advanced knowledge of best practices. The fact that breast cancer is the most commonly diagnosed cancer in Kazakhstani women and one of the top three causes of cancer-related deaths spurred her to action, and she committed to an ambitious project intended to change the way physicians care for breast cancer patients throughout Kazakhstan.

The National Research Center for Maternal and Child Health in Astana is home to the Breast Checkup Program, which is a pilot program that grew from a partnership between Nazarbayev University and UPMC. Through this partnership, the National Research Oncology Center (NROC) will open in Astana in 2017 (and the Breast Checkup Program will move from its current location into the new facility). The NROC will bring the world's most advanced technologies and clinical approaches to patients who had previously received less comprehensive care. One of those advanced technologies is tomosynthesis.

Tomosynthesis produces an advanced three-dimensional mammogram. It is more accurate than traditional mammography, and the NROC will host the first exclusive use of this state-of-the-art technology in a patient population that has not previously undergone screening mammography. Within a few years, Dr. Zuley expects that tomosynthesis will replace traditional mammography in the United States as well.

"We're giving the people of Kazakhstan the best we've got, but our continued success will depend upon ongoing support. We're committed to providing the best care we can and to advancing the use of cutting-edge technologies."

—Margarita L. Zuley, MD, chief, Breast Imaging, Department of Radiology, UPCI

Kazakhstani radiologists and technologists who have completed initial training with UPMC partners in Pittsburgh are now working at the new imaging clinic in Astana. They work alongside pathologists, medical oncologists, and surgeons who also have trained in Pittsburgh, together establishing the new benchmarks for quality breast cancer diagnosis and care in Kazakhstan. The fully equipped NROC will employ local medical specialists, nurses, and support staff to provide a comprehensive continuum of diagnosis and care for many types of cancer. Under the direction of Dr. Zuley, UPMC breast imaging experts will continue to review every case, monitor outcomes, and serve as mentors until the NROC is prepared to continue independently.





AMBITION & HOPE

The National Cancer Institute (NCI) awarded researchers at the University of Pittsburgh Cancer Institute three MULTI-MILLION DOLLAR grants in 2014. Together, they are worth nearly \$15 million. Recognition at this level of support underscores UPMC's commitment to leading the way in cutting-edge cancer research and highlights our leadership position as one of the country's premier academic centers.



GRANT ONE: We're leaders in experimental therapeutics.

Edward Chu, MD, is heading up a five-year, \$4.25 million NCI Experimental Therapeutics Clinical Trials Network grant, which will support efforts to make the latest treatments available to patients as early as possible. His group's research encompasses the first-ever early phase clinical studies of certain experimental treatments in humans, either alone or in combination with approved anti-cancer agents.



UPCI is one of only 12 cancer centers in the United States to receive this type of grant.

"We're proud to have been selected to join this elite group. Our research into the development of novel agents will allow us and others to accelerate the deployment of tailored treatments, which is the essence of personalized medicine."

—Edward Chu, MD, deputy director, University of Pittsburgh Cancer Institute and associate director, Drug Discovery Institute

Dr. Chu's team has been studying the role of poly(ADP-ribose) polymerase—or PARP—inhibitors, which target enzymes involved in the repair of DNA. By testing tumor cells for genetic mutations, researchers can identify potential sensitivities that will allow the development of highly personalized treatments. Veliparib is one PARP inhibitor in particular that the team has studied extensively, with seven Phase 1 studies over the past five years. Meticulous attention to detail is one of the reasons the clinical pharmacology lab at UPMC ranks among the top three in the nation; other NCI-affiliated cancer centers use our facilities for their own research testing.



GRANT TWO: UPCI: A Lead Academic Participating Site.

Adam Brufsky, MD, chairs the NCI Lead Academic Participating Site (LAPS) grant, awarded through the NCI's newly reorganized National Clinical Trials Network (NCTN).

The NCTN fosters cooperation and technological advances that accelerate the process of translating lab research into clinical treatments. Improved data management, standardized prioritization processes, and the consolidation of research groups result in faster, more efficient clinical trials. UPCI is one of just 30 organizations in the United States and the only organization in Pennsylvania to win an NCI LAPS grant.



