

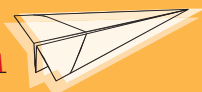
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2015

# PITTMED

“YOU DON’T  
UNDERSTAND!”

A DOC TUNES IN TO TEENS





## RUSHING

Nice piece about “The Rush to the Hospital” (Winter 2015). I have a few stories about transporting infants to the NICU at Magee from 1973–75. Your article caused me to remember the paddy wagon. I was an intern in the NICU, and we received a call from Allegheny General Hospital that they had a baby who needed phototherapy for hyperbilirubinemia. None of the Freedom House ambulances were available; so we called the police, and they showed up with an old paddy wagon with a clanging bell instead of a siren. Because the baby wasn’t really ill, and we had our own isolette and support equipment, we decided to go with them. These old cops were enthralled with the baby and wanted us to get him safely back to Magee. When we were stuck in traffic unresponsive to the clanging bell, the cop riding shotgun got out and walked ahead shouting at the drivers to “get the hell out of the way” for the baby. It was so endearing.

One more story—about a trip to Punxsutawney, Pa., to pick up another baby for phototherapy, this time with Freedom House. It was snowing, and it was a long, slow drive. When we got there, the nurses at this tiny old hospital were so glad to see us, and they made us a nice dinner. We put the baby in the isolette, and we started back. When we stopped for gas, I got out to use the restroom. When I came out, the ambulance was gone and moving down the street! I ran after it in the slush and caught up at a traffic light where I pounded on the door. They were surprised.

Thought you would be amused by these events of 40 years ago.

Lucian K. DeNicola (Res ’75)  
University of Florida—Jacksonville

## AAMC-ABLE

Just a brief note to tell you that I really enjoy reading *Pitt Med*. Your magazine stands out because of the quality of the information presented, the impressive layout, and its focus on all of the school’s missions.

As an emergency physician, it’s been



In our Winter 2015 “The Rush to the Hospital” infographic, we showed how Pitt docs paved the way for prehospital care. Illustration by Stacy Innerst.

clear to me that the University of Pittsburgh has always been a leader in prehospital care and resuscitation; thus the recent article talking about those early days (“The Rush to the Hospital”) was appreciated. And I still fondly recall meeting Peter Safar as a brand-new faculty member. I also enjoyed reading the article “The Most Kissed Face of All Time,” a story I had never heard before.

John E. Prescott  
Chief Academic Officer  
Association of American Medical Colleges

*Before his appointment with the AAMC, Prescott was dean of the West Virginia University School of Medicine and founding chair of its Department of Emergency Medicine.*

## TWO THUMBS UP

I had to stop midway through this issue (Winter 2015) and write a note. Best issue I’ve seen in a long time.

I graduated in 1979, and Peter Safar was my mentor all through college and med school. He personally taught our class CPR, demanding that we practice it to perfection: “Our patients will demand no less.” Just an incredible human being. I miss him.

Also, Ronald David was a fellow when I did my NICU rotation at Magee in 1978. He told us about two-thumb CPR in infants and, if I remember correctly, published something in *Pediatrics* about it.

Again, an incredible issue. Thanks.

John W. Blenko (MD ’79, Res ’82, Fel ’83)  
University of Maryland

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We gladly receive letters (which we may edit for length, style, and clarity).

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## RECENT HONORS

Pennsylvania Women’s Press  
Association Excellence in  
Journalism Award  
First Place, Health/Science Story  
(E. Vitone, “Don’t Spare the Horses”)

## EDITOR’S NOTE

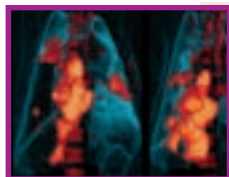
In February, this magazine lost a dear friend and former contributor, Edwin Kiester Jr., who died in Essex, Mass., at the age of 87. Ed, a Pitt alum, wrote 2,000-some articles (for magazines like *Parade*, *The Atlantic*, *Science*, *The Smithsonian*, *Reader’s Digest*, and *Pitt Med*) and 24 books (including, with his wife, Sally, *Better Homes and Gardens’ New Baby Book*, which sold more than 4 million copies); he was an honorary inductee of the Sigma Xi Scientific Research Society. Ed’s interviewees included Chiang Kai-shek and William Shatner. He parachuted into Vietnam as a journalist, sat in a trench on Pork Chop Hill in Korea, and served in World War II in occupied Germany, where he ran the Armed Forces Radio Network in Frankfurt when he was 19. He lived all over the world and had a nose for a story. This magazine and this editor are better for having crossed his path. —Erica Lloyd



# PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SPRING 2015

VOL. 17, ISSUE 2



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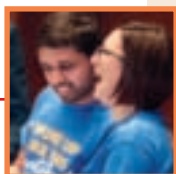
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In 2012, **HEATHER BOERNER** ["The Case for Candida"] met an HIV-discordant couple (he was positive, she was negative) who had elected to have a baby together the new-fashioned way, with help from HIV medication taken as PrEP, or pre-exposure prophylaxis. Mother and child were happy, healthy, and HIV-negative years later—an increasingly common triumph of biomedicine. Boerner learned: "I said, 'This is not the HIV I grew up with!'" For her e-book published last year, *Positively Negative: Love, Pregnancy, and Science's Surprising Victory Over HIV*, Boerner followed two couples through this journey that would've been unimaginable not long ago. Boerner is now working on expanding the book. An excerpt was recently published in *The Atlantic*.

**MICHELLE LEVEILLE** ["The Ecology Within"] created the gutsy landscapes in this issue. Don't let the fantastical fool you, though—she also sketches hyperrealistic illustrations for the Los Angeles Zoo, among other biologically inspired visual works. In college, Leveille thought she'd be an exotic bird veterinarian, but a bout with meningitis and a visit to the gross anatomy lab steered her toward the visual arts. (Birds still come to her though: She has a king vulture, Gus, and a talkative African grey parrot, Grayson.) At one point, she advertised herself online as an "anatomical illustrator"—"Boy did that backfire!" she says. We'll leave it to your imagination what kinds of photos she received.

## COVER

Through rigorous studies, Elizabeth Miller has found ways to get teens to open up about thorny issues. She's become an übergodmother for the youth of Pittsburgh and beyond. (Cover: Ghislain & Marie David de Lossy, Corbis © 2015.)



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Pitt scientists tackle the human microbiome, trillions of bitty bugs that outnumber our own cells tenfold. This teeming mass of micro-organisms seems to hold the power to tame our immune systems.

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BY ROBYN K. COGGINS

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W

hen I look up in the universe, I know I'm small, but I'm also big. I'm big because I'm connected to the universe, and the universe is connected to me.

—Neil deGrasse Tyson

*Quelle chance!* We are not biologically autonomous: The company we keep includes 10,000 (and counting) species of microbes that inhabit our bodies. We have many more bugs in us, and on us, than we do our own cells. For the most part, the microorganisms that inhabit us are not pathogens; many are active contributors in the story of our physiology—as we are to theirs. (Don't miss this issue's "The Ecology Within" to find out what Pitt people are learning about this "microbiome.")

We walk around with 8 million microbial genes—more than 360 times as many as our "own" genes. Scientists refer to the DNA that makes up our microbiome as our "second genome." Its influence on our health rivals, and may even surpass, that of the DNA we inherited from our parents. (That first, inherited genome, our human genome, it should be noted, was cowritten by a committee of microbes—and likely continues to be. A great deal of our nuclear DNA comes from viruses, including oncogenes that drive cancer. Further, all of our mitochondrial DNA stems from a bacterium that was probably engulfed, long, long ago, by an archeal cell.) These organisms get into us, become a part of our biology, and then, may, as they leave us, take a piece of our biology with them. It's not unlike the relationship between pollinating insects and flowering plants; as a bee flies from flower to flower, it both collects and deposits pollen with each visit.

Humans play unwitting host to other company, as well. Motherhood is a peak time for cellular and molecular travelers. In pregnancy, cells pass through the placenta from the mother to the fetus and vice versa. In her first trimester, one of every 50,000 of the cells in her body is her child's. More plentiful are fragments of the fetus's genome floating in a mother's bloodstream; those fragments account for 6 percent of the total DNA in her plasma. (New noninvasive prenatal testing developed here at Pitt by David Peters and Aleksandar Rajkovic can detect certain fetal chromosome anomalies in a mother's blood.)

The number of fetal cells in a mother's blood climbs throughout pregnancy, then plummets after birth; but some stay for good, often founding colonies in organs throughout the mother's body. Animal studies have borne evidence that these cells, some of which are stem cells, can probably heal her skin, repair injuries in her heart, and even cross the blood-brain barrier to seed new neurons. Tissue from autopsies of women decades after they gave birth suggest that fetal cells may protect them from Alzheimer's disease and breast cancer.

One needn't become pregnant to benefit (or suffer) from microchimerism, this possession of cells that are both like us and "other." We carry cells from our mothers and, if we have them, likely from twins and older siblings. Nothing in nature is truly independent: As one pundit observed, "Things exist only insofar as they can be related to other things."

Fellow travelers, we are, at once, unique and derivative. There is a lesson here, writ large, for culture, the body politic, and all who inhabit our globe.



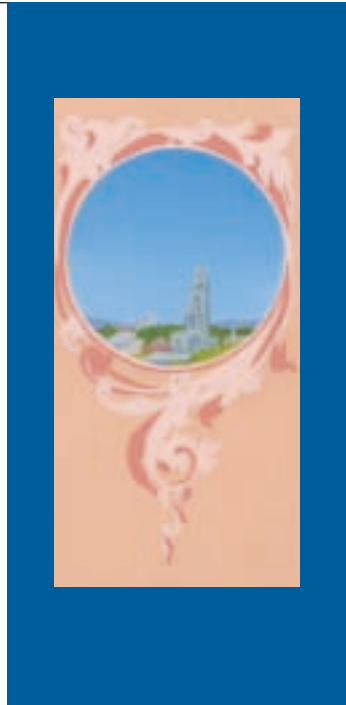
JOSHUA FRANZOS

Arthur S. Levine, MD

Senior Vice Chancellor for the Health Sciences

John and Gertrude Petersen Dean, School of Medicine





*Devoted to noteworthy happenings  
at the medical school*

## Tops for Clinical Trials

The Clinical Research Forum is making some changes to its annual Top 10 Clinical Research Achievement Awards. In the past, the organization has lauded individual researchers who led major projects that the CRF deemed innovative and probably significant to the understanding of diseases. But everyone knows research takes enormous team efforts. In appreciation of that fact, the CRF is doing things a little differently this year. “We’re really trying to make this about the science being the winner,” says Jean Bolte, project leader at the CRF. Noted.

Still, Pitt med’s hat trick on the CRF’s 2015 list is no small feat, so we’ll give our study leaders a shout out: A team under Alejandro Hoberman showed how prophylactic antibiotics prevent urinary tract infection recurrences in children with vesicoureteral reflux. Hoberman is an MD, and, among other titles, the Jack L. Paradise Professor in Pediatric Research as well as division chief of general academic pediatrics. Patrick Strollo (an MD professor of medicine and of clinical and translational science as well as director of the UPMC Sleep Medicine Center) led a multicenter study that demonstrated reductions in sleep apnea using a novel upper airway stimulation device. And Derek Angus (an MD/MPH Distinguished Professor and the Mitchell P. Fink Professor and chair of critical care medicine) with Donald M. Yealy (MD professor and chair of emergency medicine) and colleagues generated a lot of buzz when they evaluated the accepted sepsis treatment protocol in a multicenter trial.

—Micaela Corn

## FOOTNOTE

In January, the 400,000-physician-strong social network, Doximity, released its list of peer-nominated top residency institutions in the country. UPMC’s program sits at number 8 overall, just above Stanford’s and the University of Washington’s. For freshly minted MDs deciding on a training program, this can be real game-changing information. Doximity also ranked 20 residencies by specialty; UPMC’s ob/gyn residency ranked third, and otolaryngology was rated fourth.



TIM GROEN

## CARDIOVASCULAR DISEASE UNLOCKED

Just eight weeks into human gestation, a baby’s tiny heart is formed and functioning; but by birth, around one in every 100 tickers will have a structural defect. Pitt’s Cecilia Lo, armed with a multimillion dollar Bench to Bassinet grant from the National Heart, Lung, and Blood Institute, is figuring out why.

Lo, the F. Sargent Cheever Professor and chair of Pitt’s Department of Developmental Biology, and colleagues modeled the genetic basis of heart disease in 100,000 randomly mutated mice screened for cardiac irregularities using fetal echocardiograms. The team used high-throughput sequencing to identify the disease-causing mutations in mice with congenital heart defects.

“Our approach made no assumptions as to what genes are important,” says Lo, a PhD. The researchers identified nearly 100 genes causing congenital heart defects, with the unexpected finding of many genes related to cilia (hair-like organelles extending from cells), suggesting cilia play a central role in congenital heart disease.

The team was also surprised to learn that some of the mice had developed hypoplastic left heart syndrome, a rare defect of the left ventricle. “It had previously been thought you couldn’t model [the syndrome in mice], but apparently it takes multiple mutations to develop,” says Lo. The study’s results were published in *Nature* in March. —Nick Keppler



ROBIN ROMBACH / PITTSBURGH POST-GAZETTE

## Overheard Students Get Leadership Advice

In the fall, the student chapter of the American Medical Association at Pitt invited former Secretary of the Treasury **Paul O'Neill** to offer some leadership insights. He spoke to more than 100 Pitt med students about their role as stewards in the quest to make health care a safer industry. When O'Neill was CEO of Alcoa, he drastically changed the company's culture of safety. During his 13 years there, injuries were reduced to near zero. As cofounder of the Pittsburgh Regional Health Initiative in 1997, he sought to use the Alcoa safety ideas to eliminate harm to patients and caregivers. In the first 18 months of the initiative, central line infections were reduced by 67 percent. Today he works independently with hospitals to help them get people out of harm's way. Second-year Pitt med student Akash Goyal, who helped organize the AMA talk, notes, "Hearing [O'Neill's] stories of what it truly means to be a leader in today's environment was especially crucial as we begin our journey into the health care field. His words certainly inspired me to be more aware, respectful, and proactive as a future physician, and I know that they had a similar impact on others, as well." We took the occasion to gain his insights, too.

### What challenges are facing medical workers today?

As measured by injuries to workers, health and medical care is the most dangerous industry in the United States by a lot. By a whole lot. Think about it—it's really remarkable, when you think about people doing construction up on towers and buildings and [working] in foundries and factories. ... How could health/medical care be the most dangerous industry in the country?

### How can health care leaders address worker injuries?

It starts with asking yourself really fundamental questions like, *What do you believe is the central tendency of human beings?* It's a framework for how to think. At one end of the spectrum ... is a belief that people are fundamentally trustworthy and value based. And on the other end of that spectrum is, *People are ne'er-do-wells, and you can't rely on them.* And the reason it's an important question is because it defines how an individual will try to lead them.

**What would you say to inspire leaders to do better?** Ask yourself every day: *Are you part of an organization that aspires to be the best in the world at everything that you do?* And if not, what things can you do to cause that to happen? —Interview by Robyn K. Coggins

## Next Generation

**B**esides being on their way to the impressive MD/PhD combo, Medical Scientist Training Program students at the University

of Pittsburgh are on a funding roll. Four of the trainees have recently been awarded \$48,000 each in the (get ready, it's a mouthful) Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral MD/PhD and Other Dual Doctoral Degree Fellows, sponsored by the National Institutes of Health.

**Taylor Eddens** received the award for his research on pneumonia caused by a fungus called *Pneumocystis*. Eddens is in his second PhD year; his project aims to characterize *Pneumocystis* antigens and develop potential vaccines to target them, especially in patients with compromised immune systems. Eddens published two papers on his work in 2014; his thesis advisor is Jay Kolls, MD professor of pediatrics.

**Matt Hedberg** also received the Kirschstein grant. Now in his third graduate year, he studies mitogenic drivers in head and neck cancer. With his mentor, Jennifer Grandis (MD '87, Res '93), who was a Pitt Distinguished Professor of Otolaryngology and Pharmacology and is now at UCSF, he coauthored a book chapter for *The Molecular Basis of Cancer*.

**Elizabeth Oczypok**, a third-year pathology trainee focusing on pulmonary disease, received a National Institute of Environmental Health Sciences grant. She and her mentor, professor of pathology Tim Oury, an MD/PhD, will study the activation of inflammatory immune responses in asthma.

It's perhaps not surprising that local musician and second-year trainee **Josh Sturm** is interested in tinnitus. He received a grant from the National Institute on Deafness and Other Communication Disorders to study the organization of midbrain neuronal connections that may contribute to the condition. His mentor and director of the auditory research group, Karl Kandler, a PhD, is a professor of otolaryngology and of neurobiology.

In other MD/PhD award news, **Brian Rosborough**, a newly anointed PhD, won the 2014 Dr. S. Sutton Hamilton MSTP Scholar Award for "meritorious contributions to the scientific literature while completing graduate studies." The immunologist is wrapping up his MD this year. —RKC



## GET ON UP

Maybe sitting isn't pretty. A new study backed by a \$3 million grant from the National Institutes of Health will examine whether simply sitting less—rather than exercising more—can help lower people's risk of developing type 2 diabetes and heart disease.

Elizabeth Venditti, a PhD assistant professor of psychiatry who holds a joint appointment in epidemiology at the Graduate School of Public Health, joins principal investigator Andrea Kriska, a PhD in epidemiology, and colleagues to track more than 300 adults age 50 and older who are likely to develop type 2 diabetes or metabolic syndrome. Subjects will attend 22 sessions about healthy living; wear pedometers; and have their weight, blood glucose, cholesterol, and activity levels objectively monitored to determine whether they are reducing their total sitting time and losing or maintaining weight.

"There are hundreds of decisions we can make that will impact how much we move," Venditti says. "We're trying to get people to keep better track of the chunks of time they spend sitting and come up with ways to interrupt it."

—Cheryl Alkon



CATHERINE LAURE

## Ready or Clot

The brain can be an unforgiving organ. Lodged in the right place, a clot half the size of a Tic Tac is enough to cut off blood supply and bring the whole system crashing down. This is what happens during an ischemic stroke, something 130,000 Americans die from every year.

Thankfully, a new clot-retrieval procedure is gaining traction within the medical community. It's called endovascular treatment (ET).

During ET, surgeons insert a thin tube into the patient's artery by way of the groin. Once inside, X-ray-guided imaging allows the doctors to maneuver the device through the body and into the brain, where it can open blocked vessels and retrieve the offending clot.

But the proof is in the patients. A study involving 316 cases reported in a March *New England Journal of Medicine* article showed ET increases positive outcomes for patients from 30 to 55 percent compared to standard treatment.

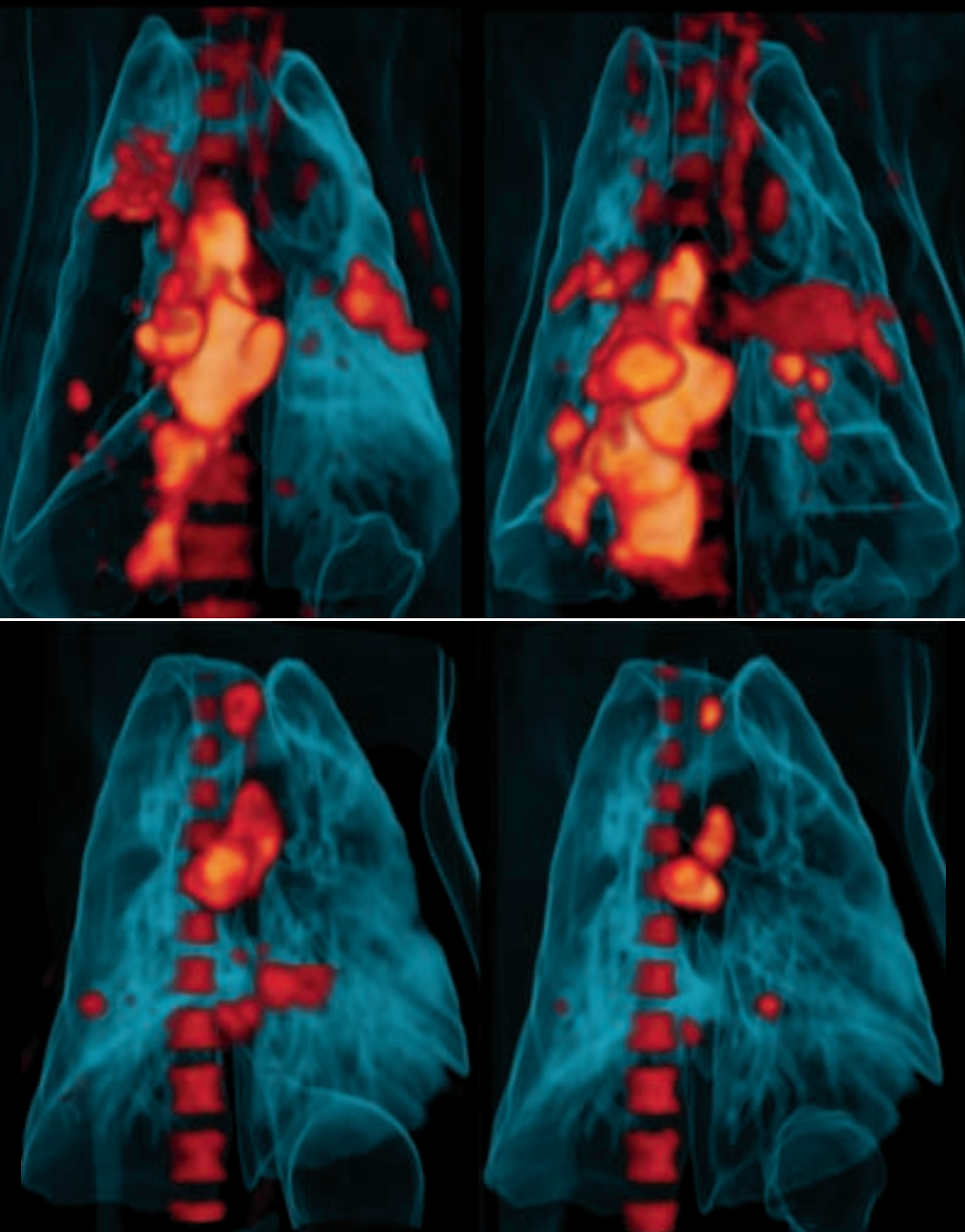
"The treatment effects are astonishing," says Tudor Jovin, an MD and director of the UPMC Stroke Institute, associate professor of neurology and neurosurgery, and leader of the University of Pittsburgh arm of the study.

