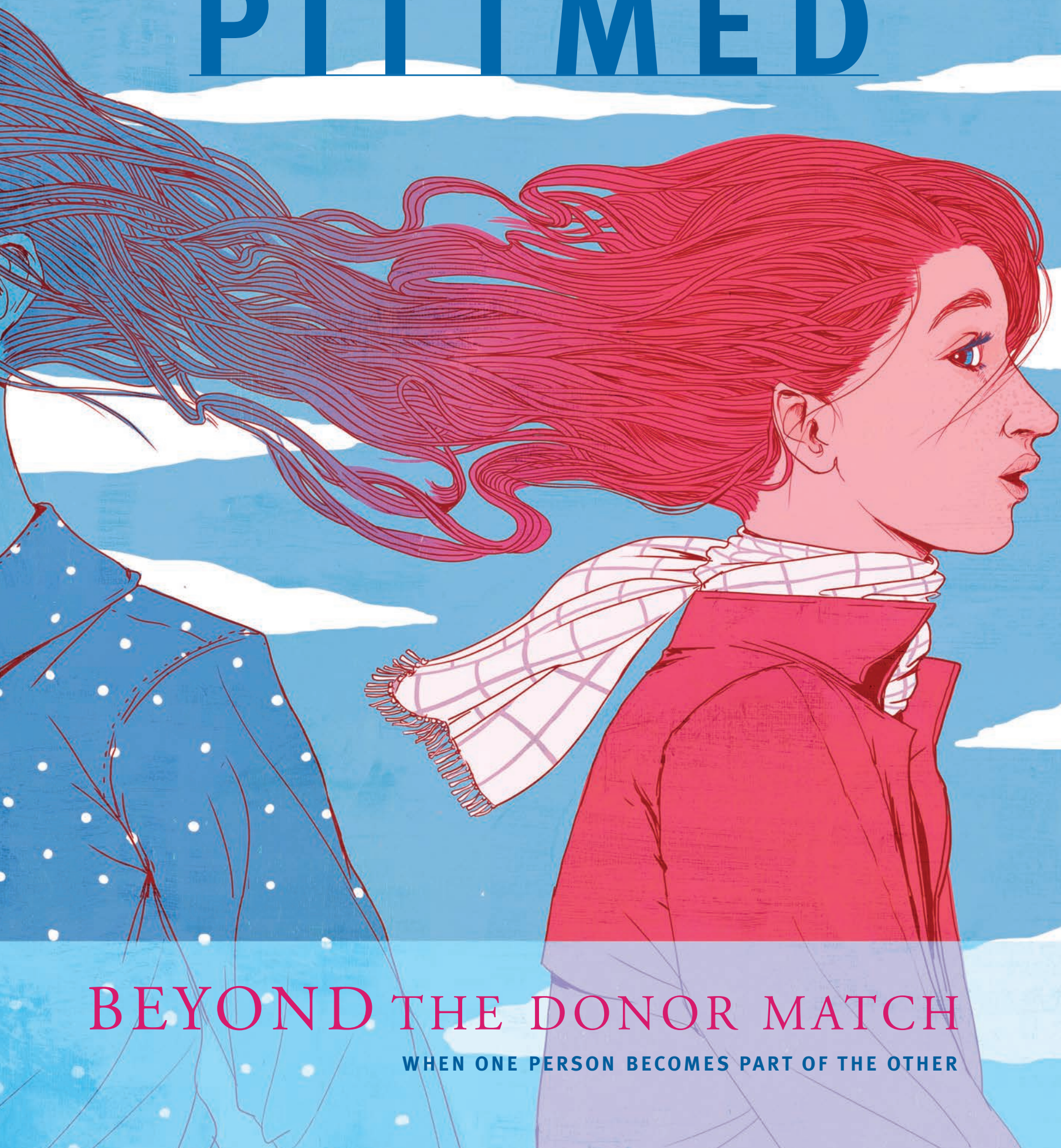


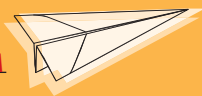
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SUMMER 2019

PITTMED



BEYOND THE DONOR MATCH

WHEN ONE PERSON BECOMES PART OF THE OTHER



FOLLOW-UP



Join in the conversation @PittMedMag.
Because you seem like someone interested
in healing and discovery.



Allison Bean MD, PhD @AlliBeanMDPhD · May 5

Someone is desperate to get that @PittMedMag news. Disclosure: I read it before I let her chew on it.



1 1 8



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Following

Learn about how @PittTweet is positioned to
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Elite athletes & members of the #military need to keep ticking in the most challenging of circumstances. Scientists are looking to these super users of the human body in the search for ways to optimize #HumanPerformance. bit.ly/2U4GRRO



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Sixty-five years after Scaife Hall first broke ground, Payette, in partnership with @mcfarchitects and @MoshierStudio, is working with @PittHealthSci on the renovation and expansion fit for the future medical education. @PittMedMag
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BREAK-FAST FRIENDS

The recent issue of *Pitt Med* made note of the passing of Henry Mankin (MD '53), a true icon of American orthopaedic surgery. I remember him well from many years ago as a fierce competitor. Around 1963–67, while I was a medical student at Pitt, he and I regularly competed for first place in line at 6:30 in the morning when the doors to the Presbyterian University Hospital cafeteria were opened for breakfast. Regardless of which of us won that daily contest, I would then be privileged to join him and the orthopaedic surgery residents for breakfast and “the first lecture of the day” on numerous occasions. How much influence he had, probably unknowingly, on my own surgical career. May he rest in peace.

Nicholas J. Feduska
MD '67
Henderson, Nev.

Editor's Note: Feduska became a kidney transplant surgeon and practiced for nearly 40 years.

BOOK AHEAD

I love receiving and reading *Pitt Med*, especially the dean's message in each issue. Please let Dr. Levine know how much I enjoy and appreciate his wonderfully written messages and that I anxiously await a compilation of all of them.

Larry Blattner, DDS, DO
Tempe, Ariz.

Editor's Note: Actually, in celebration of Dean Levine's two decades at Pitt, we are planning to compile his columns into a book. Stay tuned!

RECENT MAGAZINE HONORS

2018 National Association of
Science Writers
Excellence in Institutional Writing
(E. Vitone, “Cut Off”)

2019 Pittsburgh Black Media Federation
Robert L. Vann Media Award
Magazine/Feature
(E. Dyer, “With Love, From Haiti”)

2019 Press Club of Western
Pennsylvania Golden Quill Award
Excellence in Audio Journalism—
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(S.A. Flecker, E. Vitone, and E. Lloyd,
Pitt Medcast: “When Fred Met Margaret”)

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How new genes are born, what super users of the human body need to function. . . these are some of the issues *Pitt Med* readers have explored lately with our senior editor, **ELAINE VITONE** [“Precision Medicine for the Masses”]. In this issue, Vitone takes us on a journey with a pink-backpack-toting doctor who is about to rock our (clinical) worlds. Vitone, who has written for this magazine since 2005, also produces *Pitt Medcast*, which has been featured on several NPR-member stations. Because of her talents, this winter, *Pitt Medcast* was featured on AAAS's Sci-Mic live podcasting stage.

JENNY BLAIR [“A Whole New Ballgame”] explored a newfangled way of doing clinical trials for this issue. Blair, an MD, describes the approach as a “stunningly elegant piece of intellectual engineering” that brings the truth closer to clinicians and researchers alike. Besides writing, she enjoys drawing comics and spending time with her sheep-like dog, Mr. Noodles.

PITTMED

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VOL. 21, ISSUE 2



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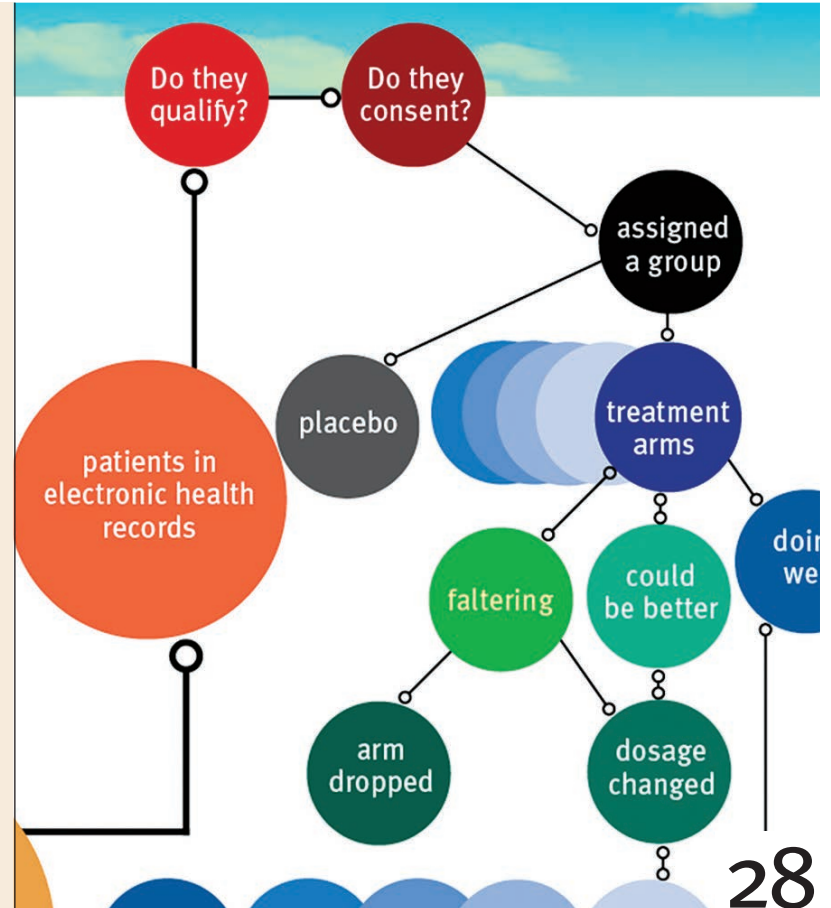
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COVER

Human chimeras: Combined organ and immune cell transplants offer new hope.
(Cover: Michael Hirshon © 2019.)



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The caterpillar is a necessary stage but becomes unsustainable once its job is done. There is no point in being angry with it and there is no need to worry about defeating it. The task is to focus on building the butterfly. —Elisabet Sahtouris

Pitt's Dr. Mylynda Massart is in a Facebook group with other family medicine physicians from across the country. Recently, one of the doctors posted a question about a couple of patients she had seen. Each patient had inherited one copy of a gene associated with a specific cancer. The posting physician wondered, *Were these patients at a heightened risk for cancer?* And, *Were there any guidelines for interpreting these tests?* She got lots of comments from the group, none of which was correct. (Though they received lots of "likes.") One person suggested there were no guidelines. (There are.) Others said that if the patients had inherited just one mutated gene, they needn't be watched closely. (They should be.) When it comes to these cancer predisposing genes, one copy puts you at high risk.

This social media thread is not an outlier. The scientific community has advanced our knowledge of genomics at a rapid pace. Yet physicians and patients are largely in the dark about how genetics really bears on wellness. Mylynda is of a very rare breed. She's a family physician and a genetics expert (an MD/PhD). She recognized during her own training the powerful impact on prevention, diagnosis, treatment, and outcome that an understanding of genetics could and should have in the clinic.

Mylynda was able to clarify the cancer genetics situation with her own post and in a phone consultation with the original posting physician. And through more formal efforts here and at the national level, she's educating primary care clinicians to help them get the right medicine to the right patient at the right time (what is called "precision medicine"). Learn how in this issue.

All physicians should be trained in contemporary genomics at a reasonably granular level, but that's not why I bring up Mylynda here. I offer Mylynda as an example of a creative thinker and innovative healer leading us to better health and likely longer lives. Our world needs more physicians like her. As I told the School of Medicine Class of '19 in my commencement address to them, we will look to their generation not only to deliver on the powerful promise of modern medical science but also to lead the way to fix the broken American health care system of which we find ourselves a part. In my address, I offered some advice to the members of this generation to help them rise to these large challenges:

Choose innovative, imaginative, and fearless words as you wrestle with setbacks and difficult diagnoses. Choose words like "how" and "why." For those pursuing research, remember that the difference between good medical science and great medical science is often in the quality of the questions asked, not their number.

Get out of your comfort zone. Know what you're good at, but also make sure you explore different cultures, interrogate ideas that are antithetical to what you believe, and examine art forms you don't get. In short, try things that don't reflect your self-image.

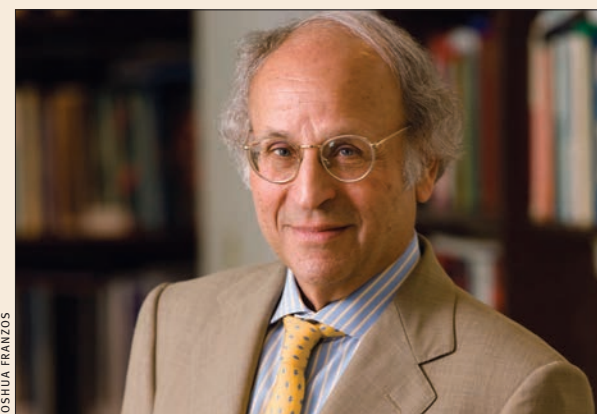
Feed your curiosity and question dogma. I'm a fan of basic science and the humanities, both of which may seem complex, abstract, remote, not practical. Yet they both can lead to transformational ideas.

In this moment, this Zeitgeist, we are looking to you to help humanity figure out how to shape a future in which we all can thrive. As physicians, we must first attend to the health of individuals and then to diverse populations; as citizens, we must also address the greatest threat, the health of our planet.

Arthur S. Levine, MD

Senior Vice Chancellor for the Health Sciences

John and Gertrude Petersen Dean, School of Medicine



JOSHUA FRANZOS



*Devoted to noteworthy happenings
at the medical school*

BETTER PREDICTOR OF YOUTH SUICIDE

Psychiatrists often use a handful of predictors to try to identify risk for suicidal behavior in young people—depressive symptoms, irritability, aggression, impulsivity, and hopelessness are a few listed by Nadine Melhem, associate professor of psychiatry at Pitt. Unfortunately, these predictors have worked only slightly better than a roll of the dice.

Throughout the past 12 years, however, Melhem and her team have developed a new model that puts a stronger focus on variability in depressive symptoms over time. (Learn more in her February 2019 *JAMA Psychiatry* paper.) After analyzing more than 600 young adults, Melhem says it's clear that fluctuations in depression are the best predictor for whether or not a young person will go on to attempt suicide.

Melhem says clinicians should shift their thinking from strictly monitoring a current diagnosis to looking at the larger picture over time. "What's important here is that these are symptoms that clinicians are already assessing, or should be assessing," she says.

—Evan Bowen-Gaddy

FOOTNOTE

In 2012, Jan Scheuermann was among the first people to have hundreds of electrodes implanted in their brain to control a robotic arm. She'd been paralyzed for 18 years before volunteering to be a Pitt research subject with technology based on studies from Andy Schwartz's lab. As she anticipated being part of history, she imagined what she might do with the arm: *I could use it to touch my husband's hand, and to gently touch my children's cheeks. I envisioned doing just that for several hours before I could fall asleep.*

Writer Raffi Khatchadourian captured the parallel journeys of Scheuermann and Schwartz in a Nov. 19 *New Yorker* story. You should read it. Give yourself some time though; it's about 13,000 words long. (The audio version clocks in at 1 hour and 24 minutes.)



Fred Brown and Rachel Pace get close to a neotropical rattlesnake.

Oakland at the Zoo

Behind a wall of glass, amid an upturned branch and pit of sand, a western diamondback slithers around its home at the Pittsburgh Zoo & PPG Aquarium. Pitt Med students peer into its case. On this spring field trip, Clinical Pharmacology course students will learn about treating venomous snakebites.

But first, it's feeding time. The rattlesnake opens wide and engulfs a dead rat whole, leaving some spectators wide-eyed and others grimacing. Later, huddled around picnic tables, the students sit with members of the school's toxicology faculty to discuss snakebite treatments and the numerous molecules swirling within venom.

Joshua Shulman, clinical assistant professor of emergency medicine, is direct with his advice: "Don't get bit. But if you do get bit, elevate the limb," he says. "You actually want the venom to spread," says Joseph Yanta (Res '13, Fel '15), assistant professor of emergency medicine.

Bites from larger snakes are less likely to transfer venom than are bites from smaller snakes, explains Shulman (MD '12, Res '15, Fel '17). So, are those big ones any less frightening? Fourth-year med student Fred Brown might need some convincing: "I'm glad there was glass between me and the snakes." —Keith Gillogly



CAMI MESA

Overheard

Flight Connections and Elaina Anglin

When **Elaina Anglin** took the MCAT in 2017, it had been 12 years since she'd graduated from Pitt with a bachelor's degree in biological sciences. Anglin was so far removed from that coursework, she feared that she'd get a low score and not be accepted anywhere. So she didn't even tell her friends and family that she was planning on applying to med school until after she had taken the MCAT. Anglin did well. It didn't hurt that she had experience in the medical field. After graduating from Pitt, she attended the Conemaugh School of Nursing in Johnstown. She worked as an ICU nurse for six years and a flight nurse for Geisinger Life Flight for five. Now Anglin is entering her second year at Pitt Med.

(By the way, Anglin also has a leg up on relieving stress. She has been an equestrian since childhood and used to compete with her horse, Junior. Now the two hit the trails as often as her studies allow.)

So, what ultimately inspired you to apply?

As I started caring for patients, I found that I became more and more interested in truly understanding what was happening in their bodies as they experienced illness and received treatment. It was fascinating how the doctors could make clinical judgments in critically ill patients based on seemingly subtle changes in hemodynamic parameters or vital signs.

What is it like being a flight nurse?

Working in the flight environment is very different from being a nurse in a hospital. Although medical command physicians are always available by radio, cell phone, or satellite phone to provide guidance, the orders that they can give are only as good as the information that is relayed to them by the flight crew. While I was still in orientation, on one of my first flights, we picked up an 8-year-old child with a significant traumatic head injury who was unresponsive. She had been struck by a car while riding her bike. I was getting the full realization at that point that I was no longer the one calling for help in an emergency; I was one of the people showing up to provide it.

Did your experience as a flight nurse make the first year of med school easier?

My background as a nurse and my experience have definitely helped me in the first year. Flight nursing requires a functional level of knowledge of a wide variety of things, so although I'm needing to learn things at a higher level and in a lot more detail now that I'm in medical school, it's very useful to be able to relate what I'm learning back to things that I've observed before in actual patients.