The nearly \$5 million grant supports our ability to enroll patients in national trials at 17 sites throughout the UPMC CancerCenter network. It is solid evidence of our position at the forefront of cancer research that will bring about a new standard of care.

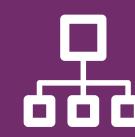
"Some of the best minds in cancer research are concentrated right here in our own academic institution. Pooling our intellectual contributions and cooperating with this vast research network allow us to participate in studies that are just steps away from major breakthroughs. That's pretty exciting."

—Adam Brufsky, MD, PhD, associate director, Clinical Investigation, UPCI

GRANT THREE: Cancer Studies in Shanghai and Singapore.

The NCI also awarded a five-year grant of more than \$4.2 million to support continuing research into the effects of genetics, environment, and lifestyle choices on cancer.

The Shanghai Cohort Study and the Singapore Chinese Health Study, led by **Dr. Jian-Min Yuan**, examine the incidence, mortality rates, and age-related outcomes of cancer in more than 81,000 Chinese men and women. Blood, urine, and other fluid samples—collected for more than 25 years—have yielded valuable information on the causes of cancer in these two populations. The findings have also led to chemoprevention trials, now underway in the United States.



With this grant, Dr. Yuan hopes to study up to 2,700 more individual cases and ensure ongoing maintenance of the studies' extensive databases and biorepositories. He and his group will also conduct follow-ups to determine cancer, non-cancer, and death outcomes.

"We anticipate that the two Asian study groups will become even more scientifically valuable over the next five years...with increasing numbers of pre-disease, biomarker-based research opportunities."

—Jian-Min Yuan, MD, PhD, associate director, Cancer Control and Population Sciences, UPCI



MEET OUR FIVE NEW ENDOWED CHAIRS

LAST YEAR, THE UNIVERSITY OF PITTSBURGH BESTOWED ENDOWED PROFESSORSHIPS UPON FIVE OF OUR RESEARCHERS—A GREAT HONOR IN ACADEMIC AND CLINICAL CIRCLES ALIKE. IN ACADEMIA, THIS IS A DISTINCTION UNLIKE ANY OTHER BECAUSE IT IS RECOGNITION OF EXCELLENCE BY ONE'S PEERS.

Endowed chairs generally include financial support and the expectation that the recipient will parlay his or her new position into extraordinary ongoing achievement. All of us at the University of Pittsburgh Cancer Institute and UPMC CancerCenter are proud of our distinguished colleagues:

YUAN CHANG, MD, became the UPMC Chair in Cancer Virology Research, focusing on how new techniques for DNA sampling can help us discover pathogens that cause chronic diseases. With fellow honoree Patrick Moore, MD, Dr. Chang identified the viruses that cause Kaposi sarcoma and Merkel cell carcinoma. UPMC funds this professorship.

ROBERT FERRIS, MD, PHD, who co-leads the Cancer Immunology Program and practices as a head and neck cancer surgeon and immunologist, is the UPMC Chair in Advanced Oncologic Head and Neck Surgery, and UPCI associate director for translational research. He spoke at the reception honoring the late **Ronald Herberman, MD**, on December 7, 2014, and served as program chair at the 2014 meeting of the American Laryngological, Rhinological, and Otological Society. Dr. Ferris's research studies the immune aspects of systemic therapy that often follows head and neck cancer surgery. UPMC funds this chair.

PATRICK MOORE, MD, MPH, leader of the Cancer Virology Program, now holds the Pittsburgh Foundation Chair in Innovative Cancer Research. Dr. Moore's research studies the link between viruses and cancer in an attempt to discover why some viruses cause cancer and some don't. A \$1 million award from the Pittsburgh Foundation funds this chair; UPCI raised \$1 million in matching funds from individuals across the community to complete the endowment.

SHIVENDRA SINGH, PHD, associate director for Basic Research and professor of Pharmacology & Chemical Biology and Urology, holds the UPMC Chair in Cancer Prevention Research. Dr. Singh studies cancer chemoprevention, a rapidly emerging sub-discipline that uses natural or synthetic agents to reverse or delay the process of carcinogenesis. UPMC funds this professorship.