As far as Jovin is concerned, ET is already the new standard of care. Or as he puts it, "You're more likely to survive if you get this procedure." —Jason Bittel

## FOOTNOTE

From multiple-award-winning documentary film to TV pilot: In *Code Black*, Ryan McGarry (MD '09) depicted the hectic and overcrowded rooms of LA County Hospital's emergency department, where he did a clerkship, and CBS has taken notice. A fictionalized series announced in January pits the ideals of doctors against systemic inequalities in the busiest ED in the nation. *Fifty Shades of Grey* actress Marcia Gay Harden is set to star, with McGarry executive-producing alongside David Semel, of *House MD* and *Heroes* fame.





COURTESY: M. TERESA COLEMAN

## RESEARCHERS' PET CT

Current treatments for multidrug-resistant tuberculosis are imprecise and lengthy—chemotherapies drag on for up to two years, and long-term side effects of the drugs are brutal. Pitt's JoAnne Flynn, a PhD, with colleagues here and at the National Institutes of Health, has taken several leaps forward on the path to treating this pernicious form of TB.

The group's study, published in *Science Translational Medicine* last December, reported several important conclusions. First, that mouse models are not adequate for evaluating TB drug efficacy—antibiotics like linezolid and AZD5847 don't work in mice, but did in Flynn's study of 20 cynomolgus macaques. The nonhuman primates were divided into untreated, linezolid, and AZD5847 groups; 87 percent of subjects in the treatment groups improved.

In addition, combined PET/CT scans during and after treatment of the macaques showed that they developed responses similar to those of humans—with lungs healing and flaring unpredictably and simultaneously, roughly correlating with bacterial burdens.

Previously, researchers could only study TB-addled tissue postmortem; with PET/CT scans, they can track development of the illness almost in real time. Here, we show PET/CT scans of macaque lungs before (left) and after two months (right). The red/yellow flares show lesions decreasing in the linezolid treatment group and increasing in the control (top row).

"I don't think we appreciated [lesion heterogeneity] until we had the ability to scan monkeys over and over again and say, 'This part's getting better; this part's getting worse' and were able to map that back to bacterial differences," says Flynn, a professor of microbiology and molecular genetics as well as immunology.

Parallel to this study, a phase 2 human trial in which linezolid was added to a failing drug regimen confirmed her team's results. —RKC

## Name Dropping

The first speaker of this year's Laureate Lecture series will be neurobiologist **Leslie Vosshall**, a PhD. On May 12—just in time for mosquito season—Vosshall will discuss the genetic basis of mosquitos' attraction to humans, focusing on the malaria- and chikungunya-infected pests in the tropics.

Her lab at Rockefeller University has been scientifically evaluating folkloric explanations behind our allure, including whether gender, age, or race contribute to a bug's swooning (answer: nope). She's found the basic mosquito equation of attraction: heat plus body odor plus exhaled carbon dioxide probably equals alive and human, AKA tasty. Her lab has shown mosquitos are choosy too, probably because of something in the blood that affects an individual human's scent. Knowing how mosquitos hunt, what their rules are, and how people can intervene could help everyone from picnickers to the 97 countries and territories in malaria's grip.

Vosshall is a Howard Hughes Medical Institute investigator, as well as the Robin Chemers Neustein Professor.

The other Laureate lecturers this year include...

**Joseph Schlessinger**, whose June 16 lecture was rescheduled from last year's series. He will present on receptor tyrosine kinases—transmembrane signals that affect cell growth and differentiation—and their role in cancers. Schlessinger, a PhD and National Academy of Sciences member, is the William H. Prusoff Professor and chair of pharmacology at Yale University.

German Cancer Research Center professor emeritus **Harald zur Hausen**, an MD, comes to Pitt on Sept. 22. His work helped establish the role of human papillomavirus in cervical cancer, for which he shared the Nobel Prize in Physiology or Medicine in 2008. The virologist's lecture will discuss dairy cattle as a source of infectious disease in humans.

Rounding out the series, **Jennifer Doudna**, PhD professor of chemistry and of molecular and cell biology at the University of California, Berkeley, will speak at Pitt on Oct. 14. The Howard Hughes Medical Institute investigator's lecture will focus on the biology of DNA loci called CRISPRs, short for "clustered regularly interspaced short palindromic repeats." Doudna is known for crystallizing and determining the structure of ribozymes and other RNAs. —RKC





DARRELL SAPP © PITTSBURGH POST-GAZETTE, REPRINTED WITH PERMISSION

## BULLETS BENEATH YOUR FEET

You wouldn't know it to stand there, but blood flows beneath the streets of Oakland. Human blood. And lots of it.

After three years of renovation and construction, in the fall of 2013, UPMC opened its nine-story Clinical Labs Building at the corner of Fifth Avenue and McKee Place. You might have noticed this if you happened to be in Oakland recently; what you probably didn't notice is the building's extensive subterranean pneumatic tube system. This pathology underground allows for patient samples—blood, urine, tissue, and more—to be whisked away for testing. Around 5,000 canisters zip beneath the streets each weekday, some 33,000 per week. Each canister, or “bullet,” is about six inches long and full of padding, the better to protect the samples within.

“[The bullet] looks exactly like what you'd see in a bank,” says Stacey Armstrong, vice president of operations at UPMC Passavant and service line owner for UPMC Presbyterian.

All of the network's 118 deposit stations are electronic. So when a nurse at Magee-Womens Hospital of UPMC draws blood for a prenatal workup, he need only type in the desired destination's station number and send the canister on its way. The bullet then snakes to the lab for testing at 20 feet

per second—far faster than a human courier could hope to travel.

Armstrong explains that each facility actually already had its own internal pneumatic tube system. But after adding 20,000 feet of tubing (there are about 8 miles' worth in all) and connecting all of UPMC's facilities across Oakland, efficiency is through the roof.

“From a patient care perspective,” says Armstrong, “you're going to have your nurses spending more time with their patients as opposed to hunting down couriers or worrying about keeping track of lab specimens.”

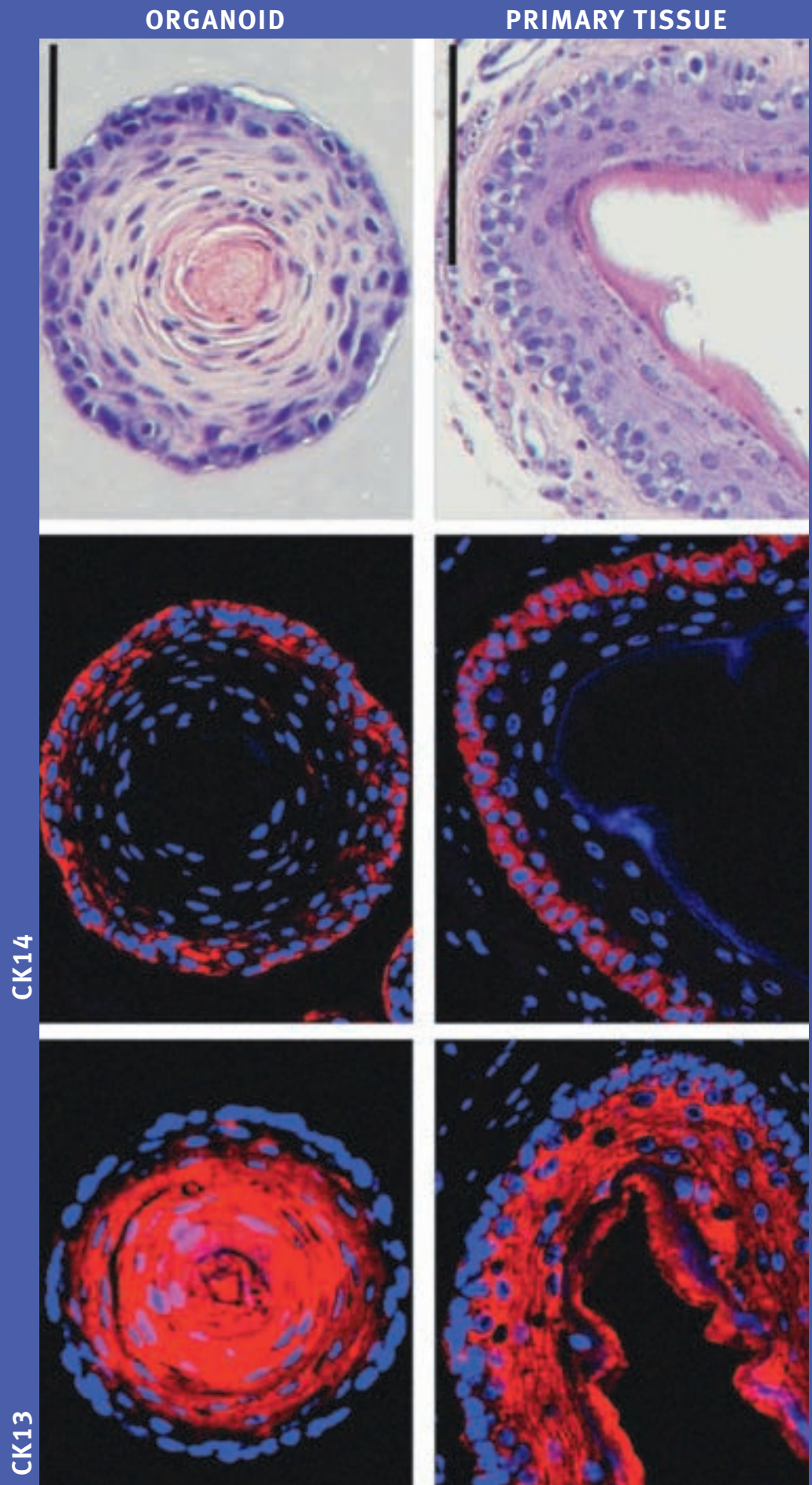
“It's a great development,” says George Michalopoulos, MD/PhD chair of pathology and Maud L. Menten Professor of Experimental Pathology at the University of Pittsburgh. “You cannot put all the potential expertise in every hospital—there aren't enough pathologists in the country to do that,” he says. “Having a centralized laboratory allows for the complicated samples to be concentrated where the experts are.”

So try not to wince the next time you sit down for a blood draw—a small part of you may be about to go on a grand adventure. —Jason Bittel

Take a ride in the tubes: [bit.ly/bbyfjBpm](http://bit.ly/bbyfjBpm)



*Explorations and revelations taking place in the medical school*



CELLULAR SURPRISE: Eric Lagasse has discovered stem cells in an unexpected location, the esophagus. These images compare esophageal tissue from mice to an “organoid,” a piece of esophageal tissue grown from the stem cells of a mouse sample. In the middle and lower rows, the red staining shows the presence of stem and progenitor cells (CK14, cytokeratin 14) and differentiated cells (CK13, cytokeratin 13), respectively. The nuclei of the cells are stained blue.



# DIGGING FOR CELLS

TURNS OUT, THE ESOPHAGUS HAS  
STEM CELLS | BY DANA YATES

Researchers once thought the esophagus was devoid of tissue-derived stem cells, the undifferentiated cells that can renew themselves indefinitely and generate highly specialized cell types. That's because stem cells from elsewhere in the body typically remain at rest until activated by injury or disease; yet all the cells in the lining of the muscular esophagus are in an active state.

The University of Pittsburgh's Eric Lagasse found it hard to believe that the esophagus lacked stem cells. "If the intestine had them [which it does], it made sense that the esophagus would, too," he says.

His research team grew pieces of esophageal tissue from mouse samples, and then conducted experiments to identify and monitor the different cells in the deepest layer of the tissue. As it turns out, the lining of the esophagus does indeed have its own stem cells; they just divide rather slowly. Lagasse, a PharmD and PhD, is an associate professor of pathology and of clinical and translational science. He also directs the Cancer Stem Cell Center at the McGowan Institute for Regenerative Medicine. He coauthored a paper on these findings with postdoctoral researcher Aaron DeWard, a PhD, and Julie Cramer (PhD '14); it was published online last year in *Cell Reports*. Financial support for the studies came from the National Institutes of Health and the Commonwealth of Pennsylvania.

The knowledge of this new source of stem cells could have applications in regenerative medicine.

One appealing thought is to use such cells to grow new esophagi for people afflicted

with esophageal cancer.

These cells might also be a source of cancer. Esophageal cancer is an especially virulent disease. It's often diagnosed at an advanced stage when it's challenging to treat and has a low survival rate. According to the American Cancer Society, approximately 15,600 people will die from the cancer in the United States this year.

The disease is associated with Barrett's esophagus, a precancerous condition in which the lining of the esophagus changes to resemble that of the small intestine. The exact cause

of Barrett's esophagus is unknown; it may be brought on by the damaging acids associated with gastroesophageal reflux disease. Lagasse and his collaborators will use their findings to investigate the cellular process behind Barrett's esophagus.


"We hypothesize that the stem cells may cause cancer by being reprogrammed to become gut cells, and then mutations happen," he says. "If we can demonstrate how the mechanism works, then hopefully we can stop the mechanism from developing into full-blown cancer." ■

## EYE (AND) TEETH

Other stem cell work at Pitt may one day restore vision to millions. Corneal blindness, often caused by injury or infection, can be treated with transplants of donor corneas. But transplant rejection and a worldwide shortage of donor corneas make using a patient's own stem cells an appealing option to explore. James Funderburgh, PhD professor of ophthalmology and of cell biology and associate director of the Louis J. Fox Center for Vision Restoration of UPMC and Pitt, was senior investigator on two recent intriguing studies:

One showed stem cells from human wisdom teeth can be turned into cells of a mouse's cornea. (Other researchers have been able to grow bone, cartilage, and neural tissue from these cells.) This was reported online in February in *Stem Cells Translational Medicine*; the lead author was Fatima Syed-Picard, a PhD, also of the Department of Ophthalmology.

In another study, the team found corneal scarring in mice can be repaired by growing stem cells from tissue extracted from the eye of a human cadaver (specifically the transparent connective tissue known as the corneal stroma) and then placing those cells on the injury site. *Science Translational Medicine* published these findings in December. The lead author was Sayan Basu, a corneal surgeon from the L.V. Prasad Eye Institute in Hyderabad, India. Today, the method developed by Funderburgh's team is being tested in a small clinical trial in Hyderabad. Although Pitt is not directly involved in the pilot study in which a few patients will receive their own corneal stem cells as a treatment, Funderburgh's team trained the Indian researchers on how to isolate stem cells. —DY



A detailed look at the body's response to thrush tells us that the immune system's innate and unlearned powers are wider than previously believed.

# THE CASE FOR CANDIDA

THE BODY HAS AN INNATE RESPONSE TO THE FUNGUS  
BY HEATHER BOERNER

Our immune system has a long memory. Exposed to a pathogen, it takes a week or two to learn that the bug is an invader—but then is never caught off guard again. Future exposure triggers a swift response. But you don't always need immune memory to fight off a microbial invasion. Consider what the University of Pittsburgh's Sarah Gaffen is learning about thrush, an overgrowth of a fungus, *Candida albicans*, that can cause painful, white lesions on the tongue or can manifest as diaper rash or a vaginal yeast infection. Common in the immunocompromised, thrush is a hallmark of HIV infection.

Apparently, in the case of *Candida*, the body's defense starts with the tongue. Yet, for a long time, "no one was looking at immunity in the mouth," says Gaffen, PhD professor of medicine in the Division of Rheumatology. But that's exactly where Gaffen and Heather Conti, a PhD and postdoc in Gaffen's lab, found a key immune protein, called interleukin-17 (IL-17), being made in response to the fungus.

IL-17, it turns out, was being made immediately—not after a learned response—by a special kind of cell, called a natural T helper 17 (nTh17) cell. Buried deep in a bed of sticky collagen on the tongue, nTh17 cells go straight from exposure to *Candida* to making IL-17 and marshaling an immune response.

Instead of taking weeks for the mice in Gaffen's lab to gather forces against *Candida*, they showed markers of immune activation within 24 hours—which indicates a natural, or innate, response.

"This finding blurs the [line] between innate or early responses and immune memory," says Gaffen.

"T cells learn and then respond to pathogens—that's what they do. We don't think of the T cell response as being innate, but the natural Th17 cell response is."

Their finding was published in *The Journal of Experimental Medicine* last fall.

## FOLLOW THE YELLOW-LIT PATHWAY

We humans have a natural colony of *Candida* in our mouths, acquired at birth. But mice do not. So Conti, Gaffen, and the team used mice to test the innate immune response to the fungus, to see how an immune system responds the first time it's exposed to *Candida*. Then, by using mice genetically engineered with cells that light up in yellow every time a cell makes IL-17, they were able to trace the immune system activity from response back to its origin.

Finding the nTh17 cells—rather than the typical Th17 cells (which make IL-17 in response to previous exposure to a pathogen)—was a surprise. "It was a combination

of process of elimination, plus perseverance, plus technical talent on Heather's part," says Gaffen. "We were finally able to see the cells, and they didn't look the way we'd expected."

Conti created a protocol to pull the cells from their bed of sticky collagen to study their response in a test tube, using a technique called flow cytometry. And sure enough, when exposed to *Candida*, the nTh17s secreted IL-17, with no adaptive response required.

## A POSSIBLE TURN FOR HIV RESEARCH

Gaffen says these nTh17 cells, whose very existence is controversial, have rarely been studied. "But our data help prove not only their existence, but also a key biological function [of nTh17]."

Conti would like to explore next how cancer therapy might affect susceptibility to fungal infections.

And there's another area they believe is ripe for exploration. The fact that nTh17 cells responded immediately to *Candida* may indicate that HIV's impact on the immune system is broader than previously thought.

HIV hobbles CD4 T cells and CD4 receptors, notes Gaffen. "So the implication—and this is not proven—is that you may lose your innate cells, too, which [could explain] why HIV patients are so exquisitely sensitive to oral thrush." ■



A new perfusion system, developed by Paulo Fontes, includes a novel recipe for the all-important fluid used and rethinks the temperature and the oxygen environment. (In the cart shown here, the organ would get a chilled bath in the sink while the machine pumps fluid into the organ.)

**NEW APPROACH  
LEARNS FROM BEAR  
HIBERNATION**  
BY NANCY AVERETT

# HOW TO PRESERVE AN ORGAN

**I**t was 1 a.m. when Paulo Fontes's (Fel '93) phone rang. The surgeon had just returned home after spending 18 hours performing liver transplants on pigs in a study at Pitt.

"The animals are walking around like they've never been operated on. They're trying to jump out of their cages," a staff member told Fontes, who quickly headed back to the lab. There, he saw that some of the pigs were livelier than many human transplant patients were immediately after surgery. "I thought to myself, *I've been putting bad livers in my patients my whole life*," Fontes says.