—Interview by Kate Benz

Next Generation

In 2013, the close-knit Pitt Med Class of 1972 created a fund to help offset the costs of student-directed research.

Since then, these alumni have raised more

than \$106,000 to help students with their projects. These recently supported projects impressed the committee with the intellectual curiosity demonstrated:

Matt Swatski, who is entering his fourth year, researches the relationship between **genetics, diabetes, and obesity**. Swatski is mentored by Erin Kershaw, chief of the Division of Endocrinology and Metabolism. His project focuses on a variant gene that is present in Samoans and helps to regulate cellular respiration, glucose homeostasis, and the synthesis of lipids. He plans to use the gene-editor CRISPR-Cas9 on mouse models to attempt to explain how the variant influences cellular nutrition. "Understanding these mechanisms could lead to better treatments for diabetes and obesity," Swatski says.

Brett Curtis studies how markers related to mitochondria also relate to delirium in ICU patients. He is a third-year student mentored by Timothy Girard, associate professor of critical care medicine. His project analyzes participants who suffered from delirium because of respiratory failure and sepsis. "There is a significant lack of knowledge of how inflammation affecting mitochondria is associated with delirium in critical illness," Curtis says.

Sheri Wang's project centers on **lymphedema**, an incurable disease where an excess of lymphatic fluid in the skin causes swelling, usually in arms and legs. Close to 10 million Americans suffer from lymphedema, and Wang, who is entering her fourth year, says she was drawn to the disease because its exact progression is not well understood. Her project mentors are the Department of Plastic Surgery's J. Peter Rubin, UPMC Endowed Professor and chair, and Lauren Kokai, research assistant professor. Wang's project engineers lymphatic channels and studies cellular signaling in certain lymphatic cells. "Ultimately, we would like to grow viable lymphatic channels as a therapy," she says. —KB

Monkey See, Monkey Graft

In 2011, Kyle Orwig and his colleagues at the Fertility Preservation Program at UPMC Magee-Womens Hospital started collecting testicular tissue from boys with cancer. They did so with the bold promise that, one day, those children could use the tissue to start a genetic family. Eight years later, Orwig, a PhD professor of obstetrics, gynecology, and reproductive sciences at Pitt, is ready to make good on that promise.

In a study published in the March issue of *Science*, he and his collaborators announced they successfully produced sperm from cryopreserved testicular tissue removed from juvenile monkeys; the tissue was grafted back at the start of puberty. What's more, the sperm resulted in a birth, a first for tissue-graft studies.

Thirty percent of boys who undergo chemotherapy will be infertile as adults; and if cancer strikes before puberty, freezing their sperm prior to the procedure isn't an option. Although ovarian tissue grafting has advanced, previous studies with testicular tissue had lackluster results. "I was surprised by how robust our results were," Orwig says. He speculates it was because his study used larger tissue samples and less cryoprotectant to preserve the samples.

Orwig's lab preserves tissue from children's hospitals nationwide. "Most children's hospitals don't have the wherewithal to do what we're doing," he says.

The next step is human clinical trials.

Talking about fertility with a young patient's parents is a "delicate discussion," he says, yet it's also empowering: "It's the first time the family can make an informed decision about their future after cure." —Elizabeth Hoover

OREGON NATIONAL PRIMATE RESEARCH CENTER



A monkey egg is fertilized with cryogenically preserved sperm derived from grafted testicular tissue.

WAIT, DON'T WAIT

Procrastinators rejoice! Actually, hold that thought. Research by Kenneth Smith, professor of medicine and of clinical and translational science at Pitt, tells us that vaccine strength wanes after inoculation. So, is it better to wait until later in the flu season to get that shot?

The answer is a big MAYBE. Sometimes flu season comes early, and you don't want to be caught unprepared. Not only that, but any gains from waiting are jeopardized if just 6 percent of the population passes on the vaccine. Really, the world doesn't need more people forgetting or opting out of vaccinations. Smith says clinicians should give patients the shot whenever they have the chance.

His main concern is maximizing the number of persons who get the flu vaccine. "Delaying is secondary to just getting vaccinated," he says. —EBG

FOOTNOTE

Picked up the phone and it was someone from Hollywood—not too many scientists can tell a story that starts like that. But Pitt's Eric Lagasse gets to. In 2018, a consultant for *Grey's Anatomy*, one of the longest-running shows in television history, called Lagasse to talk about his research. In 2012, Lagasse discovered that when hepatocytes, cells that make up as much as 85 percent of a liver, are introduced into lymph nodes of mice and pigs with liver disease, the nodes act as tiny bioreactors that incubate the growth of functional liver mass. (Lymph nodes are important for the immune system but have little to do with livers as far as we know.) The research was incorporated into one of the show's storylines, and that felt surreal for Lagasse. He visited his cousins in France last year, and they were impressed:

"That's when I shot to stardom, at least in their eyes," he says.



ABC/MITCH HAASETH



PHOTO: NATE LANGER/UPMC PHOTO ILLUSTRATION: ELENA GIAMAS CERRI

REPRESENTATION STARTS HERE

Approximately half of medical school graduates are women; yet according to a 2016 American College of Cardiology survey, less than 20 percent of cardiologists are women. To help give this field better gender representation, **Katie Berlacher** (Res '08, Fel '12), assistant professor of medicine and director of the Cardiology Fellowship Program, collaborated with Fit Education Consulting to launch *She Looks Like a Cardiologist*. The inaugural event, held in January, brought together girls from Pittsburgh-area high schools and cardiology residents, fellows, and physicians from Pitt Med and UPMC who are women. Each student in attendance was paired with a mentor, and during the morning-long event, the girls learned about the medical school application process and the importance of cardiology.

"Men and women get heart disease equally; it's not like breast cancer," says Berlacher. "The people who are treating it should represent that." Berlacher is planning a similar event to be held this year called *I Look Like a Cardiologist* which will address racial misrepresentation in the field. —Gavin Jenkins

THEY'RE IN

The country's most prestigious societies for physician-scientists have announced their newest members.

Rachel Berger, MD/MPH and professor of pediatrics and of clinical and translational science, was inducted recently into the American Society for Clinical Investigation (ASCI). **Brian Primack**, MD/PhD and Bernice L. and Morton S. Lerner Professor, joined Berger in this year's class of ASCI inductees. Berger, who also serves as chief of the Child Advocacy Center at UPMC Children's Hospital of Pittsburgh, became the first pediatrician specializing in child abuse to be inducted into the ASCI since its founding in 1908. "It is a huge honor for me and for the field of child abuse pediatrics," she says.

George Gittes, the Benjamin R. Fisher Professor of Pediatric Surgery and director of the Richard King Mellon Institute for Pediatric Research, was one of four faculty members selected to enter the Association of American Physicians (AAP). Gittes was inducted into the AAP alongside **Elizabeth Miller**, professor of pediatrics and chief of the Division of Adolescent and Young Adult Medicine at UPMC Children's Hospital of Pittsburgh; **Alison Morris**, UPMC Professor of Translational Pulmonary and Critical Care Medicine; and **Warren Shlomchik**, professor of medicine and of immunology and director of Hematopoietic Stem Cell Transplantation and Cell Therapy. —EH



Lap dogs are welcome in the virtual classroom.

TIME IS WELLNESS

Pitt Med student Vi Nguyen sits at her kitchen table in April. Clear of setting pieces, the table overlooks a south-facing window; sunlight streams into the kitchen. The room doubles as her classroom. Nguyen, who will start her second year in the fall, arranges a laptop, notebooks, and extra fine-tipped pens in pink, blue, and orange on the table's surface. She's ready to take in the day's lessons.

Like many of her fellow med students, Nguyen rarely attends class in person. She takes advantage of a program initiated 10 years ago by John Mahoney, Pitt Med's associate dean for education (until this June). In an effort to accommodate individual learning styles and to promote student wellness, Pitt Med changed how it approached coursework by making lecture attendance optional and offering downloadable live recordings (colloquially referred to as podcasts) of lectures synced with professors' slide decks. Nguyen appreciates the autonomy to choose when and how she learns.

"Every time I do go [to lecture], I am reminded that I have a relatively short attention span for passive intake of information," she says. "So it is more fruitful for me to listen to the podcast. I am able to notice when my

mind is drifting and pause [the lecture] and then rewind if I need to." Some students finish an entire semester without once attending a class lecture in person. While this may make med school sound lonely, students get to know each other in weekly small group sessions, labs, and study groups.

Michelle Zhang is also just finishing her first year at Pitt Med. When reviewing lectures on her laptop, if she is already familiar with the subject, Zhang listens to the podcast a little faster than its normal speed. She'll reduce an hour lecture to 40 minutes. Zhang says that extra 20 minutes can add up and give a student more time to socialize, exercise, or sleep.

Melissa McNeil, MD/MPH and vice chair of education for the Department of Medicine, notes that faculty members have tailored their teaching styles so that their lectures are approachable to students learning in person and via a remote location. Accommodating students who learn better at places like the kitchen table appears to be paying off.

"Wellness is multifactorial, and there are so many stressors on our students," McNeil says. "This is one thing that was easy for us to do and hugely appreciated by the students."

—Nichole Faina

Photography by Cami Mesa

INVESTIGATIONS

Explorations and revelations taking place in the medical school



Moderate activity builds up the brains of older adults.

BRAIN TRAIN

EXERCISE STRENGTHENS
THE MIND, TOO

BY ELAINE VITONE

When a rodent takes an exercise wheel for a spin regularly, new brain cells sprout up and flourish, synapses form, dopamine and serotonin spike, and new vasculature spreads. In maze challenges, cardio-mice are superior in learning and retention, compared to their couch-potato contemporaries.

It's hard to know exactly what's going on in living, breathing, exercising human brains at the cellular level since dissection is not an option. But for the last decade, Kirk Erickson—a Pitt professor of psychology with a secondary appointment in medicine—has studied brain imaging to better understand the effects of physical activity on brain structure as well as function, both emotional and cognitive.

He's found that, of all the available approaches for enhancing brain health, exercise is one of the most promising, “if not *the* most,” he says.

Back in 2011, Erickson helped confirm that the human hippocampus—which is critical to memory formation, linked to dementia, and known to deteriorate with age—actually bulked up in older adults who increased their activity for a 12-month stint.

And here's the kicker: All they did was regular, moderate walking.

One of the big remaining questions was exactly how much moderate activity is necessary to achieve these effects, says

Erickson. “We don't have a very good answer at this point.” And in a \$22 million National Institutes of Health (NIH) funded study currently under way, he hopes to find out.

The study, dubbed Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE), is enrolling adults between the ages of 65 and 80, some of whom are already experiencing some memory and cognitive losses, to participate over a 12-month period. The participants will be assigned three different levels of exercise intensity. The team will study changes in their cognitive perfor-

culture, cooking, and music. The idea is that both classes have a social aspect as well as cognitive stimulation, but only the dance class will include physical activity. (All of the above are known to improve brain health.)

Erickson has his fingers in a lot of pies. He's also collaborating with Catherine Bender, endowed professor in oncology nursing and director of the PhD program in Pitt's School of Nursing, to examine whether physical activity can fend off the cognitive deficits that accumulate in women undergoing breast cancer treatment.

Of all the available approaches for enhancing brain health, exercise is one of the most promising, “if not *the* most,” says Erickson.

mance and MRI markers of brain health, with the goal of determining whether those changes are dependent on “dose” or intensity of activity. Erickson also hopes to gain insight into whether age, genetics, or changes in the nervous system, heart, and metabolism mediate any brain gains.

For reasons no one quite understands, African Americans are at a heightened risk for early cognitive losses and have higher rates of dementia. Recently, Erickson received a five-year NIH grant to evaluate several ways of combating decline. Three times a week for six months, one group of older African American study volunteers will take an African dance class; another will take a course in African

In yet another collaboration, Erickson is teaming up with Terrence Forrester at the University of the West Indies in Mona, Jamaica. Forrester's studies have shown that malnutrition in childhood causes extremely persistent deficits in emotional and cognitive functioning, all the way up through adulthood. Together, the duo is conducting a pilot study investigating whether physical activity in such adults could improve mood, cognition, and brain health.

“For all of these adults now who had childhood malnutrition,” Erickson says, “are their cognitive deficits kind of locked in and not very malleable, or can they be modified in any way? It's a really important question.” ■



FAIR WARNING

A BETTER WAY TO
PREDICT OVERDOSE
BY KRISTIN BUNDY

PHOTO: GETTY IMAGES; TYPOGRAPHY: ELENA GALAMAS CERRI

As the opioid epidemic rages on, the Centers for Disease Control and Prevention reports that there are about 130 overdose-related deaths per day in the United States.

Despite the ongoing crisis, Walid Gellad, a Pitt physician and health policy specialist, says, “We just don’t have a good way of identifying” who is most likely to overdose. For example, Gellad notes, the way Medicare’s current risk algorithm is set up, 70 percent of overdoses occur in their low-risk group and 30 percent in their high-risk group.

“We typically think that people on high dosages of opioids are at high risk of overdose,” says Gellad. But that’s just a risk factor—not a risk prediction. “Not everyone on a high dosage will overdose.”

Risk prediction, on the other hand, digs deeper to examine the many facets of life that might influence risk. “You can have two people on the same dosage, but one can have a low risk of overdose because they’ve had a stable day, they’ve been on that dose for a long time, they don’t have a psychiatric illness, they don’t have a substance use disorder, and they didn’t

just get out of jail. Someone else might be the exact opposite.”

Gellad’s work sorts through these details. As associate professor of medicine and of health policy and management and director of Pitt’s Center for Pharmaceutical Policy and Prescribing, Gellad develops risk-prediction models for opioid overdose using machine learning.

Earlier this year, Gellad and his team published findings on the risk of overdose three months after Medicare patients were prescribed an opioid.

The algorithms successfully captured 90 percent of the overdoses in the medium- and high-risk groups. And overall, 75 percent of the participants were found to be low risk, which surprised Gellad. “We expected many more. . . . Because, in clinical practice, we’re treating a lot more people as high risk.”

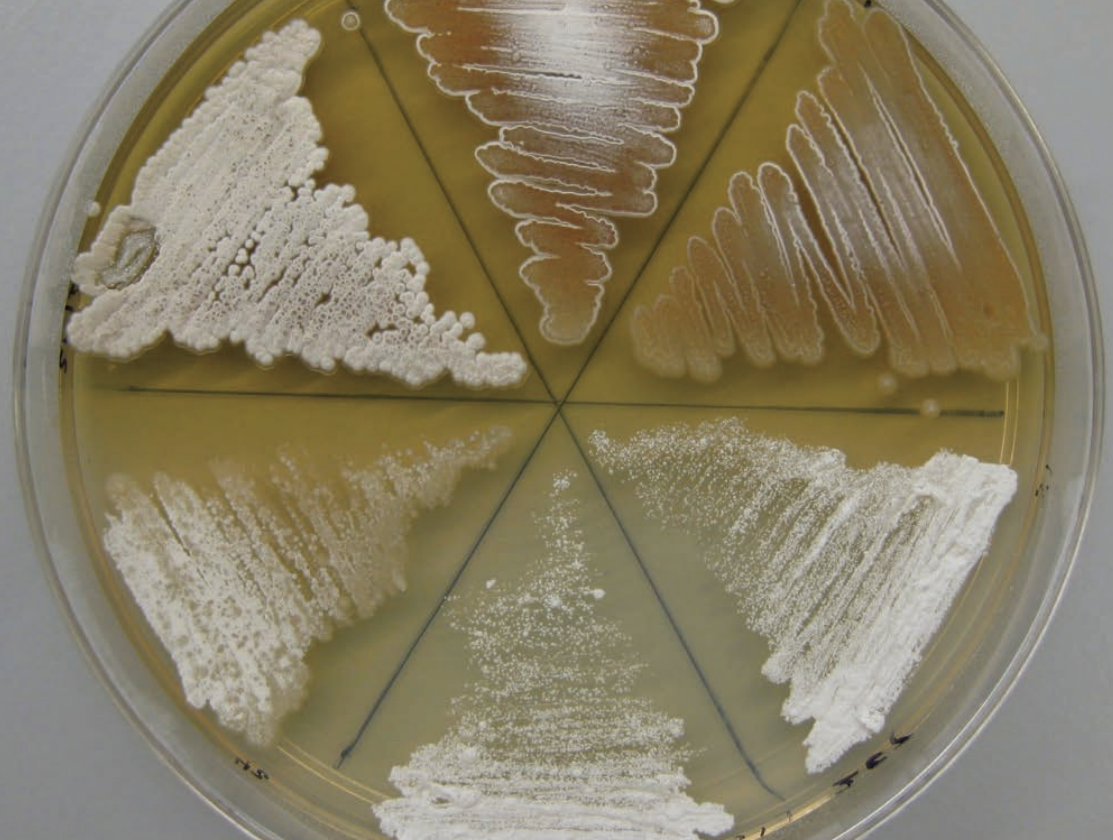
Gellad, who is also an internist at the VA Pittsburgh Health System, says this heightened perception of risk leads to a burden of hypervigilance among those who need prescription opioids and take them safely. Patients, no matter their risk classification, must provide urine

samples at each visit and answer questions like: What dosage are you taking? How often do you fill your prescription? Do you have naloxone at the ready? Gellad says, “If we can alleviate this burden in people with a low risk of overdose, it will have a big impact.”

To that end, Gellad is conducting machine-learning studies on risk prediction and opioids. In one study, which is funded by a \$1.8 million grant from the National Institutes of Health, the investigators are using Pennsylvania Medicaid claims to predict opioid overdose (and other outcomes) and explore other ways of modeling the data.

Another study is funded by the Richard King Mellon Foundation. In collaboration with Pitt’s Graduate School of Public Health and the Allegheny County Health Department, Gellad is applying machine-learning techniques to county services datasets. These include Medicaid claims, 911 calls, court records, jail records, child-welfare records, and coroner reports—all scrubbed of information identifying individuals.

This anonymized information, says Gellad, might help paint a more complete picture of overdose risk versus health care data alone. “There’s a thought that acute events in someone’s life are related to overdose,” he says. Through this collaboration, the researchers hope to better equip the county in allocating support services to those who need them. ■



In nature, superbugs are super rare. Wright's team hopes to learn new tricks from microbes that have been keeping them in check for millions of years.

TAKING CUES FROM SOIL
BY JACOB WILLIAMSON-REA

THE DIRT ON ANTIBIOTIC RESISTANCE

Each year, 2 million people in the United States battle an antibiotic-resistant infection, and of those, 23,000 die. As cases of antibiotic resistance continue to rise, the race is on to introduce new antibiotics to save these patients.

