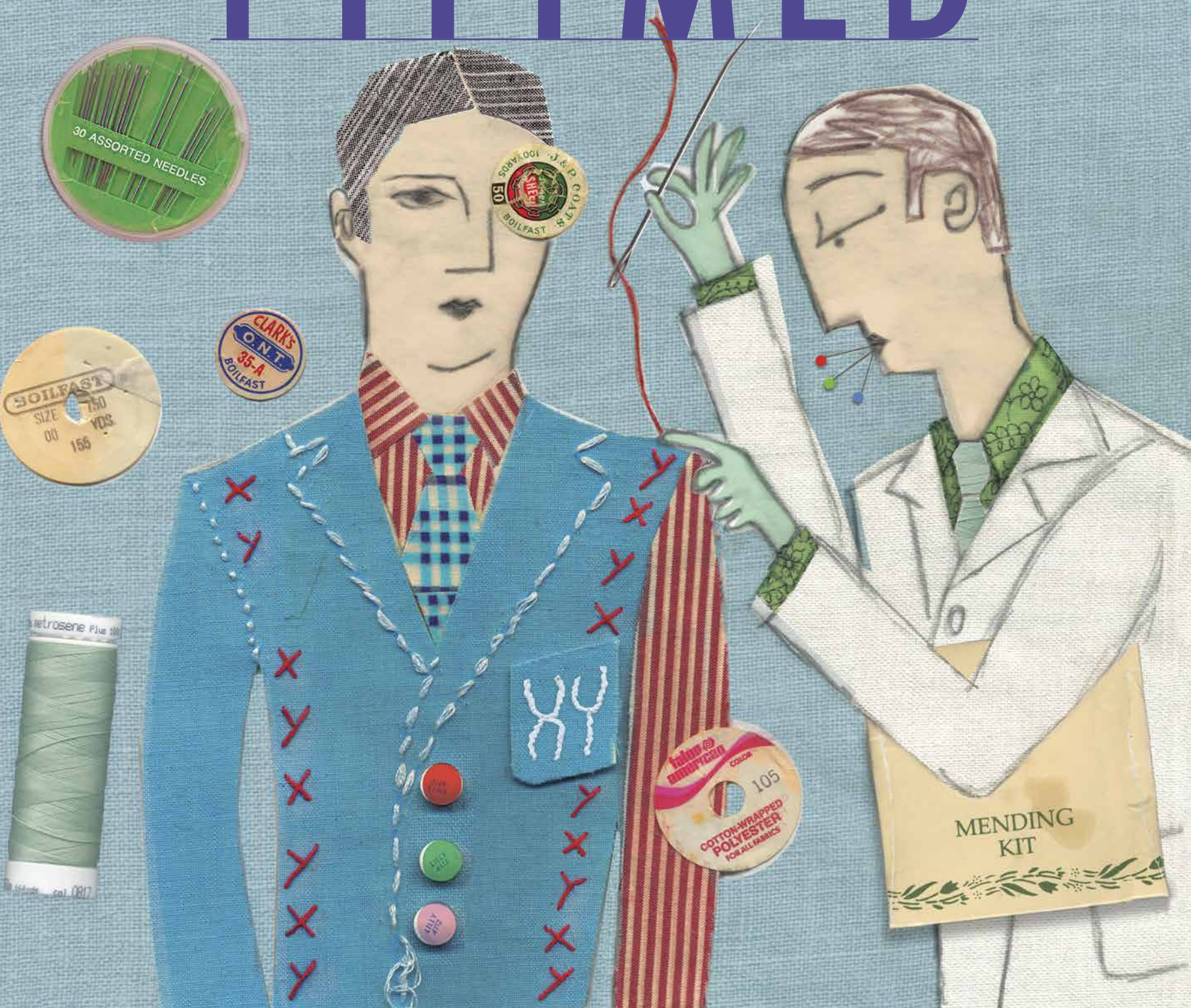
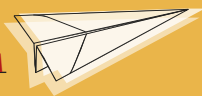


PITTMED



TAILOR MADE

TRYING ON PERSONALIZED MEDICINE



ON TWITTER

Join the conversation! Between issues, you'll get the scoop from the School of Medicine and the world of medical science at large. A few tweets from our @PittMedMag account we thought you'd like to see:

From alumnus Ryan McGarry; Jenelle Pifer's story on his multiple award-winning documentary, Code Black, appeared in our Spring 2014 issue:

@hesaidchutes (Ryan McGarry) thanks for the film shoutout @PittMedMag, now all i want is to meet my '09 classmates out at @harrisgrill #frozensmo #gilbert #getloud

Everyone loves a Fred Rogers story. We're glad we had the chance to tell you about his mentor, Pitt med's Margaret McFarland:

@PittTweet (Hail to Pitt)

Fantastic @PittMedMag piece on Margaret McFarland, Pitt psychiatry prof who mentored Fred Rogers, consulted on show: <http://bit.ly/Wnzy6c>

And our tweet on the Fred Rogers slideshow in our Winter 2013/2014 issue was often "favorited" and retweeted. In case you missed the slideshow: <http://bit.ly/1jYiazu>

CORRECTION / CLARIFICATION

We regret that in our "Next Generation" column in the Spring 2014 issue we misspelled Rachael Gordon's name. We should also have stated that Gordon (an MD student and PhD candidate) and MD student Julie Boiko's poster on introducing key junior faculty skill sets to predoctoral trainees was one of just two student projects presented at the Association of American Medical Colleges meeting.

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

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MORE WOW!

For many years, the *Pitt Med* Web site has been utilitarian. Our comrades on Pitt's Web team have made it a heck of a lot better. More interactive! Shape-shifting depending on your device! Prettier! A nice new home for our Pitt Medcasts! Check us out at pittmed.health.pitt.edu.



PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SUMMER 2014

VOL. 16, ISSUE 2



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Can someone own the alphabet?



40 1/2

CONTRIBUTORS

This is **ROBYN K. COGGINS**’ ["There’s Always Something" and many other stories] first issue as associate editor for *Pitt Med*. She’s a Minnesota native (you betcha) and casual runner who loves the Internet and counting how many dogs she sees on walks around the neighborhood. Before *Pitt Med*, she taught writing in Pitt’s English department and, many moons before that, was a server, an underwear salesperson, a barista, and a meat market clerk (for a while, all at once). On weekends, she and her brand-new husband, Clint, hold backyard writing and political conferences with local novelist Albert French. Someday, they will save the world. Coggins tweets @RojoOhNo.

Like her interview subject, *NY Times* writer Elisabeth Rosenthal, **JENNY BLAIR** ["Overheard"] was once an emergency medicine doc. Eventually both women would trade in their stethoscopes for the keyboard. Blair’s first byline appeared when she was 12; she wrote about her sister’s school bus overturning. (The kids were all right.) The story appeared on a sheet of copy paper and reached a single-digit readership. Blair won two National Headliner Awards as a medical student and resident. She went on to write about flesh-eating beetles and a man who punched a shark, among other quotidian affairs. She has contributed to *New Scientist*, *Discover*, and *The Washington Spectator*. The MD also covers city politics for the *Austin Monitor*.

COVER

Tailored medicine, easy right? All your doc has to do is take in to account your lifestyle, age, 3.2 billion base pairs, and other molecular goings-on. (Cover: Catherine Lazure © 2014)



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FEATURES

Second Lives

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Pitt med nontraditional students share “past life” experiences.

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“There’s Always Something”

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The West African Ewe people called the disease “body chewing” because the afflictions are so painful. Those with sickled red blood cells face a host of challenges, and a posse of Pitt docs are determined to make their lives better.

BY ROBYN K. COGGINS

Stitching the Pieces Together

24

More than a year into UPMC’s massive five-year plan to warehouse patient and other data, *Pitt Med* checked in with some of the effort’s masterminds to discuss the practical, ethical, and clinical issues arising.

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One size does not fit all, yet tailoring treatments is not so simple.

COVER STORY BY MICHAEL FITZGERALD

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DEAN'S MESSAGE

How do you intend to make a living? —David Levine

These words were uttered—I thought stridently—by my father on the eve of my graduation from Columbia College. I'd attended Columbia because of an abiding attraction to Manhattan and that college's eminence in the areas that most interested me in my formative years. Those years were wonderful: I immersed myself in the Russian literary masters while majoring in comparative literature; edited *The Columbia Review*; acted on the off-Broadway stage; spent a great deal of time in New York's museums. But reality had been happily remote. So with newfound angst, I considered my father's question and decided on the spur of the moment that I would become a psychoanalyst. That seemed somewhat literary and was a goal that satisfied my father.

A few years later, while in medical school, I saw Rosalind Franklin's "Photo 51"—a critical clue for determining the double helix of DNA. I thought I'd pursue a PhD in molecular biology instead of continuing as an aspirant physician.

When I noted this to my father, he said, *Fine. But if you don't finish medical school, I'm going to send you a bill for every day of tuition I've invested in you, starting with day care.* I stayed in med school, with no regret. Medicine is a noble profession that has shaped me.

Beyond their compelling role in my fiscal life, my parents—teacher and lawyer—were clearly influential at each of my many developmental stages. My mother the teacher, who came from a long line of rabbinic scholars, encouraged me to savor words and to study Latin and Greek. (This Jewish mother hoped her son would become a poet, not a doctor.) Recently, I had the occasion to reflect on others who've influenced me greatly. I shared those thoughts this May as I delivered the Petersen Lecture—marking the first endowed deanship in the 128-year history of this medical school.