It was a bittersweet realization. In the course of two decades he had assisted in and performed more than 1,000 liver transplant procedures and had recently dedicated several years to finding a better way to preserve donated livers. The lively pigs meant maybe he had found the answer.

Fontes is a Pitt associate professor of surgery and director of the machine perfusion program, a collaboration of the Starzl Transplantation Institute, the Department of Surgery, and the McGowan Institute for Regenerative Medicine. He has long been frustrated by the fact that some 20 to 40 percent of the time, donated livers cannot be used. The current technique for storing organs, cold static preservation, or CSP, relies on low temperature, 4 degrees Celsius, and no oxygenation to preserve tissue. Yet, the organs always decay some before they are placed in the recipient—some are rendered unusable.

In 2010, Fontes set out to find a better method to preserve organs. Researchers were beginning to experiment with "machine perfusion," or MP, in which an organ is placed into a device that pumps specialized fluid around tissue to ward off deterioration. He found a promising-looking apparatus made by the Dutch company Organ Assist. Using a \$1 million donation from a patient, he brought the new technology to Pittsburgh.

The next step: Find the best fluid. The human body uses hemoglobin, a molecule in red blood cells that transports oxygen from the lungs to the organs; yet red blood cells often break when perfused ex vivo by artificial pumps below the body's normal temperature.

So he explored synthetic hemoglobin products. A company in Cambridge, Mass., had created one by isolating hemoglobin molecules from red blood cells, purifying them, and then combining them chemically to create a bigger, chain-like molecule (a polymer). Their polymer could carry oxygen and would not break at lower temperatures. The FDA, however, had deemed it unsafe for in vivo use as artificial blood.

Fontes had an idea for how to fix the problem. He called the company's lead investigator and told him he wanted to alter his formula by reducing the amount of hemoglobin, changing the temperature, adding a buffer to control pH, and adding nutrients for the cells.

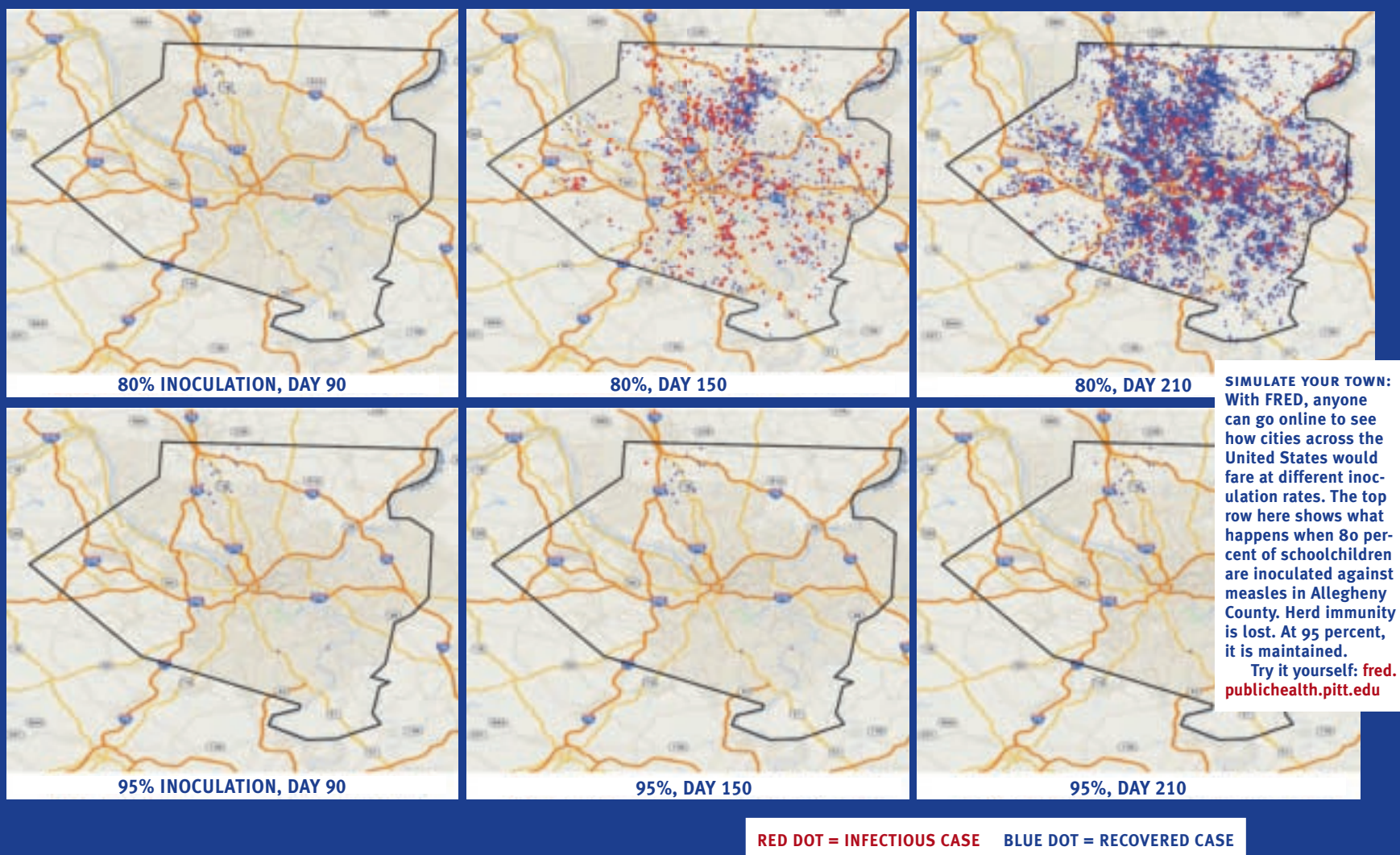
Another puzzle was getting the perfusion temperature right. Fontes wanted one that was warm enough to allow partial tissue function but cold enough to create a barrier for microbial growth. After performing some analyses and looking at studies of mitochondrial function at different temperatures (including data on the livers of hibernating bears), he settled on 21 degrees Celsius (about 70 degrees Fahrenheit).

He then took 12 pigs and transplanted into them livers that had been kept for nine hours outside their donors. Six of the livers were preserved with the MP system, the other six with the conventional system, CSP.

Then came the 1 a.m. call. Five days after the surgery, only two of the CSP pigs were still alive compared to all six of the MP pigs. Further tests revealed the MP organs were functioning better than when they were in their donors: measurements of the 100 most affected genes showed increased expression of those related to metabolic, anti-inflammatory, and regenerative functions, as well as protective mechanisms against free radicals. "If you provide oxygen," Fontes says, "you can actually improve the quality of the organ."

The results were published in the *American Journal of Transplantation* in January. Fontes hopes to start clinical trials later this year. He has founded a spinoff company, Virtech Bio LLC, which will develop MP systems for transplanting other organs, and even limbs. ■





# GONE VIRAL

**PITT TOOLS MAKE ANOTHER CASE  
FOR VACCINATIONS | BY BRETT MURPHY**

A simulation tool from the University of Pittsburgh's Public Health Dynamics Laboratory called FRED—Framework for Reconstructing Epidemiological Dynamics—shows what a measles outbreak might look like in your hometown. And the platform has gone viral.

FRED illustrates the strength-in-numbers law of nature: When one bison loses a step to an injury or age, the collective strength and speed of its herd protects it from predators. People benefit from their packs, too. In what's

known as herd immunity, infants and others who are vulnerable likely won't contract or spread an infectious disease because so many around them have a defense against it—vaccination.

The inoculated are the swift bison.

But if a population's vaccination rate drops below a certain threshold, herd immunity is lost, and a disease can blanket a city.

An outgrowth of years of research into infectious disease epidemics, FRED was produced in collaboration with Carnegie Mellon University and the Pittsburgh Supercomputing

Center. John Grefenstette, a PhD professor of health policy management in the Graduate School of Public Health, is the lead software designer and lead programmer on the project.

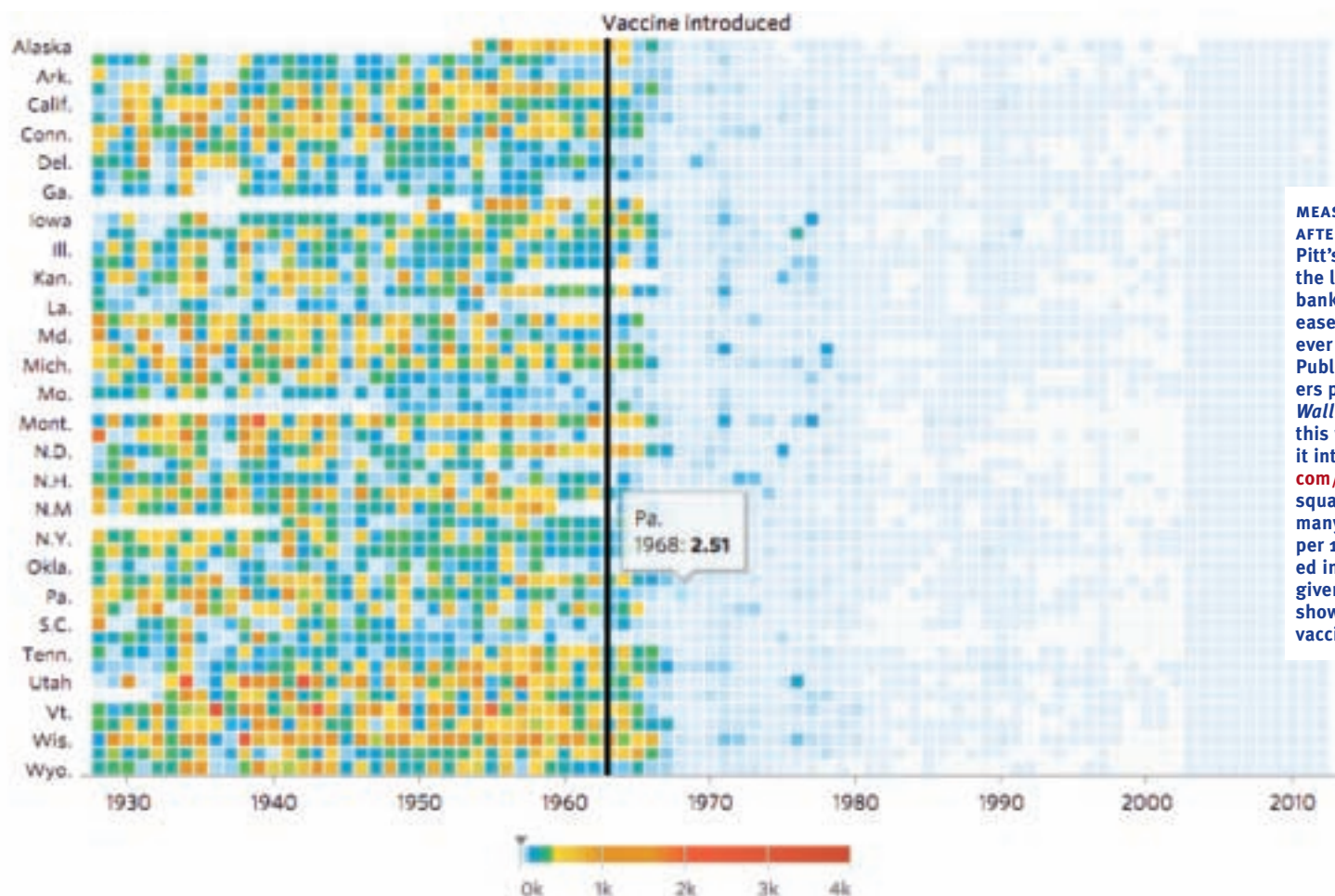
FRED can be adjusted to model an outbreak in any U.S. city, says epidemiologist and Pitt Public Health dean Donald Burke, an MD and Pitt Distinguished University Professor of Health Science and Policy, UPMC Jonas Salk Professor of Global Health, as well as professor of medicine.

The beauty of the tool is in the simplicity of its presentation. Pitt's David Galloway, a research programmer for the platform, says FRED's user-friendly interface has miles of code behind it—all applying “natural history parameters,” or how people tend to act when they're sick.

Do people stay home from work or trudge in? How sick does your daughter have to be before you keep her home from school? How close is the nearest hospital?

These are just some of the considerations churning in FRED's measles epidemic simulator. Click on the play buttons, and two simulations will unfold in the city of your choice: one where

# MEASLES



**MEASLES, BEFORE AND AFTER THE VACCINE:** Pitt's Project Tycho is the largest centralized bank of digitized disease surveillance data ever assembled. Pitt Public Health researchers partnered with *The Wall Street Journal* this winter to make it interactive ([tinyurl.com/wsajt](http://tinyurl.com/wsajt)). LEFT: Each square documents how many cases of measles per 100,000 were recorded in a given year in a given state. The line shows 1963, when the vaccine was introduced.

95 percent of schoolchildren are vaccinated and another where only 80 percent are. At 80 percent, you are likely to see the map enflame in a sea of red dots, cases spreading as the days tick on. At that point, herd immunity has been lost. About 92 percent of children across the United States have been vaccinated against measles. Pennsylvania's vaccination rate is slightly above average. In both West Virginia and Ohio, the inoculation rate is lower—86 percent.

In a recent interview with *Pitt Med*, Carl Zimmer, a science columnist for *The New York Times*, said that describing how an outbreak works can be difficult. "Visual illustrations online can help a lot," he says of the FRED simulator's accessibility for folks outside of scientific circles. "And those simulations do an elegant, simple job" of showing why herd immunity is important.

Zimmer was one of hundreds of thousands to recently come across FRED shortly after it went viral across social media this February. Pulitzer Prize-winning journalists and national media correspondents praised (in 140 characters or less) the tool's value.

"Want to see what #measles cld do in your town if vax rate = 95%? Or only 80%?" Laurie Garrett of the Council on Foreign Relations tweeted with a link. "Cool interactive frm @PittPublicHlth."

FRED isn't the only Pitt Public Health interactive tool hitting the mainstream lately. Pitt's Project Tycho, a digital database that provides open access to U.S. disease surveillance data, teamed up with *The Wall Street Journal* this winter to create interactive graphs illustrating a history of infectious diseases. The headline of the article—"Battling Infectious Disease in the 20th Century: The Impact of Vaccines."

At 90 million case files chronicling reports of 58 infectious diseases in every state before, during, and after vaccination licensure from 1888 to recent times, Project Tycho is the largest centralized bank of digitized disease surveillance data ever assembled. Wilbert van Panhuis, an MD/PhD assistant professor of epidemiology at Pitt Public Health and lead investigator for the project, says Tycho has very

real applications for researchers, policymakers, health officials, and parents. "There's a lot of misinformation out there, and people don't realize the consequences of not vaccinating," he says. "Our data help put things in perspective, historically and state by state."

This magazine (see our Spring 2014 cover story) and other publications wrote about Project Tycho as well as FRED last year, as the tools became publicly available. And now many more people know about them.

Bill Gates, who helps fund both FRED and Project Tycho through the Bill and Melinda Gates Foundation, tweeted about *The Wall Street Journal* article to his 21 million-plus followers.

Burke says these painstakingly researched platforms can help people make better choices. "We, as a society, don't do a great job thinking through complex systems," he says of problems like the current measles outbreak.

"Having these tools literally allows you to turn the knobs and think about the consequences of certain actions."

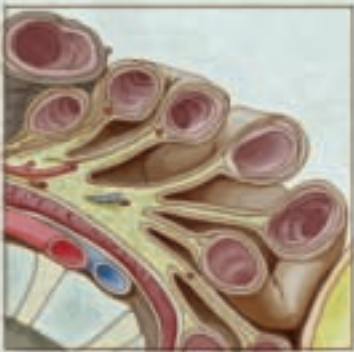


*Ginkgo pneumoloba*

*Papilio paranasal*



**FIG. C:**  
I. LITUS DETAIL



*Colon transtagnum*

*Intestinum litus*



TAXONOMY OF THE HUMAN MICROBIOME

BY ELAINE VITONE

ILLUSTRATIONS BY MICHELLE LEVEILLE

# THE ECOLOGY WITHIN

Your inner ecology, like this fantasy bio-landscape, is a dynamic community in a delicate balance. In that wild kingdom of your microbiome—where trillions of microscopic organisms outnumber your own cells tenfold—the gut is king. Intestinal flora produce a lion's share of molecules that rule the immune system, with effects rippling throughout the body.

As an intern at the UPMC Eye & Ear Institute, Andrew Goldberg (Res '90) met a middle-age man who swore he'd succeeded in curing himself of a pesky outer-ear infection after all his previous ear, nose, and throat docs had failed.

ENTs see this all the time: Give a patient a course of antibiotic drops, and maybe the problem clears up or maybe a chronic infection surfaces. So one day, this particular patient took matters into his own hands. *Whatever's in my good ear, I want to get over to my bad ear*, he told Goldberg. *So I just took some wax from my good ear and put it in my bad ear. And within a couple days, I was fine.*

*Cilia aquaherba*

*Ova evolutione*



The story of the Earwax Man has become something of a legend among scientists in an emerging field, the study of what's called the human microbiome. As Goldberg, professor of otolaryngology at the University of California, San Francisco, has shared this anecdote in his presentations, people have come up to him afterward sharing similar yarns dating back as far as the 1930s. One septuagenarian said his med school mentor swore by a cup of curative earwax that he kept in his office.

For centuries, improvements in hygiene and sanitation have saved innumerable lives. But as rates of asthma, allergies, and other inflammatory diseases steadily rise in the Western world, scientists now wonder whether we are seeing the cumulative effects of the pendulum swinging too far. It seems that, along with the bath water, we may have thrown out too many of the microorganisms that have co-evolved with us in a mutualistic relationship; we pro-

intestines—widely regarded as the throne of the microbiome, seating most of the microorganisms that populate our persons—a host of maladies ranging from asthma to psychiatric disorders quiet down.

The microbiome consists of trillions of microbes that make vitamins, ease inflammation, and influence everything from whether we can tolerate our breakfast cereal to how well our meds work. Their collective DNA has been called our “second genome,” and perhaps the best part about this genome is that, unlike the first one, which we're more or less stuck with for life, the microbiome's is highly modifiable. When we give our microbial helpers what they need to seed and succeed, they spring back to health—and so do we.

A number of University of Pittsburgh faculty members are exploring this inner ecology, and University officials are in the beginning stages of planning a new microbiome center

least proving helpful in how he explains the disease process to patients—they understand the concept immediately and intuitively.

“Patients appreciate it, although I certainly wish I had something more concrete to deliver. It's always, you know, *It's coming.*”

## BRINGING UP BIOME

One of the most troubling unsolved mysteries in pediatrics remains necrotizing enterocolitis (NEC). In severe cases of this disease seen in premature infants, sections of the intestines swell, wither, die, and must be removed, says Michael Morowitz, MD assistant professor of surgery at Pitt. About one third of NEC patients require surgery, and many of those children don't survive after the procedure.

Since the 1990s, a number of likely contributing factors have been sleuthed out at Pitt, including inflammatory cytokines, nitric oxide, and a

**The microbiome consists of trillions of microbes that make vitamins, ease inflammation, and influence everything from whether we can tolerate our breakfast cereal to how well our meds work.**

vide them a home, and they, in turn, keep our immune systems in check. With the rise of next-generation sequencing, which enables researchers to detect and sequence the DNA of all microorganisms within a given sample, we're learning more about them than ever.

The balance of our bodily ecosystem is delicate, Goldberg explains. Think of it like a lake. If the temperature of the water increases, cold-water species decline. Algae become overgrown, choking off oxygen and killing helpful bacteria. Fish die, and the wetland birds that feed on them thin in number.

Many changes in our health have rippling and far-reaching effects we've never been able to explain; and increasingly, scientists are wondering whether the microbiome might hold the answers. For example, if you treat sinus disease, somehow, pulmonary disease improves, too. If a person develops lung disease, cardiovascular disease tends to go along with it. And study after study has contended that if a body takes probiotics down the hatch to introduce new microflora to the

at Pitt (which is fertile ground for discovery in this area, with its strengths in interdisciplinary biomedical research, bioinformatics, computational modeling, and a wealth of clinical data available through UPMC, the largest academic health care center and payer/provider in the country).

In October, Pitt awarded its 2014 Dickson Prize in Medicine (which honors a leading American investigator engaged in “innovative, paradigm-shifting biomedical research”) to microbiome luminary Jeffrey Gordon, who famously linked gut microbiota to both obesity in the Western world and undernutrition in developing countries.