The solution might be just beneath our feet.

Most therapeutic antibiotics come from bacteria that naturally produce antibiotics. “Thousands of these antibiotic-producing bacteria live on a barely visible speck of soil,” the University of Pittsburgh’s Erik Wright notes. They’ve been producing antibiotics to protect themselves for millions of years.

Surprisingly, in the natural world, resistance has remained at astonishingly low levels, says Wright, an assistant professor of biomedical informatics. With a \$1.5 million Director’s New Innovator Award from the National Institutes of Health, Wright hopes to learn a few of nature’s tricks.

“We want to know how soil bacteria have avoided antibiotic resistance for so long, and how that might inform our clinical use of antibiotics.”

Clinical and agricultural antibiotic use consists of one antibiotic compound at a high dose. The natural antibiotic producer *Streptomyces*, however, uses small amounts of many different antibiotic compounds, specifically tailoring them to individual threats. “This led us to consider a nature-guided approach, or biomimicry,” Wright says.

Wright will use mass spectrometry, which details chemical structures of molecules and will allow the team to analyze how different streptomycetes respond to threatening microorganisms. The researchers can then watch how *Streptomyces* changes defensive-compound secretions: what exactly each streptomycete produces, whether bacteria target competitors as groups or individuals, and more.

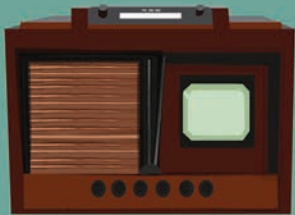
Additionally, by comparing the DNA

sequences and other genomic features of organisms, he’ll study the synergistic potential of *Streptomyces*. Natural antibiotic cocktails produced by different streptomycetes might have frequently occurring compounds that appear together, which would suggest certain combinations are more successful.

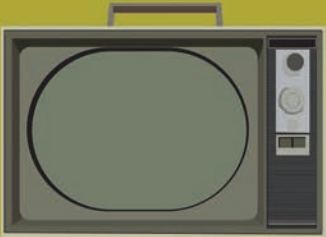
“Maybe we’ll discover information that we wish we had well before we started using antibiotics,” says Wright. “Or maybe this will encourage us to take a step back to understand how best to use them.”

“The dream is that this research will lead to the use of antibiotic cocktails, instead of individual compounds. This would allow us to not only tailor treatments, but possibly make antibiotic resistance a thing of the past.” ■

Editor’s Note: In our next issue, catch more news on the drug-resistant bacteria front: Phage viruses, from a Pitt lab, cured a life-threatening infection in a double-lung transplant patient.



Berg



Massart



IMPERFECT PITCH

HOW USEFUL IS A REPORT
FROM A COMPANY LIKE
23ANDME TO YOUR HEALTH?
THE PROMISE AND PERIL
OF PERSONAL GENOMICS

How do we separate hype from reality as personal genomics companies ramp up ads, social media, and celebrity influence campaigns that directly target consumers? In February, we sat down with two University of Pittsburgh experts to discuss how the heavy consumer pitch can cloud medical practice, science, understanding, and the road ahead for medical education as personal genomics becomes increasingly relevant in the clinic. The discussion was taped live from the Sci-Mic Podcast Stage at the 2019 meeting of the American Association for the Advancement of Science in Washington, D.C. The following has been edited for brevity and clarity. For the full discussion, listen to the episode at bit.ly/2YM6pCt.

Today, millions of people are raising their hands for genetics testing through direct-to-consumer personal genomics companies like 23andMe. And even though there are disclaimers that the reports they're getting back are not for diagnostic or medical decision-making purposes, for many consumers the

reports raise questions that you, Mylynda and Jeremy, would find familiar, given your expertise in the emerging field known as precision medicine, also known as personalized medicine.

Let's start there. What is precision medicine? What's your elevator speech for laypeople?

Jeremy Berg: Precision medicine is using genomic information in addition to other factors to try to customize diagnosis, and potentially treatment, of a wide range of diseases.

Mylynda Massart: When I explain precision medicine to my patients or to my family, it's really about taking all of the factors that lead up to our individual health. So, looking at our genetics and all of our environmental factors, such as our nutrition, our exposures in our local environments, even our traumas.

There are some compelling stories and videos out there from these companies: origin stories, reunions of long lost family members. There are also stories along the lines of, for example, a woman who didn't know about her Ashkenazi Jewish heritage, and the mail-order test results told her that she had an 80 percent chance of developing a deadly cancer. So she followed up with her doctor, had preventative surgery, and, lo and behold, every woman in the family has this genetic variant, and this is life changing, life saving.

But what kind of information are we—the consumers—really getting from these companies, and what do we need to be thinking about as we try to process this information?

JB: In terms of the technology, most of the direct-to-consumer tests are not whole-genome sequencing, but are a sampling of known variations across the human genome. So it's a very incomplete picture of your whole genetic background.

But more important than that is: All of this is really complicated. In some cases, there are variations that are so-called highly penetrant, [meaning they] are very predictive. If you have this [gene] variant, then

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Editor in Chief of AAAS's *Science* family of journals

Mylynda Massart
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Coinvestigator, All of Us Pennsylvania

you are certain or very likely to have a particular disease. The archetype of that is sickle cell anemia. You have two copies of each gene. If you have two copies [of a particular variation in a hemoglobin gene], you have sickle cell disease; if you have one copy, you have sickle cell trait.

But for most other diseases or other traits, things are much more complicated, where there are lots of variations, and they all contribute a little bit [in addition to] other factors like environment and exposures and experience.

And that complexity tends to get lost in the sort of cartoon version of the reports that come back. And one concern that I have is that consumers take it much more seriously or uncritically than they should for their own benefit.

MM: I think that when the direct-to-consumer testing market first opened up, it was really fun, and that's really what the key term was. It was engaging, the general society was learning more about genetics and genetics terminology, and they were having fun doing it. Now, the level of results [is] increasing in clinical utility. There are results coming out now on *BRCA* mutations [for breast cancer], genes that may contribute to risk of Alzheimer's disease or Parkinson's disease, and a lot about pharmacogenomics—how genetics affect the metabolism of everyday medications (which can result in adverse reactions, or toxicity levels, or drugs simply not working or being therapeutically effective at all).

And to me, the part about that that's so important is that while it's still fun and interesting and engaging, these results now need to be brought into the clinical world and interpreted from a clinical perspective. And the doctors out there really need to recognize the limitations of these tests: How much is actually accurate? What is left that perhaps didn't get tested? And what we call residual risk. How do you explain to a patient and the general population the limits of the capacity of this testing to really be informative?

And then on the flip side, a lot of these tests are done in [approved] labs and are probably very accurate. But the FDA has passed some pretty strict regulations that these tests, to be used clinically, need to be repeated and confirmed [in order to determine how to

apply a result to] an individual's care plan.

Regarding these reports about “risk,” can you clear up that term?

JB: One very fundamental aspect is the difference between absolute risk and relative risk. So if you have a test result, and it says you have a 10 times higher risk than that of the general population based on your genetic variation, it depends what the baseline risk is. If the absolute risk for the population is 1 percent, and you have a tenfold higher risk, it means you have a 10 percent absolute risk, which may be worrisome or not, depending on what the condition is and so on.

But tenfold sounds really scary! Ten percent, not so much.

The other [aspect is that] the uncertainty in the models that leads to these risk predictions is pretty substantial. The models are based on some outrageously gross simplification of everything, because that's the best we can do. Conveying the uncertainty in the risk is something that I think really gets lost in the shuffle.

MM: Even with *BRCA*, having one copy of that mutation does not guarantee that someone will ever develop breast cancer in their lifetime or ovarian cancer in their lifetime. It simply is, again, about risk, and having a general-population understanding of risk and where these risks fit in, what they mean, and what are the preventative interventions that could be put in place to reduce their risk.

JB: The tests are never going to be deterministic. Genetic determinism—meaning, if you knew your genome sequence, and we understood everything, you could predict your whole future life—is just absolutely false. And the studies that [disprove genetic determinism] go back decades and decades, looking at identical twins, where their genomes, for all intents and purposes, are identical. Some traits are closely shared, but a lot of other traits, including getting different diseases, aren't.

MM: Right. And I think that's where this greater concept of precision medicine comes into play. Taking the genetics component and recognizing what it does contribute as well as its limitations. And then really starting to understand, and using computer-assisted technology for all the other types of exposures

and data and family histories, and then being able to better refine that predictive model. Even so, it's unclear whether that will ever reach 100 percent, but it will increase in its predictive aspect as technology develops.

What is needed to bring us further along in precision medicine and bring all of its promise into reality?

JB: Well, one of the obvious things is more data, and Mylynda can talk more about that. Then, the challenge is still substantial—to do the computer analysis to try to develop better risk models.

A lot of genetic data originally were focused on people who had reason to believe that they have a risk for a particular disease. [For example], if you test people who think they have a [higher] risk for breast cancer because they have a family history of breast cancer, and you identify a gene. So you'll identify particular variations in that population of patients. [But] then the question is: What's the prevalence of that same genetic variation in a general population that doesn't have any risk for breast cancer? And that's the sort of thing that can now be done with these larger studies.

MM: The All of Us study is about putting together that million-person research cohort to gather a vast amount of data, to bring it together and organize it in a way that researchers can finally start looking at all those different layers that contribute to precision medicine. And there were a lot of things that had to line up to finally be able to do a study of this size. We had to have the computing technology, the ability to store [and analyze] all that data. And the cost of these analyses needed to come down. Now, someone can have their genome sequenced for \$500 to \$1,000. All of that had to line up to create this large project that's being funded through the National Institutes of Health.

Also, one of the large emphases of the All of Us study is to collect that data from a very diverse population. We're trying to understand the components that lead to strong health and to longevity, as well as the components that lead to disease and illness. We need to look at a vast population that's very diverse to apply that to unique communities and have something that's meaningful.

—Interview by Elaine Vitone



PRECISION MEDICINE FOR THE MASSES

MYLYNDA MASSART BRINGS
GENOMICS TO PRIMARY CARE

BY ELAINE VITONE

PHOTOGRAPHY BY JOHN ALTDORFER

A few years ago, Mylynda Massart was mentoring a young man who was struggling with depression. To add insult to injury, his trial-and-error search for the right treatment was *itself* a series of unfortunate events, one awful side effect after another.

Distraught, the mentee blurted out: *It's the 21st century. Why can't we just look at my genetics and know what to prescribe the first time?!*

And that, in a nutshell, is one of the biggest frustrations in medicine right now, for both patients and physicians.

In some specialties, precision medicine is already the standard of care. Genetics guide therapy for cancer, for example, as well as many rare diseases treated by medical geneticists. Sadly, in primary care clinics—the front lines that see most patients most of the time—we're just not there yet.

But it *is* coming, says Massart, an MD/PhD assistant professor of family medicine at Pitt, who teaches genomics and precision medicine to Pitt Med students as well as practicing physicians.

Researchers are optimistic that the table is finally set to build an understanding of the enormous variability of sickness and health, of disease progression and remission, of response to treatment and its opposite. Scientists hope to clarify the interplay among genes, environment, and exposure. The reasons why one identical twin can get a chronic disease and not the other.

Massart told her mentee that he was justified in his anger. And in fact the research on his very question—which depression meds are right for which patients—was looking promising, but still not ready for prime time in clinical care.

Today, more than 200 medications, which are used in treating dozens of diseases, have some genetic considerations. For some, there's an indication right on the FDA-approved product labeling. And yet most frontline clinicians have no idea this is the case. Massart knows because she asks them to venture a guess when she gives talks. Most docs guess 20, maybe 30 tops. When she tells them the answer, it's like a bolt of lightning.

"They're all shocked. *Two hundred?!* They're

all pulling up their phones and clicking on the FDA site," says Massart, who is 5'2" and likely to be spotted with her pink backpack as she ferries to and from three clinical and academic offices. She's a self-described storyteller by nature. (It's a Jewish gene, she says with a smile and a shrug.)

The science is evolving faster than practicing physicians can keep up.

And with the advent of genetic testing from companies like 23andMe, which deal directly with consumers rather than providers, patients are showing up at doctors' offices with genetics reports. The physicians are confronted with questions for which their training never prepared them. (See our Tough Questions discussion starting on p. 12 for more on this.) So referrals to genetic counselors—of whom there is a dire national shortage—are growing. Patients can wait several months to get in, and a lot of very scary Google results can show up in the meantime.

As one of only a handful of primary care physicians in the country with training in genetics, Massart is uniquely qualified to straddle these two worlds and begin what will likely be a long, hard effort to bridge them. And here at Pitt/UPMC—which established the UPMC Genome Center, the Pharmacogenomics Center of Excellence, and the Institute for Precision Medicine—she feels she's at exactly the right place and time to do it.

This summer, Massart and Philip Empey, PhD assistant professor of pharmacy and therapeutics in Pitt's School of Pharmacy and associate director of the Institute for Precision Medicine, will open a primary care clinic for

precision medicine. It will serve as a testing ground for new services for patients, as well as for new educational tools to help other physicians and pharmacists provide these services.

And a lot of education is needed, Massart says. Physicians need to understand what's covered in health risk reports from companies like 23andMe and how to explain those results to patients. They need to understand the FDA guidelines regarding direct-to-consumer test results—what they can and cannot do with information from those reports, when to order repeat testing, and what labs to order them from. Also, they need to know where to store genomic data in the electronic health record and then how to integrate those data into patient care.

At the new clinic, some patients will come for a visit or two to address a specific concern. Some will stay for their long-term primary care needs at this multidisciplinary clinic. Some will be referred to the appropriate genetics services (neonatal genetics, pediatric genetics, oncology genetics, etc.).

Lucas Berenbrok, assistant professor of pharmacy and therapeutics, will be on-site offering his expertise in pharmacogenomics, or how genetics contribute to medication response.

Massart and her team see triaging genetics cases appropriately—and teaching other primary care docs to do the same—as one of their most important charges.

To help other clinicians catch up, they'll build teachable moments into every interaction with referring physicians: souped-up consultation reports, recommended readings, and FYIs on deeper-dive materials that they're creating, like precision-medicine lectures and online courses.

Massart strongly believes genomics is something that primary care docs can pick up. They're already trained to do 70 to 80 percent of pulmonology, cardiology, endocrinology, and so on, she says. "We know where our boundaries are and when we need to phone a friend, . . . whether it's calling for guidance or actually referring the patient to that specialist."

She aims to *be* that friend—and eventually work herself out of that job.

The clinic doesn't have a name yet. For now, it's in a temporary home in the UPMC Matilda H. Theiss Health Center, the site of Massart's family medicine practice. "There are some messages on that phone over there with some early referrals," she says in her office on a recent spring afternoon. "Our hope is to officially launch around July."

The new clinic is a dream realized for Massart, who is 47. Her career has been a kind of timeline of historic moments in the pursuit of bringing precision medicine to the masses; everything seems to have been building to this.

Massart got her BS in cell biology from the University of Illinois, then went on to grad school in biochemistry and genetics at the University of Utah, which was one of many sites where

That work further characterized the genes' associated mutations, which affect about 1 in 40 with Ashkenazi Jewish ancestry. (In the general population, it's 1 in 500.)

BRCA was kind of a signpost moment for precision medicine, Massart says.

It was the first oncogene to go commercial in a big way. For the first time, people could see the coming storm. "I think that just gave so many people a sense of having some power and control over a disease that we feel so powerless against," says Massart.

Meanwhile, Massart's new friends were inviting her to shadow them in their clinics and sit in on case conferences. She found their collaborative process riveting. These genetic counselors (experts in both the science of genetics and the psychosocial aspects of counseling) and medical geneticists (often MDs who diagnose and treat diseases with

they documented the children's symptoms (episodic paralysis and stiffness and unusual eye movements) and collected blood samples to bring back to Utah. Years later, Swoboda helped lead the international collaboration that identified the gene for AHC.

In the second half of med school, which Massart completed at Oregon Health and Science University in Portland (she'd transferred there to be near her grandparents), she was sure she was going to be a medical geneticist. That went out the window when a couple of things happened in 2004.

First, she fell in love with primary care. That clinical rotation was filled with a little bit of everything and everyone, from babies to 90-year-olds—basically, paradise for Massart, a people person. And her attending could tell. Three weeks into her clerkship, he and his partner sat her down and said, *Mylynda, this*

Today, more than 200 medications, which are used in treating dozens of diseases, have some genetic considerations. For some, there's an indication right on the FDA-approved product labeling. And yet most frontline clinicians have no idea this is the case. Massart knows because she asks them to venture a guess when she gives talks. Most docs guess 20, maybe 30, tops. When she tells them the answer, it's like a bolt of lightning.

the Human Genome Project took place. Massive, room-sized sequencers were housed in her adopted haunt, the Eccles Institute of Human Genetics, with its prominent double-helix staircase.

By chance, Massart fell in with a new crowd, geneticists. The first of these fast friends was a genetic counselor who reached out with an invitation for Massart to participate in a study that was recruiting among Salt Lake City's Ashkenazi Jewish community, of which Massart was a member.

That community, which largely retained shared genetics over time, was ideal for study. Ashkenazi Jews became central to many ground-floor findings in genetics.

A University of Utah faculty member, Mary-Claire King, had identified the breast cancer genes *BRCA1* and *BRCA2*. A start-up called Myriad Genetics formed around subsequent research in which Massart participated.

significant genetic components) would discuss the histories of patients and their families, review photos, and plot out pedigrees on the whiteboard. Together, they'd come up with a diagnosis and a plan.

"They were brilliant," Massart says. For the rest of grad school, she snuck over to watch them in action every chance she got. "I would set up an experiment that needed to go for two hours and run down through the hospital."

Kathryn Swoboda, a neurologist, medical geneticist, and University of Utah fellow who was joining the faculty, hired Massart for a postdoc position in her lab. Through Massart's first two years of medical school (she started her MD after completing her PhD), they characterized a very rare disorder called alternating hemiplegia of childhood (AHC). With cases so few and far between, studying these children meant traveling the world.

The pair grew close with these families as

is an intervention. You are not a specialist. You are a primary care doctor, and you just need to accept it.

Then, that same week, her pink flip phone rang. An emergency department physician was on the line, calling from Italy. One of the kids in Swoboda's registry had checked into the hospital with influenza, and the doc was terrified of messing up. He had to know: What did a child with this infection need in the context of this rare disorder?