My pediatrician, Chauncey Wyckoff, was a giant in my eyes. (Even though he was one of the few men I've known who was shorter than me.) In his day, Dr. Wyckoff was one of the country's notable academic pediatricians. My older cousin Donald Glaser, who went on to win the Nobel Prize in Physics, engaged me in science as a child. (Our families shared a duplex, and Don and I grew up together.) At Columbia, the eminent author and critic, Lionel Trilling, taught me to reason as critically as a scientist must, although that was surely not his intent. In medical school, internist Clifford Pilz taught me to pay attention to every nuance in a patient's being. In residency, Max Cooper—then a pediatrician and fledgling researcher and now one of the country's most important immunologists—illustrated the immediacy of basic science in its nexus with clinical care. At the NIH, the inspirational Wallace Rowe and Sherm Weissman set me on the path of thinking about what causes cancer (as I still do) and becoming a molecular biologist after all. (I didn't have to drop out of medical school!) Each one of these mentors imprinted something in me. Their bright light has helped me navigate a path that has presented extraordinary clinical, research, and leadership opportunities.

I cannot put my pen aside without noting one of our own lodestars here at Pitt, esteemed medical educator and vice dean Dr. Steven Kanter, will soon be assuming the deanship at the University of Missouri-Kansas City School of Medicine. Throughout the last two decades, he has ignited idealism and intellectual integrity in our students. I, like many others here, shall miss him greatly.

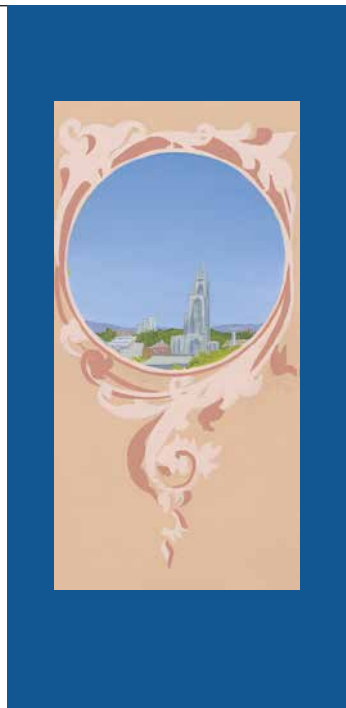
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Senior Vice Chancellor for the Health Sciences

John and Gertrude Petersen Dean, School of Medicine



JOSHUA FRANZOS



*Devoted to noteworthy happenings
at the medical school*

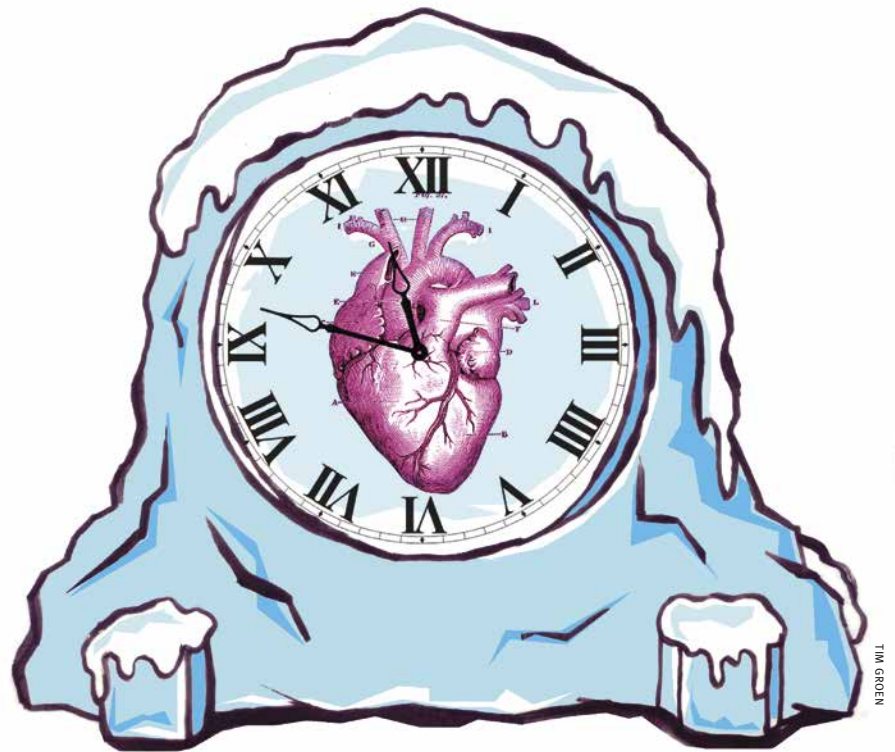
RANKS SWELL IN TOP SOCIETIES

Thirteen Pitt med physician-scientists are among the newest members of two prestigious medical societies. This year, the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP) chose eight and five of their new members, respectively, from Pitt.

The ASCI chooses physician-scientists younger than 50 whose biomedical research it deems “outstanding.” The society elects up to 80 new members annually; this year, it chose 76 total. Pitt med profs honored included Cristian Apetrei, an MD/PhD; Carlton Bates, an MD; Hülya Bayir, an MD; Peter Lucas, an MD/PhD; Linda McAllister-Lucas, an MD/PhD; Mary Phillips, an MD/MD (Cantab); Aleksandar Rajkovic, an MD/PhD; and Yutong Zhao, an MD/PhD.

With 58 ASCI members to date, Pitt outnumbers Yale, Vanderbilt, and UCLA.

The AAP, cofounded in 1885 by William Osler, recognizes excellence in basic and clinical science. Of 62 inductees this year, Pitt’s were Yuan Chang, an MD; Patrick Moore, an MD/MPH; David Hackam, an MD/PhD; David Lewis, an MD; and Sally Wenzel, an MD. —*Jenny Blair*



A Matter of Time

A patient with severe trauma and massive blood loss who is also in the throes of cardiac arrest needs special care. But what to focus on? The quickly bleeding wound? The arrest? Emergency medicine physicians and trauma surgeons could use a few extra minutes.

Cue EPR, emergency preservation and resuscitation. Pitt’s late Peter Safar (MD Distinguished Professor of Resuscitation Medicine) with colleagues, including Samuel Tisherman (MD ’85, Res ’93, and longtime Pitt professor of critical care medicine and of surgery), developed the procedure in preclinical studies. EPR involves flushing out the patient’s blood and pumping cool saline into the aorta. With no blood, brainwaves, or breathing, this paused state will allow surgeons to repair damage, Tisherman predicts. He’ll know more as clinical trials unfold at UPMC Presbyterian and at several other academic medical centers, including the University of Maryland, to which Tisherman has recently moved.

The Department of Defense–funded trial of EPR officially began in April at UPMC Presbyterian. So when the right patient comes into the emergency department, the EPR team is primed to “race against the clock,” says Tisherman. —*Robyn K. Coggins*

FOOTNOTE

Pitt med’s Peter Shaw lent his knowledge and, ever so briefly, his visage to the movie *The Fault in Our Stars*. As head of Children’s Hospital’s adolescent oncology program, Shaw was uniquely qualified to advise on the film, which focuses on a romance between two teenage patients. With his guidance (and the dean’s help securing Children’s as a filming location), the producers managed to create an oncology ward accurate “down to a box of alcohol swabs on a cart.”



Overheard Sticker Shock

Here in the United States, we pay \$2.7 trillion each year for health care, and that number is increasing. Though the Affordable Care Act has made health insurance possible for millions of Americans, whether it will help control costs is in doubt. We talked about the issue with this year's School of Medicine commencement speaker, **Elisabeth Rosenthal**, an MD. In her *New York Times* series "Paying Till It Hurts," she examines how incentives built into our health care system drive up the price of drugs, tests, and procedures.

Why are health care cost discussions taboo in this country?

We have this weird notion that if you talk about value or cost-effectiveness in health care, you're on that slippery slope to talking about death panels and [saying], "It's not worth saving someone." It's a big misconception that talking about costs means your life is not worth it. It means, "Let's think about how to spend our health care dollars wisely."

Also, a lot of people are making a lot of money in our health care system right now, and they don't really want to talk about high prices. Their first concern is to figure out how they can keep their piece of that \$2.7 trillion health care pie.

How can patients keep their own health care expenses under control?

We're in a really difficult moment for individuals. All our plans are asking people to pay far more of their medical expenses. That does make people more cost conscious, but we're not giving them the tools or the information they need. One thing I would push for in the near future is to have more price transparency.

So would health care price transparency be an effective national reform?

I would put that pretty high up. There are a lot of things we can do. A lot of people say we should just have price regulation or single-payer, which would also work. It's not like it's a great mystery what we could do—the mystery is what we're willing to do.

The question in the end is going to be, "Will all of that private market stuff be sufficient?" Or are we going to need to do what almost every other country does, which is to have some form of national price setting or price regulations? —Interview by Jenny Blair

Faculty Snapshots

Famed faculty members Bernard Fisher, Thomas Starzl, and Julius Youngner each received a Chancellor's Medal this spring from outgoing Chancellor Mark A.

Nordenberg. Fisher (MD Distinguished Service Professor of Surgery) dramatically altered our understanding of cancer biology and fought for scientifically sound treatments for breast cancer, including lumpectomy and tamoxifen. Youngner (ScD Distinguished Service Professor Emeritus of Molecular Genetics and Biochemistry) was instrumental in creating the killed-virus polio vaccine and is known for other microbiology advances (including trypsinization, the basis for modern cell culturing, and fundamental studies of interferon). For more on Starzl (MD/PhD Distinguished Service Professor of Surgery), the man who made liver transplantation a reality, see p. 6.

The Chancellor's Medal celebrates those who leave "an indelible mark" on the University—Nordenberg called the trio "health care heroes" in his remarks.



FROM LEFT: Fisher, Youngner, and Starzl.

Carolyn Coyne and Yoel Sadovsky's July 2013 paper in *PNAS* won the Cozzarelli Prize; the National Academy of Sciences celebrates just one biomedical sciences paper with the award each year. Their study showed how the placenta may protect a pregnancy against viral infections. Coyne is a PhD associate professor of microbiology and molecular genetics. Sadovsky is an MD, Elsie Hilliard Hillman Professor of Women's and Infants' Health Research, and professor of obstetrics, gynecology, and reproductive sciences, as well as of microbiology and molecular genetics. Elizabeth Delorme-Axford (PhD '13) is the first author on the paper.