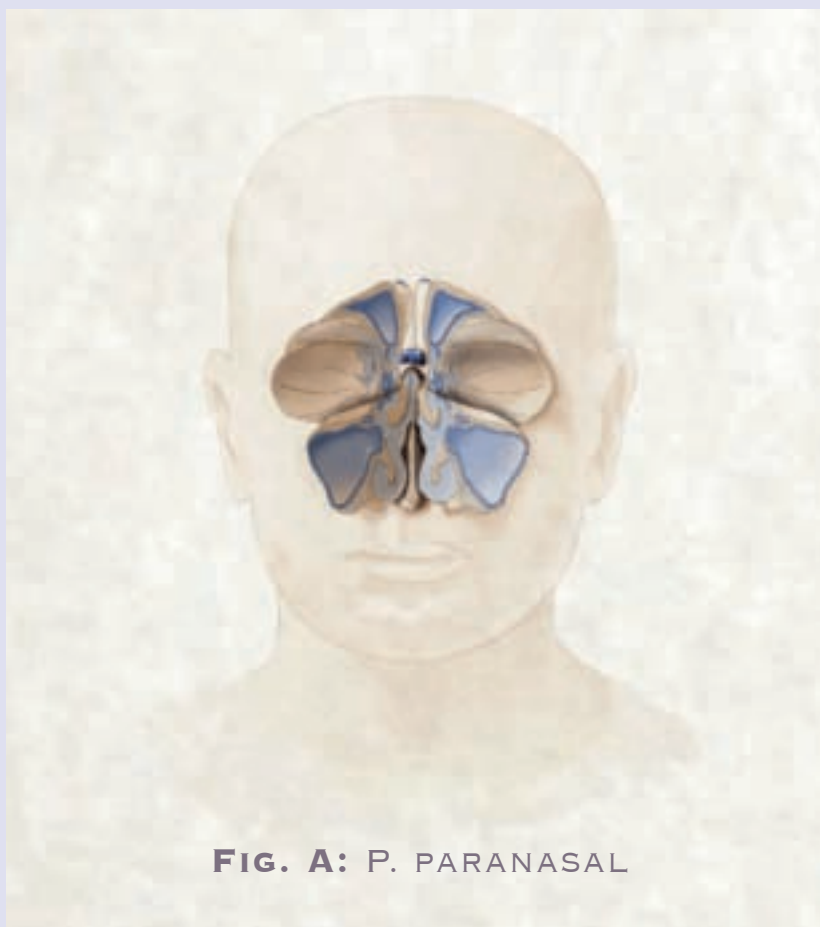
In 2007, the National Institutes of Health (NIH) launched the Human Microbiome Project. Eight years later, industry is racing to cash in on its promise, and the public is clamoring for new hope in treating everything from autism spectrum disorder to food allergies. But in terms of evidence-based medicine coming to the clinic, we're just not there yet, says Goldberg. On the upside, the idea of the microbiome is at

toll-like receptor called TLR4.

But all along, bacteria have remained a top suspect in NEC for several reasons: Many babies are cured of NEC with antibiotics. X-rays of these infants show guts full of gas bubbles—which are almost certainly produced by abnormal bacteria. And cases of NEC sometimes occur in clusters in a neonatal intensive care unit (NICU).

Morowitz calls preemies the “Wild West” of the microbiome. Rather than spending their first days colonizing their bodies with typical neonatal microbes—from the birth canal, from their environments, and from milk—preemies are isolated in a NICU and take antibiotics intravenously. Those born before 35 weeks receive nutrition intravenously or through feeding tubes. “All bets are off,” he says.

In an NIH-funded study based at Magee-Womens Hospital of UPMC, Morowitz has been analyzing stool samples from preemies, prospecting this wild frontier. Thus far, NEC seems to be more about complex interactions—no rabble-raising Lilliputian species (or gang thereof) has emerged as the culprit. So now, his team is



**FIG. A: P. PARANASAL**

We used to think the sinuses were sterile, but that didn't fly with Andrew Goldberg.

digging even deeper, developing techniques to sequence not just the DNA of microflora but also the RNA and proteins.

So far, Morowitz has learned that the preemie microbiome is guided by certain principles: First, preemies' guts—regardless of whether they're healthy or sick—are generally full of “very unfriendly” organisms. Second, even if two babies have the same bacterial species, each one will have her own individual strain that is markedly distinct, down to the level of individual genes. Third, the NICU environment is highly influential—preemies are populated by microbes found on the countertops, bed rails, and computers in the unit. And fourth, certain microorganisms with beneficial health properties in healthy newborns (e.g., *Bifidobacterium* and *Bacteroides*) are nowhere to be found in the intestines of premature infants.

Since his initial funding from the NIH, Morowitz has pursued other microbiome projects. In March 2014, he reported in the *Journal of Pediatric Surgery* a surprising difference he found between appendicitis

patients and healthy youngsters. His team found *Fusobacterium* (best known as a gum-disease bug)—and lots of it—in the ill-fated appendixes, whereas control organs had none. This may help us better understand appendicitis, he says—which is another great unsolved mystery.

In another project, with collaborators Jillian Banfield, a PhD professor of Earth and planetary science and environmental science, policy, and management at UC Berkeley, and Joseph Carcillo, MD associate professor of critical care medicine at Pitt, Morowitz is studying the effects of the hospital environment on the gut, skin, and mouth microbiomes in children ages 1 to 9. (Most of what we know about the microbiome in this setting pertains to adults.) A few basic principles have emerged in these new Pitt studies, as well:

For one, the microbes of the skin and of stool samples—which should be very different—are actually quite similar in the ICU. “Which is not good,” Morowitz says. “My vision is that we'll be checking these things

twice a week, and if skin bacteria doesn't look like it should, then [we'll] do something about it. What that would be is up for debate.”

Typically, in a healthy body, microbes coexist; little populations of many, many stripes live together peaceably. “But what happens in the ICU is you tend to get some individual, sort of obnoxious species that overtakes all others and grows to very high amounts.” (Other groups have shown in animal models that this can be a sign of an impending bloodstream infection, he notes.)

Also keeping NICU staff on their toes: In intensive care units, the microbiome changes drastically over the course of a few days. “Whereas in healthy individuals, it doesn't change much over time unless they change their diet or start on antibiotics.”

Morowitz notes that clinicians generally don't think much about bacteria, besides how to wipe them out in the case of infection. “But I think that over the next 5 to 10 years there will be a change, where all clinicians recognize that there are a lot of good organisms on the body, too, and part of caring for the patient will involve caring for the microbiome and making sure that the microbiome is appropriate for their age and place in life.”

## GUT DEALINGS

In the early '80s, Stephen O'Keefe, MD professor of medicine at Pitt, was investigating malnutrition prevention and treatment in rural Africa when he noticed something intriguing about his patients. As he was conducting lactose tolerance tests, which measured gases in the patients' exhalations, he learned that much of the air rising from their guts to their gullets came in the form of methane—not hydrogen, as is typically the case in Westerners. Clearly, something very different was at work in what was then called the “bacterial flora.”

Years later, when he moved to the States and began practicing as a GI, O'Keefe was amazed to see how much more prevalent polyps and colon cancer were among African Americans than rural Africans—about a hundred times as prevalent. “And one of the obvious differences was their diet,” he recalls. The puzzle pieces began to slide into place.

With funding from the American Institute for Cancer Research, O'Keefe documented these dietary differences, then examined the



microbiota within the individuals and found a striking contrast between the two continents. In a 2013 paper in the *American Journal of Clinical Nutrition*, the team tested the hypothesis that it wasn't so much the food itself that determined colon cancer risk, but rather, how the food affected the microbiota, and in turn, the byproducts—or metabolites—that they produce.

A little gut primer: Your small intestine lives on the same goodies you live on, the amino acids, fats, and sugars forged by your digestive system. But by the time your food reaches the end of the line—the colon—anything absorbable is gone. What's left is indigestible residue—fiber, that is—which microbes in the colon process and break down into short-chain fatty acids. Among them is butyrate, which is not only the major energy source for the cells within your colon, but also their peacekeeper. Butyrate controls the rate of cell turnover and proliferation in the organ's lining. It also suppresses inflammation and keeps the walls snug and secure, protecting actively dividing cells inside from troublemakers, like carcinogens.

Essentially, butyrate is your ultimate colon cancer queller—a gift of your gut bacteria, for the small price of room and board.

The 2013 paper showed the correlation between metabolite production and colon cancer risk. In April, *Nature Communications* published an NIH-funded follow-up study showing this mechanism at work in the two populations whose striking contrast first gave O'Keefe pause 30 years ago: rural Africans, with their high-fiber and low-protein diet, and African Americans, whose diet is exactly the opposite. O'Keefe and his Dutch collaborators, Willem de Vos and Erwin Zoetendal of Wageningen University and Research Centre, showed that by switching the diets of these populations for as little as two weeks, their butyrate levels flip-flopped.

And so did their rates of epithelial-cell proliferation—a biomarker for colon cancer risk.

## FUNGUS O'LUNG-US

When the NIH announced the Human Microbiome Project, they invited grant proposals for studies of the nose, mouth, skin, gut, and urogenital systems, but not of the lung. Even as recently as 2007, the thinking

was that the lung—though incessantly exposed to the external environment—was sterile. You see, when you culture lung tissue samples, you almost never get anything to grow, unless that person has a raging infection like pneumonia, explains Alison Morris (MS '03), MD associate professor of medicine and immunology at Pitt.

The NIH—specifically, the National Heart, Lung, and Blood Institute—soon came around, and Morris and Elodie Ghedin, a PhD and former Pitt faculty member who is now a professor of biology and public health at NYU, applied for and were awarded a spot in the multicenter Lung HIV Microbiome Project.

COPD (chronic obstructive pulmonary disease) is on the rise in people with HIV. Morris's was among the first groups to investigate the reasons why. When starting out as a scientist, she studied a fungus called *Pneumocystis jirovecii*, a common cause of fatal pneumonia in the early days of the AIDS epidemic. She went on to show that it plays a part in HIV patients' continued vulnerability to COPD, as well.

In comparing the lung microbiomes of HIV-positive and HIV-negative people, she has found surprisingly similar bacterial populations. However, there are some significant differences. Her studies with the Lung HIV Microbiome Project show that the lungs of people with the virus are far more likely to house *Tropheryma whippelii*, a bug that causes a rare disease in the GI tract. (It does not cause the GI disease in these HIV patients. "We don't yet know how it gets [in the lungs] or what it's doing," says Morris.)

In addition, people who are on antiretroviral therapy for HIV actually have worse airway obstruction than HIV patients who are not. "What we think may be going on is that as their immune system gets better, they may be more able to react to things"—including the harmless flora of the microbiome. "That [reaction] causes inflammation that damages the lung."

Getting in on the ground floor of the lung microbiome took a lot of front-end work; lung tissue sampling requires an invasive procedure called bronchoscopy. Luckily, the Pitt Men's Study—a longitudinal public health research initiative that's been following HIV-positive men in Pittsburgh since the start of the epi-

demic—has provided a wealth of samples and dedicated volunteers.

Yet, bronchoscopy accesses the lungs through the oral and nasal route, which Morris calls a "veritable sewer." Microbes along the respiratory tract move, mix, and mingle as we breathe and cough. Establishing how best to minimize the nonlung microbes in the samples, and rule out the ones that do manage to sneak in, took three years. Computational modelers from the University of Michigan helped sort out which microorganisms thrive in which environment.

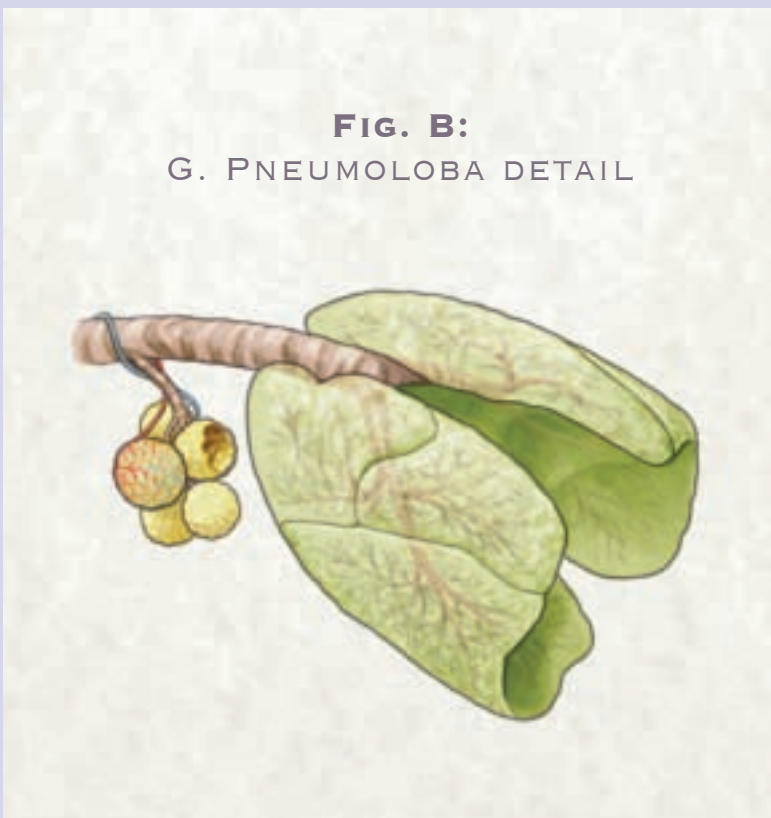
With lessons learned from the Lung HIV Microbiome Project, Morris and collaborators launched a new study called GRADS (Genomic Research in A1AT and Sarcoidosis). Its foci, sarcoidosis and alpha-1 antitrypsin deficiency, are two very different diseases, but both are suspected to be at least partly fueled by infection. GRADS will integrate for the first time information from our first and second (microbiome) genomes as well as clinical information on these diseases in the hope of identifying biomarkers that can help physicians track disease progression and response to therapy. Co-led by Naftali Kaminski (formerly of Pitt and now MD professor of medicine at Yale) and Steve Wisniewski (PhD professor of epidemiology at Pitt Public Health), GRADS is funded by an \$8.3 million grant from the NIH. Now nearing the end of its highly successful enrollment stage, the multicenter study is shaping up to be the largest study of both of these diseases to date.

## IRRITABLE BIOME

In any ecosystem, from the rivers of Allegheny County to the vegetable garden in your backyard, the health of the community goes to pot when a species gets too greedy and crowds out its competition. The same goes for the microcosm in your gut. In one extreme and dreaded example of this, a complication of antibiotic therapy known as *Clostridium difficile* infection, the little bacterial dictators can bring you to death's door. And sometimes, the cure—ironically, more antibiotics—can do you in.

Hence, the growing acceptance of a new therapy called fecal microbiota transplantation (FMT), which is exactly what it sounds like: transplanting fecal specimens from healthy donors to reseed a doomed intestinal tract with diverse microflora (under close medical supervi-

**FIG. B:**  
**G. PNEUMOLOBA DETAIL**



Alison Morris and collaborators cultivated protocols for lung microflora studies.

sion, of course). It may soon become the standard of care for *C. diff*—trials at medical centers around the world, including UPMC, have seen high success rates thus far.

Some scientists are hopeful that FMT might help sufferers of other diseases that are also believed to result at least partly from imbalances in the intestinal microbiome—namely, ulcerative colitis and Crohn’s disease, which together are known as inflammatory bowel disease, or IBD. Michael Morowitz (see “Bringing up Biome”) and Alka Goyal, MD assistant professor of pediatrics at Pitt, are conducting a novel FMT trial for IBD in pediatric patients at Children’s Hospital of Pittsburgh of UPMC.

To hear Pitt’s David Binion, MD professor of medicine, tell it, there’s no more perfect place to study the role of the microbiome in IBD than here—quite a vote of confidence given that he himself has Crohn’s. Pitt, he points out, is the home of Richard Duerr, MD professor of medicine, of human genetics, and of clinical and translational science, who for the last 15 years has been a major player in characterizing IBD’s implicated genes, particularly those

involved with the interrelationship between the immune system and the microorganisms in the GI tract.

Pitt, Binion says, has three coauthors of the American College of Gastroenterology’s *C. diff* physician guidelines: Binion himself; Scott Curry, MD assistant professor of medicine; and Brian Zuckerbraun, chief of trauma surgery and an MD associate professor.

Pitt is in collaboration with MIT on a project called OpenBiome, which is screening FMT donors and banking the samples so that patients in desperate need can get FMTs more quickly.

“And I’ll go ahead and say it,” Binion adds. “We are one of the leaders when it comes to handling observational natural history data”—that is, systematically tracking every imaginable metric of the patients who’ve consented to participate (that adds up to some 16,000 clinical visits, 2.4 million lab results, and 112,000 prescriptions so far) and linking them to clinical outcomes. This unique asset has been lacking in gut microflora research until now, he says.

“You can generate all the information in the world about genetics and the microbiome, but then you have to link it to the human data. That’s where we believe the discoveries are going to come from.”

## UPWIND AND DOWNSTREAM

Goldberg, of the famous Earwax Man story, has actually spent his entire microbiome-research career investigating micro-organisms not in the ears but in the sinuses.

Several years ago, he became involved with a study of biofilms—the sticky, antibiotic-resistant microbeasts long suspected as the reason why some sinus infections tend to spring back no matter how many different antibiotics you throw at them. The effort evolved into an intensive, years-long project that in 2012 resulted in a game-changing *Science Translational Medicine* paper. Therein, Goldberg and his UCSF collaborators proved once and for all that the sinus cavities, in both sickness and in health, are loaded with microflora; for centuries, we’d assumed the sinuses were sterile, except in disease states. The difference, the team found, was that healthy people had more diversity of species, more even distribution among them, and greater bacterial counts overall.

And for the first time ever, their paper showed that something akin to a probiotic for the sinuses—introduction of helpful bacteria to chronically inflamed cavities—could prevent infection in an animal model.

Goldberg continues to learn more about the teeming community within your face; several papers are out for review. In one, his team defines subcategories representing the range of courses chronic sinus infection can take—four “sinotypes” that are each microbiologically and immunologically distinct. In another paper, he traces what he believes to be the mechanisms behind the link between improved sinus health and improvement in asthma symptoms, a curious downstream effect that has long confounded explanation.

Eventually, Goldberg hopes to go back to where this all started for him, the ear. But as yet there aren’t enough resources to do so.

“We have a bandwidth problem,” he says. “There are so many things we want to do.”

But, you know. It’s coming. ■





“YOU DON’T

ELIZABETH MILLER HELPS OTHERS

TUNE IN TO TEENS | BY JENNY BLAIR

# UNDERSTAND!”

The patient who transformed Elizabeth Miller's life was 15 years old when the two met in 2000. At a Boston-area clinic where Miller volunteered, the girl walked in to ask for a pregnancy test. It was negative. Miller asked the usual domestic violence screening questions. The patient “looked at me rather strangely,” recalls Miller. Turning up nothing of note, she then talked to the girl about birth control options and sent her home with condoms.

Two weeks later, Miller learned that the girl had suffered a severe head injury after her boyfriend pushed her down a flight of stairs.

“It was there, staring me in the face,” Miller recalls of the abuse the girl must have been enduring at the time. “And I totally missed it.”

PHOTO | GHISLAIN &amp; MARIE DAVID DE LOSSY, ©CORBIS





The tragedy ignited her interest in adolescent relationship abuse. Trained in medical anthropology, Miller began to cast not only a physician's, but also a social scientist's, eye on the problem, and to draw in an unusually wide variety of people to solve it. Today, as associate professor of pediatrics and chief of the Division of Adolescent and Young Adult Medicine for the University of Pittsburgh's Department of Pediatrics and Children's Hospital of Pittsburgh of UPMC, Miller, an MD/PhD, brings together activists, researchers (including other social scientists and epidemiologists), health care providers, social workers, and youth themselves in partnerships to grapple with partner abuse and many other forms of adversity that burden young people.

Since her arrival in 2011, Miller has built a research powerhouse—one with rich community and academic ties, a thriving multi-

disciplinary clinic, and a strong commitment to youth empowerment and social justice. The Center for Adolescent and Young Adult Health, or CAYAH, treats kids from all walks of life, including young people tangled in the juvenile justice system, those whose family lives are fragile, those in foster care or who have aged out of that system and find themselves homeless.

Her colleagues call her Liz. She's warm, has a genius for connecting people, and stands 5' 1" tall. "Energetic" is an understated description of Miller. At the moment, she is involved in 18 active grants and holds \$2 million just in federal funds. During this time of extremely tight federal funding, Miller has launched one National Institutes of Health and two Centers for Disease Control and Prevention R01 grant-funded studies this year. Here are just a few topics she's exploring: racial disparities in men's reproductive decisions, partner violence against Native American women, and alcohol-fueled sexual violence among college students.

One colleague calls her a "force of nature."

In a sense, she's an übergodmother for the youth of Pittsburgh and beyond whose work may change the odds for her own patients as well as young people who will never meet her. And her efforts are helping other professionals understand this population better.