Did they tell you I'm only a medical student? Massart said. *I'm not a doctor.*

They did, he said. But this is such a rare disease. And the family gave me your name. They said you're one of only three experts in the world.

Massart gave him the best advice she had (treat him as you would any other child, but keep an eye on his lactic acid), then got back to her evening routine. It was her toddler's bedtime. After tucking Noah in for the night,

she sat down at her computer to write a paper due the next day. She doesn't remember what the assignment was, exactly. But she does remember what came out of her reeling mind and onto the page:

A treatise on why genetics belong in primary care.

Genetics have context, she realized. Genetics are part of a broader picture—a person, a life, a family. And though the term *precision medicine* wasn't part of the lexicon at that time, medicine was clearly moving to the molecular level. "And we were never going to have enough geneticists in the world to handle the magnitude of health issues that involve genetics," Massart says.

Massart and her young family moved to rural Idaho in 2009. For five years, she practiced family medicine with a focus on genetics. It was gratifying from the start. To her knowledge, there was only one genetic counselor in the entire state, and zero medical

health care more than ever before," she says. "They really want to understand this."

The 1960s *Star Trek* reruns were a staple of Massart's childhood. Through her teens, her family taped *Next Generation* on VHS so they could watch together when her dad got home. And she's propagated the Trekkie gene in her own offspring, she reports. "Last night we watched the season five finale of *Discovery*."

The tricorder-wielding doc of the future was pretty much what Massart thought she was slowly working toward during her training. Like, wave a device across the patient, and *beep*, diagnosis. Or at least: Type-type, click-click—maybe even scan a fingerprint—and *beep*, medical record, complete with DNA data. And that thinking was, *ahem*, logical, given the times. At the 2000 White House press conference announcing the completion of the Human Genome Project, the

a natural fit for All of Us Pennsylvania, both because of her background in genetics and her work in underserved communities. (Massart is medical director of the UPMC Matilda H. Theiss Health Center, a family medicine practice in Oak Hill.) To make research as relevant as possible to as many Americans as possible, diversity in the All of Us cohort is key; Massart leads the statewide effort to help it live up to its name.

Prescribing for depression and many other maladies is like throwing a dart at the dartboard, says Massart. "Most of the time you don't hit the bullseye with that first drug. . . . We're pretty much shooting blind."

So back the patient comes a few weeks later. Then, the physician must consider: Is the problem that this is the wrong dose, or the wrong class of antidepressant altogether? The dart-throwing can go on for months, and in that time, a lot can happen.

Did they tell you I'm only a medical student? Massart said. I'm not a doctor. They did, he said. But this is such a rare disease. And the family gave me your name. They said you're one of only three experts in the world.

geneticists. It was very if-you-build-it-they-will-come, says Massart. "I just showed up, and these genetic cases just started walking in the door." First, a man with cystic fibrosis. Then, a brother and sister with a rare genetic disorder. Then, a woman with some printouts of data from a little start-up called 23andMe.

In 2013, Angelina Jolie went public with her own *BRCA* status and subsequent decision to undergo preventive double mastectomy. From then on, genetic testing start-ups—both consumer-facing and physician-focused—seemed to sprout up like weeds, says Massart. She thinks Myriad Genetics paved the way for these companies, which quickly mounted aggressive marketing campaigns. Representatives fanned out to doctors' offices. TV and social media ads turned science terms into household words.

Now, patients come to see Massart with health reports from these companies all the time. "Patients are taking ownership of their

effort's leader, Francis Collins, called our newly sequenced genetic code "the book of life." By many scientists' predictions, DNA would directly inform treatment by the end of the aughts.

We've since learned that the genome is no open book. Genetics, environment, and exposure riff off of one another in complicated ways. To better understand this perplexing interplay, the National Institutes of Health launched the Precision Medicine Initiative in 2015. Its primary charge: to build a 1-million-participant study called All of Us, which would include both genomic data and electronic health record data over time—at least 10 years, and hopefully longer.

All of Us recruitment launched right here in Pittsburgh, led by Steven Reis, MD associate vice chancellor and Distinguished Service Professor of Medicine, who directs Pitt's Clinical and Translational Science Institute. When he met Massart, he recognized she was

"I share the story of my own family," says Massart. "My grandmother committed suicide during that time. That's the worst possible outcome, right? But there are many other negative outcomes. People lose their marriages. They drop out of school. They lose their jobs. They may start [abusing] drugs and alcohol."

It's not yet possible to look at genetic test results and know exactly what to prescribe—but we're getting closer, says Massart. For now, physicians can rule out at least some of the many medication options. Throwing fewer darts can mean less suffering.

In the world Massart's young Trekkies will inherit, she hopes fewer people will wind up sick in the first place. That's the ultimate mission of precision medicine.

So Massart is doing all she can to get primary care docs up to speed. "I want them to be far ahead of the game—preventive and proactive," she says.

Steady as she goes. ■



Philip Empey

JUST DOING IT

More than 200 FDA-approved medications already have genetic considerations in their labeling. But the tests required to find out if you can safely take the drug can be expensive. This is one reason why frontline doctors haven't yet caught up with the rapidly evolving science known as pharmacogenomics, or "how DNA contributes to medication response," explains Philip Empey, who leads Pitt's new Pharmacogenomics Center of Excellence and is Mylynda Massart's cofounder at the new primary care precision medicine clinic.

To prove pharmacogenomics is worthwhile on a broad scale—in terms of improving patient outcomes, or saving costs, or getting people to the right meds faster—it has to be systematically implemented, then its use needs to be tracked and fine-tuned. In other words, to prove it's worth doing, you have to do it.

To help nudge precision medicine out of this classic chicken-and-egg conundrum, the Pharmacogenomics Center of Excellence recently launched a five-year, 150,000-participant study. Through a partnership between Pitt Pharmacy and the Clinical and Translational Science Institute, volunteers across Western Pennsylvania will undergo a panel testing for more than 4,600 genetic variants in nearly 1,200 genes.

Of those 1,200 genes, 13 have shown an especially high level of clinical utility and are now relevant to prescribing practices for some 40 medications. Results from related genetics tests will be incorporated into the UPMC electronic health record, which is getting an upgrade to help guide physicians through genomics-based prescribing practices. For example, if a doc tries to prescribe a drug that the patient's genetics suggest wouldn't do diddly to help, a warning window will pop up on the screen.

When physicians or pharmacists in the UPMC system see one of these pop-up windows, Massart explains, they'll also see an option to click and read more—maybe a paragraph or so—and then get back to their patient. "And then, . . . in the evening or on a break or at lunch, they could watch perhaps a 15 minute CME video, and learn even more in-depth."

Test results for those 13 genes, by the way, will be accessible for patients in the UPMC system.

Empey believes pharmacogenomics will make a difference for at least some patients. Determining which patients is what this study aims to do. —EV



Patients receiving new kidneys and livers must take damaging anti-rejection drugs for the rest of their lives. Now researchers hope to train the immune system instead of just tamping it down.



SCIENTISTS ARE TEACHING THE BODY TO ACCEPT NEW ORGANS

BY GINA KOLATA FROM *THE NEW YORK TIMES*

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It was not the most ominous sign of health trouble, just a nosebleed that would not stop. So in February 2017, Michael Schaffer, who is 60 and lives near Pittsburgh, went first to a local emergency room, then to a hospital where a doctor finally succeeded in cauterizing a tiny cut in his nostril.

Then the doctor told Schaffer something he never expected to hear: “You need a liver transplant.”

Schaffer had no idea his liver was failing. He had never heard of the diagnosis: Nash, for nonalcoholic steatohepatitis, a fatty liver disease not linked to alcoholism or infections.

The disease may have no obvious symptoms even as it destroys the organ. That nosebleed was a sign that Schaffer’s liver was not making proteins needed for blood to clot. He was in serious trouble.

ILLUSTRATION | MICHAEL HIRSHON

The news was soon followed by another eye-opener: Doctors asked Schaffer to become the first patient in an experiment that would attempt something that transplant surgeons have dreamed of for more than 65 years.

If it worked, he would receive a donated liver without needing to take powerful drugs to prevent the immune system from rejecting it.

Before the discovery of anti-rejection drugs, organ transplants were simply impossible. The only way to get the body to accept a donated organ is to squelch its immune response. But the drugs are themselves hazardous, increasing the risks of infection, cancer, high cholesterol levels, accelerated heart disease, diabetes, and kidney failure.

Within five years of a liver transplant, 25 percent of patients on average have died. Within 10 years, 35 to 40 percent have died.

“Even though the liver may be working, patients may die of a heart attack or stroke or kidney failure,” said Abhinav Humar, a transplant surgeon at the University of Pittsburgh Medical Center who is leading the study Schaffer joined. “It may not be entirely due to the anti-rejection meds, but the anti-rejection meds contribute.”

Kidneys in particular may be damaged. “It is not uncommon to end up doing a kidney transplant in patients who previously had a lung or liver or heart transplant,” Humar added.

Patients usually know about the drugs’ risks, but the alternative is worse: death for those needing livers, hearts, or lungs; or, for kidney patients, a life on dialysis, which brings an even worse life expectancy and quality of life than does a transplanted kidney.

A GLIMMER OF HOPE

In 1953, Peter Medawar and his colleagues in Britain did an experiment with a result so stunning that he shared a Nobel Prize for it. He showed that it was possible to “train” the immune systems of mice so that they would not reject tissue transplanted from other mice.

His method was not exactly practical. It involved injecting newborn or fetal mice with white blood cells from unrelated mice. When the mice were adults, researchers placed skin grafts from the unrelated mice onto the backs of those that had received the blood cells.

The mice accepted the grafts as if they were their own skin, suggesting that the immune system can be modified. The study led to a scientific quest to find a way to train the immune systems of adults who needed new organs.

That turned out to be a difficult task. The immune system is already developed in adults, while in baby mice it is still “learning” what is foreign and what is not.

“You are trying to fool the body’s immune system,” Humar said. “That is not easy to do.”

Most of the scientific research so far has focused on liver and kidney transplant patients for several reasons, said James Markmann, chief of the division of transplant surgery at Massachusetts General Hospital.

Those organs can be transplanted from living donors, and so cells from the donor are available to use in an attempt to train the transplant patient’s immune system.

Far more people need kidneys than need any other organ—there are about 19,500 kidney transplants a year, compared with 8,000 transplanted livers. And those transplanted kidneys rarely last a lifetime of battering with immunosuppressive drugs.

“If you are 30 or 40 and get a kidney transplant, that is not the only kidney you will need,” said Joseph R. Leventhal, who directs the kidney and pancreas transplant programs at Northwestern University.

Another reason to focus on kidneys: “If something goes wrong, it’s not the end of the world,” Markmann said. If an attempt to wean patients from immunosuppressive drugs fails, they can get dialysis to cleanse their blood. Rejection of other transplanted organs can mean death.

The liver intrigues researchers for different reasons. It is less prone to rejection by the body’s immune system. When rejection does occur, there is less immediate damage to the organ.

And sometimes, after people have lived with a transplanted liver for years, their bodies simply accept the organ. A few patients discovered this by chance when they decided on their own to discard their anti-rejection drugs, generally because of the expense and side effects.

An estimated 15 to 20 percent of liver transplant patients who have tried this risky strategy have succeeded, but only after years of

taking the drugs.

In one trial, Alberto Sanchez-Fueyo, a liver specialist at King’s College London, reported that as many as 80 percent could stop taking anti-rejection drugs. In general, those patients were older—the immune system becomes weaker with age. They had been long-term users of immunosuppressive drugs and had normal liver biopsies.

But the damage caused by immunosuppressive drugs is cumulative and irreversible, and use over a decade or longer can cause significant damage. Yet there is no way to predict who will succeed in withdrawing.

TRICKING THE IMMUNE SYSTEM

The more researchers learned about the symphony of white blood cells that control responses to infections and cancers—and transplanted organs—the more they began to see hope for modifying the body’s immune system.

Many types of white blood cells work together to create and control immune responses. A number of researchers, including Markmann and his colleague, Eva Guinan of the Dana-Farber Cancer Institute, chose to focus on cells called regulatory T lymphocytes.

These are rare white blood cells that help the body identify its own cells as not foreign. If these regulatory cells are missing or impaired, people can develop diseases in which the body’s immune system attacks its own tissues and organs.

The idea is to isolate regulatory T cells from a patient about to have a liver or kidney transplant. Then scientists attempt to grow them in the lab along with cells from the donor.

Then the T cells are infused back to the patient. The process, scientists hope, will teach the immune system to accept the donated organ as part of the patient’s body.

“The new T cells signal the rest of the immune system to leave the organ alone,” said Angus Thomson, director of transplant immunology at the University of Pittsburgh Medical Center.

Markmann, working with liver transplant patients, and Leventhal, working with kidney

transplant patients, are starting studies using regulatory T cells.

At Pittsburgh, the plan is to modify a different immune system cell, called regulatory dendritic cells. Like regulatory T cells, they are rare and enable the rest of the immune system to distinguish self from non-self.

One advantage of regulatory dendritic cells is that researchers do not have to isolate them and grow them in sufficient quantities. Instead, scientists can prod a more abundant type of cell—immature white blood cells—to turn into dendritic cells in petri dishes.

“It takes one week to generate dendritic cells,” Thomson said. In contrast, it can take weeks to grow enough regulatory T cells.

The regulatory T cells also have to remain in the bloodstream to control the immune response, while dendritic cells need not stay around long—they control the immune system during a brief journey through the circulation.

“Each of us is taking advantage of a different approach,” Markmann said. “It is not clear yet which is best. But the field is at a fascinating point.”

What about patients who already had an organ transplant? Is it too late for them?

“I get asked that question almost every day I am seeing patients,” Leventhal said.

For now, the answer is that it is too late. These patients are not candidates for these new strategies to modify the immune system. But researchers hope that situation will change as they learn more.

“SOMEONE HAS TO BE FIRST”

When Michael Schaffer, the Pittsburgh patient, was told that he needed a liver and that he could be the first patient in the group’s clinical trial, he shrugged. “Someone has to be first,” he said.

Schaffer began a search to find a living donor, a close relative willing to undergo a major operation to remove a lobe of liver—or a stranger whose cells were compatible and who

was willing to donate.

The Pittsburgh scientists told him how to proceed. Ask immediate family, then relatives, friends, and colleagues. If that failed, he would have to start advertising with fliers and posts on Facebook.

Schaffer is one of eight brothers. Four were older than 55, too old to safely undergo removal of part of their liver. The three younger brothers were in poor health.

He moved on to nieces and nephews. Three agreed to donate, and one, Deidre Cannon, 34, who was a good match, went forward with the operation.

It took place on Sept. 28, 2017. Afterward, Schaffer was taking 40 pills a day to prevent infections and to tamp down his immune system while his body learned to accept the new organ.

But now he has tapered down to one

pill, a low dose of just one of the three anti-rejection drugs he started with. And doctors hope to wean him even from that.

His case may be intriguing, but he is just one patient. The scientists plan to try the procedure on 12 more patients and, if it succeeds, to expand the study to include many more patients at multiple test sites.

For Schaffer, it has all been worthwhile. He is active, working with a teenage grandson to replace the tiles on his kitchen floor. He shovels snow and mows lawns as a favor for his neighbors, and helps take care of his grandchildren after school.

“My goal is to live to be 100 and get shot in bed by a jealous husband,” Schaffer said. ■



Humar



Thomson

MASTER CONDUCTORS

In late 1989, transplant giant Thomas Starzl invited a Scottish immunologist named Angus Thomson, one of the few people in the world other than Starzl studying the anti-rejection drug FK506 (now called tacrolimus), to visit Pittsburgh. Yet what Thomson would concentrate on for decades to come was another interest of Starzl’s.

Around the time that Thomson visited, Starzl had proposed that donor immune cells that came along with a transplanted organ might have helped some long-surviving transplant recipients delay or avoid rejection. The hypothesis was contrary to the prevailing view that donor immune cells instigated rejection. But Thomson, now Distinguished Professor of Surgery and Immunology, thought that Starzl was onto something and accepted his invitation to join the faculty at Pitt.

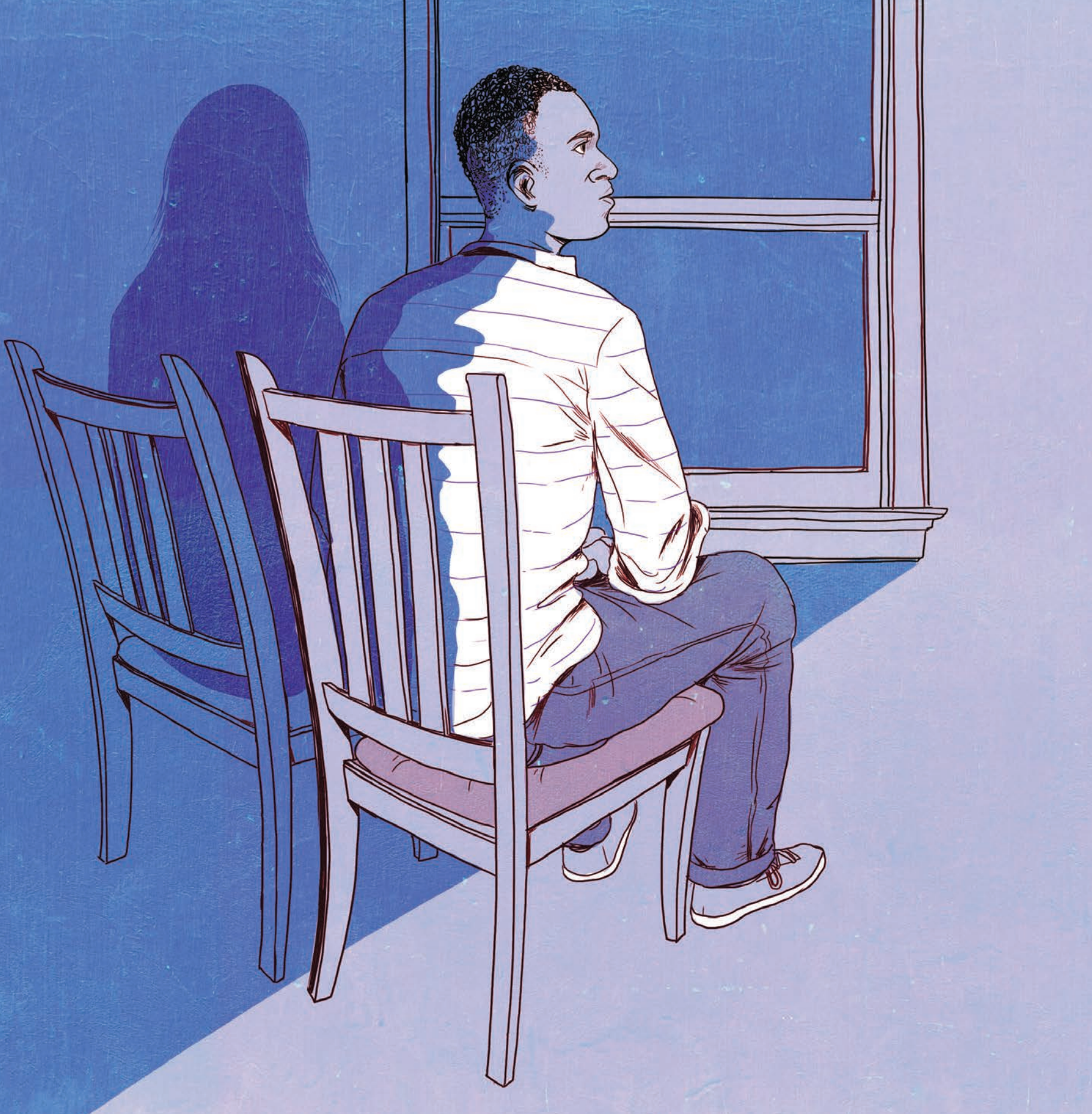
Throughout the next two decades, Thomson and his team studied donor regulatory dendritic cells (DCregs)—immune cells now thought to be important in moderating how a transplant recipient’s immune system responds. He calls dendritic cells the “conductors of the immunological orchestra,” because they can dictate how other immune cells behave.