Coyne

David Lewis received the 2014 American Psychiatric Association Award for Research in Psychiatry. Lewis is the MD chair of psychiatry and UPMC Professor of Translational Neuroscience at Pitt. In addition, his department won a \$10 million grant from the National Institute of Mental Health to support the Silvio O. Conte Center for Translational Mental Health Research toward efforts in detailing the disease process of schizophrenia.



Sadovsky

Pitt's chair of orthopaedic surgery, Freddie Fu (MD '77), was awarded the Kappa Delta Elizabeth Winston Lanier Award (a.k.a. the "Nobel Prize of Orthopaedic Research") at the American Academy of Orthopaedic Surgeons' 2014 annual meeting. Fu, the David Silver Professor of Orthopaedic Surgery, investigates "double bundle" ACL reconstruction, which more closely mimics the knee's natural anatomy than traditional reconstruction methods. —RKC



Lewis



Fu

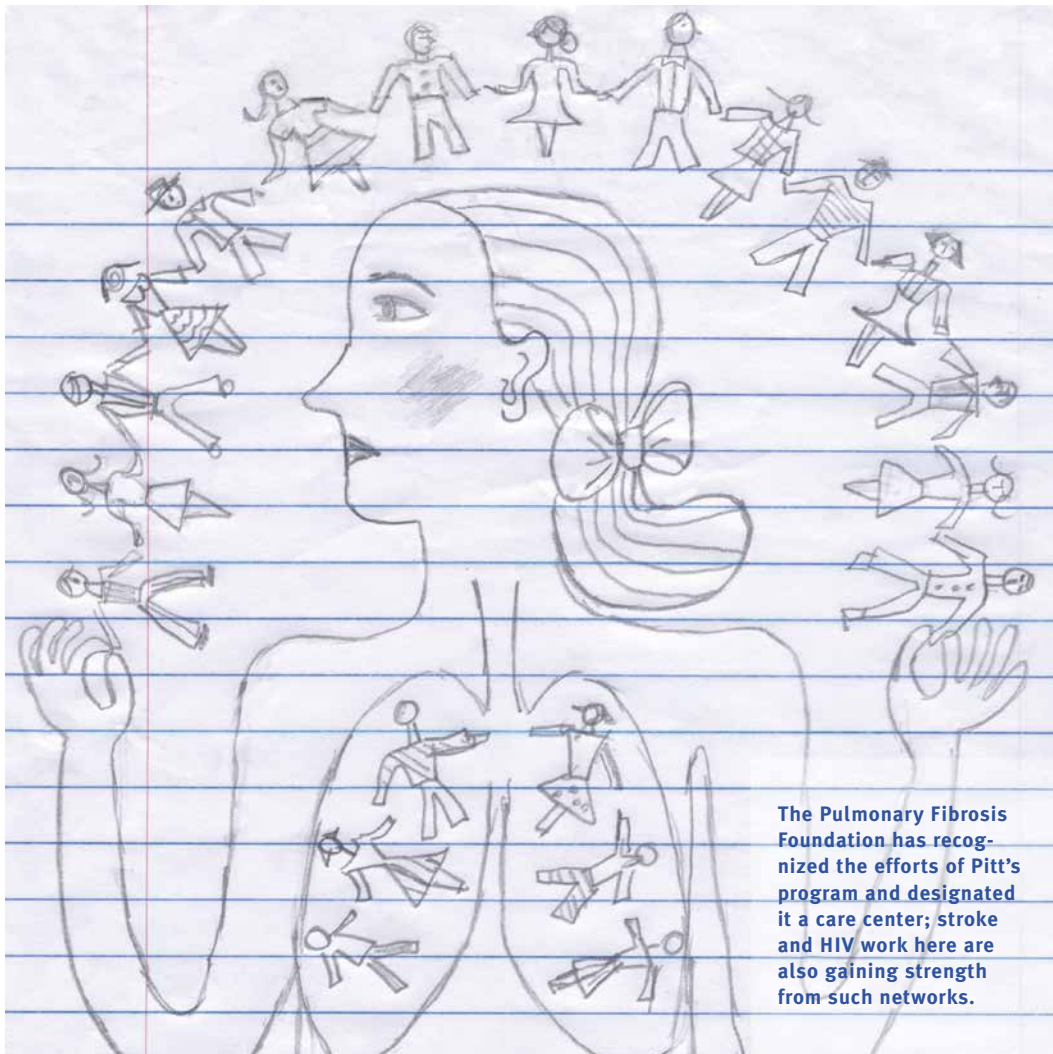
Centered

It's all about networking. At least it seems that way of late at the School of Medicine.

The Pulmonary Fibrosis Foundation has named Pitt's Center for Interstitial Lung Disease one of nine designated centers in its new Care Center Network and PFF Patient Registry Program. The centers will track treatment and outcomes to establish best practices and standardize care for the currently incurable and multifarious disease.

The National Institutes of Health has named Pitt one of 25 new regional stroke centers in an effort to jump-start clinical trials to prevent and treat strokes—currently America's fourth-leading cause of death and number-one cause of serious, long-term disability. Affiliates of the National Institute of Neurological Disorders and Stroke Trials Network will share results of their multi-disciplinary studies across member sites. The "StrokeNet" will create a long-range approach to research, decreasing setup costs of starting new trials.

Pitt's Microbicide Trials Network has been awarded \$70 million to help prevent the spread of HIV. A group led by coprincipal investigators Sharon Hillier (PhD professor and vice chair for faculty affairs in obstetrics, gynecology, and reproductive sciences) and Ian McGowan (MD and PhD professor of medicine in gastroenterology, hepatology, and nutrition) will develop vaginal and rectal gels, rings, and films that can kill or block transmission of the virus. —RKC



The Pulmonary Fibrosis Foundation has recognized the efforts of Pitt's program and designated it a care center; stroke and HIV work here are also gaining strength from such networks.

CATHERINE LAZURE



GREG KAVALEC

The dean, with a few structural models of items he's focused his lab on over the years. FROM LEFT (and most recent): KillerRed, a fluorescent protein (the novel use of which has allowed the further detailing of the cell's response to DNA damage); UV-DDB (a protein which binds to damaged DNA and initiates its repair); and SV40 (an oncogenic virus). Also shown is this magazine.

INAUGURAL DEANSHIP

He's not just senior vice chancellor for the health sciences and dean of the med school anymore. Arthur S. Levine, MD, is now the John and Gertrude Petersen Dean; he holds the first endowed deanship in the history of this medical school. Chancellor Mark A. Nordenberg conferred the honor at a ceremony this May with a proud handshake, a little ribbing, and a medal worthy of an Olympian.

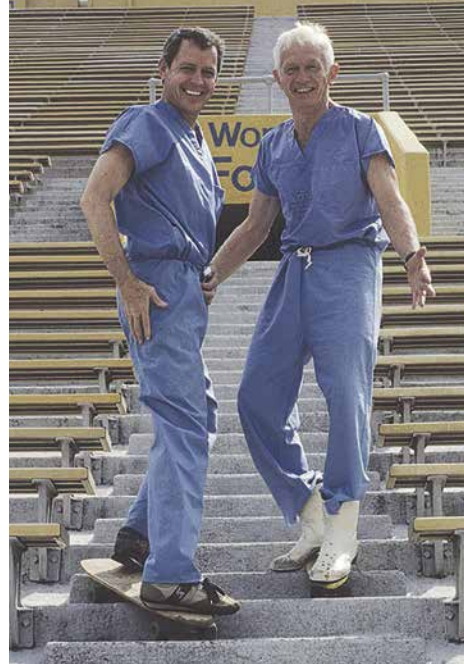
Levine, dean since 1998 (after three successive search committees had failed to find the right person, by the way), has led the med school into the ranks of the top five institutions receiving NIH funding. He has appointed 30 of 31 department chairs, created 10 new departments, and lured five National Academy of Sciences members to join the faculty.

"The institution transcends departments," Levine said of the present-day school, increasingly known for its interdisciplinary collaborations.

At the event, Levine gave a lecture recounting both his and the School of Medicine's histories, referring back to his great grandfather and the first diploma granted by the school in 1887.

Levine attributed his and the school's strength, in part, to stellar faculty, donors like the Petersens, and first-rate staff like his assistant, Gina Deible. He said he's "a catalyst dependent upon substrate."

His portrait (left), painted by Greg Kavalec, was unveiled after the lecture and will hang in the Scaife Hall auditorium. —RKC



EPIC TALE OF AN EAGLE SCOUT

Thomas E. Starzl—MD/PhD Distinguished Service Professor of Surgery and famed transplantation surgeon—was recently inducted into the National Academy of Sciences. He joins the ranks of Alexander Graham Bell, Thomas Edison, Margaret Mead, and other scientific juggernauts (including six other Pitt faculty members).

Don't know much about Starzl? Then check out the Official Dr. Thomas E. Starzl Web Site (www.starzl.pitt.edu). The site was officially launched in April 2014; archivists and the great doc spent much of 2013 filling out the site with photos (including those shown here of him as an Eagle Scout and, decades later, skateboarding with eminent surgeon Hank Bahnson) and archival materials. "After responding to many requests over the years for information about his background, accomplishments, and impact on the legacy of transplantation and transplant immunology," says archivist Ashley Taylor, Starzl "wanted the archive Web site to provide a singular, official destination for those wishing to learn more about him and his work." In addition, all 2,257 Starzl publications are available digitally through the University Library System (d-scholarship.pitt.edu). Yup, we said 2,257. —RKC

Appointments



Vignali

Dario Vignali, a PhD, has been recruited to Pitt from St. Jude's Children's Research Hospital, where he was vice chair of the immunology department. At Pitt, he will be a professor in and vice chair of the Department of Immunology and colead the Cancer Immunology Program at UPCI. Vignali, along with **Robert Ferris**, an MD/PhD, will also run the new Tumor Microenvironment Center—an important hub for cancer and immunological studies.