JIAN-MIN YUAN, MD, PHD, associate director for Cancer Control and Population Sciences, professor of Epidemiology, and co-leader of the Cancer Epidemiology and Prevention Program, holds the Arnold Palmer Chair in Cancer Prevention. He is tracking the long-term development of cancer and other chronic diseases within two population cohorts in China and Singapore in order to identify better prevention strategies. The Arnold Palmer Foundation funds this chair.

The University of Pittsburgh Cancer Institute and UPMC CancerCenter are grateful for the philanthropic support that makes these professorships possible. By demonstrating commitment to research at the highest level, these endowments reflect our dedication to our work and help us to attract tomorrow's leaders in cancer research.

CIRCLE OF HOPE

The Circle of Hope honors individuals, family foundations, and privately held companies that make contributions of \$10,000 or more in a calendar year. This list recognizes those who were members in 2014.

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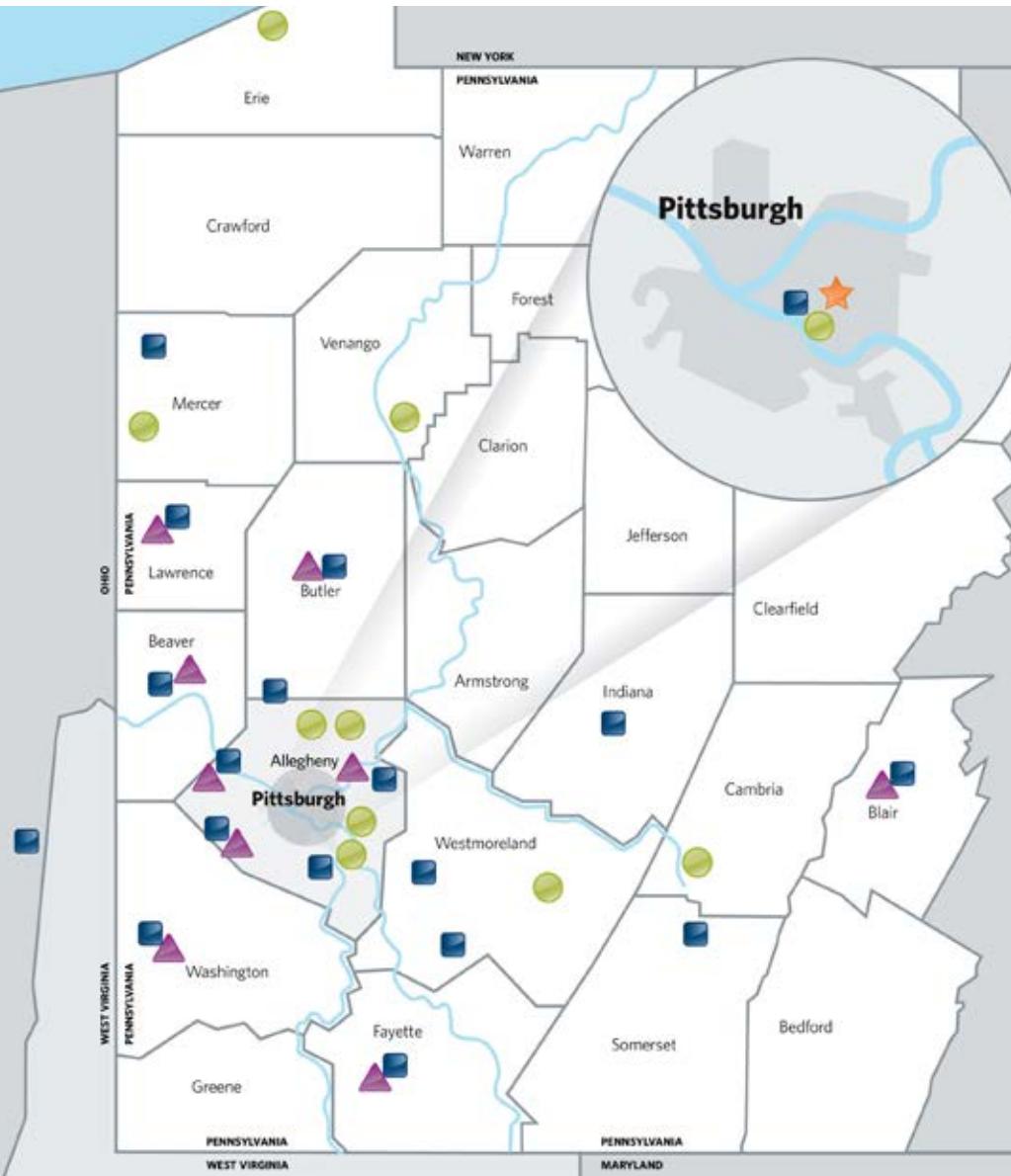
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UPMC CancerCenter, partner with University of Pittsburgh Cancer Institute, is internationally recognized for its leadership in the prevention, detection, diagnosis, and treatment of cancer. Hillman Cancer Center in Pittsburgh, established in 2002 with a generous gift from the Hillman Foundation, is UPMC CancerCenter's flagship site, housing both laboratory and clinical areas.