In collaboration with Abhinav Humar, Pitt’s Thomas E. Starzl Professor of Transplantation Surgery and clinical director of the Starzl Transplantation Institute, Thomson’s lab also demonstrated in animal models that DCregs derived from organ donors could control the immune system of transplant recipients and prolong donor organ survival.

In 2017, with funding from UPMC’s new Immune Transplant and Therapy Center, Thomson and Humar started a clinical trial that would transplant liver lobes and DCregs from living donors. Michael Schaffer (featured above) became the first person in the world to receive DCregs from a donor. “It was a humbling moment,” says Thomson, “one that 20 years ago I would not have imagined would happen.”

Schaffer is doing well and slowly being weaned off anti-rejection medications. And as this magazine went to press, 11 other patients had successful transplants as part of the trial.

—Arvind Suresh



A new combined lung/bone marrow transplant is saving the lives of some very sick patients. Not only that, but when successful, these patients are gaining the immune systems of the donors, so they can lead lives free of immunosuppressant drugs.

BEYOND THE DONOR MATCH

WHEN ONE PERSON BECOMES PART OF THE OTHER

BY SHARON TREGASKIS

Among the mementos in the Rangos Research Center office of pediatrician Paul Szabolcs hangs a front-page news story published in 2010. In the accompanying photo, confetti showers down on a slight 16-year-old as health care providers and fellow patients celebrate her release from the local bone marrow transplantation unit.

When they met in 2009, Szabolcs recalls, the flaxen-haired youngster was in a precipitous decline. At just 4'5" and 48 pounds, Daphne (we've changed patient names in this story) required intravenous nutrition and high-flow oxygen supplementation; her muscles were so depleted she could no longer walk independently. Diagnosed as an infant with the same hereditary immune deficiency that had killed her older brother before his fourth birthday, she had endured recurrent respiratory infections for six years. Still, she acted in local theatre productions, excelled in her Advanced Placement courses, earned her driver's permit. When she couldn't attend school in person, she participated by Skype.

A transplant of stem cell-rich cord blood, Szabolcs's specialty, could replace Daphne's delicate immune system with one vigorous enough to protect her lungs. But she was too weak to endure the radiation and chemotherapy that precedes such transplants. And those persistent respiratory

ILLUSTRATIONS | MICHAEL HIRSHON

infections had inflicted such extensive damage, a new set of lungs was equally imperative—and risky. The drugs used to prevent organ rejection would only accelerate her immune decline. “It would have been futile and irresponsible to offer any kind of [conventional] transplant,” says Szabolcs. “We would have killed her.”

Together with her pulmonologist, Szabolcs—now chief of the Division of Blood and Marrow Transplantation and Cellular Therapies at UPMC Children’s Hospital of Pittsburgh—proposed a novel solution, then garnered the myriad institutional and federal approvals required to proceed. Her doctors would seek a single deceased donor to furnish both bone marrow and lungs. If their scheme worked, Daphne would be cured of her hereditary immune dysfunction and spared the side effects caused by lifelong use of the medications necessary to prevent rejection.

The procedure they envisioned would take months. If a size- and tissue-matched donor

coexisted in harmony, without the aid of immunosuppressant therapy.

Clinicians refer to that outcome as “immunological tolerance,” and it’s been commonplace in bone marrow transplantation since the procedure was pioneered in the 1950s. In the field of lung transplantation, however, Daphne’s experience is the stuff of fantasy. Among those who live a full decade after receiving their new lungs, 75 percent experience chronic rejection. And they’re the lucky ones—45 percent of recipients die within the first five years of their transplant surgery.

“This equates to the prognosis of a moderate cancer, and it’s supposed to be a life-saving transplant,” says associate professor of medicine John F. McDyer, director of Pitt’s Lung Transplantation Translational Research Program. “There’s a lot of room for improvement.”

It’s no surprise that of all the solid organs, lung transplants are the most difficult to manage, says Mark Gladwin, the Jack D.

marrow failures—people with idiopathic pulmonary fibrosis, sickle cell, scleroderma, and a condition McDyer has studied extensively known as short telomere syndrome. So far, their program has garnered more than \$12 million in combined funds from the National Institutes of Health and UPMC. Already, they’ve enrolled 10 patients and performed five combined lung and bone marrow transplants.

Bone marrow transplantation was pioneered in the 1950s as a curative treatment for leukemia, in which cancer emerges within the bone marrow. First, doctors blast the patient’s leukemic cells with radiation and chemotherapy (what’s called myeloablative conditioning); then they replace the immune system they obliterated with donor marrow. When the donor marrow starts cranking out red and white blood cells, a state clinically known as engraftment, the transplant is considered a success. In the early years, only identical twins were eligible to receive transplants. In time, it became obvious that absent a twin,

“When she started getting sicker and sicker, there was a part of me that started trying to prepare myself for a life without her. It’s amazing that she’s here.”

could be identified in time, the marrow would be harvested and processed to deplete the most immunologically aggressive cells, then frozen. The lungs would be transplanted immediately. If Daphne survived that surgery, she would spend a few months on immunosuppressants while regaining her strength, then proceed with chemotherapy, radiation, and finally transplantation of the cryopreserved bone marrow.

“Quitting was not her nature,” says Szabolcs. “So I felt that it was my obligation to come up with a plan that, while without precedent, still carried hope.”

By the time Szabolcs and his colleagues reported on the case in a 2014 letter to the *Journal of Allergy and Clinical Immunology*, their former patient was attending college on a full scholarship and giving campus walking tours. This fall she’ll commence graduate studies in computational analysis and public policy. And for eight years and counting, her own cells and those of her donor have

Myers Professor, chair of the Department of Medicine, and director of the Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute.

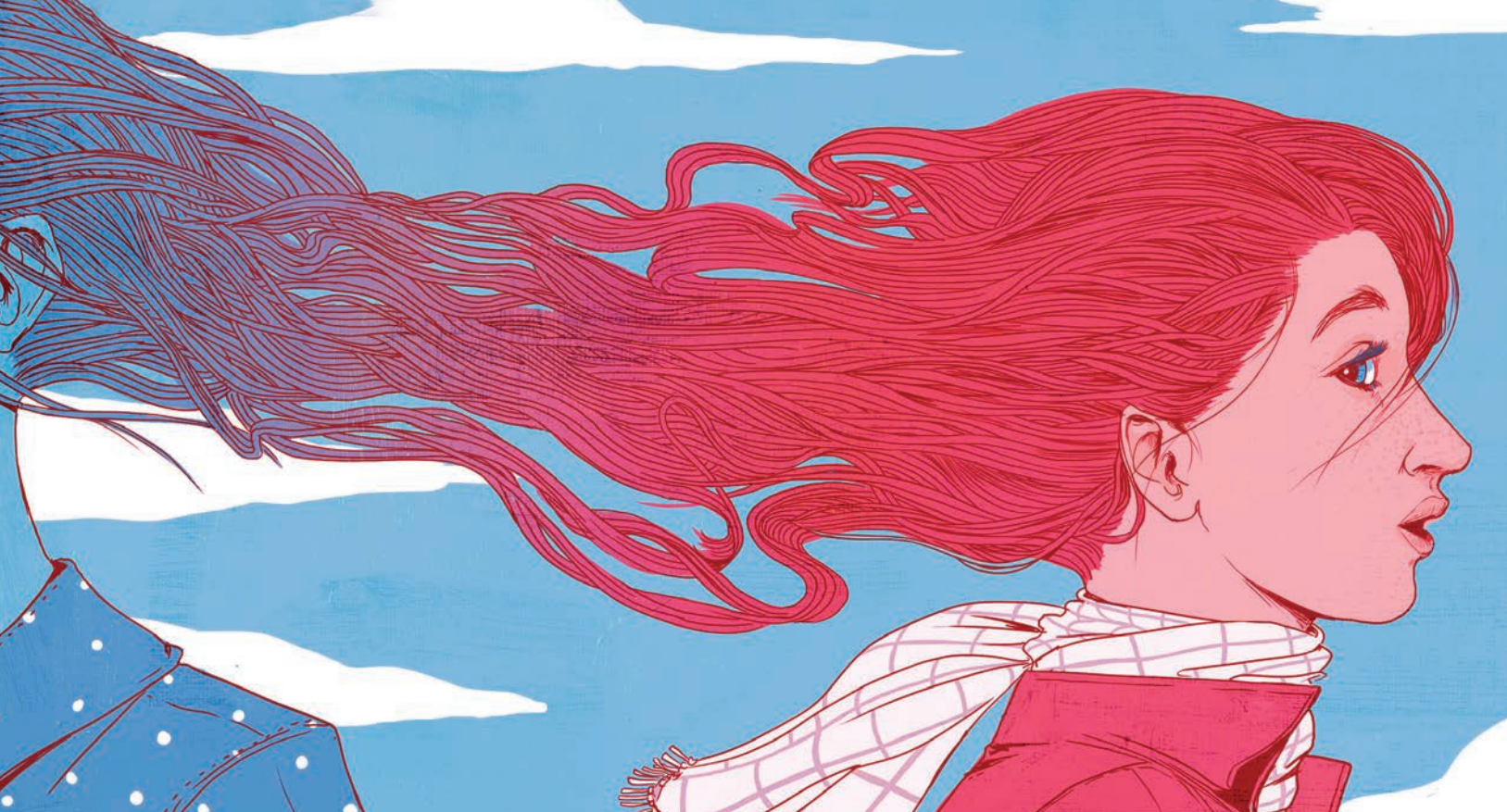
“The lungs are always exposed to viral and bacterial infections, which stimulate inflammation and increase the risk of activating the immune system. The activated immune system will also attack the donor’s lung in a process called rejection,” he says. “The idea of combining the bone marrow from the donor with the lungs from the same donor could be a breakthrough by eliminating the risk of the bone marrow attacking the lungs.”

Like Szabolcs, McDyer joined the Pitt faculty in 2011—recruited by Gladwin. And soon after they met, the two started laying the groundwork for a joint clinical and research program to continue the work Szabolcs began in 2009. They teamed up with Jonathan D’Cunha, Pitt’s surgical director of adult lung transplant, and expanded the effort to include more adults plagued with both lung and bone

more distant matches were sufficient—and far more widely available. It also became obvious that the myeloablative regimen necessary to kill every leukemic cell lingering in the marrow posed significant hazards. Even today, says Szabolcs, the regimen kills one in 10 or more patients.

Whether the patient has leukemia or is about to undergo a novel combined lung and bone marrow transplant, the trick is finding the delicate balance where a patient survives both conditioning and the physiological chaos that can ensue when host and donor immunology clash. “When you don’t have to kill every last leukemic cell [for instance], you want to dial back the intensity of the conditioning,” says Szabolcs. “But there’s a possibility the patient’s stem cells may recover.”

That’s what happened in 2016, when Szabolcs and McDyer did their first lung and bone marrow transplant at Pitt. Madeline was 10 when she was diagnosed with secondary combined immune deficiency. Within a year,



her health had deteriorated to the point that her parents were told they could take her home on palliative care, or contact Szabolcs and the pediatric lung transplant team at Children's to explore whether she could enroll in their clinical trial. She was 11 when she was added to the transplant waiting list. She received her new lungs in September 2015; a month later she celebrated her 14th birthday at the Ronald McDonald House in Pittsburgh. Her new bone marrow was transplanted in January 2016. Today, she's applying to college.

"That was a thing I didn't think she would get to do," says her mother. "When she started getting sicker and sicker, there was a part of me that started trying to prepare myself for a life without her. It's amazing that she's here."

Like Daphne, Madeline achieved immunological tolerance. Her mother still urges her to avoid people who are sick and wash her hands often, but Madeline has no need for immunosuppressant therapy to protect her lungs from rejection. Her donor bone marrow takes care of the job, simultaneously fending off the ear infections, pneumonias, and other ailments that plagued her during childhood.

But unlike Daphne, whose native immune system was totally obliterated and replaced in full—a state known as full donor chimerism—some of Madeline's own stem cells survived. As a result, her blood contains mature cells derived both from her own bone marrow and that of her donor's, a state known as mixed chimerism.

Szabolcs and his collaborators don't yet

understand why Daphne's immune system exhibits full chimerism while Madeline's is mixed. Both outcomes have long been documented among bone marrow transplant recipients, with mixed results. "Even with full dosing," says Szabolcs, "some patients reject [the bone marrow transplant], some fully engraft, and some live with fully mixed chimerism. It wasn't something people could control; it just happened."

Chimerism first attracted scientific attention in the 1940s—cattle twins sometimes exhibited two distinct immune types, antigens acquired during their mutual gestation. Later, doctors reported similar cases among humans. Evidence of such chimerism in nature suggested that clinicians might be able to induce the state in transplant patients, subverting or short-circuiting the dangerous scenario of donor and host immune systems clashing.

In the early '90s, when Szabolcs was a postdoctoral fellow in New York City, he heard Pitt transplant pioneer Thomas Starzl give a talk on the subject at Rockefeller University. Starzl had started documenting mixed chimerism among liver transplant recipients, some of whom had successfully abandoned their anti-rejection medications. He had a hunch that the key to their immunological tolerance was derived from what he dubbed "passenger leukocytes." That is, white blood cells from donors were hitching a ride on transplanted livers; in the process, they were conferring mixed chimerism to the recipients.

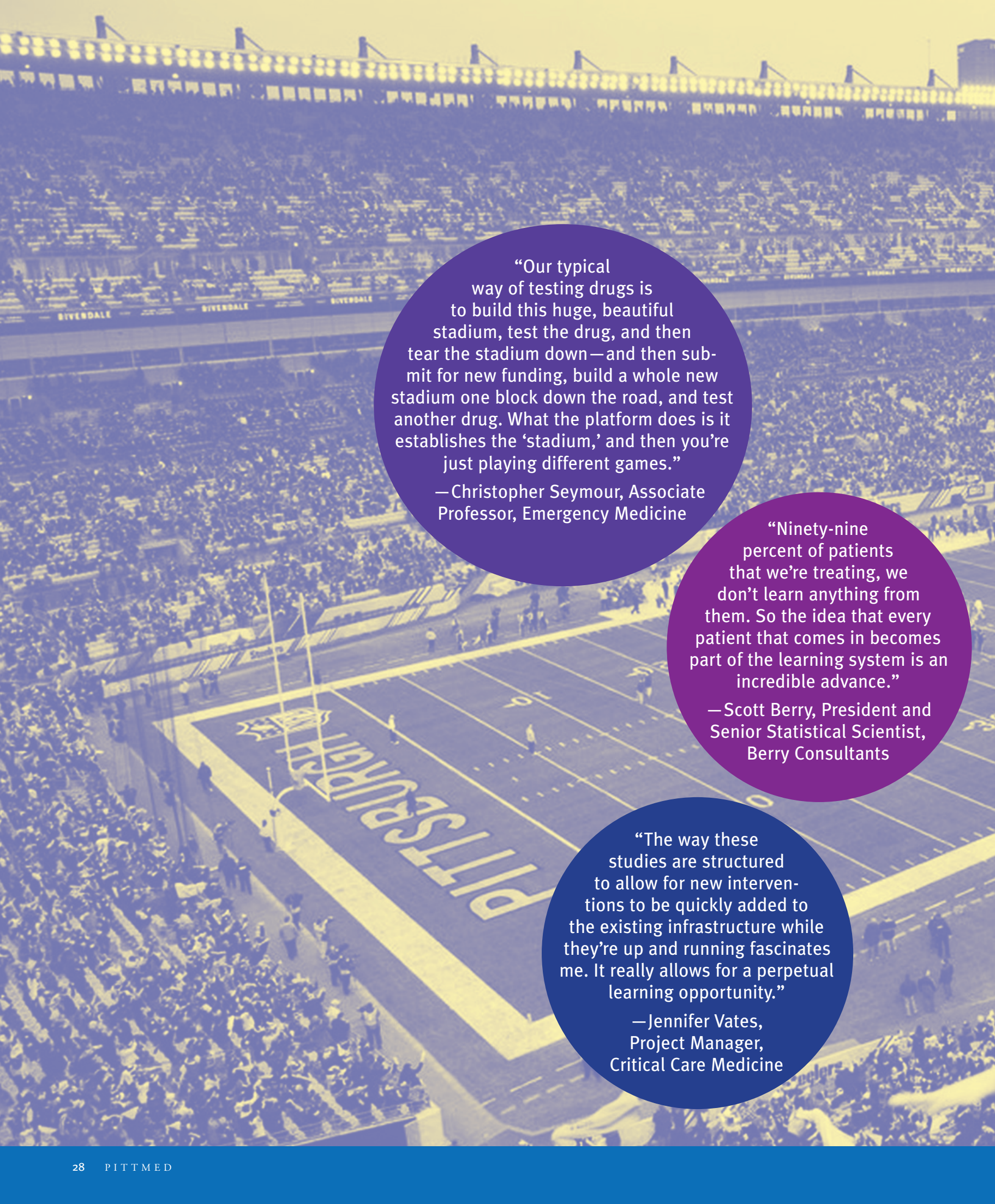
Starzl hypothesized that those donor-

derived leukocytes were the key to immunological tolerance. In his subsequent experiments, says Szabolcs, Starzl simply transfused donor bone marrow—recipients didn't receive myeloablative conditioning and the donor cells weren't processed to reduce the risk of undue aggression against the recipient.