Ferris

Luis De la Torre, an MD, comes to Pittsburgh by way of Hospital Angeles Puebla in Mexico, where he was the head of the hospital's Colorectal Center for Children. Now an associate professor at Pitt, De la Torre is the founding director of another such center at Children's Hospital of Pittsburgh of UPMC that will provide diagnostics, consultations, a broad range of treatments, and emotional support to patients and their families. The center's radiologists, gastroenterologists, psychologists, surgeons, and specially trained nurses will work with patients with anorectal malformations, Hirschsprung disease, and those with functional problems after related procedures.



De la Torre

Hoby Hetherington, a PhD, joins Pitt as a professor in the Department of Radiology. Hetherington made a name for himself at Yale for his work on high-field magnetic resonance spectroscopy. Now Hetherington will lead Pitt's Magnetic Resonance Research Center, as he and colleagues investigate the behavior of neurotransmitters in epilepsy patients using imaging techniques he developed. He also investigates brain tumors and traumatic brain injury.



Hetherington

Roderick O'Sullivan, a PhD, has joined UPCI and the faculty at Pitt after leaving the Salk Institute for Biological Studies, where he was a postdoc. O'Sullivan, an assistant professor of pharmacology and chemical biology, was the first author of a recent study investigating the alternative lengthening of telomeres pathway, a contributor to cell division in 10–15 percent of cancers. O'Sullivan's lab at Pitt will continue this research as his team works to understand the relationship between telomere structure and function in this peculiar but significant pathway. —Zach Nichols



O'Sullivan



PHOTO COURTESY CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC/TIM GROEN, PHOTO ILLUSTRATION

ROOM WITH A VIEW, OF THE LITTLEST ONES

When a newborn lands in the neonatal ICU, it's a rough road of separation for new parents like Erin and Ryan Hayes. But the NICUs at Children's Hospital of Pittsburgh of UPMC and Magee-Womens Hospital of UPMC are easing some parental worries with NICVIEW—a camera system mounted above incubators that parents can securely access.

"It was nice," Erin Hayes says, "to be able to see my baby on there, see both of them." Twin boys Tristan (pictured) and Maddox, born last November at just 25 weeks, were in both hospitals during their respective six- and four-month stays. The Hayeses tuned in during lunch breaks at work and at bedtime to view their little ones between visits.

"[Parents] can feel comforted that, even though they can't be with the baby, the baby is okay," says Beverly Brozanski, MD medical director of Children's NICU and professor of pediatrics and of obstetrics, gynecology, and reproductive sciences at Pitt.

Parents can check in during six designated times each day and share

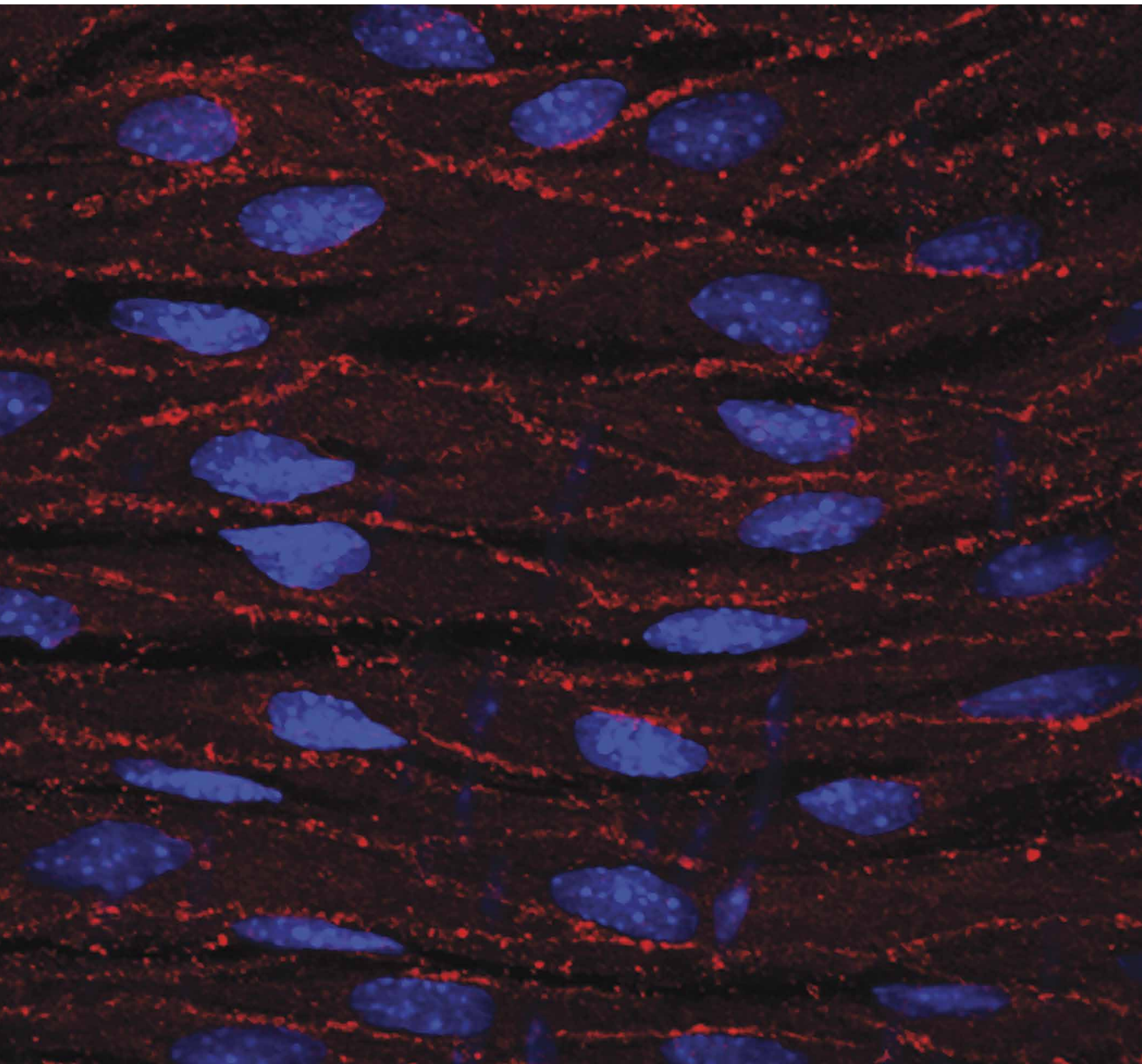
login information with family; folks from 29 states and five countries have connected since December, Brozanski says. "When family—their parents, sisters, and brothers—can log in to see the baby, they understand a little bit more about what the parents are going through."

By the end of June, Magee had some 30,000 logins to its 62 cameras, and Children's reported more than 20,000 to its 31. (Children's plans to add more cameras this year.) Brozanski thinks of the service as part of the big transition from hospital to home.

"Family-centered care is very important to newborn medicine. We're discharging this baby—this very medically fragile child—to a family that hasn't had the baby home yet," she says. "Anything we can do to help ease that transition and allow the family to feel more connected is definitely worthwhile."

And don't worry: Maddox and Tristan are home and doing well.

—Robyn K. Coggins



Hemoglobin is critical to maintaining safe levels of nitric oxide in the body. ABOVE: Hemoglobin alpha (red) seen in a layer of endothelial cells taken from a mouse artery. The blue stains cell nuclei. OPPOSITE PAGE: Hemoglobin alpha (red) and the enzyme nitric oxide synthase (light green) meet up (yellow) in the endothelial cells of a mouse artery.

N.O. IN BALANCE

HEMOGLOBIN HELPS NITRIC OXIDE
STAY IN CHECK | BY DANA YATES

Found in car exhaust, smog, and cigarette smoke, nitric oxide (NO) was, at one point, mainly seen as a pollutant. In 1992, however, the journal *Science* named NO “Molecule of the Year” for its crucial role in the normal function of the heart, lung, brain, pancreas, uterus, and liver, among many other organs. Six years later, Robert Furchgott, Louis Ignarro, and Ferid Murad were awarded the Nobel Prize in Physiology or Medicine for their discoveries related to NO in the cardiovascular system. (As these scientists pursued the mysterious gas behind heart health, Pitt alum John Hibbs Jr. was describing NO’s biochemical pathway in relation to the immune system.)

As a signaling molecule, or biological go-between, NO helps cells work together. It is produced in the cells that line blood vessels and affects many vital activities, such as blood vessel dilation, inflammation reduction, and blood clot prevention. NO is routinely used in clinical settings. For example, medications that release NO are used to treat high blood pressure and heart failure in adults, and NO gas helps newborns with pulmonary hypertension.

NO can do a body good. But, of course, the gas is also a known danger. An overabundance of NO can lead to major medical conditions, including septic shock. Striking approximately 750,000 Americans each year, and killing 28–50 percent of those people, according to the National Institute of General Medical Sciences, sepsis is caused when the body produces an overwhelming amount of NO to destroy an infection.

This reaction leads to low blood pressure

and blood clotting, and a lack of oxygen can cause organ failure.

With so much at stake, it’s essential to maintain a careful balance of NO in the body. So what keeps it in check? The answer is hemoglobin, reports Adam Straub, a PhD assistant professor of pharmacology and chemical biology and investigator in the University of Pittsburgh’s Heart, Lung, Blood, and Vascular Medicine Institute.

When Straub was a postdoctoral research fellow at the University of Virginia, he was lead author of a paper that showed hemoglobin, the protein in red blood cells that carries oxygen, controls the diffusion and signaling of NO in the blood vessel wall. The paper was published in November 2012 in *Nature*.