Kristy Trautmann, executive director of the FISA Foundation, a Pittsburgh women's health and disability rights organization, puts it this way: "Liz embodies what it means to take research and use it to change the world."

**W**hen you show up to your appointment at the CAYAH clinic in Oakland, you get a warm welcome even if you're three hours late. They'll try to fit you in, Miller having long ago done away with the clinic's old "15 minutes late, get rescheduled" policy.

There's no TV in the waiting room; Miller has seen to that. But there is a shelf of free books gathered by a staff member's 6-year-old daughter. Rainbow stickers and LGBTQ SafeZone pam-

phlets are on display around the clinic, along with posters advertising research studies and support groups. A new Gender and Sexual Development Program is housed here, drawing gender-variant kids from three states. (Homeless queer youth can also visit a free downtown clinic just for them that Miller helped establish by bringing together several existing organizations.)

In the exam room, you don't have to get undressed before the provider arrives (another Miller policy). You aren't required to get a pelvic exam if you want birth control. If you need a breast exam but don't feel safe or comfortable in a gown, you can leave your T-shirt on.

"CAYAH clinicians create a safe space for youth to talk about tough subjects like drug use, their sexuality," says Pitt assistant professor of pediatrics Heather McCauley whose social epidemiology research focuses on girls in the foster care system and LGBTQ youth.

Unsafe at home? Not enough to eat? Got a complex mental health situation?

"We don't bat an eye," says Joanne Goodall, a nurse practitioner.

Gabrielle (not her real name) can vouch for that.

"I was in a hole, a dark hole," recalls the 21-year-old, who has severe asthma and a tough home life. For a long time, Gabrielle's illness was out of control, with well over a dozen hospitalizations in one especially bad year. As she struggled to cope with her medical problems, a turbulent family situation and the deaths of loved ones turned her world upside down.

"I kind of shut down," she recalls. "I didn't know how to talk to people."

That gradually changed. Talking to Goodall, Gabrielle began to open up, express her feelings, and eventually take control of her health. Social worker Gary Sadler helped her solve practical problems on the homefront, while clinical director and Pitt assistant professor of pediatrics Jonathan Pletcher (MD '94) helped her deal with her depression and anger. Goodall told Gabrielle to call her any time, and earned the young woman's trust by returning all calls within a day. People at the clinic, Gabrielle says, take care of her as if she were their own.



Elizabeth Miller is like an übergodmother for the young people of Pittsburgh.

CAMI MESA

BOONE SPEED / ©GETTY



Adolescence can seem, all at once, a time of limitless possibility and intense pressure.

“[Goodall] makes me feel like maybe I’m talking to an aunt or maybe a grandma,” Gabrielle says. “She just has that spark to her. She makes you feel real comfortable. She’s always open. And she’s always, always, always there to listen.”

The clinic’s staff, Miller stresses, are there to lend an ear and support.

If the provider finds out you’ve missed appointments or skipped your meds or run away or gotten in trouble with the police, the response is gentle and constructive. If you’re struggling with a gigantic bill or have run out of food, a social worker can make calls to help you. Gabrielle says Goodall makes sure she has a bus ticket if she doesn’t have a ride home.

“You don’t say, *What’s wrong with you?*” says Goodall of the clinic’s approach to trou-

bled kids. “You say, *What happened to you?* . . . [and] *What else can we offer you to help?* . . . Kids refer their friends.”

It is, in a sense, a clinic that keeps saying *yes* when what many kids are accustomed to hearing is *no*.

Even in supportive families, chronic disease can isolate an adolescent.

Eighteen-year-old Sydney (not her real name) has an uncommon condition that causes chronic pain. She’s used to educating her own physicians about it.

When she began to see Pletcher a year and a half ago, she was impressed.

Not only was he already familiar with her illness, but the big-picture questions he asked were spot on:

“How do I get through school? How do I

maintain relationships with friends? How do I feel every day knowing I’m probably going to wake up and go to sleep in a lot of pain?” Sydney says.

“For the first time, I talked to someone who understood the medicine behind what was wrong and could help from that aspect, but [also] wanted to know about every aspect, and how it changed my life.”

Letting youth tell their own stories forms the backbone of much of Miller’s research. After her 15-year-old patient was attacked in 2000, she began a series of 53 interviews with young women referred by care providers and social workers who knew that the girls had experienced abusive relationships; Miller was intent on learning how



to better spot warning signs of such violence.

What she heard was a story about teen pregnancy that providers and researchers had overlooked.

In one of her very first interviews, Miller heard from an 18-year-old who'd had a baby at age 16. The reason: Her boyfriend had flushed her birth control pills down the toilet. He told their friends, against her wishes, that they were starting a family.

"I didn't want to start a family. I wanted to finish school," the young woman told Miller.

"It was story after story of abusive partners actively, like explicitly, trying to get a young woman pregnant when she didn't want to be," Miller recalls.

"Everybody talks about girls who get pregnant on purpose to trap their boyfriends. But not the other way around." What Miller discovered in these interviews appeared in 2007 in *Ambulatory Pediatrics*.

With a 2010 paper in *Contraception*, Miller became probably the first in the domestic violence literature to quantify what she dubbed "reproductive coercion," in which a male deliberately promotes unwanted pregnancy and/or controls pregnancy outcomes in his female partner. This behavior often accompanies partner violence, and the combination doubles the risk of unintended pregnancy. In that study of 1,278 patients at five Northern California family planning clinics, one in five adolescent girls and young women reported reproductive coercion.

Many of these patients don't typically volunteer this information to providers. Reproductive coercion can be the hidden reason behind seemingly irresponsible behaviors like "losing" one's birth control pills, not showing up for contraceptive appointments, or "sexual acting out," a loosely defined term that includes impulsive, precocious, injurious, or otherwise concerning sexual behavior.

When she gives talks to women's health providers, Miller says, "Something about the reproductive coercion piece really clicks. Every one of them is sitting there thinking about a patient of theirs where they assumed she was just being irresponsible."

In the digital age, much abuse takes place

online. A project of the National Domestic Violence Hotline called *loveisrespect* routinely hears from young people whose partners text them obsessively, then get angry if there's no quick response. Or they'll threaten them online. Or they'll post compromising photos of them publicly. Or keep tabs on them through social media.

Two in five youth, both male and female, reported such abuse in a first-of-its-kind study that Miller and her colleagues published in *Pediatrics* last November. Those who had

**One organization routinely hears from young people whose partners text them obsessively, then get angry if there's no quick response. Or they'll threaten them online. Or they'll post compromising photos of them publicly. Or keep tabs on them through social media. Two in five youth reported such abuse in a first-of-its-kind study that Miller and her colleagues published in *Pediatrics* last November.**

experienced this so-called cyberdating abuse in the last three months were more likely to be physically and sexually abused in the course of an intimate relationship. The study focused on students using school-based health services in California.

As part of a long-term strategy to reduce relationship violence, Miller is collaborating with Pitt sociology professor Lisa Brush, a PhD, and McCauley, an ScD, on a social science study. In it, groups of adolescent boys draw what they think it means to be a man and brainstorm online about the cultural messages they receive about manhood.

Some of the boys' beliefs, like the idea that men shouldn't hit women because their job is to protect them, might seem positive. But they "merely reinforce traditional atti-

tudes about what you should be as a man," McCauley says. Less conducive still to gender equity is the idea that men need more sex than women do, so they're entitled to demand it or look for it outside an otherwise monogamous relationship.

The work grew from Miller's studies of the Coaching Boys Into Men initiative, in which high school coaches of boys talk to their charges about alternatives to relationship violence.

Miller found that the program can lead to an increase in positive bystander intervention—by 25 percent at three months—as well as to a relative reduction in abuse perpetration. After a year of follow-up, nonparticipants increased their rates of partner abuse by 15 percent relative to participants. (Though after a year, positive bystander interventions dropped off compared to right after the sports season.)

Although the program is doing good things, it doesn't shift the young participants' beliefs about hypermasculinity. (Hypermasculinity can be thought of as the embrace of exaggerated stereotypically male behaviors, including aggression and sometimes even violence.) The social science studies are meant to explore why, with an eye toward tweaking future interventions.

Thanks in large part to Miller's research, the Planned Parenthood Federation of America has rewritten its partner-violence screening guidelines to include efforts to identify reproductive coercion, and the American Congress of Obstetricians and Gynecologists is doing the same. In the meantime, the American Academy of Pediatrics is suggesting that practitioners place a greater emphasis on long-acting reversible contraceptives like the intrauterine device. Those methods are harder for a hostile partner to sabotage than, say, packages of birth control pills.

To Miller, such translation of research into changes in policy and practice is the whole point. "The reason that I do research is because I'm an advocate," Miller says.

"You know that old feminist adage, 'The

personal is political?” Brush asks. “What is so special about Liz Miller is that for her, the clinical is political.”

**E**lizabeth Miller grew up bicultural and bilingual in Kobe, Japan. She is the daughter of a Japanese mother and a father from Gulfport, Miss. (Her parents met on a boat to Taiwan and married years later.) “Airlifted” back to Gulfport to stay with relatives during her childhood summers, Miller says she was traumatized by the racism and poverty she witnessed there.

One of her cousins in Gulfport got pregnant at age 16. She says those kinds of early experiences have fed her interest about how social determinants affect health.

During medical school at Harvard, she did a summer project in Japan on health care for the homeless. Later, for her PhD in anthropology, she focused her dissertation on sex trafficking in Japan and grew passionate about understanding gender-based violence, especially that directed at women and girls.

Miller became board certified in internal medicine and pediatrics, also earning her Japanese medical license and practicing in Kobe for a year. It was as a Harvard faculty member that she became a school physician for an area district, grew intrigued by adolescent health, and met the teen who inspired so much of her subsequent work.

But whither adolescent medicine? The Society for Adolescent Health and Medicine first met in 1969. Yet, as an official subspecialty, adolescent medicine has been around only since 1994, with the first fellowships accredited four years later. To some observers, why adolescent medicine needs to exist at all is unclear. Can't teens just go to pediatricians and twentysomethings to internists or other adult providers?

With its many complex changes in biology and social roles, Miller says, adolescence is second only to infancy in its dynamism. She's heard pediatricians and other physicians say things like, *They're too difficult*, and *Teens will be teens*, and *They just need to grow up*.

Adolescent medicine specialists' offerings include gynecologic and sometimes obstetric care for girls and young women; care for young adults with conditions like cystic fibrosis that until recent decades would likely

have killed them in childhood; and help for children with complex medical or psychosocial problems transitioning to adulthood.

Young adults aren't quite like other adults, either. Neuroscience suggests that cognitive development isn't complete until the early to mid-20s. Adolescence is also a time when full-blown mental illnesses, like depression or schizophrenia, can manifest themselves.

For Miller though, part of the joy of caring for adolescents and young adults is because of their very vulnerability.

“Maybe as researchers, practitioners, and advocates for adolescents we are drawn to this population because they are so often misunderstood and marginalized,” Miller says.

Even for kids in tenuous situations, adolescence can be a breathless time of self-discovery.

Gabrielle, the CAYAH patient, is feeling a lot more centered these days. With some paperwork help from Goodall, she is now applying to school, a process she says is “on a roll.” Her goal? To become a medical assistant.

Gabrielle adds that ever since she's been seeing Goodall she's “been okay. Everything about me has been going uphill.”

**W**hen she was recruited from UC Davis, Miller says, she fell in love with Pitt. For one thing, Children's was trusted in the community. And thanks to previous head Pamela Murray, an MD/MPH, the division already had a firm commitment to vulnerable youth populations, with contracts in place to serve local colleges, mental health agencies, and Pittsburgh's juvenile-justice facility.

As codirector of community engagement for the Clinical and Translational Science Institute's Community PARTners Core, Miller helps find ways to link the community with the academy.

Stephanie Walsh is chief operating officer of the human services agency Auberle, which offers programs like foster care, work-readiness training, and drug treatment to at-risk children and families primarily in southwestern Pennsylvania.

When Miller visits Auberle's child-service workers, Walsh says, she connects “as though she's always been a member of that team,” discussing research in an understandable way and giving them tools they can use.

For example, suppose a teenage girl enters foster care after having run away for a few months. Rather than looking at her as an incorrigible runaway or just checking to see if she is all right, Miller would encourage staff to ask themselves if the girl might have been forced into sexual activity—and teach them how to explore that possibility with open-ended questions.

So rather than asking, *Have you ever been abused?* Walsh says that now that question might go something like this, “*You know, I worked with a young girl once, and this happened to her. I don't know if you have any friends that that's happened to, but I thought I'd just share that.*” It's a way to say... *If this has happened to you, I am aware that this can happen, and I'm capable of talking to you about it.*”

Miller has learned that youth are much more likely to open up when clinicians and frontline staff share how common unhealthy relationships are, describe what they mean by “unhealthy” and “abusive,” and offer information to share with their friends.

At the FISA Foundation, access to people doing solid science both at Pitt and nationally allows Trautmann and her colleagues to make evidence-based decisions about violence prevention for women and girls.

For example, Miller's study of the outcomes of Coaching Boys Into Men directly inspired FISA's work to encourage the program's adoption locally. Moreover, FISA is now better positioned to talk to grantees about the emerging evidence and best practices that can strengthen their proposals.

Before, says Trautmann, “we were doing our very best, and I think we were doing it in the smartest possible way. But we didn't have access to all this information.”

“Liz has galvanized the University and hospital system and community to carry out more rigorous research that helps us to solve the health problems of adolescence,” says David Perlmutter, an MD, who holds the Vira I. Heinz Chair, is a Distinguished Professor of Pediatrics, and leads the Department of Pediatrics at Pitt, as well as serving as scientific director and physician-in-chief at Children's.

He adds, “When I go around town now, people say, *David, thank you for bringing Liz Miller to Pittsburgh.*” ■



Organ	Tumor type	Gene	Mutation Type
Adrenal	Pheochromocytoma (sporadic & MEN)	RET	Missense activating mutations of the kinase function
Bladder	Carcinoma	ERBB2	Activating mutations, amplification
Bladder	Carcinoma	CDK4	Amplification
Bladder	Carcinoma	MCL1	Amplification
Bladder	Carcinoma	MDM2	Amplification
Bladder	Carcinoma	MYC	Amplification
Bladder	Carcinoma	MYCL1	Amplification in bladder; RLF-MYCL1 translocation in lung
Bladder	Carcinoma	CCND1	Amplification, polymorphism (G870A)
Bladder	Carcinoma	RAF1	Amplification, mutation
Bladder	Carcinoma	CDKN2A	Deletion
Bladder	Carcinoma	CDKN2B	Deletion
Bladder	Carcinoma	PTEN	Deletion
Bladder	Carcinoma	NF1	Deletion, Truncation
Bladder	Carcinoma	AR	Loss expression
Bladder	Carcinoma	ARID1A	Mutation
Bladder	Carcinoma	ARID1A	Mutation
Bladder	Carcinoma	BRAF	Mutation
Bladder	Carcinoma	CCND3	Mutation
Bladder	Carcinoma	CREBBP	Mutation
Bladder	Carcinoma	EGFR	Mutation
Bladder	Carcinoma	FANCA	Mutation
Bladder	Carcinoma	FGFR3	Mutation
Bladder	Carcinoma	HRAS	Mutation
Bladder	Carcinoma	JAK2	Mutation
Bladder	Carcinoma	KDM6A	Mutation
Bladder	Carcinoma	MLL3	Mutation
Bladder	Carcinoma	NOTCH1	Mutation
Bladder	Carcinoma	NRAS	Mutation
Bladder	Carcinoma	PIK3CA	Mutation
Bladder	Carcinoma	RB1	Mutation
Bladder	Carcinoma	TP53	Mutation
Bladder	Carcinoma	TSC1	Mutation
Bladder	Carcinoma	KRAS	Mutation (G12C)
Bladder	Carcinoma	AKT1	Mutation, amplification
Bladder	Carcinoma	JAK1	Mutation, amplification
Bladder	Carcinoma	FGFR1	Mutation, Fusion (NTM-FGFR1)
Bladder	Carcinoma	BCL2	Overexpression
Bladder	Carcinoma	MRE11A	Single nucleotide polymorphism
Bone	Ewing Sarcoma	ETV4	Fusion / translocation with EWSR1
Bone	Multiple Osteochondroma	EXT1	Mutation
Bone	Hereditary multiple exostoses (HME)	EXT2	Mutation
Bone	Carcinoma	IDH1	R132
Bone	Carcinoma	IDH2	R172
Bone	Carcinoma	MYCN	Amplification
Bone	Carcinoma	ALK	F1174L
Bone	Embryonal carcinoma and medulloblastoma	SUFU	Heritable constitutional mutations, genomic duplications and point mutations
Bone	Carcinoma	SMARCB1	Mutation (or allelic loss/deletion)
Bone	Carcinoma	SMO	Mutations, esp W535L, R562Q, R199W, L412F
Bone	Carcinoma	SMO	Mutations, including D473H, E518K, codons 225, 223, 391, 388, 400
Bone	Carcinoma	TERT	Point mutations
Bone	Carcinoma	IDH1	R132H
Bone	Carcinoma	IDH2	R172
Bone	Carcinoma	GPR124	SNP
Bone	Carcinoma	LMO1	Translocation/amplification, mutations, overexpression
Bone	Carcinoma	LMO3	Translocation/amplification, mutations, overexpression
Bone	Carcinoma	BARD1	Tumor suppressor; oncogenic isoform
Bone	Carcinoma	PHOX2B	
Bone	Carcinoma	ESR1	Activating mutation in ligand-binding domain

As they dig deep into the human genome, pathologists are finding increasingly more precise—and complicated—molecular information for clinicians. The table shown here is a small excerpt from a 611-gene resource (the Cancer Genomics Resource List 2014) that Marina Nikiforova and 15 colleagues spent two years compiling. They tracked next-generation sequencing–based cancer tests and where they were offered; tests for nearly 400 of the mutations were only offered at one or two institutions.

## GETTING PERSONAL WITH THE GENOME

BY ROBYN K. COGGINS

# PATHOLOGICAL FUTURES

“I remember the first time I saw DNA,” says molecular pathologist Marina Nikiforova, an MD, with a gleam in her eye. “You can see DNA forming,” she says. “You can see it by eye.”

Anyone can: Break the cell membrane with enzymes and pull away proteins to unzip that familiar ladder shape. With the right temperature and a little patience, it’ll appear—white, gauzy wisps swirling in a test tube, the schema for our entire being exposed.

“It’s like long strands, just folding, folding, folding.... It was one of the most fascinating, important moments,” Nikiforova says.

Swiss scientist Friedrich Miescher first discovered DNA and RNA in 1869. In 1995, when Nikiforova first saw the human genome, it hadn’t been sequenced yet; technologies that transform that test tube gossamer into useful information were still in their infancy. While it takes about eight hours for a cell to replicate its DNA, to decode 99 percent of the human genome took researchers around the globe nearly 15 years, culminating in 2003.



Pitt pathologists are going submolecular.

SIGRID GOMBERT, © MEDIA BAKERY



Patients are already seeing benefits from this initiative. Yet, “personalized medicine” or “precision medicine” has a way to go to before it’s fully realized.

Modern pathology has a huge role to play in bringing it about. And the more pathologists are enamored with the still stubbornly mysterious and maddeningly complex fabric of life, the more we all stand to benefit.

**P**icture the classic college lecture hall: The brilliant professor broadcasts her knowledge to her students in the least time-intensive manner possible. Some students don’t understand the material, but those individual needs are not within the purview of a 200-seat classroom. They’d better ask a classmate (or Google) for clarifications. This teaching method certainly isn’t guesswork, but it’s probably not the best way to teach individual students, either. That’s medicine in the pre-genetic sequencing era: *Here’s a treatment—we have reason to believe it works for most people. Good luck, dear patient.*

Now picture those upper-level science courses of undergrad and graduate school, with smaller enrollments, more intimate seminar settings. Boom, that’s precision medicine—the class is grouped into students with similar backgrounds and needs, which means instruction, though not quite one-on-one, is much more specialized. In medical parlance: *Here’s a treatment we know targets this subtype of this ailment, and we have several more treatments in the toolshed.* Or as Nikiforova puts it, “Now the doctor won’t just pick any drug and give it.” She’ll use evidence-based genetic profiles to get it right on the first try.

Precision medicine isn’t at the tutor-pupil level just yet, and may never be—despite some reporters’ claims that we’d get made-to-order drugs once the human genome was sequenced, that’s unlikely to happen. (You wanted your own pharmaceutical brand? Sorry.) More likely, molecular pathologists like Nikiforova and other biologists will narrow in on increasingly specific disease markers, and, in response, more targeted drugs will be manufactured as both primary and secondary treatments.