"They didn't have the specific objective to engraft stem cells and build the immune system," says Szabolcs. "Our primary point is to transfer the immune system from the donor, and then there's a realistic possibility that tolerance could also develop."

To better understand what's going on with their own patients—both teens and adults, several with significant comorbidities—Szabolcs and McDyer spend a lot of time in their respective labs, analyzing bloodwork and cells washed from their patients' bronchial passages, looking for clues to long-term prognoses. In addition to making sense of how chimerism relates to immunological tolerance, they're also documenting the myriad forms mixed chimerism takes. Already, they know that certain cell types in the bone marrow exhibit asymmetrical host-donor ratios, even in the same patient—but the implications of those differences remain murky. They're also investigating how close matches must be for a successful outcome.

"These are patients who don't have other options," says McDyer. "We tell them it's a lot of risk, and we learn a lot from each patient, and we'll do our best—we'll do everything we can to get them through it." ■



“Our typical way of testing drugs is to build this huge, beautiful stadium, test the drug, and then tear the stadium down—and then submit for new funding, build a whole new stadium one block down the road, and test another drug. What the platform does is it establishes the ‘stadium,’ and then you’re just playing different games.”

—Christopher Seymour, Associate Professor, Emergency Medicine

“Ninety-nine percent of patients that we’re treating, we don’t learn anything from them. So the idea that every patient that comes in becomes part of the learning system is an incredible advance.”

—Scott Berry, President and Senior Statistical Scientist, Berry Consultants

“The way these studies are structured to allow for new interventions to be quickly added to the existing infrastructure while they’re up and running fascinates me. It really allows for a perpetual learning opportunity.”

—Jennifer Vates, Project Manager, Critical Care Medicine

PITT DOCS HAVE REIMAGINED
HOW TO TEST TREATMENTS
BY JENNY BLAIR

A WHOLE NEW BALLGAME

In March 2009, two California schoolchildren came down with a cough and fever. Within weeks, the Centers for Disease Control and Prevention had pinpointed their symptoms to a brand-new swine flu. Both children recovered, but their illnesses heralded the global H1N1 pandemic, which killed an estimated 284,000.

After the pandemic, the University of Pittsburgh's Derek Angus, Distinguished Professor and Mitchell P. Fink Professor, Critical Care Medicine, recalls soul-searching and lament among clinician-researchers who hadn't been able to respond fast enough. "Here in Pittsburgh, for several weeks, we were inundated with terribly ill H1N1 patients; and yet by the time we got [a] trial up and running, the epidemic was over," Angus says. Virologists around the world isolated the organism very rapidly, he points out. "[But] we couldn't even answer the simplest clinical question."

There had to be a better way—a way to efficiently, affordably learn what every patient has to teach, then to apply those lessons faster. Sepsis, cancer, and other daunting diseases also demand answers faster than traditional trials can provide them.

Angus and his colleagues started thinking about how to fuse randomized clinical trials with clinical practice. Within five years, Angus published a landmark paper in the *Journal of the American Medical Association* proposing a new approach to clinical trials. The approach is a novel combination of a few forward-looking methods that had met with success in other trials.

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CIRCLE CHARTS | ELENA GIALAMAS CERRI

The old way of structuring trials is like building a sports stadium, playing one game, then dismantling it. Angus's team proposed a permanent stadium, a platform ready for game after game. Not only that, it would be embedded in the electronic health record, make incremental changes as it gathers information, and be ready to ask and answer new clinical questions on short notice. It would piggyback unobtrusively on clinical care: UPMC clinicians would invite patients as appropriate; trial organizers would let the system automatically capture blood pressure, adverse events, etc. without having to deploy the usual army of research coordinators and staff. The platform creates what Angus calls a learning health care system.

This April, almost exactly 10 years after the H1N1 epidemic began, Pitt began enrolling patients in one of the world's first trials that combines the electronic health record with a new, efficient, safety-focused randomization process. The system is powered by software created by the Texas-based Berry Consultants. The approach, called REMAP (randomized, embedded, multi-factorial, adaptive platform), may transform the way doctors learn from patients—and how they care for them.

trial
starting

The platform can be adjusted for other experimental therapies.

Do they
qualify?

Do they
consent?

The algorithm watches the results throughout.

patients in
electronic health
records

placebo

New participants are likely to be randomized to the better performing arms. Likewise, patients already enrolled who don't respond well to their assigned experimental treatment may be reassigned to groups that seem to be responding better.

faltering

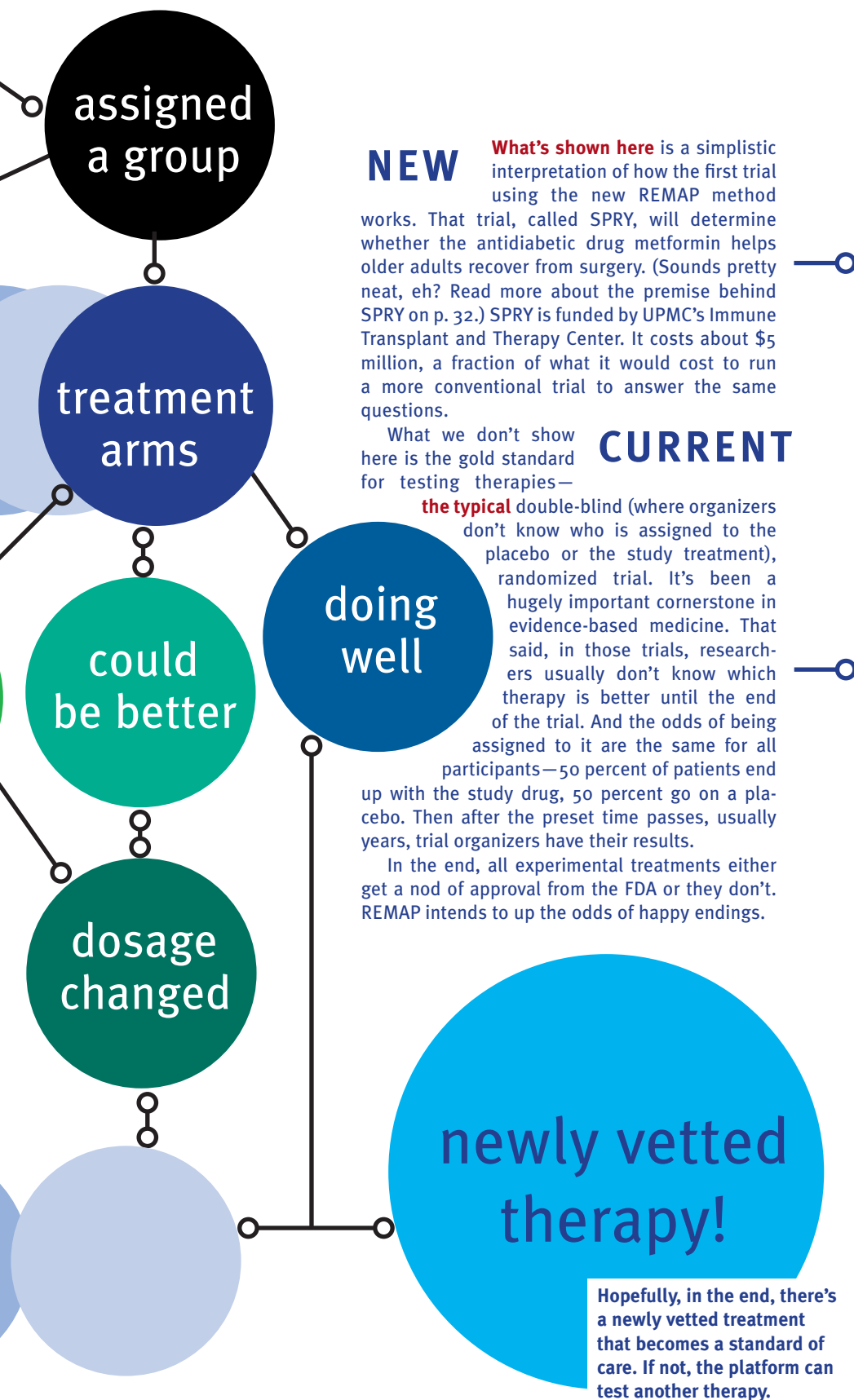
arm
dropped

The odds of being assigned to the best therapy go up as enrollment proceeds and researchers learn more.

refined treatment arms

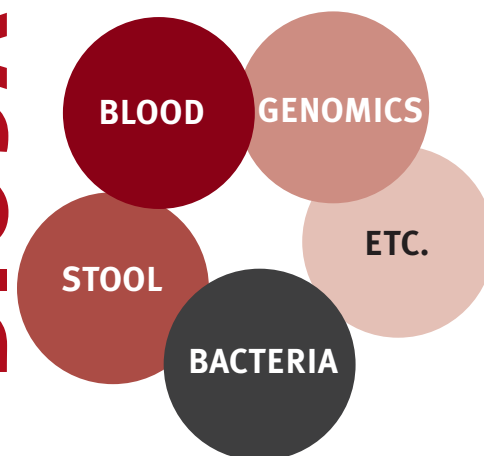
New treatment arms are introduced in response to what's been learned.

TRY, TRY AGAIN



BIOSAMPLES

The trial will build a vast biorepository—a bank of 422,000 blood samples and 60,000 stool samples collected from SPRY participants over multiple time points. These sample proteins, genes, and microbiota could yield new insights for many years to come.



FUTURE

Pitt's Derek Angus imagines that REMAP-type trials may one day become part of

everyday care. Experimental treatments for cancer, sepsis, and other highly complex problems are particularly well-suited to this approach.

"In a way, it would seem intolerable to ever let your bedside clinician with imperfect knowledge try to make a decision under uncertainty when an overarching adaptive platform may have more knowledge about the best odds of treatment than anything else," Angus says.

It makes sense that a smart algorithm working with smart docs in everyday clinical settings would make trials smarter. Let us count the ways . . .

CONVENTIONAL TRIALS

SLOW

Unwieldy

Expensive
(might never get
off the ground)

Results might
be too broad—
treatment effect is the
average from many trial
participants; yet people
respond to treatments
in different ways

... Or too
narrow—effect
might not apply
to patients who
differ from trial
participants in
some way

Randomization
might seem risky
or unfair

HOW SURGERY IS LIKE AGING

Surgery is hard on the body, which ramps up inflammation as a response to the stresses of the operation and anesthesia. This can lead to postsurgical complications. Inflammation also underlies many aging processes, and high-risk surgery in frail individuals is a little like the aging process. So a therapy that boosts resiliency after surgery might, by the same token, promote healthier aging, too. The Strategies to Promote Resiliency (SPRY) clinical trial—Pitt's first in the overarching REMAP platform—is testing whether the commonplace diabetes-control drug metformin might be such a therapy. Metformin intrigues anti-aging researchers because it has a wide range of beneficial effects, including reducing inflammation and extending life span in other organisms. If it reduces complications in postsurgical patients over a few months, it might slow aging, too.

And metformin is just one of many possible therapies the research team can test. Even non-drug interventions like physical rehab before the operation could be added as treatment arms.

THE NEW WAY

GO

Can be run
at a fraction of
the cost

Automated

- Integrates with the electronic health record
- Screens for potential patients to enroll
- Captures clinical data

Streamlined
into existing
care

• Broad
enrollment, yet can
apply to diverse groups
of patients

• Adjusts enrollment criteria as
trial “learns” that some types of
patients benefit more

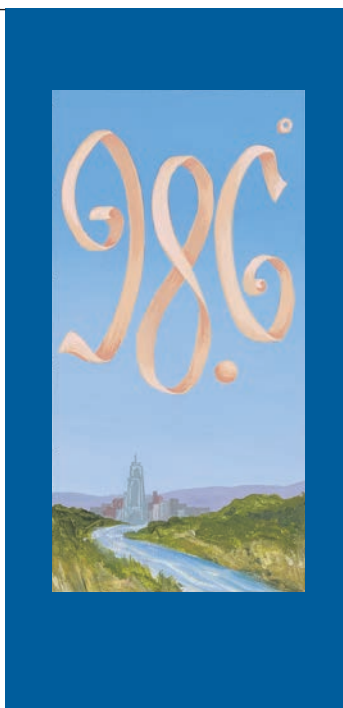
• Tests various treatments and
patient types in multiple
combinations, adding
new trial arms along
the way

It “plays
the winners.”
A machine-learning
algorithm tracks which
trial arms are yielding better
outcomes and adjusts to
randomly assign more par-
ticipants to the more
effective arms

“That’s the concept behind SPRY—to create a platform where we would allow patients, should they consent, to be randomized to different strategies that are almost like anti-aging strategies,” Pitt’s Derek Angus says.

Using the new trial design, principal investigator Matthew Neal, Pitt’s Roberta G. Simmons Assistant Professor of Surgery, says, “we can study drugs like metformin in a leaner, more efficient way, so that every new exciting drug that has the potential for prehabilitation, or has the potential to be an anti-aging strategy, is not sidelined by the burden of eight-digit trial budgets, which would make it prohibitive.” ■

*People and programs
that keep the school
healthy and vibrant*



BOOSTER SHOT

In November, four Pitt professors with positions at UPMC Hillman Cancer Center were each awarded a portion of a \$1 million grant from the **Breast Cancer Research Foundation (BCRF)**. The funding is part of the foundation's record-breaking \$63 million donation, which was split among 300 of the world's top scientists and is intended to span the entire spectrum of cancer research, from basic cell biology to developing new treatments.

Wendie Berg, an MD/PhD professor of radiology, **Leisha Emens**, an MD/PhD professor of hematology/oncology, and **Steffi Oesterreich** and **Adrian Lee**, each a PhD professor of pharmacology and chemical biology, were among the scientists chosen across six continents to receive the BCRF grants.

"It's exciting," says Berg, who specializes in breast imaging at UPMC Magee-Womens. "A lot of years of life are lost, and treatments have improved but are still fundamentally limited by the stage of detection." She notes that doctors want to catch breast cancer early on "and not cause harm in the process by doing extra procedures that are unnecessary."

Emens, who is coleader of the Hillman Cancer Immunology and Immunotherapy Program, praised the BCRF for the grant. "They allow a lot of flexibility for investigators to explore areas that more traditional grants don't necessarily support," she says. "Having [BCRF's] support gives us all a foundation to move our research forward and make rapid progress."

—Kate Benz

FOR INFORMATION ON GIVING TO THE SCHOOL:
Jennifer Gabler at 412-647-3792 or
jjennifer@pmhsf.org
www.giveto.pitt.edu

ELECTRONIC SAVIORS

BANDED TOGETHER

BY EVAN BOWEN-GADDY

In 2007, Jim Semonik knew he needed a colonoscopy. His father had died from colon cancer four years earlier, and now, as a 31-year-old, he had lost his appetite, he was having

several bowel movements each day, and blood appeared in his stool.

Semonik's fear was validated when, following a colonoscopy, he was diagnosed with stage IIB colorectal cancer. Only 11 percent of colon cancer patients are younger than 50.

David Medich, associate professor of surgery and chief of the Division of Colon and Rectal Surgery at the University of Pittsburgh, started Semonik on chemotherapy and radiation treatment in mid-2008.

From the age of 23, Semonik had worked as a DJ and promoter of industrial music, a mix of electronica, rock, and punk. He brought CDs to the long radiation sessions, and he'd listen to industrial music bands, like 16 Volt, Chemlab, and KMFDM.

"It was a dark kind of music," Semonik says.

Semonik credits the aggressive music and the treatment he received from Medich's team with his ability to overcome the disease. One afternoon, while receiving radiation treatment and tuning in to his favorite genre, he decided to use one to help the other.

"I'm on borrowed time already, so I may as well do my best with it," says Semonik. "I started contacting everyone I knew. Every record label that I had worked with, every band that I had worked with, whether it be local, international."

Semonik's idea: create a compilation album of industrial music featuring artists from around the world. The proceeds would go to cancer research. But before he could start producing albums, Semonik needed to beat cancer.



Semonik (shown here) recruited 83 bands to support cancer research and people with cancer.

In September 2008, Medich removed Semonik's two tumors, along with his gallbladder and 18 inches of his large intestine.

"I had to relearn how to walk, had to retrain my digestive system, had to wear an ileostomy bag," says Semonik.

Following a bout with pancreatitis and a reversed ileostomy, Semonik got started on the project. With 83 bands lending their music, he released *Electronic Saviors: Volume 1* in 2010. The album raised more than \$20,000 for various organizations, supporting people with cancer and cancer research. He decided to make additional volumes, and in 2016, after the release of *Volume 4*, he donated \$5,000 to Medich and his research team. This year, following the release of *Volume 5*, Semonik donated another \$7,500 to Medich. The money will be used to study different methods of chemo-radiation that free patients of the need for surgery.

"When I tell you I wouldn't have made it without music, I can tell you the same about him," says Semonik of Medich.

Semonik's compilation albums have raised more than \$70,000 for cancer-related charities in eight years, and he remains cancer free. ■

MATCH RESULTS CLASS OF 2019

ANESTHESIOLOGY

Eng, Alexander
Westchester Medical Center/New York Medical College
*Westchester Medical Center/New York Medical College
Huynh, Jamie
UC San Diego Medical Center/
University of California, San Diego
*Scripps Mercy Hospital, California
Jayakumar, Sachidhanand
Yale New Haven Hospital, Conn.
Kamal, Fariha
University of Michigan Hospitals
Kocher, Matthew
UPMC/University of Pittsburgh, Pa.
Ligus, Zachary
Strong Memorial Hospital/University of Rochester, N.Y.
Makonza Goto, Rudo
Vanderbilt University Medical Center, Tenn.

DERMATOLOGY

Anderson, Alyce
McGaw Medical Center/Northwestern University, Ill.
*UPMC/University of Pittsburgh, Pa.

EMERGENCY MEDICINE

Ahn, Jennifer
UPMC/University of Pittsburgh, Pa.
Frodey, Brian
Albany Medical Center/Albany Medical College, N.Y.
Juarez, Jose Miguel
Mount Sinai Hospital/Icahn School of Medicine, N.Y.
Lehtihet, Nadia
MedStar Washington Hospital Center/
Georgetown University, D.C.
Markovtsova, Anastasia
Stanford University Programs, Calif.
Massey, Denzel
Madigan Army Medical Center, Wash.
Reseland, Eric
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Yourish, Harmony
UPMC/University of Pittsburgh, Pa.