“We used to think that NO just went everywhere in the body, but it’s actually highly regulated,” says Straub.

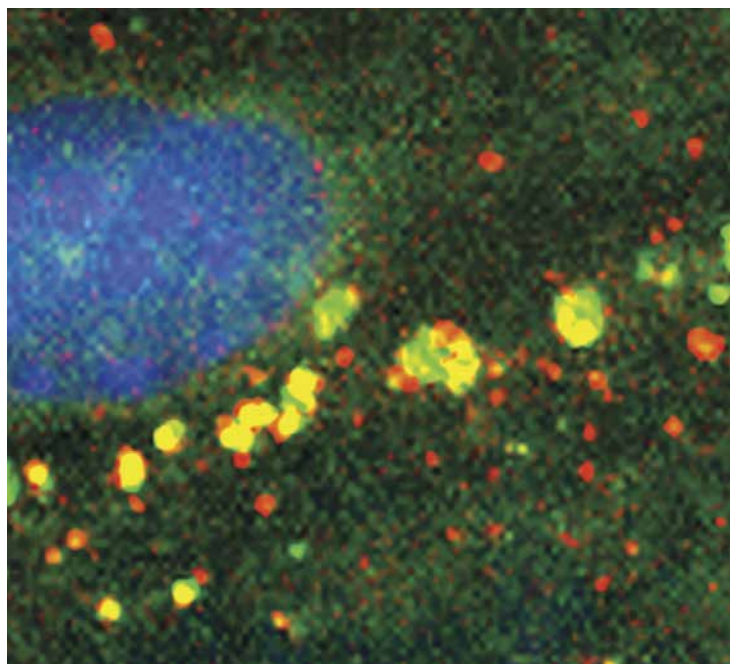
Simply put, hemoglobin controls NO by deactivating it. The process, Straub explains, is similar to that of a garden hose; hemoglobin acts like a nozzle, regulating the amount of NO and how much blood vessels dilate. What’s more, researchers are also finding hemoglobin in cell types other than red blood cells, including in the brain, lungs, and kidneys.

“This shows a much wider impact in the body in terms of how NO affects many functions, such as how neurons talk to each other in the brain and how immune cells talk to each other about inflammation,” says Straub.

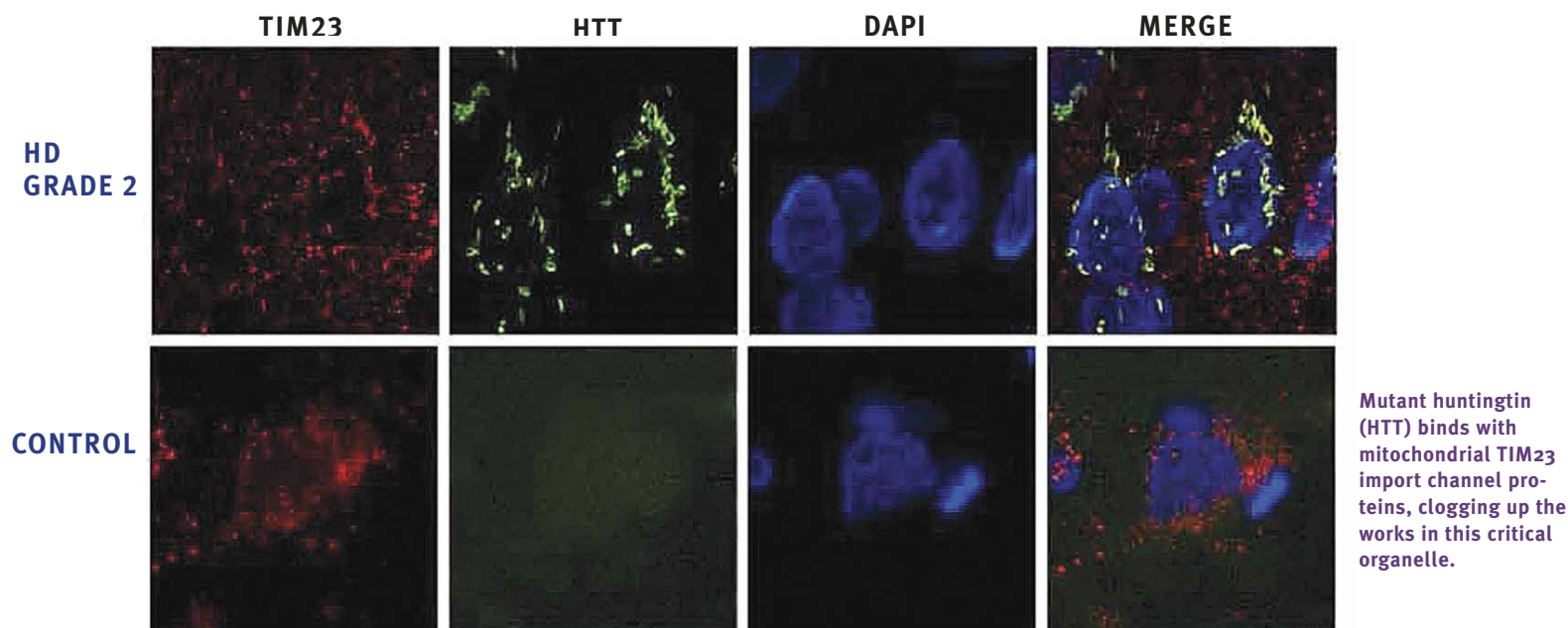
Today, Straub’s work adds to a long and

thriving legacy of NO research at Pitt. Those investigations have ranged from identifying the human gene that ultimately triggers NO production, to understanding how the molecule contributes to organ transplant rejection, to studying how to increase NO levels in order to treat heart and lung problems.

To that end, Straub’s latest research involves the development of peptides that disrupt hemoglobin’s NO-deactivation mechanism. The result is a decrease in blood pressure and possibly even a complete reversal of hypertension. So far, animal models have



shown promising outcomes in this area of study, and Straub is exploring the next steps for future inquiry. ■



DAMMING EVIDENCE

AN UPSTREAM CAUSE OF HUNTINGTON'S
DISEASE | BY JENIFER LIENAU THOMPSON

It is sometimes surprising to be reminded that the law of parsimony almost always applies—even in a field as intricate as neurodegenerative disease. But, as a University of Pittsburgh team reported in *Nature Neuroscience* this May, Huntington's disease (HD), a protracted and “universally fatal” neurodegenerative disorder, is actually caused by a case of clogged cellular plumbing.

More than 30,000 Americans suffer from HD—an untreatable condition.

Symptoms of the disease often emerge in mid or even late life, after which patients may live another 15 years or so. Most of the damage is to the brain—the cortex and striatum—where neurons die slowly. Because neurons rarely regenerate, the effects of HD accumulate and escalate over a lifetime; hallmark symptoms range from involuntary muscle movement to cognitive and psychological dysfunction.

Researchers have known that HD is associated with a mutation influencing the production of huntingtin protein (HTT). They also knew that deaths of neurons in the brain cause the devastating symptoms of the disease.

Pitt's Robert Friedlander, who is chair and Walter E. Dandy Professor of Neurological Surgery, and colleagues wanted to establish how the mutant protein huntingtin actually caused these cells to die. It involved years of painstaking investigations, but they figured it out.

It all comes down to the mighty mitochondria—which produce the power that fuels all cellular function.

Mitochondria need some 1,200 different proteins to generate all this energy. Most of those are assembled in the cell's cytosol and imported through protein channels in the mitochondrial membrane. Without a full complement of functional proteins, mitochondria cannot operate properly.

Friedlander and his colleagues suggested that mutant HTT might have a proclivity for binding to protein import channels—passageways in the mitochondrial membrane through which proteins emigrate from the fluid inside of cells. Mitochondrial dysfunction and cell death in HD might be explained, they thought, if mutant HTT were shown to block functional proteins from getting inside the mitochondria.

Using neurons from the brains of both humans and mice with HD, the researchers were able to follow the problem upstream to its source—an import channel defect. In particular, mutant HTT binds with all three of the proteins that make up a channel called TIM23. Once clogged by mutant HTT, TIM23 can no longer import critical functional proteins, and the cell gradually weakens and dies.

Elizabeth Jonas, an MD on Yale University's medicine and neurobiology faculty, wrote a study review of the paper in *Nature*

Neuroscience; she noted later in an interview that the Pitt work is “thought-provoking.”

“These findings will definitely be of interest to anyone in the field of HD, but also to people working on any problem that involves aggregations of abnormal proteins that could block channels,” Jonas says.

“Friedlander's team found that synaptic mitochondria are more susceptible [to clogged plumbing in HD],” she adds. “That was tremendously exciting. ... Why doesn't the disease manifest until so late in life? It must mean that only a few of the many mitochondria are affected at first—and that slows down the synapses just enough to make the patient not able to run track or answer a question on an exam. Over the course of the patient's life, the synapses are taking more and more hits, and those hits are accumulating until finally they reach some threshold, and we see the full clinical manifestations.”

Friedlander's team also wondered, *Could we protect neurons by boosting levels of the three proteins that make up TIM23?* It wasn't easy to find out. Says Friedlander, “it is very, very difficult to transfect the three proteins that make up the TIM23 complex, especially into the primary neurons”—the first casualties of HD.

This phase of the study took five years.

It turns out that overexpressing the proteins that make up TIM23 can “rescue” neurons subjected to mutant HTT—unprecedented findings that were well worth the wait. ■



D IS FOR BABY

THE APPARENT LINK
BETWEEN VITAMIN D
AND PREGNANCY HEALTH
BY KATY RANK LEV

Preeclampsia is a puzzle to medical researchers—no one knows what causes it. Characterized by high blood pressure and protein in the urine of pregnant women, preeclampsia causes seizures, disability, and even maternal or infant death. The only cure is delivery, which can mean a premature induction or cesarean section if a mother's symptoms are severe.