UPMC CancerCenter

Partner with University of Pittsburgh Cancer Institute

LOCATIONS

★ UPMC SHADYSIDE CAMPUS

Hillman Cancer Center
Mary Hillman Jennings Radiation Oncology Center

▲ RADIATION ONCOLOGY CENTERS

- 1 Jameson Radiation Oncology¹
- 2 Heritage Valley Radiation Oncology, Beaver¹
- 3 Heritage Valley Radiation Oncology at UPMC West¹
- 4 UPMC/St. Clair Hospital Cancer Center¹
- 5 Washington Health System Radiation Oncology¹
- 6 Uniontown Hospital Radiation Oncology, Robert E. Eberly Pavilion¹
- 7 UPMC CancerCenter Radiation Oncology at UPMC East
- 8 Butler Health System Radiation Oncology¹
- 9 UPMC CancerCenter Radiation Oncology at UPMC Altoona

■ MEDICAL ONCOLOGY CENTERS

- A UPMC CancerCenter Medical Oncology, New Castle
- B UPMC CancerCenter Medical Oncology, Beaver
- C Trinity Tony Teramana Medical Oncology¹
- D UPMC CancerCenter Medical Oncology, Sewickley

- E UPMC CancerCenter Medical Oncology, Upper St. Clair
- F UPMC CancerCenter Medical Oncology, Jefferson
- G UPMC CancerCenter Medical Oncology, Washington
- H Arnold Palmer Medical Oncology, Oakbrook Commons²
- I Arnold Palmer Medical Oncology, Mt. Pleasant²
- J UPMC CancerCenter Medical Oncology, Uniontown
- K UPMC CancerCenter Medical Oncology, Windber
- L UPMC CancerCenter Medical Oncology at UPMC Mercy
- M UPMC CancerCenter Medical Oncology, Indiana
- N UPMC CancerCenter Medical Oncology, Greenville
- O UPMC CancerCenter Medical Oncology, Monroeville
- P Butler Health System Medical Oncology¹
- Q UPMC CancerCenter Medical Oncology at UPMC Passavant-Cranberry

● DUAL CENTERS (RADIATION AND MEDICAL ONCOLOGY)

- 1A UPMC CancerCenter at UPMC Horizon
- 2B The Regional Cancer Center, Erie
- 3C UPMC CancerCenter at UPMC Passavant
- 4D UPMC CancerCenter, Natrona Heights

¹In partnership with UPMC CancerCenter

²A partnership of Exela Health and UPMC CancerCenter

³A partnership of UPMC CancerCenter and Memorial Medical Center



University of Pittsburgh
Cancer Institute
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UPMC CancerCenter connects patients to the integrated expertise of leading clinicians, academic researchers, specialty programs, and treatment centers. By partnering with the University of Pittsburgh Cancer Institute (UPCI), designated as a Comprehensive Cancer Center by the National Cancer Institute, we are accelerating the breakthroughs in our labs into clinical practice around the world. Backed by the collective strengths of UPMC and UPCI, UPMC CancerCenter is transforming cancer research, care, and prevention—one patient at a time.

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For information about supporting cancer research efforts and patient care at UPMC CancerCenter and the University of Pittsburgh Cancer Institute, contact us at 412-623-4700.

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