FAMILY MEDICINE

Clark, Elizabeth
Thomas Jefferson University Hospital, Pa.
Dhillon, Harbir
St. Joseph's Medical Center, Calif.
Huang, Cecilia
Long Beach Memorial Medical Center, Calif.
Ounis, Hibaa
Kaiser Permanente Woodland Hills Medical Center/
UCLA, Calif.
Taormina, John
UPMC St. Margaret/University of Pittsburgh, Pa.

INTERNAL MEDICINE

Abboud, Andrew
Massachusetts General Hospital/
Harvard University, Mass.
Allen, Matthew
University of Virginia Health System
Birda, Vaibhav
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Brown, Frederick
Barnes Jewish Hospital/Washington University, Mo.
Campbell, Tracy
MedStar Washington Hospital Center/
Georgetown University, D.C.
Chang, He
University of Iowa Hospitals and Clinics

Corredera, Erica
New York—Presbyterian Hospital/
Weill Cornell Medical Center
Fair, Katherine
University of Washington Affiliated Hospitals
Gordon, Rachael
UPMC/University of Pittsburgh, Pa.
Hatheway, Clark
California Pacific Medical Center
Huang, Jenny
Scripps Clinic/Scripps Green Hospital Program, Calif.
Joolharzadeh, Pouya
Barnes Jewish Hospital/Washington University, Mo.
Keil, Spencer
UPMC/University of Pittsburgh, Pa.
Macklin, Michael
UPMC/University of Pittsburgh, Pa.
McNamara, Laura
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Morrison, Amanda
Vanderbilt University Medical Center, Tenn.
Namboodiri, Hima
LAC+USC Medical Center/University of Southern
California
Nguyen, Felix
Barnes Jewish Hospital/Washington University, Mo.
Oh, Adrianna
UPMC/University of Pittsburgh, Pa.
Priedigkeit, Nolan
Brigham & Women's Hospital/
Harvard University, Mass.
Robinson, Darve
Yale New Haven Hospital, Conn.
Roy, Priya
University of Wisconsin Hospital and Clinics
Sestito, Samuel
Vanderbilt University Medical Center, Tenn.
Spehar, Stephanie
University of Michigan Hospitals
Tang, Yicheng
UPMC/University of Pittsburgh, Pa.
Wagner, Phillip
UPMC/University of Pittsburgh, Pa.
Wang, Linda
Beth Israel Deaconess Medical Center/
Harvard University, Mass.

INTERNAL MEDICINE/PEDIATRICS

Axline, Michael
Virginia Commonwealth University Health
System Program
Linn, Alexandra
Hospital of the University of Pennsylvania

INTERNAL MEDICINE/PSYCHIATRY

Robbins-Welty, Gregg
Duke University Medical Center, N.C.
Saliu, Ololade
University of Iowa Hospitals and Clinics

INTERNAL MEDICINE/ WOMEN'S HEALTH

Koenig, Leah
UPMC/University of Pittsburgh, Pa.
Pace, Rachel
UPMC/University of Pittsburgh, Pa.

NEUROLOGICAL SURGERY

Kashkoush, Ahmed
Cleveland Clinic/Case Western Reserve University, Ohio

NEUROLOGY

Johnson, Erica
Mayo Clinic/Mayo Clinic School of Health Sciences, Minn.
*UPMC/University of Pittsburgh, Pa.
Madill, Evan
*Stanford University Programs, Calif.
Mehta, Amol
New York—Presbyterian Hospital/
Columbia University Medical Center
Wang, Jia-Yi
*Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Wechsler, Paul
New York—Presbyterian Hospital/
Weill Cornell Medical Center

NEUROLOGY—PEDIATRIC

Carson, Ross
Boston Children's Hospital/Harvard University, Mass.

OBSTETRICS/GYNECOLOGY

Dong, Shirley
Ohio State University Medical Center
Sakai, Nozomi
University of North Carolina Hospitals
Szeto, Libby
Montefiore Medical Center/Albert Einstein College
of Medicine, N.Y.
Vasudeva, Isha
UConn Health/University of Connecticut

OPHTHALMOLOGY

Arnett, Justin
UC San Diego Medical Center/University of California,
San Diego
*Englewood Hospital, N.J.
Blecher, Nathaniel
*Barnes Jewish Hospital/Washington University, Mo.
Jones, Peter
*UPMC/University of Pittsburgh, Pa.
Keppel, Kevin
Cleveland Clinic/Case Western Reserve University, Ohio
*UPMC/University of Pittsburgh, Pa.

ORAL/MAXILLOFACIAL SURGERY

Biron, Gregory
UPMC/University of Pittsburgh, Pa.
Cooper, Kristopher
UPMC/University of Pittsburgh, Pa.

ORTHOPAEDIC SURGERY

Bhagal, Sumail
UPMC/University of Pittsburgh, Pa.
Judy, Ryan
Temple University Hospital, Pa.
Kohut, Kevin
University at Buffalo, N.Y.
Mahjoub, Adel
Cooper University Hospital/Rowan University, N.J.
Obioha, Obianuju
Rush University Medical Center, Ill.
Su, Favian
UCSF Medical Center/University of California,
San Francisco

OTOLARYNGOLOGY

Mathews, Fasil
SUNY Downstate Medical Center, N.Y.

PATHOLOGY

Kikuchi, Alexander
University of California, San Francisco Affiliates



On March 15, Pitt held its annual Match Day ceremony at Alumni Hall. ABOVE LEFT: Class of '19 grads Michael Matt, Michael Axline, and Amol Mehta pose for the Pitt Med cover photo booth. ABOVE CENTER: Eman Bascal cheers as her husband, Ahmed Kashkoush, learns he has matched with Cleveland Clinic. ABOVE RIGHT: Rachel Hughes (left) and Shirley Dong pose in the photo booth while celebrating that they matched at New York University Langone Medical Center and Ohio State University Medical Center, respectively.

PEDIATRICS

Arjunan, Akshaya
UPMC Children's Hospital of Pittsburgh/
University of Pittsburgh, Pa.

Berken, Jonathan
Lurie Children's Hospital of Chicago & McGaw Medical
Center/Northwestern University, Ill.

Brayer, Samuel
Cincinnati Children's Medical Center/University of
Cincinnati, Ohio

Brueckmann, Ilona
Lurie Children's Hospital of Chicago & McGaw Medical
Center/Northwestern University, Ill.

Chen, Cathy
UC San Diego Medical Center/
University of California, San Diego

Hughes, Andrew
Children's Hospital of Philadelphia/University of
Pennsylvania

Hughes, Rachel
NYU Langone Medical Center & Bellevue Hospital

Karim, Sabrina
Boston Children's Hospital/Harvard University, Mass.

Koff, Kelsey
University of Washington Affiliated Hospitals

Matt, Michael
Cincinnati Children's Medical Center/University of
Cincinnati, Ohio

McAuley, James
Comer Children's Hospital/University of Chicago
Medical Center, Ill.

Mena, Jennifer
Montefiore Medical Center/Albert Einstein College of
Medicine, N.Y.

Park, Andrea
Riley Hospital for Children/Indiana University

Ray, Mondira
University of Washington Affiliated Hospitals

Russell, Margaret
UPMC Children's Hospital of Pittsburgh/
University of Pittsburgh, Pa.

PHYSICAL MEDICINE AND REHABILITATION

Mantik, Christopher
Casa Colina Hospital, Calif.

PSYCHIATRY

Atuahene, Brittany
Yale New Haven Hospital, Conn.

Becker, Claire
Western Psychiatric Institute and Clinic/University of
Pittsburgh, Pa.

Bisbey, Meghan
Western Psychiatric Institute and Clinic/University of
Pittsburgh, Pa.

Brockman, Ida
Western Psychiatric Institute and Clinic/University of
Pittsburgh, Pa.

Chernoff, Eva
Mount Sinai Hospital/Icahn School of Medicine at
Mount Sinai, N.Y.

Goldschen, Lauren
Brigham & Women's Hospital/Harvard University,
Mass.

Krivinko, Joshua
Western Psychiatric Institute and Clinic/
University of Pittsburgh, Pa.

Nguyen, Julia
UNM Psychiatric Center/University of New Mexico

Njoku, Ihuoma
University of Virginia Medical Center

Strobl, Eric
Vanderbilt University Medical Center, Tenn.

Transue, Emilie
Strong Memorial Hospital/University of Rochester, N.Y.

Zimmerman, Eric
Western Psychiatric Institute and Clinic/
University of Pittsburgh, Pa.

PSYCHIATRY/FAMILY MEDICINE

Kruszka, Gillian
UPMC/University of Pittsburgh, Pa.

RADIATION ONCOLOGY

Karukonda, Pooja
Duke University Medical Center, N.C.
*University of North Carolina Hospitals

Sivananthan, Aranee
University of Chicago Medical Center, Ill.
*UPMC/University of Pittsburgh, Pa.

Sutera, Philip
Johns Hopkins Hospital, Md.
*Allegheny General Hospital, Pa.

RADIOLOGY—DIAGNOSTIC

Atcheson, Kyle
Wake Forest University Baptist Medical Center, N.C.
*Presence Resurrection Medical Center, N.C.

Moulton, Joseph
Yale New Haven Hospital, Conn.
*UPMC/University of Pittsburgh, Pa.

RADIOLOGY—INTERVENTIONAL

Khan, Abdullah
UC Davis Medical Center/University of California, Davis
*Santa Clara Valley Medical Center, Calif.

RESEARCH

Ernst, Sara
UPMC/University of Pittsburgh, Pa.

SURGERY—GENERAL

Anto, Vincent
UPMC/University of Pittsburgh, Pa.

Boulay, Lauren
Morristown Medical Center/Mount Sinai
School of Medicine, N.J.

Darby, Jennifer
Loyola University Medical Center, Ill.

Donovan, Ashley
Ohio State University Medical Center

Griffith, Brian
University of Michigan Hospitals

Hossain, Mir Shanaz
Cleveland Clinic/Case Western Reserve University, Ohio

Kahler, Dylan
Temple University Hospital, Pa.

Kreger, Alexander
University Hospitals Cleveland Medical Center/
Case Western Reserve University, Ohio

Li, Binghau
Creighton University, Neb.

Liu, Annie
Duke University Medical Center, N.C.

Meyyappan, Thiagarajan
UPMC/University of Pittsburgh, Pa.

Ramos, Anna
UPMC/University of Pittsburgh, Pa.

Sanin, Gloria
Wake Forest University Baptist Medical Center, N.C.

SURGERY—PRELIMINARY

Donnell, Drew Michael
Ohio State University Medical Center

Hersh, Beverly
Zucker School of Medicine at Hofstra/Northwell, N.Y.

Jani, Ronak
Brigham & Women's Hospital/
Harvard University, Mass.

Lewis, Daniel
UPMC Mercy/University of Pittsburgh, Pa.

Liu, Shih-Dun Stanley
San Joaquin General Hospital, Calif.

Lu, Michael
UPMC Mercy/University of Pittsburgh, Pa.

Nikonova, Elena
Shands Hospital/University of Florida

SURGERY—THORACIC

Fisher, Bryant
UPMC/University of Pittsburgh, Pa.

UROLOGY

Lee, Austin
University of Rochester Medical Center, N.Y.

Myrga, John
UPMC/University of Pittsburgh, Pa.
*UPMC/University of Pittsburgh, Pa.

*Indicates location of transitional or preliminary year
of medical or surgical training.



CLASS NOTES

'60s

Growing up in Wilkes-Barre, Pa., **John Godleski** (MD '69) noticed many community members struggling with their health. "They had lung diseases related to their work in the mines," he says. This sparked his interest in inhaled particles and air pollution. His work was among the first to document health effects from ambient air particles, specifically on the cardiovascular and pulmonary systems. Godleski, former director of pulmonary pathology at Brigham and Women's Hospital and former professor of pathology at Harvard Medical School and Harvard T.H. Chan School of Public Health, retired from academia with an emeritus title in 2017. Through his eponymous company, he continues his work as a consultant on environmental particle inhalation. He also explores the possible link between talc powder in female pelvic tissue and ovarian cancer. Godleski and his wife of 50 years, Mary Lou Moss Godleski, run a house museum in Mineral Ridge, Ohio, called the Moss Ancestral Home.

'70s

When his local hospital's surgical team shrank, **Gregory Jones** (MD '79), medical director of Montgomery County Ambulance District (MCAD), realized major trauma cases in his rural Kentucky area might fare better at major hospitals in Lexington, 30 minutes away. He asked three such hospitals if MCAD could bring them there, and all three refused. To this, Jones replied, "Get ready, because we are coming." Come they did, and as a result, outcomes

improved drastically. The practice soon became standard of care.

Curious about how the district's STEMI patients (a type of heart attack that benefits from prompt catheterization), in particular, would benefit from a beeline to cath labs in Lexington, he then began a formal study—but never finished it because it was so stunningly beneficial, he says. Other counties quickly followed suit.

For these and many other initiatives, the Kentucky Ambulance Providers Association named Jones Medical Director of the Year in 2018.

'80s

Clydetta Powell (Pediatrics Resident '79, Child Neurology Fellow '82) has been appointed the designated federal officer for the National Clinical Care Commission, an advisory commission mandated by the U.S. Congress. Throughout the next three years, the commission, which consists of 23 members from academia, private practice, patient advocacy groups, and federal agencies, will evaluate federal programs in diabetes and deliver a report of their findings and recommendations to Congress and to the U.S. Secretary of Health and Human Services. At the U.S. Department of Health and Human Services, Powell directs the Division of Health Care Quality. Previously, she served as medical officer for infectious disease in the U.S. Agency for International Development.

After screening around the world, from London to New Delhi, and snagging several best documentary awards along the way, *Burden of Genius: Dr. Thomas Starzl's Journey into Organ Transplantation* came home to Pittsburgh for a debut at the Carnegie Science Center in April. Showings throughout the film's weeklong run featured guest speakers, including Starzl protégés **George Mazariegos** (Critical Care Medicine '92,



Velma Scantlebury (Fel '88), **Joy Starzl**, and film producer **Carl Kurlander** take a selfie at the Pittsburgh debut of *Burden of Genius* in April.

Transplant Surgery Fellow '93), chief of the pediatric transplant program at UPMC Children's Hospital of Pittsburgh; **Velma Scantlebury** (Transplant Surgery Fellow '88), associate director, Kidney Transplant Program, Christiana Care Hospital, and author of *Beyond Every Wall: Becoming the 1st Black Female Transplant Surgeon* (2018); and **Ngoc Thai** (MD '97, Transplant Surgery Fellow '04), who is director of the Center for Abdominal Transplantation and chair of surgery at Allegheny Health Network.

Kenneth Shestak (Plastic Surgery Resident '85) is chief of plastic surgery at UPMC Magee-Womens Hospital and a professor in Pitt's Department of Plastic Surgery. Shestak focuses his clinical work on cosmetic and reconstructive surgery of the breast and body. He's also a dedicated educator. Shestak remains connected to alumni as the executive director of the Futrell Society of Pitt Plastic Surgery Alumni. His textbook, *Reoperative Plastic Surgery of the Breast* (Lippincott Williams & Wilkins, 2006), tackles problems resulting from reconstructive and cosmetic surgeries.

'90s

As a Pitt Med student, **Thomas Lomis** (MD '92) studied under Bernard Fisher and the late Charles Watson. As medical director of the Valley Breast Care and Women's Health Center in Van Nuys, Calif., Lomis says he is grateful to have learned from the best. He researches targeted therapies for breast cancer as principal investigator of clinical trials conducted through Translational Research in Oncology (TRIO-US) at UCLA. Both the Every Woman Counts program and Valley Breast Cancer Foundation help his hospital staff provide free services, including mammograms, breast reconstruction, biopsies, and breast prostheses. "We treat



HON-DERMAS

Pitt dermatologist Alaina James and residents Jonathan Lee and Hasan Khosravi led six Pitt Med students on a UPMC Dermatology Brigade to Honduras in March. In a short week, they



packed in a lot—assessing and treating 520 patients, performing 18 surgical procedures, and presenting lectures to local med students. Financial support from the Medical Alumni Association and School of Medicine dean's office helped make the trip happen for the students, who included Maria Evankovich, Caroline Kettering, Carlos Morillo-Hernandez, Motunrayo Lydia Olawaiye, Pragosh Saini, and Sophia Zhang. "It was an enriching, humbling experience reminding us why we entered medicine," says Zhang. Brigade members are shown here with translators and other providers and patients.

more patients than anyone else in California," he says.

Margaret Larkins-Pettigrew (MD '94, Ob/Gyn Res '98) is the director and Edgar B. Jackson Jr., MD, Endowed Professor for the University Hospitals Health System in Cleveland.

She develops programs that increase health care access for Northeast Ohio's "high-potential individuals"—those facing economic or social barriers to care—and addresses how UH's employees "care both for one another and for patients." Her clinical practice focuses on enhancing quality of life for women living with HIV. Larkins-Pettigrew founded WONDOOR (Women and Neonates Diversity Outreach Opportunities and Research), a nonprofit that "works locally and globally to educate providers to become specialists for folks in low- to middle-resource communities." As an adjunct professor at UPMC Magee-Womens Hospital, she expands international practice opportunities for faculty and residents. Pittsburgh's Gateway Medical Society will honor her this October with their Lifetime Achievement Award.

'00s

As a pediatric dermatologist at Massachusetts General Hospital and faculty director of pediatric dermatology at Harvard, **Elena Hawryluk** (Cell Biology and Molecular Physiology PhD '07, MD '09) focuses on pediatric melanoma. What makes these cases unusual, she says, is that children haven't experienced the risk factors that come with age, namely sunburns. And because pediatric melanoma presents differently—as changes in birthmarks or pink, bleeding bumps—the cancer is difficult to diagnose. The Dermatology Foundation recently recognized Hawryluk with the Pediatric Dermatology Career Development Award for her research on atypical pediatric pigmented lesions.

—Rachel Mennies, Brian Salvato, and Elaine Vitone

SPOTLIGHT

MOALLI HAS DESIGNS FOR WOMEN

For a third of women, the badges of childbirth and long life come at an unexpected and embarrassing cost—pelvic organ prolapse. That's a condition where the bladder, uterus, or rectum bulge into the vagina, or even outside the body. More than 10 percent of American women find it bothersome enough to undergo surgical correction.