Lisa Bodnar (Fel '04), an MPH/PhD assistant professor of epidemiology at the University of Pittsburgh Graduate School of Public Health and of obstetrics, gynecology, and reproductive sciences as well as psychiatry at the School of Medicine, notes that preeclampsia, which affects 3.4 percent of pregnant women in the United States, accounts for 18 percent of maternal deaths associated with births each year.

Bodnar, a trained dietitian, has been interested in pregnancy since she was an undergraduate at the University of North Carolina at Chapel Hill, where she examined folate levels in pregnant women. She has been intrigued by the effects of diet and nutrition on gestation ever since.

When Bodnar returned to her native Pittsburgh for a reproductive biology postdoctoral fellowship at Magee-Womens Research Institute, where she's now on the faculty, she began researching pregnancy and vitamin D, a unique nutrient in that we both absorb it from our food and synthesize it in our skin following exposure to the sun.

"People have always related vitamin D to bone health and calcium metabolism," she says. But about a decade ago, the literature began to suggest it could also be important for other reasons, including placental function and regulating placental inflammation. "I felt like preeclampsia was a really obvious direction to take the research from there."

She and her team recently examined vitamin D levels in blood samples from pregnant women collected as part of the Collaborative Perinatal Project (CPP)—a 12-center study conducted from 1959 to 1966. Bodnar's investigation focused on samples gathered in the first 26 weeks of gestation, roughly 700 being from women who later developed preeclampsia and about 3,000 from women who did not. The samples were well preserved and able to be tested for vitamin D levels four decades later.

Bodnar's team controlled for factors that can influence vitamin D status—including smoking, diet, ethnicity, and physical activity—and found a correlation between vitamin D deficiency and the rate of severe preeclampsia. In fact, sufficient vitamin D intake was associated with a 40 percent reduction in the incidence of severe preeclampsia. There was no relationship between vitamin D and mild preeclampsia. (Severe preeclampsia is believed to stem from a different root cause than mild preeclampsia.) Her results were published in *Epidemiology* in March.

Bodnar's study, it's important to note,

supports a correlation between vitamin D and preeclampsia—not causation. Her ongoing research explores how the body metabolizes vitamin D to better understand the link between this deficiency and adverse pregnancy outcomes. She believes vitamin D will prove to be a key component of a healthy pregnancy.

In October 2013, the *American Journal of Epidemiology* published another paper by Bodnar's group examining ethnicity and preterm birth. In CPP participants of African American and Puerto Rican descent (populations that are more susceptible to vitamin D deficiency than whites), Bodnar's team found that incidences of premature birth decreased by as much as 30 percent as vitamin D levels increased. In white women, the team found no such relationship between vitamin D and preterm birth. The researchers also found that vitamin D deficiency was most strongly associated with cases of preterm birth involving placental damage resulting from inflammation.

What excites Bodnar most about her work is its potential for a wide impact, should the causal relationship pan out in other studies now under way.

"Even if [vitamin D deficiency] is only related to a small subset of adverse outcomes, the treatment is so simple, so inexpensive, and so safe," she adds.

"Vitamin D and other nutrient deficiencies are attractive to study because they are modifiable." ■



THE NONTYPICAL STUDENT IS PRETTY TYPICAL
AROUND HERE | BY ELAINE VITONE

SECOND LIVES

Zoya Voronovich's (MD '14, shown left) family is "kind of obsessed with the brain and the mind," she says with a hint of a Russian accent—they immigrated to Colorado when she was 11. Her grandmother was a psychiatric nurse and served with Russia's military in World War II. Her uncle and aunt both trained in Russia as neurologists. "It runs in our blood."

But, much as the family stories intrigued her, once she got to college, she still couldn't see herself pursuing an MD. She was an indie rock DJ at her campus radio station—not one of those Type A premeds. "The U.S. conception is that medicine is very competitive, and I always thought you have to be perfect to do this ... It seemed overwhelming." She started out declaring biochem, but then added two more majors—quantitative economics and finance. After graduation, she worked for a business consulting firm, then moved on to work primarily in the retail sector.

"But then, once I became more confident in my career in the corporate world, I thought, *Maybe I could do [med school]. Maybe I have the support to explore this. Maybe I have a little more guts to see what it takes.*"

Voronovich, 31, is one of 19 students in the University of Pittsburgh School of Medicine Class of 2014 alone who are "nontraditional"—generally, the 25-and-up set who enter medicine as a second career (two from this class enrolled with PhDs). Voronovich came to Pitt after hearing through word of mouth that it was a nontrad-friendly school—a rep the School of Medicine has lived up to, in her experience.

Yeah, Pitt med students are super smart, of course. And they have a lot more to offer. Officials at Pitt's School of Medicine believe that training creative, thoughtful people to become doctors—people who bring a range of life experiences to the table—will result in better doctoring, better medical science, and a better health care system. As a result, Pitt has become the alma mater for many "nontraditional" students.

PHOTOGRAPHY | CAMI MESA

"Dr. Pettigrew is a great example," she says. Each year, right after the White Coat Ceremony, Chenits Pettigrew, an EdD assistant dean for student affairs and faculty diversity, and director of diversity programs at Pitt med (and just named a Man of Excellence by the *New Pittsburgh Courier*), hosts an annual dinner for nontrads.

"He touched base with me several times," says Voronovich. "I saw him first day of Anatomy, when I was feeling very overwhelmed." She saw him recently, on Match Day, too, when she learned she'll be starting her neurosurgery residency at the University of New Mexico.

Pettigrew has learned to tune in to the particular concerns of this crowd—whether or not their study strategies (which might be a little rusty) are working effectively; whether or not their career plans (which have less time for detours) are on track; whether their partners and family members (who might include gestating babes, elderly dependents, and anyone in between) are faring well amid the rigors of med school.

Pettigrew's own family has been there—twice. His wife, Margaret Larkins-Pettigrew (MD '94, Res '98), came to Pitt med at age 34 after starting out as a nurse. Their son, Gaetan Pettigrew (MD '12), was a dancer in New York before he enrolled at age 27.

"My job is to get to know who they are and what they are interested in," says Pettigrew. "How is this affecting their lives?"

For Voronovich and her husband, med school has been uniquely challenging. He is a tenured professor in the University of Colorado's

Leeds School of Business and couldn't relocate, so he stayed behind with this blended family's four children, ages 6, 13, 16, and 18.

"It's always cheaper for me to travel [to Colorado]. I feel like I've been on the run for the last four years," says Voronovich. But, some 36 months of phoning, Skype-ing, and frequent-flier-mile-ing later—she's moving to Albuquerque, just a seven-hour drive from home, making the family's final phase of bimodal living somewhat easier.

And she's realizing a dream, graduating from a top institution for all-things-brain—Pitt's Department of Psychiatry is among the highest-funded by the National Institutes of Health. Aided by her background in statistics and analysis, at Pitt med she researched deep brain stimulation in Parkinson's disease patients, as well as treatments for traumatic brain injury in elderly patients. She also contributed to two review papers. Now, she has in the works a project on the potentially fatal infection within the brain known as ventriculitis; that effort arose from her work on a pediatric neurosurgery team in Kijabe, Kenya, last summer and this spring.

Voronovich hopes to continue both her research and her global health work. She'll add a few new stories to the family lore—like that of a middle-school-aged boy she met in Kenya who was hospitalized for a brain abscess for nearly two months. "He was a heartbreaker. As he got better and was able to be more active, he got friendlier and started hanging out with us.

"When I think of kids like him, it really inspires me to keep going and help children like him for the rest of my life."

In **Dan Van Roekel's** (MD '14) previous career, he started out as a "best boy"—a second-in-command grip on a film lighting crew. Having completed a combined BA in drama and a BFA in studio art from Tufts University and the School of the Museum of Fine Arts, he cut his teeth in the Boston area film industry doing electrical and grip work, then made the move to editing. Van Roekel was a sound editor and assistant editor for *NOVA* for three years and a technical arts instructor at MIT's visual arts program for seven, before he applied and was accepted at Pitt med (after spending two years catching up on science requirements at the University of Massachusetts Boston).

As it turns out, the sensibilities and skills he used in his former life have plenty of applications for Van Roekel, now 42, who recently matched in the very visual and technical field of radiology (at MedStar Georgetown University Hospital, Washington, D.C.).

And his teaching experience lends itself well to the fine art of bedside manner. "You kind of see them struggle and need more help. You can't judge them. You need to be compassionate," he says.

Through his documentary film work, he encountered the more difficult emotional aspects of the human story with the focused gaze of an editor's eye. Van Roekel did a service trip in rural Haiti the summer after his first year of med school.

After residency, Van Roekel hopes to return to work along these lines—perhaps through telemedicine. He is researching ways to combine radiology with global health—for him, that would be an ideal complement to the hours he'll spend in the radiology reading room.

He doesn't want to be disconnected from the people he's there to help. "That goes with the documentary, the storytelling, the human part of it. ...

"Every time you look at [an imaging study], you have to have an image of a patient in your head. That drives you to make sure you find out what's wrong."



Jamil Alhassan (BS '11 who is in the Class of 2017), has dreamed of getting an MD since he was a kid. He grew up in Southwest Philadelphia, in a single-parent household, and worked two jobs in high school to help support his family. He came to Pitt for his bachelor's and, with guidance from fraternity brothers, learned the standards to hold himself to if he wanted to be med school material. By spring of his senior year, he was an RA, a biology TA, a student representative for the University's Board of Trustees, and a homecoming king—all while pulling a 3.94.

"College changed my life," he says.

Then, that spring, he contracted meningitis.

Since, apparently, four years of very little sleep and five cups of coffee a day (plus extra espresso shots) had pushed his body too far, he decided to put off med school, as much as it pained him.