As we approach this more precise era in medicine, we expect the role of professor will be taken up by the treating physician. Yet, clinicians often are unclear about the meaning of the mutations that sequencing discovers. Someone needs to translate. That’s a pathologist’s job. (Already pathologists make or confirm 60 to 70 percent of diagnoses in UPMC

hospital patients.)

But heck, some *pathologists* are overwhelmed by the genetic stew of possibility. The magnitude of this problem is hard to overstate; clinical interpretation and translation are a real challenge beyond sequencing. So getting more precise medicine to patients is going to take some seriously skilled pathologists.

Consider: Every person has his or her own 3 billion base-pair recipe, and those base pairs tend to vary in about 2 million ways—some harmful, some not. Let’s take a moment to look at the ingredient list.

The genome is the whole shebang—all the genetic material in a human. When scientists say we’ve “mapped the human genome,” they mean we’ve determined the sequence of nucleotides in a given sample of DNA. It’s important to emphasize that researchers have mapped a human genome, not the definitive blueprint for humanity. Each individual has variations therein. (For the curious: Anonymous volunteers donated DNA for the Human Genome Project. Nobody involved in the massive effort knows exactly whose samples were used.)

From big to small on the genetic continuum: We’ve got 23 pairs of chromosomes (a total of 46), which help pack 6 feet of DNA into each human cell. That wispy DNA is made up of base pairs—cytosine, guanine, adenine, and thymine—which pair C-G and A-T, over and over billions of times to make us who we are.

The ATCG nucleic acid pairings determine how proteins are expressed and which enzymes a cell rallies to trigger our basic biological processes like metabolizing drugs or digesting sugars. Variations within these pairs, called single nucleotide polymorphisms, or SNPs, are common within a population, but sometimes result in nonsense or missense alterations.

With some 20,000 genes and more than 100,000 proteins, there’s a lot of room for error. And that’s just the coding part of the genome. Something like 95 percent of the human genome is noncoding—what scientists used to call “junk” but now suspect contains the power switches to the coding parts. The epigenome, or chemical tags that ride on the backbone of DNA but are separate from the genetic sequence, influences which of these switches get flipped.

So, variations in any part of this biological formula can influence or directly cause disease (or not). There are parts of the genome that are totally unstudied. Even the known

parts are extremely complex and vary by individual. Because the genome is so incredibly large, sometimes genomic pathologists focus on just the exome—the 1 percent or so of the human genome that happens to harbor most mutations related to disease. In short, the future of medicine—precision medicine—is a veritable flood of possibility.

Well then, how is this new era evolving?

Today’s pathologists work on a scale from macro to molecular. Anatomic pathologists look at the big stuff, the gross tissues themselves. After the anatomic pathologist slips the slide under a microscope, he narrows down to the micro-anatomy of cells, sometimes on a FISHing expedition, known more technically as “fluorescence in situ hybridization”—a colorful dye-job that helps scientists see cellular structures.

Nancy E. Davidson, an MD, director of the University of Pittsburgh Cancer Institute and UPMC CancerCenter and Distinguished Professor of Medicine at Pitt, wrote in a March *Journal of the American Medical Association* editorial on breast biopsies that this “critical tissue diagnosis from the anatomic pathologist directly determines patient management. That diagnosis is based on morphology, the relationship between cellular and architectural features.”

Yet that examination itself is subject to interpretation, depending on who’s doing the biopsy, how it’s sampled, and who looks at the tissue. Though this step yields undoubtedly important clinical information, the sample demands a closer look.

More recently, pathologists have been able to zoom in further, down to the submicroscopic, the molecules, the DNA and RNA themselves. (RNA transcription is yet another layer in this molecular genetic jumble.) This closer look is expected to be somewhat more objective, notes Davidson.

“Will cytopathology die? No,” says Nikiforova. “All this [molecular approaches] will be in conjunction with traditional pathology . . . to improve patient management.”

Spurred by the sight of DNA, Nikiforova soon thereafter completed a clinical pathology residency and a fellowship in molecular diagnos-



Nikiforov



Nikiforova



Michalopoulos



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ously. But cancer is an especially fertile ground to put precision medicine to the test.

"I hate to use the expression 'low-hanging fruit,'" says George Michalopoulos, MD/PhD chair of Pitt pathology, "but because we have the normal genome of the individual and the cancer genome, we'll make comparisons." In other words, comparing a tumorous sample and a healthy sample from the same person can indicate how the tumor came to be. This is opposed to more nebulous and tangled genetic associations, like the many genes correlated with alcoholism or heart disease, that have muddier (or are missing) comparison points.

Generally, doctors have identified cancers by origin in the body—lung, breast, brain. But, like the brain-pancreas mutation example shows, cancer knows no borders.

Two genes famous for showing up in various cancers are BRCA1 and BRCA2, which are on chromosomes 17 and 13, respectively; when functioning properly, these genes produce proteins that help repair DNA and ultimately suppress tumors. A mutation at one

mutations—known to signal aggressive, recurrent prostate cancer. Their findings, published in the *American Journal of Pathology* last September, will be used to appropriately gauge treatment after prostate cancer is identified. To get there, the team had to sequence 289 RNA samples some 1,300 times. (And, in another study, to be published, a group at Pitt has identified gene fusions in advanced breast cancer, including an estrogen-receptor related fusion that blocks antihormone action.)

One of the most successful cancer drugs to date, Gleevec, also targets a fusion site, notes Jeremy Berg, PhD director of Pitt's Institute for Personalized Medicine. Known generically as imatinib, the drug has been heralded as a cancer breakthrough for its success treating chronic myelogenous leukemia and some gastrointestinal tumors—nearly doubling five-year survival rates for the former to 59 percent.

Imatinib targets the activity of the product of chromosome 9's ABL1 gene and its cell division processes. When fused with the BCR gene, activity of the overexpressed protein goes

which he half-seriously offers a solution:

"There should be a national draft for biologists—everybody should do two years of biology research. It's just so many years of work to be done." Right now, researchers are devoting their entire lives to studying one or two genes. In Michalopoulos's view, that pace is too slow.

If you talk to young pathologists about modern pathology's methods, Nikiforova says "they will tell you, *This is unprecedented; this is the most exciting part of pathology*. They all want to learn and to know and to be part of it. For older generations of pathologists, it's very difficult to learn about this and to get engaged in the process."

Pitt pathology, for its part, has anticipated and anteceded the larger field's trends. Yousem, who was the former vice chair of the pathology department, saw the writing on the wall a dozen years ago and insisted that his colleagues get focused. "I gave everybody two years' notice and said, *We're going subspecialty* . . . We were probably the second hospital in the country after

**A brain cancer patient's mutation profile happened to show a rare marker that usually appears in pancreatic cancer. A pathologist noticed it and was able to offer an atypical but clinically appropriate course of treatment. The next month, with the exact same two docs, the roles were reversed.**

of those points increases the risk of breast and ovarian cancers by double-digit percentages. Patients found to have a BRCA mutation may elect preventive surgeries or have more frequent exams to catch abnormal tissue earlier.

But the concept of mutation itself isn't as cut and dried as it sounds. There are many ways a gene can mutate: It can fuse with a nearby gene or swap positions. It can mismultiply and drop an important element or gain an extra nucleotide. Pathologists and oncologists are increasingly turning to analysis of these sequence variations to trace disease, as well as trace its progression.

Researchers are learning that gene expression itself exists on a continuum of degrees, with some debate on the middle-of-the-road expressions. This is a deeper, more ambiguous part of making medicine more precise.

A recent study headed by Michalopoulos, with Jianhua Luo, an MD/PhD professor of pathology, and Joel B. Nelson, the Frederic N. Schwentker Professor and chair of urology, identified eight fusions—those smushed

haywire; imatinib selectively interferes with that process, stopping irregular protein and enzyme production.

Berg, who's also associate senior vice chancellor for science strategy and planning in the health sciences, as well as Pittsburgh Foundation Professor of Personalized Medicine and of computational and systems biology, wonders whether scientists should be looking for more fusion targets (rather than "point mutations," or single alterations).

He also stresses that genomic findings "need to be correlated with outcomes. . . . It's also important not to say that with these molecular tools, all these ambiguities are going to go away, because they'll initially get more ambiguous."

The deeper we dig, the more we find—which means more knowledge and also more to synthesize.

Michalopoulos, the Maud L. Menten Professor of Pathology, says that despite advances in technology and bioinformatics, the field is facing serious knowledge gaps, for

Mass. General to go [that route]."

Back then, Yousem told pathologists with an interest in liver, "*Your life is liver; you live, breathe liver. And as part of you living, breathing liver, you have to go and live and breathe with your clinician colleagues so that you can see what they're interested in from a research perspective and from a patient care perspective.*"

The move might seem contradictory at first—if we know that cancer's originating organ, for instance, may not matter, why organize that way? Yousem's bet was that focusing in would allow everyone to broaden out. In other words, if pathologists could dig deeper, they could eventually find connective roots that a group of generalists stuck at the surface would miss. Being more precise allowed everyone to see a bigger picture.

That focus resulted in specialized clinical tests that no other institution had, or even has—physicians from all over the country send, for instance, thyroid samples to Pitt for one-of-a-kind analysis.

Getting to this position meant redoubling the department's focus on technology. As Pitt

snagged Nikiforova and Nikiforov in 2006, the school began expanding research space in the UPMC Clinical Labs Building to the seventh and eighth floors and hired more than 35 staff members. (For more on the lab and what runs beneath it, see p. 7.) The Nikiforovs joined Sanja Dacic, MD/PhD professor of pathology and director of the FISH and Developmental Laboratory, to grow molecular testing at Pitt. And just last October, molecular and genomic pathology rented the astoundingly fast, million-dollar HiSeq 2500.

Were it not such an expensive machine, one might run a palm over its cover like that of a sleek sports car. Whereas the lab's older MiSeq machine—a real workhorse—can pump out more basic next-generation sequencing results in about seven days, the HiSeq can do so-called “deep” sequencing, processing 96 patient samples—nearly 5,000 genes—in about 10 days. This is the Rolls-Royce of sequencing technology; machines like these have helped pathologists worldwide identify at least 140 genes mutated in cancer, with more expected.

Here's how it works. A lab tech injects chopped-up DNA base pairs into special gel on a plate or in thin tubes that are then zapped by electrodes. The different nucleotides are tagged with dye and lurch forward in response to the electrodes—how far forward they go signals their composition to the machine. The sequencer scans what happens and assembles the data into a probable genetic sequence (ACTGCGGAT...). This process happens over and over to validate the results—redundancy is a pathologist's friend, and that repetition is what makes the sequencing so deep and precise. Because the human genome is so large, pathologists can only sequence segments of DNA at a time. Once they have all the sequenced pieces, there's a bit of guesswork involved in putting it back together again.

On a tour of the lab, Nikiforova explains that the relatively zippy Rolls-Royce is for research only. “We didn't convert it to clinical yet because we're still working on validation” she says. “In clinical lab you have to be very strict.”

She would know: Pitt-based pathologists are duly focused on developing clinical tests that are reproducible, validated, and accurate, including Nikiforov's much-praised ThyroSeq NGS panel, which detects cancer in fine needle aspiration biopsies of the thyroid. This targeted next-generation sequencing approach allows many patients with cytologically indeterminate thyroid nodules to avoid surgery, which is the standard of care.

This February, at the Association for Molecular Pathology meeting, Nikiforova presented on

a Pitt-developed sequencing panel for brain tumors, which quantifies them from benign to aggressive. “Nobody's doing this worldwide,” she says—that is, mapping mutations, fusions, and anything tumor-specific that can help in both diagnosis and prognosis. Her collection of brain tumor markers isn't quite ready for the clinic, but Nikiforova expects it will be soon. “It's a need within the community,” she says, “but nobody [else] has designed it yet. And we do it in our lab, using our own resources, and our minds, and our energy.”

That last bit is the real key. Precision medicine might sound like a story of technology, and it is to some extent. But the clincher is people—knowledgeable pathologists like the Nikiforovs and Yousem and Michalopoulos who keep current on a tsunami of research, who can combine gross pathology with sequencer outputs and apply the results to real-world decision-making.

Again, some of that process is automated, as it should be. Once a sample goes through the MiSeq, the machine pops out a multicolored report highlighting disadvantageous mutations while marking neutral mutations with a smiley face. The reporting software, developed by fellow-turned-assistant professor Somak Roy, an MD, matches mutation results to ongoing clinical trials that the patient might enroll in, as well as potential drug therapies that might benefit that individual—usually several of each, which a trained pathologist must help the clinician decipher. (Roy is also assistant director of the molecular and genomic pathology lab.)

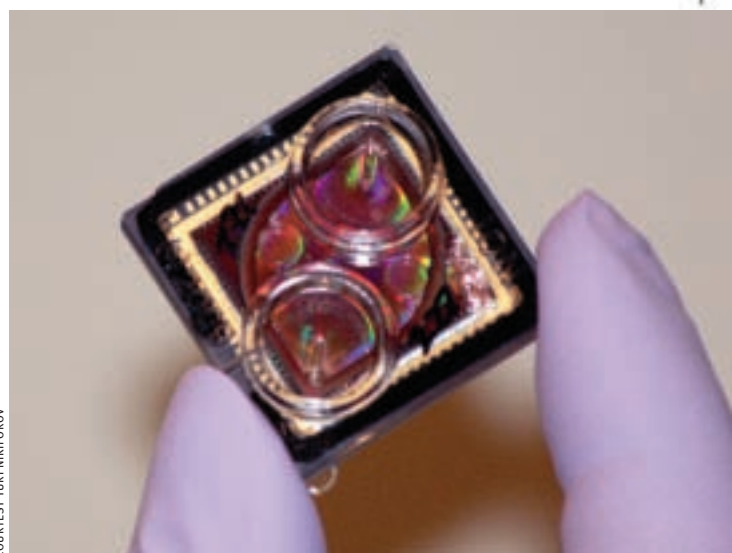
What's really impressive is the way Pitt pathologists are taking the tiny pictures that have emerged from genomic testing and piecing them back together again—that paradox of the tiny-turned-big. Nikiforova and 15 other researchers assigned by body-site specialty formed a working group from more than a dozen institutions throughout the United States. They cross-referenced known genes, mutations, and panels; compiled them; and sussed out patterns ripe for exploit. Their Cancer Genomics Resource List 2014 was published in the *Archives of Pathology & Laboratory Medicine* in December.

The working group found 611 genes for which next-generation sequencing is offered; of those, “tests for 393 genes were only offered by one or two institutions.” That means there

are lots of homegrown testing panels that could be shared across labs and institutions. There's also, as always in this field, a lot more to learn. The idea behind the resource list was to help academic and hospital laboratories, as well as for-profit ventures, develop tests themselves and consolidate knowledge.

Beyond that, Nikiforova wants to focus even further, on patients whose tumor mutations don't blip on the existing panels. She ticks off her ambitions in an avalanche. She's still amazed by the minutiae of the minutiae of life:

“We're developing sequencing of not only 50 genes, but sequencing of more than 5,000 genes at the same time. And [those]



COURTESY YURI NIKIFOROV

After a sample has been analyzed on a traditional slide, pathologists isolate the DNA and place it on a chip like this one for next-generation sequencing.

will be sequenced for mutations and for all messenger RNA expression. Exome and transcriptome analysis”—those protein coders and the full set of RNA molecules. “And we'll look at mutations, we'll look how genes are expressed”—she reminds that genes can be highly expressed or have low expression. “We'll look at gene fusions at the same time, copy number changes. Maybe some gene is amplified, [or there are] multiple copies of the gene present. That might serve us differently with a therapeutic target.

“So we're just expanding and going for deeper sequencing of samples that we [didn't] previously identify any mutations in. And this is a huge kind of effort that we are developing.”

She stops herself. “We're kind of pushing the boundaries. It's very difficult.” ■





Boy or girl? The biology is not always clear. And confusion and agony can persist for decades beyond the maternity ward. Arlene Baratz and Katie Baratz Dalke are helping smooth the way for children born with intersex conditions.

# LET'S TALK ABOUT SEX

## BIOLOGY THAT ISN'T BINARY

BY MICAELA CORN  
WITH ERICA LLOYD

In 1990, Arlene (MD '84, Res '90) and Mark (MD '84, Res '90) Baratz's 6-year-old daughter, Katie, had a surgical procedure to repair a hernia in her groin. Hernias are common, and are treated fairly easily with surgery. What's far less common is for a young girl's hernia to be caused by a partially descended testis—which is exactly what Katie's surgeon found on his operating table.

How can a girl have testes? Good question. Male and female gonads and genitals actually develop from indifferent precursors, and every embryo has two sets of ducts, the Müllerian and Wolffian, that can develop into internal reproductive structures. A number of genes, especially the SRY gene located on the Y chromosome, direct gonadal and genital development. The presence of the SRY gene on a Y chromosome typically signals the indifferent gonads to develop into testes, which produce the hormones known as androgens. The androgens in turn (principally, testosterone) are responsible for the development of indifferent genitalia into male external structures. At the same time, the testis secretes the hormone Müllerian-inhibiting substance (MIS), which prevents the Müllerian ducts from developing



into female internal structures. The absence of a Y chromosome with SRY, on the other hand, results in ovarian development. Without testosterone from the testis, female external structures develop, rather than male ones. (In addition, prenatal hormone exposure likely influences areas in the brain associated with hormone secretion in adolescence and adulthood.) This is a highly oversimplified explanation of what typically happens. Along the way, any number of hormonal signals can go astray; that's where things become anything but straightforward—in the delivery room and beyond.

Katie, for example, has complete androgen insensitivity syndrome (CAIS): a condition in which a Y chromosome triggers the development of testes, but for various reasons, the body doesn't respond to the androgens produced

there. The result is that the fetus with XY (typically male) chromosomes develops external female structures. The baby will look like a girl—and, typically, like Katie, grow up to identify as a girl—but will have internal testes in place of ovaries, fallopian tubes, and a womb.

When they learned of Katie's testes, all that Arlene (a radiologist) and Mark Baratz (a Pitt orthopaedist) knew of

intersex conditions was what they had been taught in medical school. "They were all called 'types of hermaphroditism' at that time," Arlene Baratz says ("male pseudo-hermaphrodite" being the term used to describe Katie's biology). "And we were told that when you diagnosed someone with one of these conditions, you did whatever you could to normalize their body. . . . And you had to do it early, so they wouldn't know about it, and then you never told them."

Before the era of informed consent, physicians often made decisions about gender assignment in cases of what are now known as "disorders of sex development" (DSD), which sometimes involved irreversible surgeries on ambiguous genitalia or other tissue, without involving the families. The thought was that the parents might reject the child. Today, parents are, of course, involved in all decision making, notes Selma Feldman Witchel (MD '78, Fel '83), cochair of the DSD Committee at Children's Hospital of Pittsburgh of UPMC. The DSD Committee is a multidisciplinary team with representation from urology, genetics, pathology,

and endocrinology; Arlene Baratz is the family/patient representative. Witchel, who is a Pitt associate professor of pediatrics, says the team gathers information from the family, physical examinations, hormone levels, imaging, and genetic testing to offer the best recommendation reflecting which gender a child will most likely identify with. At Children's, members of the DSD team are also involved in the care of gender-questioning children, adolescents, and young adults. "We are very aware that binary concepts of sex and gender are inadequate, and we need to be open to how individuals see themselves," says Witchel.

The Baratzes opted to leave in the testes, and let Katie eventually decide whether she wanted them. And they decided to be open with their daughter about CAIS, but it took some years to fully explain.

"I think I told her [in the early conversations] that most women have a nest inside their bodies where a baby can grow," Arlene Baratz says, in a 2011 documentary, *The Truth of My Sex*. And when Katie asked if she had that nest, too, her mother told her no, "but you will be a mommy, and you'll have a very lovely family, and it will be very exciting, because you'll be adopting your children."

"It really kind of changed my world," recalls Katie (now Katie Baratz Dalke) in the documentary. "I remember even as, like, a 9-year-old feeling sad whenever I saw pregnant women."

As Katie reached her teen years, her parents explained the details of her anatomy and genetics. Katie felt betrayed; a secret had been kept from her. "My doctors all knew about it . . . strangers, like people who just happened to be in the office when I was there, knew more about me than I did."

**T**alking about sex biology is not something our society is particularly good at, and diverse sex biology (or identity) even less so. The binary model is deeply embedded in our collective psyche. When a new baby is born, or even beforehand, what's the first thing everybody wants to know? *Is it a boy or a girl?*

Yet estimates of how many individuals present with DSD range from one in a hundred (according to the Intersex Society of North America) to one in 4,500 (per the National Institute of Child Health and Human Development). It depends on the variations you include. A 2006 world "Consensus Statement on Management of Intersex Disorders" includes

Klinefelter syndrome—that results when boys have more than one X chromosome; the incidence of Klinefelter alone is one in 800.