One version of the surgery involves inserting polymer mesh materials through an incision in the vagina to hoist the pelvic organs back into place; but in April, concerns about safety and efficacy led the Food and Drug Administration to stop the sale of mesh for this purpose.

Still, the clinical need remains, says Pamela Moalli (Res '98, Fel '00). She's an MD/PhD professor of obstetrics, gynecology, and reproductive sciences at Pitt and a pelvic reconstructive surgeon at UPMC Magee-Womens Hospital.

Together with Steven Abramowitch, PhD associate professor of bioengineering at Pitt, Moalli has spent the past decade working to create a better mesh. Recently, the pair secured a \$2.5 million National Institutes of Health grant for the continuation of this work.

The problem with currently available mesh materials, Moalli says, is that they weren't designed to be used in the vagina. They're repurposed from hernia surgery, and most are made of knitted polypropylene. The materials sometimes deform and wrinkle under the vertical strain of the pelvic organs, which might cause pain and erosion. Polypropylene is also quite stiff, which can cause the tissue to thin over time.

Moalli and Abramowitch created softer 3D-printed mesh, designed to hold its shape while also holding the pelvic organs up. They hope their new materials will make pelvic organ prolapse surgery safer and more effective for the hundreds of thousands of women who need it.

"Issues that negatively impact quality of life and are specific to women often do not get the attention that they deserve in research," Moalli says. "This is an opportunity to develop solutions for women that are designed based on an understanding of the uniqueness of female anatomy and biology." —Erin Hare



CAMI MESA

Moalli

CHARLES A. COLTMAN JR. NOV. 1, 1930–NOV. 28, 2018

Charles Coltman Jr. (MD '56) liked to close meetings with a quip: "Everyone opposed to adjourning, please remain seated," recalls biostatistician John Crowley of his former boss.

Coltman, who died in November 2018, enjoyed a prolific career as a physician and cancer researcher.

Well known for his precise, military bearing, garnered through a 20-year career in the U.S. Air Force, Coltman also possessed a softer, more humorous side.

Crowley, now chief of strategic alliances with the nonprofit Cancer Research and Biostatistics, worked under Coltman during his tenure as chair of SWOG (formerly the Southwest Oncology Group). Even today, Crowley's speech is littered with "Coltmanisms," like referring to the latest cancer-drug combo as "alphabetagooferdust" or "difungomuctane."

"He commanded respect just by his presence, but his leadership was much more than that," Crowley says. "He really knew the field and commanded respect with his knowledge."

Guiding SWOG from 1981 to 2005, Coltman championed randomized clinical trials, technological innovations, and the use of statistics. Coltman also cofounded the San Antonio Breast Cancer conference, today the premier international conference on breast cancer, and forged enduring relationships between American and Japanese cancer researchers. As a researcher, he inves-

tigated renal, gastrointestinal, and lung cancers, as well as therapies for lymphoma. He co-led the study that established the chemotherapy regimen known as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) as the standard of care for patients with advanced-stage, aggressive lymphoma.

"He made you want to do your best for him," Crowley says. —Adam Reger



Harrison

ANTHONY MILLER HARRISON

DEC. 6, 1938–JAN. 28, 2019

When Department of Surgery chair Timothy Billiar (Fel '90, Res '92) was a resident, he and his peers

called attending surgeon Anthony Harrison (Res '65) "the best intern on the service." Harrison, whose intern year was long behind him by then, earned the admiring nickname because, Billiar says, "He'd come in before the interns, who are supposed to be the first ones in the hospital, and he'd have already seen patients and written notes."

Harrison, who served as professor of surgery at the University of Pittsburgh beginning in 1992, died in January. Before joining the faculty, Harrison in 1970 helped found General Surgical Associates, which grew into one of the region's largest surgical practices.

His patient-centered approach included checking on patients multiple times a day and sharing his home phone number.

In an era of increasing specialization, Harrison's ability to handle just about any surgical procedure set him apart.

"In the same morning, he might operate on a pancreas, do a vascular surgery, and perform

a thyroidectomy," says Distinguished Professor of Surgery Andrew Peitzman (Res '84), who also trained under Harrison.

"If someone came in with an unusual condition, and you asked, 'Have you ever seen this before?' Tony's answer was always, 'Yes, I've done it multiple times,'" says Brian Zuckerbraun (Res '05), chief of the Division of General Surgery.

The department is working with Harrison's family to establish the Anthony M. Harrison Chair of Surgery in his memory. For information, contact Gary Dubin at gdubin@pmhsf.org or 412-647-9113. —AR



Hess

MICHAEL L. HESS

AUG. 10, 1942–APRIL 13, 2019

When Michael Hess (MD '68, Res '71) taught medical students about heart failure, he would throw the class a football and a beach ball. The props, says his longtime colleague Maureen Flattery, an NP, helped demonstrate the difference between a nondilated heart (football) and one that is diseased and dilated (beach ball). "His cardiac physiology lectures were famous."

Hess, a widely published authority on cardiovascular physiology and the medical management of cardiac transplantation, as well as the recipient of seven outstanding teacher awards from Virginia Commonwealth University (VCU), died in April.

In the mid '70s, heart transplant cases were considered strictly surgical; Hess saw a need for more comprehensive care. One Friday in the hospital, he introduced himself to pioneering heart-transplant surgeon Richard Lower. By the following Monday, Lower's post-op patients were in Hess's care.

Hess was named professor of medicine in cardiology in 1980 and went on to garner many more leadership roles at VCU: He led the heart failure transplant program, the Division of Cardiology, the Division of Cardiology's laboratories and research, and the advanced heart failure program. In 2013, Hess established the university's cardio-oncology program, which he directed until he retired in 2018.

In 1981, claiming he had "no one to talk to," Hess cofounded the International Society for Heart and Lung Transplantation, of which he served as the first president. ISHLT, which remains the world's leading society of transplant physicians and surgeons, operates the International Registry for Heart and Lung Transplantation. —Kristin Bundy

IN MEMORIAM

'40s

SIDNEY N. BUSIS
MD '45
MARCH 22, 2019

GEORGE J. DUSCKAS SR.
MD '45
MARCH 8, 2019

HAROLD E. GORDON
MD '49
MAY 19, 2019

'50s

ROBERT C. TARTER
MD '56, RES '60
MARCH 6, 2019

MORTON I. BERKOWITZ
MD '57
JAN. 1, 2019

DANIEL J. WOOTEN
RES '71
MAY 19, 2019

JOHN ROBERT HAYS
MD '58, RES '63
JAN. 30, 2019

'60s

LAWRENCE A. ROSEN
MD '61
MARCH 2, 2019

EDWARD J. ZIVIC
MD '62
DEC. 24, 2018

JAY L. JENKINS
RES '64, FEL '66
MAY 19, 2019

ROBERT M. HASSAN
MD '68
MARCH 27, 2019

HENRY B. WESSEL
MD '69
FEB. 24, 2019

'70s

JOHN SUTHERLAND
BEACHLER
MD '70, RES '75
MARCH 18, 2019

JAMES M. MCGREEVY
MD '73
JAN. 29, 2019

DOMINGO G. OTTONELLO
FEL '75
FEB. 28, 2019

'80s

MICHAEL GEORGE LICINA
MD '80
APRIL 24, 2019

WILLIAM H. GAMBLE
RES '81
APRIL 25, 2019

MARTIN P. ONTELL
PHD '81
JUNE 21, 2018

FACULTY

MARYANN A. DONOVAN
MARCH 3, 2019

CHARLES R. FITZ
FEB 22, 2019

TRANSFORMATION KEITH ON GENDER AFFIRMATIONS

BY KRISTIN BUNDY

One of the first plastic surgery cases in which Jonathan Keith (MD '06, Res '13) scrubbed in as a med student was a male-to-female vaginoplasty. "I'd never seen anything like it," he says. "It was transformative and powerful. And it all stemmed from, what I felt to be, the imagination and creativity of one man."

Training under J. William Futrell, former professor and chair of plastic surgery at Pitt, Keith became inspired to care for transgender patients. Futrell was the only surgeon performing gender-affirming surgeries in Pittsburgh at the time, and Keith saw that his practice improved people's outlook.

After the vaginoplasty, Keith says, "I saw how much the surgery affected the patient's life, and how she really changed."

The rates of suicide attempts are alarmingly high among transgender people—46 percent of trans men in this country and 41 percent of trans women, according to the American Foundation for Suicide Prevention. Keith wants clinicians to "open their eyes to the reality of the situation." People are dying because of how they feel in their own bodies.

In 2018, Keith became the first plastic surgeon in New Jersey to perform a female-to-male phalloplasty. But the road getting there was a rocky one. The taboo of gender-reassignment surgery was an ever-present barrier in Keith's training. It would take several twists of fate and chance encounters with people from Pitt, actually, that would get him to finally establish a transgender-centered practice.

The first obstacle was Futrell's retirement, which occurred while Keith was still in med school. "When the only person with the

expertise retires [from an institution], the progress just kind of goes away," he says.

Keith buried the idea of serving the trans community for years until later in his residency, when a fellowship led him to Ghent University Hospital in Belgium. There, Keith met Stan Monstrey—who had studied under Futrell decades earlier.

"Monstrey ran a highly productive and respected gender-affirming surgery program out of the hospital where I was learning microsurgery," says Keith. Monstrey was then, and still is, traveling the world, training others on gender-confirmation surgery.

This opportunity reinvigorated Keith's interest, he says. "The surgery was creative and dovetailed with the things that I like to do, which is very large, complex multidisciplinary surgery." Gender-affirming surgery requires a team of specialists from plastic surgery, urology, gynecology, and anesthesiology. Outside the operating room, internal medicine docs, psychologists, infectious disease experts, and other specialists get involved.

In 2014, the U.S. Department of Health and Human Services reclassified gender-affirming surgery, changing it from experimental to a proven therapy. Medicare started covering it, and Medicaid and private insurance companies followed suit.

That's when the pent-up demand became apparent, says Keith, who had already performed scores of feminizing or masculinizing "top surgeries" for trans patients. "Patients started talking to each other and funneling

very organically by word-of-mouth into my office," he says.

Despite the uptick in demand, three years passed before Keith was ready to perform "bottom surgery."

"Basically it took from 2015, when I first started seeing patients, until 2018 to have all the pieces [and players] in place . . . to design the surgery itself and to know that I was able to do it safely," says Keith. "That's when we started."

He performed his first phalloplasty in February 2018 and his first vaginoplasty in May of the same year. After taking months to monitor his patients for major post-op complications and seeing none, Keith felt comfortable continuing with the program. Beginning in November 2018, Keith had one gender-affirming surgery scheduled biweekly through spring 2019.

As assistant professor at Rutgers New Jersey Medical School and codirector of Rutgers Center for Transgender Health, Keith's guiding principle working with trans patients is respect. That, he says, means "really delving deep into what they want."

Keith recalls Futrell's bravery decades earlier, when reassignment surgery hovered on the fringe of plastic surgery.

In the spirit of Futrell's commitment to the trans community, Pittsburgh will once again become a hub for people wishing to transition. Pitt and UPMC are planning a transgender health care center in the Three Rivers region. ■

COURTESY UNIVERSITY HOSPITAL, NEWARK, N.J.



Jonathan Keith



YOUNG LOVE AND DISEASE

What has been the most surprising reaction to Rachael Lippincott's novel *Five Feet Apart*, about two teens with cystic fibrosis falling in love in between treatments? Outrage over the lobster.

There's no way they would have lobster in the hospital! Lippincott recalls the mom of a cystic fibrosis patient telling her, joking about a cafeteria meal her characters eat. Lippincott says with a laugh, "I was like, *Yeah, that's totally fair!*"

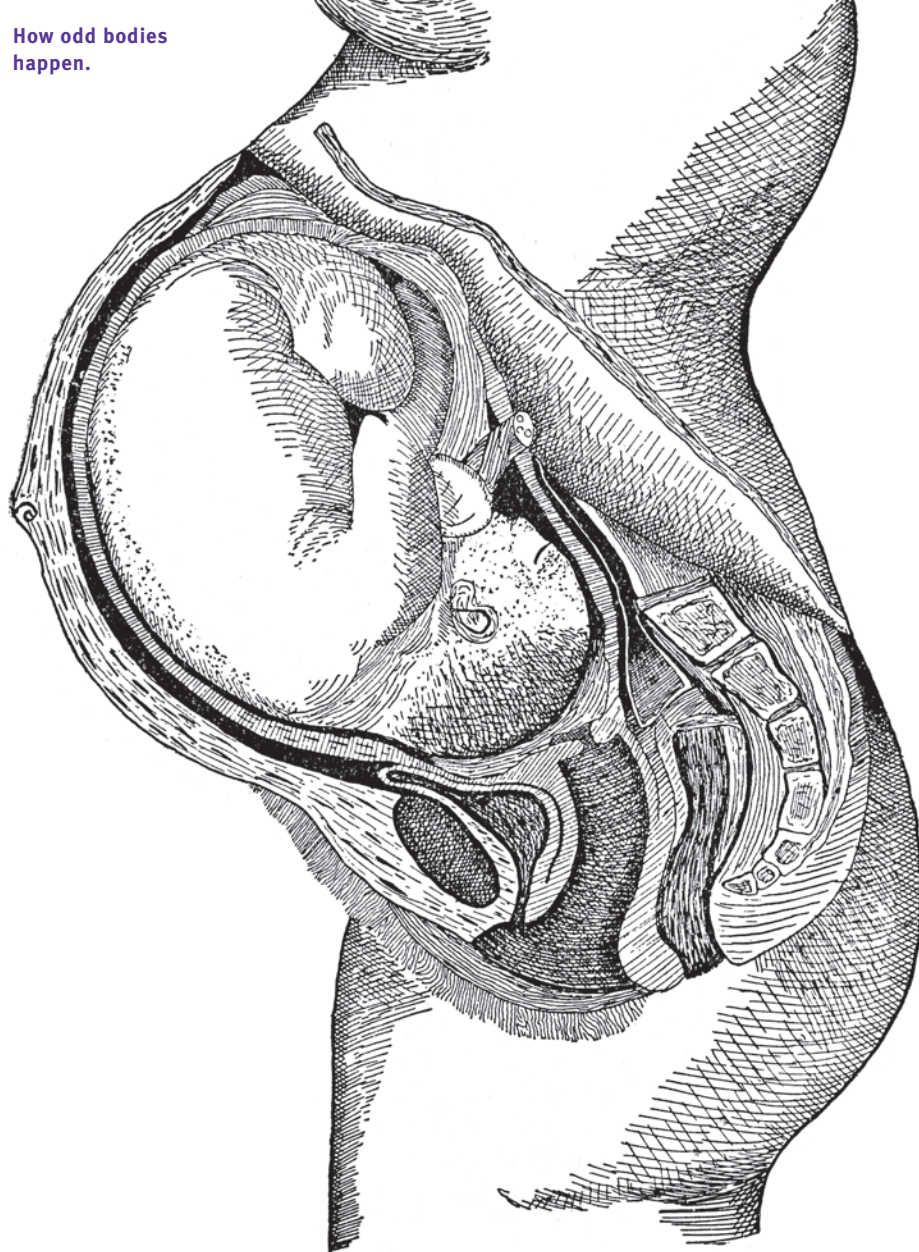
Despite the lobster, Lippincott, age 24, was conscious of accurately portraying the experiences of patients and families living with cystic fibrosis, a lifelong disease that clogs up lungs and other organs with mucus.

Lippincott wrote the book after her mentor at Pitt, young adult author Siobhan Vivian, told her that Simon and Schuster was looking to adapt the screenplay of *Five Feet Apart* into a novel. Fresh out of studying writing as an undergrad at Pitt (Lippincott graduated in '17), she submitted a draft to the publisher—and landed the gig. As of this writing, *Five Feet Apart* has been on *The New York Times* Bestseller List for more than 20 weeks.

The movie came out this March. (That included a scene with an eight-lobster feast; Lippincott's lobster was more subdued, a pasta dish.) Justin Baldoni, the director, collaborated on the screenplay with Claire Wineland, a vlogger and patient activist who died recently at 21. Then "I watched a bunch of Claire's videos," Lippincott says. That's one way Lippincott learned about the physical, mental, and emotional impact of the disease. She also scoured the Cystic Fibrosis Foundation site, scrolled through countless CF Reddit forums, and watched other CF vloggers describe drug trials, hospital stays, and daily routines.

Lippincott says speaking with patients and families has been the best part of writing the novel. "Places where they saw themselves in the book have been incredible," Lippincott says. "Honestly, their opinion matters most of all." —Prachi Patel

How odd bodies happen.



GETTY IMAGES/SCANNED 1892 ENGRAVING

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Unless otherwise noted, for information:
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FOR REAL! TWEEN SCIENCE

We take it for granted that human bodies are mostly the same. But two recent news stories show that we don't always develop in expected ways. In Bangladesh, a woman had a baby; then, 26 days later, she had twins. Turns out, she had two uteruses! And in Portland, Ore., another woman had all her organs backwards, on the opposite side of her body than where they'd be typically.

"We have a genetic blueprint for how we form, left to right, front to back, with everything in the right place," says Michael Tsang. He is a University of Pittsburgh biologist who researches how bodies develop. "All our dimensions are specified very early on in the embryo," when we are tiny specks in our mothers' wombs.

Usually, a uterus is formed from two tubes that fuse together. But the Bangladeshi woman had a rare hiccup in her DNA (a mutation), so the fusion didn't happen. That caused the two uteruses.

And usually, our heart fits into a cavity on the left side of the chest. Our other organs pack into our bodies in their particular spots, too. The woman from Oregon had a one-in-a-million condition where left-right patterning is completely reversed.

Luckily, "the complete reversal meant her organs still had space to form and function properly," says Tsang. So perfectly properly, in fact, that her condition wasn't discovered until medical students examined her body after she died at the age of 99! —Lela Nargi

Is there a topic you'd like us to explore? Drop us a line at medmag@pitt.edu.



UNIVERSITY OF PITTSBURGH ATHLETICS

YOU CROSSED THE GOAL LINE TOGETHER YEARS AGO.

Let the end zone celebration pick up where it left off at **Medical Alumni Association Weekend, Sept. 20-21**. Huddle up for a tour of the Steelers and Panthers' training facilities, class dinners, welcome back reception, documentary screenings, lunch with student innovators, and a student-led tour of Scaife Hall. While at the training facilities, you'll meet with Pitt Med faculty who take care of standouts from the Steelers, Penguins, Panthers, and Pittsburgh Ballet.

Reunion Classes:

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