Instead, Alhassan worked in Camden, N.J., as a corps member of Teach For America. In this life as a science teacher, he would create elaborate study guides that used humor to liven up the lesson plans (the characteristics of life, featuring Lil Wayne, was a favorite). He also implemented a class culture he called Students Will Achieve Greatness, or SWAG—a rebranding of the kids' word for coolness and swagger.

Each time students did something to help the efficiency of the class as a whole, they earned SWAG points, which Alhassan painstakingly tabulated along with their grades and posted on the classroom wall. Scores of 80 to 90 percent were dubbed BAs, 90 to 94 MAs, and 95 on up PhDs. And along with these awards Alhassan displayed his own "wall of achievement"—homecoming king photos, newspaper clippings from his college step shows, his Pitt degree. Proof that yes, even for someone who grew up in a neighborhood much like this, success can, and does, happen.

The students' grades improved. Attendance

went up. Kids rolled into his classroom during lunch just to hang out. Between his first and second year at Teach For America, Alhassan wrote a book chapter on educating Black men at the invitation of a professor at Howard University.

When Alhassan, now 24 and a Schweitzer

Fellow, talks about doctoring, it sounds a lot like his teaching philosophy: Building relationships. Treating the whole person—even the whole family. (Family medicine is one specialty he's considering.) Health, like education, stems from deep and complex roots. "It takes a village." ■





Kaarin Michaelsen (MD '14), 42, who double-majored in biology and history at Stanford University, chose the latter as her path the first time around, earning her history PhD from Berkeley and starting a tenure-track position at the University of North Carolina, Greensboro in 2003. As an historian, Michaelsen examined how 19th-century Britain's medical education system for women affected the professional identities of those doctors (among other topics). These schools, she learned, were interested in producing a very specific kind of woman physician—"public spirited," they called it. The idea was: Go out, found clinics for women, children, and other underserved populations. "And what's interesting is that those clinics had longevity. ... They became the founding institutions of the NHS [Britain's publicly funded health care system]."

But in all that sifting through old charts and physicals, she realized she didn't just want to teach about medicine—she wanted to do it. When it came time to apply for tenure, she realized it was time to move on. And at that point, Michaelsen had been flying to Pittsburgh every weekend for six years. Her husband was on the faculty at Carnegie Mellon University, and their two kids had gotten into campus daycare

tory and medicine—together, as well. Throughout the last four years, she's established medical history discussion groups and given a talk on Britain's rabies epidemic in the late 19th century. And next winter, she'll be teaching a history of medicine course through the Department of Surgery.

For her scholarly research project, Michaelsen studied *Scope* and *Scalpel*—like productions dating all the way back to the 1880s. (She herself was one of the head writers for Pitt's production.) She found generations of MDs-in-training poking fun at the faculty, and themselves, and commenting on larger issues in the profession. "One thing that particularly struck me as a scriptwriter was that virtually nothing had changed in the intervening decades. I was just being more overt about it than they were."

Michaelsen matched for an anesthesiology residency at Pitt. The teacher in her is alive and well in the physician she's become. "You have to educate the family about the disease, the prognosis. You get to know them really well, which was something I did a lot with my students. And then you have to manage all these different competing interests at once, which reminded me of trying to manage different classes."

"It felt familiar and comfortable and fun. And I remember thinking, *Yeah. This is home. This is where I want to be.*" ■

there and not in Greensboro. "Coming to med school in Pittsburgh was probably going to be the best way to keep everyone together."

Happily, at Pitt, she's found ways to keep her two professional passions—his-

In his life before his MD, **Tom Miller** (MD '14), 33, was a paramedic-slash-writer (an EMT/MFA). For a year, the Harvard and Notre Dame-educated Wisconsin native worked full-time for an ambulance service that answered 911 calls in Pittsburgh's East End. ("If nothing else, I figured good stories would come of it.")

He then switched to part-time when he landed an adjunct teaching gig at Duquesne University.

"I eventually came to the conclusion that I was having more fun on the ambulance than I was teaching comma placement," Miller says, so he used his tuition discount to complete the last of his premed requirements. (Organic Chemistry, he adds, is kinda weird when your former student—the one who was so upset about that B he got in English last year, naturally—is suddenly your classmate. "We'd sort of wave awkwardly to each other.")

With the start of med school just a few months away, Miller got the itch to revisit his MFA manuscript, a collection of overlapping folkloric tales spanning several centuries that was aimed primarily at a scholarly audience. He realized what he really wanted to write now were the kinds of stories he enjoys reading for fun—fantasy à la J.K. Rowling and George R.R. Martin.

And—long story short—Miller is now a newly minted MD-slash-author.

The novel, which is tentatively titled *The Philosopher's War* and will be printed by Simon & Schuster in July 2015, takes place during World War I. In this alternate version of history, a poorly understood branch of science (basically, magic) was discovered around 1800.

In addition to birthing this metaphorical baby—this novel he gestated through four years of late-night writing, rewriting, and pitching to literary agents (he sent the manu-

script to 30 in all)—Miller and his wife, Abby, also welcomed a baby boy, Owen, in March.

Needless to say, the last four years, which culminated in Miller's match with the University of Wisconsin's emergency medi-

cine residency, have been a constant exercise in triage. And when asked what made this magic act doable for his family, Miller's answer is simple:

"You find a way. You make the time for things that are important." ■



OH, THE PLACES YOU'VE BEEN

Pitt med students have taken all sorts of scenic routes along the way to this medical school: previous careers, parenthood, pilot training. There are too many interesting “nontrads” to mention them all, but we couldn’t resist introducing you to a few more here. —Zach Nichols



CHRISTOPHER BARNES, 27
MOLECULAR PHARMACOLOGY PHD PROGRAM (3RD YEAR)
FROM: HUNTERSVILLE, N.C.
NAIMA SHARAF, 28
STRUCTURAL BIOLOGY PHD PROGRAM (5TH YEAR)

FROM: QUITO, ECUADOR

Barnes was a high school football standout who also played for UNC Chapel Hill. Sharaf lived in Ecuador and Australia before coming to the United States. The two met while working in the same lab, where, Sharaf says, Barnes would come work on weekends when she was there. With other colleagues, the couple was just awarded a patent on a nuclear magnetic resonance (NMR) device that allows users to observe the inner structure of living cells. Now at Pitt together, Barnes and Sharaf have two sons, ages 4 and 1.

Barnes on this “ideal situation”: “Graduate school is actually a pretty good time to have a family, especially in the PhD program, because that’s when your schedule is the most flexible. And especially here at Pitt; our medical insurance is great.”



KIMBERLY BELL, 27
MD CLASS OF 2017
FROM: PITTSBURGH, PA.
LEANING TOWARD: OB/GYN

Bell, a mother of two, attended Pitt as an undergrad, earning a BS in ecology and evolution while enlisted as a medic in the Army National Guard. Motherhood has taught her compassion, she says, and military service, discipline.

On treading the nontrad path: “If somebody tells you that you can’t do it because of your background, don’t listen to them and try anyway.”



BRIAN NOLEN, 34
MD CLASS OF 2015
FROM: PITTSBURGH, PA.
LEANING TOWARD: INTERNAL MEDICINE & ONCOLOGY

Nolen started out working for a biotech company,

where he quickly grew bored of the nine-to-five and started volunteering as an EMT. Then, in 2008 and 2011, respectively, Nolen received his MPH and PhD in human genetics from Pitt, focusing his research on the treatment of gynecological cancers. It was working alongside clinicians at the University of Pittsburgh Cancer Institute, he says, that made him realize the grass was greener.

The long view: “I think I have a little perspective in knowing that each test is not the end of the world and probably not the most important thing I’ll ever do in my life.”

PATRICK POLSUNAS, 33
MD CLASS OF 2017
FROM: NEW YORK CITY, N.Y.
LEANING TOWARD: ORTHOPAEDIC SURGERY & PHYSICAL MEDICINE & REHABILITATION

Polsunas has worn many hats and—as a longtime triathlete—run, biked, and swum many races. He’s worked as a carpenter, yoga instructor, and children’s mental health coordinator. He sees medicine as “a natural progression” from his time teaching yoga and helping kids.

His advice for would-be nontrads: “Don’t be afraid, going into it, that you won’t have anyone to interact with. And when you do get there, embrace those interactions.”



JANELLE WHITNEY, 28
MD CLASS OF 2017
FROM: MIDDLEBURG, PA.
LEANING TOWARD: OB/GYN

Whitney had her first child, now 8 years old, while pursuing a bio major at MIT. After graduation she stayed for another year at MIT to teach. Since then, Whitney and her husband have had two more children (4 and 2 years old).

On seeing it both ways: “Being a mother, I really got exposed to health care from the patient’s perspective a lot more than my classmates.”



MEGAN WRIGHT, 33
MD CLASS OF 2017
FROM: CALIFORNIA (ALL OVER THE STATE)
LEANING TOWARD: ONCOLOGY (THIS WEEK!)

In her many former lives, Wright has taught art at Evergreen State College in Olympia, Wash.;

flipped houses as a carpenter in Olympia and Albuquerque, N. Mex.; and co-owned and managed a microbrewery in Ventura, Calif. Then she realized that, as someone who’s always loved seeking out new challenges to conquer, she’d feel right at home in an ever-evolving field like medicine.

On how her old skills serve her now: “I see waitressing as gangbusters useful. How do you go and approach somebody and—in less than 5 minutes—put them at ease, take care of them, make suggestions? ... Your face time is actually very short, but [the customer or patient] leaves with a very positive experience.”



TOLANI OLONISAKIN, 22
MD CLASS OF 2017
FROM: LAGOS, NIGERIA
LEANING TOWARD: UNDECIDED

Olonisakin began college at 16, majoring in biology, but spent her undergrad years researching black holes in an astrophysics lab. She then felt the pull of another powerful force, the desire to “benefit mankind.” She says that though physics is “science in its purest form,” particles swerving around distant black holes have little to do with helping people. So she spent the year before enrolling at Pitt doing research on sickle cell disease. Now, as a second-year in Pitt’s Physician Scientist Training Program, she’s studying innate immunity in the lungs.