"There's a real need to find a common language," Arlene Baratz says.

The world consensus statement, published in a period of increasing acceptance for sex variability, did away with the hermaphrodite-based terminology that the Baratzes first learned. Yet the current DSD lexicon is not embraced by everyone.

"I think clinicians often don't realize how the terms that they use can be hurtful to patients," says Arlene Baratz. "Just the term 'disorders' is very controversial in the community. People feel like, *Well my body is different; why is that a disorder?* It's pathologizing."

Patients can become disengaged, or demanding, about the terminology used to define them or their conditions, Arlene Baratz notes. Clinicians react. "The whole interaction ends up making people feel like they don't want to go for medical care," she says. "It has led to health disparities."

To combat some of this, and to be the social support for others that she wishes she'd had as a young mom, Arlene Baratz is a board member and medical and family adviser to the AIS-DSD Support Group and moderator of the AIS-DSD Parents Group. In 2014, she helped draft a policy that got the community "a seat at the table" (from study inception to goals and design) for two currently National Institutes of Health-funded DSD research projects. Arlene Baratz is also a founding member of Accord Alliance (which promotes integrated, comprehensive care in the DSD community) and sits on the board of Advocates for Informed Choice (which advocates for children born with DSD in legal and other spheres). In February, she gave a talk at the medical school, "DSD 101: Dealing with Reproductive Diversity."

With Katie, who is now a psychiatrist at the University of Pennsylvania, Arlene Baratz cochairs the committee on patient perspectives as part of an ongoing effort to update the 2006 world consensus statement, the earliest papers from which are expected to be published by summer's end. A separate nomenclature committee has acknowledged the need to replace "DSD." Baratz is hopeful: a number of patients sit on that committee.

"When I look back, I can see that [change] is happening," she says. "It always seems very slow while you're doing it, but it's such a different world from when my family was young, and I'm very grateful for that." ■





# MATCH RESULTS

## CLASS OF 2015

### ANESTHESIOLOGY

Dilla, Andrew  
Oregon Health & Science University  
Lu, Shu  
Massachusetts General Hospital/Harvard University  
Steen, Talora  
Brigham & Women's Hospital/Harvard Univ., Mass.  
Sween, Lindsay  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.

### DERMATOLOGY

O'Neill Dulmage, Brittany  
McGaw Medical Center, VA/Northwestern Univ., Ill.

### EMERGENCY MEDICINE

Babalola, Kathlene  
Albert Einstein Medical Center, Pa.  
End, Bradley  
Ohio State University Wexner Medical Center  
Espinoza, Joaquin  
Oregon Health & Science University  
Fritz, Christie  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
Kingsley, Evan  
Temple University Hospital, Pa.  
Lee, Ted  
University of New Mexico  
McCann, Sean  
Presence Resurrection Medical Center, Ill.  
Morley, Julia  
UPMC/University of Pittsburgh, Pa.  
Romero, Cynthia  
Vanderbilt University Medical Center, Tenn.  
Sabedra, Alexa  
University of Cincinnati Medical Center, Ohio  
Shestak, Christopher  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
Taylor, Shameeke  
University of Chicago Medical Center, Ill.  
Wang, Xiao  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
Zhang, Richard  
University of Chicago Medical Center, Ill.

### FAMILY MEDICINE

Alger, Mikaela  
Swedish Medical Center/University of Washington  
Duff, Kyle  
Washington Hospital, Pa.  
Harding, Mark  
Robert Wood Johnson Medical School/  
Rutgers University, N.J.  
Huynh, Leticia  
University of Tennessee  
Kamprath, Sagar  
UPMC St. Margaret/University of Pittsburgh, Pa.  
Knox, Jordan  
University of Utah Affiliated Hospitals  
Martz, Rebecca  
Christiana Care Health System, Del./  
Thomas Jefferson University  
Rhem, Marla  
UPMC St. Margaret/University of Pittsburgh, Pa.

### INTERNAL MEDICINE

Arboleda, David  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
Bilan, Victor  
Yale-New Haven Hospital, Conn.  
Calderon, Luis  
Georgetown University Hospital, Washington, D.C.  
Chin, Katherine  
UPMC/University of Pittsburgh, Pa.  
Chung, Jeffrey  
Barnes-Jewish Hospital/Washington University, Mo.  
Fu, Polly  
UCSF Medical Center, Calif.  
Gillum, Megan  
Duke University Medical Center, N.C.  
Hudak, Stephen  
UPMC/University of Pittsburgh, Pa.  
Jochum, John  
UPMC/University of Pittsburgh, Pa.  
Karpenshif, Yoav  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
Kaus, James  
Mount Sinai Beth Israel, N.Y.  
Leef, George  
Stanford University, Calif.  
Li, Allen  
UPMC/University of Pittsburgh, Pa.  
Lopez, Carlos  
North Shore-LIJ Health System, N.Y.  
Lu, Bonnie  
UPMC/University of Pittsburgh, Pa.  
McCloskey, Karen  
New York University  
Nakajima, Erica  
Vanderbilt University Medical Center, Tenn.  
Nidadavolu, Lolita  
Rhode Island Hospital/Brown University  
Nolen, Brian  
UPMC/University of Pittsburgh, Pa.  
Nuñez, Eduardo  
Rhode Island Hospital/Brown University  
Plonka, Caitlyn  
University of Chicago Medical Center, Ill.  
Rao, Anjali  
UPMC/University of Pittsburgh, Pa.  
Rattan, Puru  
Emory University, Ga.  
Raymond, Dahlia  
Hahnemann University Hospital/Drexel University, Pa.  
Rocco, Joseph  
UPMC/University of Pittsburgh, Pa.  
Rosasco, Maria  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
Rosborough, Brian  
Massachusetts General Hospital/Harvard University  
Tefera, Leben  
University Hospitals Case Medical Center/  
Case Western Reserve University, Ohio  
Wong, Jeffrey  
Brigham & Women's Hospital/Harvard University,  
Mass.  
Wu, Alexander  
Cleveland Clinic/Case Western Reserve Univ., Ohio  
Xu, Peter  
University of Southern California

Younes, Ramee  
Olive View-UCLA Medical Center, Calif.  
Zhang, Janie  
University of Michigan Hospitals  
Zhong, Diana  
Barnes-Jewish Hospital/Washington University, Mo.

### INTERNAL MEDICINE— GLOBAL HEALTH

Kensler, Caroline  
UPMC/University of Pittsburgh, Pa.

### INTERNAL MEDICINE— PEDIATRIC

Cohen, Sarah  
Duke University Medical Center, N.C.  
Dhar, Abhishek  
Baylor College of Medicine, Texas  
Gilman, Alana  
Vanderbilt University Medical Center, Tenn.  
Holt, Stephanie  
UPMC/University of Pittsburgh, Pa.  
Janiczek, Jonathan  
University of Cincinnati Medical Center, Ohio  
Jimenez-Bacardi, Adria  
Jackson Memorial Hospital/University of Miami, Fla.  
Langmann, Gabrielle  
UPMC/University of Pittsburgh, Pa.  
Lott, Margaret  
Jackson Memorial Hospital/University of Miami, Fla.

### INTERNAL MEDICINE— PRELIMINARY

Sink, Jacquelyn  
UPMC/University of Pittsburgh, Pa.  
Wolf, Joel  
North Shore-LIJ Health System, N.Y.

### INTERNAL MEDICINE—PRIMARY

Mattson, Jennifer  
New York University  
Nwadiuko, Joseph  
Johns Hopkins Bayview Medical Center, Md.

### INTERNAL MEDICINE— WOMEN'S HEALTH

Samberg, Diana  
UPMC/University of Pittsburgh, Pa.

### MAXILLOFACIAL SURGERY

Ahani, Kaveh  
UPMC/University of Pittsburgh, Pa.  
Shupak, Raymond  
UPMC/University of Pittsburgh, Pa.

### NEUROLOGICAL SURGERY

Chen, Stephanie  
Jackson Memorial Hospital/University of Miami, Fla.  
Nwachuku, Enyinna  
UPMC/University of Pittsburgh, Pa.

### NEUROLOGY

Agudelo, Christian  
Jackson Memorial Hospital/University of Miami, Fla.  
Goodheart, Anna  
Brigham & Women's Hospital/Harvard Univ., Mass.

### NEUROLOGY—PEDIATRIC

Triplett, Regina  
St. Louis Children's Hospital/Washington University, Mo.



Love was in the air this match day. All seven of Pitt med's declared couples matched together, including Rahul Shah and Alana Gilman, pictured here, who are bound for Vanderbilt University Medical Center.

## OBSTETRICS/GYNECOLOGY

Benabou, Kelly  
Women & Infants Hospital/Brown University, R.I.  
Duvet, Mildred  
Lehigh Valley Hospital, Pa./University of South Florida  
Fang, Nancy  
University of Colorado  
Grady, Cynthia  
Louisiana State University  
O'Neill, Elizabeth  
UPMC/University of Pittsburgh, Pa.  
Phillips, Jaclyn  
George Washington University, Washington, D.C.  
Vij, Ruchika  
Ohio State University Wexner Medical Center  
Wang, Nan  
Ohio State University Wexner Medical Center

## OPHTHALMOLOGY

Duerr, Eric  
Bascom Palmer Eye Institute/University of Miami, Fla.  
Kim, Jocelyn  
Georgetown University Hospital, Washington, D.C.  
Shah, Samir  
Hines VA Hospital/Loyola University, Ill.  
Zhou, Siwei  
UPMC/University of Pittsburgh, Pa.

## ORTHOPAEDIC SURGERY

Labrum, Joseph  
Harbor-UCLA Medical Center, Calif.  
Schott, Trevor  
Massachusetts General Hospital/Harvard University  
Zhao, Emily  
UPMC/University of Pittsburgh, Pa.

## OTOLARYNGOLOGY

Dixit, Ronak  
UPMC/University of Pittsburgh, Pa.  
Pendleton, Kelsey  
UPMC/University of Pittsburgh, Pa.  
Sukato, Daniel  
SUNY Health Science Center, Brooklyn, N.Y.

## PATHOLOGY

Abel, Jacob  
University of Tennessee  
Kang, Liang-I  
Barnes-Jewish Hospital/Washington University, Mo.

## PEDIATRICS

Barney, Angela  
Jackson Memorial Hospital/University of Miami, Fla.  
Bernard, Heather  
Children's Hospital of Pittsburgh of UPMC/  
University of Pittsburgh, Pa.  
Bowles, Austin  
University of Utah Affiliated Hospitals

Cohen, Adam  
Children's National Medical Center/  
George Washington University, Washington, D.C.  
Dreyzin, Alexandra  
Children's Hospital of Pittsburgh of UPMC/  
University of Pittsburgh, Pa.  
Frazer, Lauren  
University of North Carolina Hospitals  
Gupta, Rachelle  
Massachusetts General Hospital/Harvard University  
Liu, Mona  
Mattel Children's Hospital/UCLA, Calif.  
McDaniel, Lauren  
Johns Hopkins Hospital, Md.  
Oparaji, Judy-April  
Walter Reed National Military Medical Center,  
Bethesda, Md.  
Papa, Rebecca  
North Shore-LIJ Health System,  
Cohen Children's Medical Center, N.Y.  
Ross, Megan  
University of Colorado  
Shah, Rahul  
Vanderbilt University Medical Center, Tenn.  
Stone, Mary Katherine  
Lurie Pediatrics, McGaw Medical Center/  
Northwestern University, Ill.

## PHYSICAL MEDICINE & REHABILITATION

Bean, Allison  
Mount Sinai Health System, N.Y.  
Haas, Matthew  
Rehabilitation Institute of Chicago, McGaw Medical  
Center/Northwestern University, Ill.  
Pfoff, Marissa  
UPMC/University of Pittsburgh, Pa.  
Steere, Hannah  
Spaulding Rehabilitation Network/  
Harvard University, Mass.

## PLASTIC SURGERY

Shakir, Sameer  
Hospital of the University of Pennsylvania  
Zammerilla, Lauren  
University of Texas Southwestern Medical Center

## PSYCHIATRY

Amin, Priyanka  
UPMC/University of Pittsburgh, Pa.  
Ciuffetelli, Gary  
UPMC/University of Pittsburgh, Pa.  
Hoffman, Gil  
UPMC/University of Pittsburgh, Pa.

## RADIATION ONCOLOGY

Binks, Joshua  
University of Arizona Affiliated Hospitals

Iheagwara, Uzoma  
UPMC/University of Pittsburgh, Pa.  
Kang, John  
Strong Memorial Hospital/University of Rochester, N.Y.  
Ling, Diane  
UPMC/University of Pittsburgh, Pa.  
Rhieu, Byung Han  
Johns Hopkins Hospital, Md.

## RADIOLOGY—DIAGNOSTIC

Narendra, Divya  
Strong Memorial Hospital/University of Rochester, N.Y.  
Srivastava, Udayan  
University of Texas Southwestern Medical Center  
Sun, Ellen  
Brigham & Women's Hospital/Harvard University, Mass.  
Taylor, Kevin  
Vanderbilt University Medical Center, Tenn.

## SURGERY—CARDIOTHORACIC

Mallios, Demetrios  
University of Southern California

## SURGERY—GENERAL

Caparosa, Ellen  
Thomas Jefferson University, Pa.  
Cutler, Jessica  
Monmouth Medical Center, N.J./Drexel University  
Evans, Megan  
Lehigh Valley Hospital, Pa./University of South Florida  
Huang, Bernice  
NewYork-Presbyterian Hospital/Columbia University  
Medical Center  
Landreneau, Joshua  
Cleveland Clinic/Case Western Reserve University, Ohio  
Lee, Tiffany  
University of Texas Southwestern Medical Center  
Puyana, Salomon  
Kendall Regional Medical Center/  
University of South Florida  
Rieser, Caroline  
UPMC/University of Pittsburgh, Pa.  
Severance, Sarah  
Indiana University  
Shterental, Sebastian  
North Shore-LIJ Health System, N.Y.

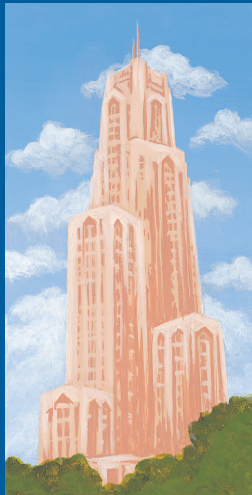
## TRANSITIONAL MEDICINE

Ukeje, Kene  
Walter Reed National Military Medical Center,  
Washington, D.C.

## UROLOGICAL SURGERY

Ayyash, Omar  
UPMC/University of Pittsburgh, Pa.  
Chen, Leo  
Stanford University, Calif.





## CLASS NOTES

## '60s

People keep asking **Catherine DeAngelis** (MD '69), who stepped down as editor-in-chief of *JAMA* in July 2011, how she came to be the first woman and first pediatrician to get that gig. So she's writing a memoir, *JAMA Mama*, in response. Last year, the Johns Hopkins University Distinguished Service Professor Emerita published a book on patient care and professionalism with Oxford University Press. She serves on the University of Pittsburgh Board of Trustees and teaches at Hopkins. This April, the esteemed "Dr. De" will be awarded the Howland Medal of the American Pediatric Society, one of the highest awards in pediatric medicine, bestowed annually for distinguished service in the field.

**Robert Kisilevsky** (PhD '69) hand-carved his own chess board, its pieces, and its storage case from wood local to Kingston, Ontario, Canada, where the Queen's University professor emeritus of pathology and molecular medicine now lives. And before he founded his own biotechnology company, Neurochem, (now Bellus Health) in 1993, he carved out the insights that were key to the company's work in amyloids, narrow protein deposits found in several disease states. Kisilevsky revealed mechanisms of amyloid deposits, then developed compounds to remove them and block their formation—work that has applications in Alzheimer's, adult-onset diabetes, and malaria. Kisilevsky says Pitt was a good choice for him. "Not only did I get the training, but I found my wife there, too." Barbara (Smatsky) Kisilevsky, a School of Nursing graduate, has published widely on a fetus's ability to hear voices from inside of the womb.

## '70s

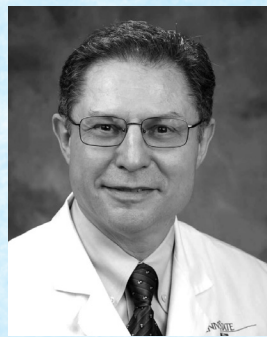
The Joseph P. Kennedy Jr. Intellectual and Developmental Disabilities Research Center at the University of Chicago, directed by **Nancy Schwartz** (MS '67, PhD '71), has been awarded more than \$1 million this year in grant support, mostly from the National Institutes of Health, to examine the mechanisms of brain injury and genetic disorders. Among the group's many research endeavors is the use of nanoparticles to treat disorders associated with intellectual disability caused by abnormal folding of proteins. In Schwartz's own research, she focuses on genetic abnormalities implicated in chondrodystrophies, disorders that affect the development of cartilage. Schwartz is also the postdoctoral dean at the University of Chicago.

## '80s

**Vincent Verdile** (Emergency Medicine Resident '87), a former Pitt emergency medicine faculty member, is now the Lynne and Mark Groban Distinguished Dean and professor of emergency medicine at Albany Medical College and executive vice president for health affairs at Albany Medical Center. Under Verdile's leadership, Albany has established a new simulation center for medical students and practicing physicians and updated its admissions process to incorporate multiple mini interviews—standardized scenarios the faculty pose to med school applicants to take a deeper look at the whole person. Verdile is one of the longest-tenured deans of a U.S. medical college.

## '90s

**Vitaly Gordin** (Anesthesiology Resident '95, Pain Management Fellow '96) went to medical school in Latvia straight out of high school. After 10 years of practicing anesthesiology in the former Soviet Union (plus three more in the States), he completed a fellowship in pain management at UPMC. Gordin appreciates the time with patients his role affords and enjoys "crosslinks with multiple specialties." Gordin's research interests include evidence-based support for interventional pain management procedures, including cortical steroid injections to the cervical and lumbar spine, and their efficacy compared with other such standard procedures as physical therapy or medication. The Penn State Milton S. Hershey Medical Center vice chair of anesthesiology for chronic pain management, director of pain medicine, and professor of anesthesiology works with former Pitt classmate **Lisa Sinz** (Anesthesiology Resident '95, Anesthesiology/Critical Care Fellow '96), who directs Penn State's simulation lab.



Gordin

## '00s

**Manny Hernandez** (MD '00) jokes about when he used to get evaluations back in medical school that said his personality was well suited for emergency medicine. "I think that some of the clinical specialties may have seen that as a polite way of giving me some feedback. I saw it as a compliment." Hernandez recently authored a chapter, "Assessing Your Needs," in a new textbook from Cambridge University Press titled *Emergency Department Leadership and Management: Best Principles and Practice*. Hernandez, who earned his MBA in 2006, divides his efforts between part-time clinical work at the University of Florida in Jacksonville and a full-time leadership position with the health care advisory services practice for CannonDesign, a design firm.



Kibbe

When **Melina Kibbe** (Surgery Resident '02) returns to Pitt this May for the first time in 13 years, she'll give the Richard L. Simmons Lecture at the 2015 Department of Surgery Research Day (and hopefully partake in a few pierogies while she's in town, she says). At Northwestern University, Kibbe studies novel nitric oxide-based therapies for patients with vascular



disease who undergo vascular interventions. She was recognized by President Obama with a Presidential Early Career Award for Scientists and Engineers in 2010 for this work. Among her many titles are Edward G. Elcock Professor of Surgical Research and vice chair of research in the Department of Surgery at Northwestern, as well as cochief of the Vascular Surgery Service at the Jesse Brown VA Medical Center. And this January, she added editor-in-chief of *JAMA Surgery* to the list.

**David Levinthal** (Neuroscience PhD '04, MD '06) wants gastroenterologists to ask for help. At both the bench and the bedside, the Pitt assistant professor in the Division of Gastroenterology, Hepatology, and Nutrition focuses on functional gastrointestinal and motility disorders. Because patients with such disorders often need psychological care, Levinthal aims to put psychosocial issues on the radar for gastroenterologists everywhere. His cross-disciplinary spirit will drive a project he began recently as a member of the inaugural class of the American Gastroenterological Association's Future Leaders Program. In his new role, Levinthal will network, receive mentoring, and explore ways the AGA can help young investigators organize and gain funding for multi-investigator scientific teams that span departmental and even institutional boundaries. "My goal has always been to move the field forward. As a researcher and a clinician at a medical center, I've done that in a microcosm. The

AGA is the flagship for the field."

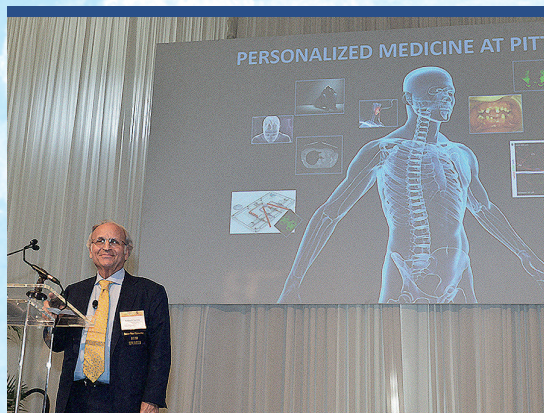
## '10s

As a Pitt med student, **Adrienne Clark** (MD '11) joined the Global Health Interest Group on campus and traveled to Guanajuato, Mexico, to establish global health research opportunities for Pitt

students and help strengthen ties between Pittsburgh's Mexican immigrant communities and their family members back in Guanajuato. The experience led Clark, now a fourth-year chief psychiatry resident at the University of Pennsylvania, to spend a month this past winter teaching at the University of Botswana and conducting clinical work at Sbrana Psychiatric Hospital in Lobatse, Botswana. She was selected by her chair as the program's first resident to serve in this role. Clark will begin a fellowship in child and adolescent psychiatry at Children's Hospital of Philadelphia this fall. —*Keightley Amen, Micaela Corn, and Keith Gillogly*



Clark



Presentations and celebrations at the Palm Beach Winter Academy: Addressing the crowd (photos on left)—Dean Arthur S. Levine and Pitt's personalized medicine czar Jeremy Berg. Soaking up the sun at the poolside reception (above)—MAA prez Jan Madison with speakers Lisa Parker and Steve Shapiro, and friends George Fechter and Chris Fulton.

## SNOWBIRDS OF A FEATHER

Many universities have special winter events in Florida that offer educational and other alumni relations programs, but none do it quite like Pitt. Eleven years ago, Arthur S. Levine (the John and Gertrude Petersen Dean and senior vice chancellor for the health sciences), a team from the Health Sciences Foundation, and a few "snowbirds" down in Naples, Fla., began planning a one-day program that would showcase University of Pittsburgh researchers, clinicians, educators, and others shaping the future of health care.

The first program speakers addressed just over 100 attendees on topics ranging from diabetes prevention to Alzheimer's disease imaging techniques developed at Pitt.

For Winter Academy's decennial this March, a gaggle of more than 400 guests fraternized at the Florida west coast event; Richard (MD '74) and Diane Maloney cochaired the host committee. What's more, Winter Academy has been such a hit that it branched out four years ago to Florida's east coast, when Margaret LaManna (MD '76), who spurred the bicoastal idea, hosted the event at her residence. More than 200 alumni and friends gathered this year at the Palm Beach Mar-a-Lago Club, owned by Donald Trump; the event was hosted by Herb and Barb Shear. The group gathered for talks on personalized medicine and pharmacogenomics, but the academy isn't just lectures—the flock also enjoyed fine food and poolside ambiance. —*Robyn K. Coggins*

**FOR INFO ON NEXT YEAR'S EVENTS: MICHAEL LAFRANKIE, [LMICHAEL@PMHSF.ORG](mailto:LMICHAEL@PMHSF.ORG)  
412-647-9071**



## LISA M. GRANDINETTI

AUG. 12, 1976–FEB. 27, 2015

**A**s a dermatology resident at the Cleveland Clinic, Lisa Grandinetti was struck by how much skin conditions affected quality of life for her patients who also had gastrointestinal diseases, even when their GI symptoms were under control. From the time she joined UPMC in 2009, she began receiving GI referrals. And as this roster grew, she became convinced that the 30 percent of people with celiac disease and inflammatory bowel disease (IBD) who also suffered from rashes, psoriasis, and skin ulcers needed specialized coordinated care. She realized this dream two years ago when she opened the first gastrointestinal dermatology clinic in the country as its founding director. Patients traveled from as far as the Carolinas to see her.

Grandinetti, a nonsmoker, was diagnosed with stage 4 lung adenocarcinoma in October 2014 and died four months later.

She was assistant professor of dermatology at the University of Pittsburgh and director of the dermatology residency program. And Grandinetti was known to make time for patients at a moment's notice. Once, she quietly paid out of pocket for a man's cab fare across town when he couldn't afford the trip. Likewise, she had an open-door policy with her residents, says Melissa Pugliano-Mauro, a dermatology colleague at UPMC, making herself available to them day or night.

"She really served as a mentor for me, even though we were the same age," Pugliano-Mauro says. "She was a really good role model to just say, 'Gosh, you're never too young to take the opportunity to have an impact on a department.'"

—Micaela Corn and Elaine Vitone



Grandinetti

## IN MEMORIAM

### '40s

FALK K. ARNHEIM  
MD '43A, RES '44  
JAN. 31, 2015

JAMES F. CULLETON  
MD '43  
JAN. 23, 2015

JAMES GIACOBINE  
MD '44  
JAN. 20, 2015

J. FRASER JACKSON  
MD '44  
MARCH 8, 2015

ROBERT McCHESNEY  
COYLE  
MD '45  
JAN. 1, 2015

PERRY H. ENGSTROM JR.  
MD '47  
JAN. 22, 2015

WILBUR S. MELLON JR.  
MD '48  
MARCH 13, 2015

### '50s

JOHN DAVID RODGERS  
MD '50  
FEB. 27, 2015

STEPHEN C. BRUNO  
MD '51  
JAN. 15, 2015

RALPH J. MILLER SR.  
MD '52  
FEB. 24, 2015

DAVID C. BORECKY  
MD '53  
FEB. 28, 2015

JOSEPH A. CIPCIC  
MD '54  
JAN. 9, 2015

LOUIS A. HERRMANN  
MD '54  
JAN. 21, 2015

SAMUEL LOWERY  
MD '55  
FEB. 3, 2015

DAVID B. RAAB  
MD '56  
MARCH 10, 2015

NICK L. TEREZIS  
MD '56  
MARCH 16, 2015

EDWARD J. CARNEGIE  
MD '57  
JAN. 11, 2015

JAMES N. FISHER  
MD '58  
MARCH 13, 2015

### '60s

MICHAEL J.  
SHAUGHNESSY  
MD '65  
FEB. 22, 2015

### '70s

RICHARD S. GEHL  
MD '70  
MARCH 10, 2015

JERRY K. LYNN  
PHD '72  
DEC. 25, 2014

DANIEL J. O'DONNELL  
MD '75  
APRIL 3, 2015

RONALD J. PENKROT  
MD '77  
MARCH 21, 2015

### FACULTY

ERNEST STERNGLASS  
FEB. 12, 2015

## ANIL PUROHIT LONE, BUT NOT ALONE

**W**hen Anil Purohit (Res '11) opened his first cardiology clinic in Lilongwe, Malawi, a line of 50-some patients stretched out the door. Some had sold items from their homes to pay for transportation there. Nearly all were suffering from serious heart complications.

The third-year cardiology fellow and clinical instructor of medicine has been in Malawi since August 2014 as part of an NIH-funded Fogarty International Center Global Health Program for Fellows and Scholars. (Only 20 clinicians nationwide were selected.) His yearlong project focuses on the effects of aspirin as a primary prevention strategy for cardiovascular disease in HIV patients. "Aspirin is the most powerful medication we have in Malawi to treat cardiac illness," he says. (In place of potassium supplements normally indicated for congestive heart failure, he prescribes three bananas a day.)

But as the only cardiologist in the country, he soon found the heart-health needs of an entire population on his shoulders.

"It took me a month, but I finally realized my role here in

Malawi is not to put these bandages in these big holes and to save lives [immediately]. My role here is basically to . . . build capacity and train Malawians."

In November, Purohit gave a three-day lecture series at the Malawi College of Medicine, teaching medical students and clinical officers (similar to physician assistants) how to interpret electrocardiograms. There were a couple of ECG machines available, he recalls, but no one had ever been taught how to use them. In the clinic, "that's probably the biggest impact I can make," he says. "Our role at the end of the day is not to take over. It's to teach and transfer these skills so that the Malawians can be in charge of their own health." —MC



Purohit is the only cardiologist in Malawi.

## MARVIN GRUBMAN A MAN, AN ISLAND, AND A VACCINE

BY JASON BITTEL

For 36 years, Marvin Grubman (PhD '72) began his workday with a decontamination shower. Then, each night before leaving the lab, he'd take another. And if his work that day meant visiting a room housing an infected animal, that'd be two more showers—one upon entering the room, another before exiting.

That's just how it goes when your office is on a restricted island where you're tasked with fighting infectious diseases for the Department of Homeland Security. Grubman was a lead scientist with the Plum Island Animal Disease Center, just off the northeast coast of Long Island, until he retired in 2013.

"It's not an easy place to work," he says with a laugh.

Grubman has worked with many diseases throughout his career, but none of them more intimately than a potentially fatal one that infects cloven-hooved animals like cattle, sheep, and pigs. You know it as foot-and-mouth disease.

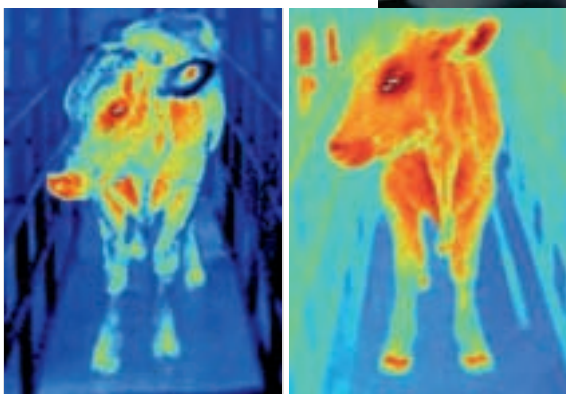
Not to be confused with hand, foot, and mouth disease, an illness common in children, foot-and-mouth disease is one of the most infectious diseases among animals and is potentially fatal. The virus causes lesions on the gums, lips, and tongue, as well as blisters on the animal's feet that can result in lameness. Thankfully, it's exceedingly rare for people to contract foot-and-mouth.

In 2001, the United Kingdom's livestock industry suffered more than 2,000 cases of foot-and-mouth. Because the virus spreads so quickly—from contact between animals, aerosols, or even inanimate objects like tractors—the UK opted to slaughter more than 10 million sheep and cattle in a desperate attempt to stop the outbreak. Some estimates put the total cost of containment at well over \$16 billion.

The goal of the Plum Island facility is to ensure that a similar fate never befalls the United States. And thanks to Grubman, the chance of that may now be smaller than ever.

In 2012, Grubman developed a novel vaccine

for foot-and-mouth disease that has two major benefits. The first is that the vaccine contains no active virus, which means it can be produced on the mainland. (The United States forbids any endeavor that would allow the



Grubman in his lab at Plum Island before his recent retirement. He has developed an experimental vaccine for foot-and-mouth disease. **LEFT:** His Plum Island colleagues investigated the use of infrared technology to identify infected animals (red indicates elevated temperatures).

active virus to make landfall, including scientific research—hence Plum Island's whole Fortress of Solitude-esque setup.)

The second benefit is that the vaccine can be identified in a blood sample, so livestock owners can differentiate between animals that have been infected and those that have been inoculated. This last bit means we'd only have to euthanize truly sick animals in the event of an outbreak, as opposed to every animal exposed to an infected one.

To create the vaccine, Grubman produced the virus's outer protein shell, or capsid, without the infectious ribonucleic acid center—kind of like a hollow M&M. Once inside an animal, its immune system spots the defanged capsid and creates antibodies to fight off the virus. It took seven straight years of tinkering before Grubman got this latest iteration of the vaccine, a combination of a hollow shell and virus-suppressing interferon, to work properly.

"I remember when we first got the results," he says. "It was amazing."

Grubman was amazed that it worked at all, and also amazed that it worked so quickly to

protect the test pigs. "This was the first demonstration that any approach could so rapidly protect naturally susceptible animals," he says.

Larry Barrett, director of the Plum Island Animal Disease Center, called the discovery the biggest news in foot-and-mouth disease research in the last 50 years.

Grubman is a touch more modest.

"There's still lots and lots and lots to do," he says, "but, over time, this will be improved and one day soon, hopefully, it can be used in the field."

Grubman and his wife, Annette, have since moved to Atlanta to be near their daughter, Susan. The couple also has a son, David, who got his law degree from the University of Pittsburgh and still resides in the area. Marvin still serves on the editorial board for the *Journal of Virology*.

Though he's been retired for two years now, Grubman keeps in touch with his colleagues at Plum Island to see how the vaccine is progressing. He says one of the things he misses about work is the sheer pursuit of it all, the constant struggle to make the vaccine better, but so far retirement agrees with him.

At the very least, there aren't as many showers. ■

COURTESY THE DEPARTMENT OF HOMELAND SECURITY







TOP PHOTO: WWE's Paige in a tongue wagging contest at Children's Hospital. MIDDLE PHOTO: Paige hugs Addison Mercurio. BOTTOM: Matthew Watts with WWE's R-Truth; Sin Cara looks on.

## SUPERSTARS LARGE AND SMALL

March was a good month for October Twisdale. He turned 6, celebrated the three-month anniversary of a heart transplant, and got to spend an afternoon hanging out with his heroes—professional wrestlers from WWE (World Wrestling Entertainment).

"I think he has a new best friend," said October's mom, Kristine Henzy, while watching her son craft a miniature WWE belt out of felt with the big-bearded, three-time world champion Daniel Bryan.

October was born with hypoplastic left heart syndrome and total anomalous pulmonary veins. You'd never know it to look at him though. His parents could hardly keep up as he weaved through the crowd laughing and getting all the wrestlers' autographs.

Seven-year-old Addison Mercurio, who was being treated for aplastic anemia, was a little more shy—at least around the male wrestlers. (Who wouldn't be intimidated by WWE's Sin Cara in a full-face lucha libre mask?) But that didn't stop her from getting a "no boys allowed" pic with WWE's Brie Bella and Paige.

Addison's father, Adam Mercurio, said that later that night, they noticed Paige on television wearing a bracelet Addison had given her. "It meant the world to her and all the other kids there."

The event was held as part of WWE's ongoing commitment to Connor's Cure, a fund created in honor of Connor Michalek, an 8-year-old fan who died last year from a rare tumor that affects the brain and spinal cord. The fund supports pediatric brain and spinal cancer research and helps with costs borne by families whose children are undergoing care. Connor's father, Steve Michalek, was also in attendance.

"I'm really proud of what this event has become," he said.

That same evening, Connor "The Crusher" Michalek was inducted into WWE's Hall of Fame and honored with its first Warrior Award.

—Story by Jason Bittel, Photography by Martha Rial

# CALENDAR

FOR ALUMNI & FRIENDS

## MEDICAL ALUMNI ASSOCIATION EXECUTIVE COMMITTEE BOARD MEETING MAY 13, 6 P.M.

For information:

Pat Carver at 412-648-9741, cpat@pitt.edu

\*Please consider becoming an MAA board member.  
(Teleconferencing is available for four annual MAA meetings if you are not a local physician.)

## MEDICAL ALUMNI ASSOCIATION REUNION WEEKEND MAY 15-18

Reunion Classes:

1955, 1960, 1965, 1970, 1975,

1980, 1985, 1990, 1995, 2000, 2005

For information:

Pat Carver at 412-648-9741, cpat@pitt.edu

## MAY 15

11 a.m., Graduation Luncheon  
Alumni Hall, J.W. Connolly Ballroom

5 p.m., Grand Opening Reception  
Pittsburgh Athletic Association

6:30 p.m., *The Sound of a Modern Symphony*  
Heinz Hall for the Performing Arts

7 p.m., Scope and Scalpel: *Modern Family Medicine*  
Central Catholic High School, McGonigle Theater

## MAY 16

9 a.m., Breakfast with the Dean and  
Today's Medical Students  
Scaife Hall, 11th Floor Conference Center

6 p.m., Reunion Gala: Dinner and Dance  
Twentieth Century Club

## MAY 17

11:30 a.m., Farewell Alumni Reunion Brunch  
Wyndham Pittsburgh University Center

2 p.m., Scope and Scalpel: *Modern Family Medicine*  
60th Reunion Celebration  
Central Catholic High School, McGonigle Theater

## MAY 18

4 p.m., Class of 2015 Graduation Ceremony  
Soldiers & Sailors Memorial Hall & Museum  
For information:

Ashley Knoch at 412-648-9059, akk57@pitt.edu

## WHITE COAT CEREMONY AUGUST 9, 3 P.M.

Scaife Hall Lecture Rooms 5 & 6  
Reception immediately following  
Petersen Events Center Lobby

For information:

Pat Carver at 412-648-9741, cpat@pitt.edu

## PHILIP S. HENCH DISTINGUISHED ALUMNUS AWARD DINNER

AUGUST 9, 6:30 P.M.

University Club, 123 University Place

For information:

Pat Carver at 412-648-9741, cpat@pitt.edu

COURTESY UNIVERSITY OF PITTSBURGH'S GRAHAM HATFULL, DEBORAH JACOBS-SENA, WELKIN POPE OF ARTS AND SCIENCES; ALSO: PITT'S JAMES CONWAY, ALEXANDER MARKOV, ALEXIS TRUET OF THE SCHOOL OF MEDICINE.



This looks like a glow-in-the-dark corn dog; it's really a virus that attacks bacteria.



## FOR REAL! TWEEN SCIENCE

At any moment, a microscopic arms race could be under way inside you. Humans are in a constant battle against invisible “bugs” that make us sick. But some bugs, like the bacteria that give us food poisoning, are often under attack by even smaller bugs—viruses called bacteriophages (phages, for short). A phage’s only mission in life is to make more phages. It needs bacteria—more specifically, bacteria’s protein-assembly machinery—to reproduce. Phages use special protein keys to “pick” locked ports in cell walls and inject their own genetic material (DNA or RNA) into carefully chosen host cells. Phage genes then hijack the bacteria and force them to build armies of new phages inside themselves. One type of phage forces the bacterium to make more and more new phages until it explodes, sending thousands of them out on the prowl for more victims. Others are sneakier—they slip phage genes into the bacterial DNA, and as the bacterium multiplies, so do the secret plans to build new phages. Over time, many generations harbor these phage plans until something turns the phage genes on. Then the bacteria start to manufacture the thousands of new phages that will eventually kill off their own cells. But don’t feel too sorry for bacteria—they can actually defend themselves from phage attacks. One lucky mutation can change the lock so that the phage can no longer pick it. Eventually, though, a fortunate phage’s “key” mutation will fit the lock, and then the arms race rages on.

As evil as they sound, phages could be allies in our battle against human disease. Because they are specific in their targets, scientists think that we could treat bacterial illness with a mixture of different types of phages. Maybe such treatments would work better than drugs (antibiotics) often prescribed today.

—Jennifer Lienau Thompson

Thanks to phage hunters and Pitt profs Roger Hendrix and James Conway, who filled us in on the wily ways of these microbes. The “corn dog” phage shown above was originally isolated by Pitt’s Bill Brucker.

For more kids’ stuff: [www.howscienceworks.pitt.edu](http://www.howscienceworks.pitt.edu)





THE OWL, 1973

# WHERE THE THEATER USED TO BE

If you’ve ever gotten directions along the lines of *Turn left at the joint that’s not there anymore*, you might be a Pittsburgher, or at least a Pitt alum.

And if you remember this street corner, you’re old enough to benefit from a **charitable gift annuity (CGA)**. It’s a way to provide yourself and/or a loved one with a guaranteed income for life, and receive a tax deduction, while building a stronger future for Pitt. You can even designate a specific area that your gift will benefit, like the medical device researchers at the McGowan Institute for Regenerative Medicine—they’ve got spiffy green-design labs down on the Mon now, where LTV Steel used to be. Or the up-and-coming docs at the new Children’s Hospital of Pittsburgh of UPMC in Lawrenceville—you know, where St. Francis Hospital used to be.

The examples below are based on a minimum gift of \$10,000.

AGE	RATE	YEARLY INCOME	ESTIMATED DEDUCTION
55	4.0	\$400	\$2,327
60	4.4	\$440	\$2,638
65	4.7	\$470	\$3,282
70	5.1	\$510	\$3,946
75	5.8	\$580	\$4,468
80	6.8	\$680	\$4,946
85	7.8	\$780	\$5,615
90	9.0	\$900	\$6,271

To learn more, contact:

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Because of varying restrictions, Pitt is not able to offer gift annuities in some states.