On being heard: “There’s a lot of great work being done here at Pitt. [The people I interviewed with] just seemed very interested in what I was doing and what I talked about. They made me feel heard. It was really refreshing.” ■

Elaine Vitone contributed to this report.



“THERE’S ALWAYS SOMETHING”

MORE TO COME
WITH SICKLE CELL
BY ROBYN K. COGGINS

The shape of the reds was very irregular, but what especially attracted attention was the large number of thin, elongated, sickle-shaped and crescent-shaped forms. These were seen in fresh specimens, no matter in what way the blood was spread on the slide, James B. Herrick wrote in 1910, six years after his intern Ernest Irons showed him a peculiar specimen under a microscope.

The blood came from 20-year-old Grenada native Walter Clement Noel, who was in Chicago to attend dental school. On his voyage from Barbados, Noel had developed an intense

sore on his ankle—similar to more than 20 others that had scarred his legs throughout his childhood in Grenada—which another doctor had treated with iodine. By the time Noel reached Irons and Herrick (an early adopter of microscopic blood exams and best known for having first described myocardial infarction), he had been coughing for five weeks and was feverish, dizzy, and jaundiced.

But the mysterious part of his illness showed in his blood. After Irons, then 27, first examined Noel he performed a smear and noticed “many pear-shaped and elongated forms” on the slide. Thus began a two-and-a-half year search for a diagnosis, following and studying Noel until he returned to Grenada after dental school to open a practice. Herrick published his 1910 paper, and by the 1920s, enough similar cases surfaced that the disease was coined “sickle cell anemia.”

However, the disease had been known elsewhere for centuries. One history traced the condition through a family in Ghana back to the 1670s. In Nigeria, the Igbo people called sufferers *ogbanje*, or “children who come and go” as evil spirits targeting families. The Ewe in Ghana, Benin, and Togo called the illness “body chewing” and the Adangme, “body biting”—alluding to the extraordinarily painful nature of the affliction.

More than 5 million people worldwide, most of whom have Sub-Saharan African, Middle Eastern, or Mediterranean ancestry, are affected by sickle cell disease (SCD)—a set of recessive, inherited blood disorders. (People of Latin American, Saudi Arabian, and Indian heritage also get SCD.)

Maylen Johnson (not her real name), a Pittsburgh native who’s quick to laugh, has the SC type of sickle cell disease, meaning her father and mother each carried a different variant of the SCD trait. Now 40 (but you’d never guess it with her smooth skin and girlish cheekbone freckles), Johnson has been hospitalized for complications related to the disease so many times it’s hard to keep track.

She and her twin brother were diagnosed at around 6 months old. Their mother noticed

they cried more than usual and had trouble sleeping. “She could tell when we tried to crawl that something was hurting,” Johnson says. Her aunt also had SCD and died at age 55; her grandmother, two nephews, and a niece are carriers.

Every red blood cell in our bodies contains hemoglobin, a knotty-looking protein that transports oxygen from the lungs through the rest of the body. Hemoglobin can typically be broken down into alpha and beta subunits. The problem in sickled cells

resides in the beta part—it stems from just one nucleotide change, which causes one amino acid change, and results in structurally abnormal hemoglobin.

These irregular hemoglobin molecules clump together, stiffening red blood cells and altering their shape, which prevents them from moving smoothly through the blood vessels, especially capillaries. The result is oxygen loss, anemia, stabbing pain, and sometimes tissue death.

As a child, Johnson was physically active, though it sometimes led to complications. In high school, she ran track and was on the cheerleading team. She wanted to swim, *Who doesn’t love to swim?* she asks. But she couldn’t handle the cold pool water—even a short dip meant hospitalization for a bad cold or pneumonia. Same thing happened to her brother.

“We didn’t understand then why we couldn’t do a lot of the things that ‘normal’ kids could do,” she notes.

“I always used to say that the pain felt like a piano dropped on me. When it’s at its peak, it’s very, very painful.”

At least that level of pain isn’t constant for Johnson—she experiences it three to five times per year. She mostly deals with chronic lower-level pain in her back, hips, and legs.

Life-sucking pain and fatigue are probably the most infamous of SCD’s manifesta-

tions. People with SCD might also experience leg ulcers and jaundice (like Noel), swollen hands and feet, clogged blood vessels, strokes beginning in childhood, multiple organ failure, cognitive deficits, and lung disease (more on these last two in a moment). The extent of symptoms often depends on which of the four main types of sickle cell disease a patient has—HbSS, or sickle cell anemia, is generally most severe. In 1960, the average lifespan of someone with SCD was just 10 years. Today, thanks to improved infection treatment, preventive medi-

cine, and blood transfusions, the average has jumped to about 50.

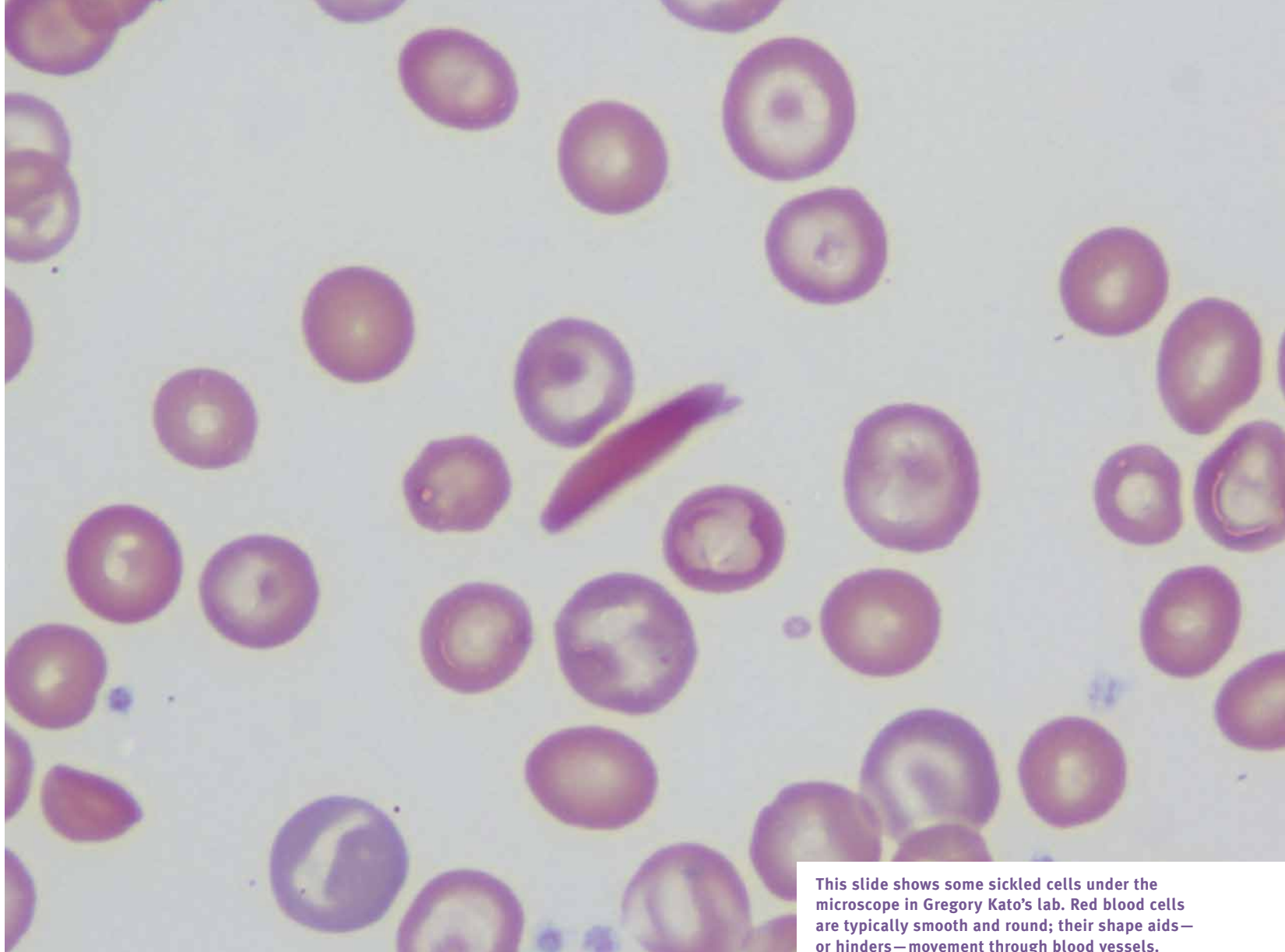
Often, the best doctors can do are blood transfusions to alleviate bad pain crises and to reduce the risk of strokes.

A stem cell transplant—from bone marrow, umbilical cord blood, or peripheral blood—can cure the disease. But such a transplant, of course, comes with risks of rejection and infection. And finding a donor can be extremely hard. The best match usually comes from a healthy sibling; yet many parents, once they have a child with SCD, opt not to risk having more children with the disease.

Johnson takes hydroxyurea (the only FDA-approved SCD drug), pain medication, and occasional blood thinners. She has had the same primary care physician her entire life and has been seeing Enrico Novelli, MD director of UPMC’s Adult Sickle Cell Disease Program, for years. For lung checkups a few times a year, she visits Pitt professor of medicine Mark Gladwin.

Since he arrived at Pitt from the National Institutes of Health in 2008, Mark Gladwin—MD division chief of pulmonary, allergy, and critical care medicine and director of the multidisciplinary Heart, Lung, Blood, and Vascular Medicine Institute (VMI)—has summoned a diverse and multitalented sickle cell team that’s tackling the disease

The Ewe people in Ghana, Benin, and Togo called the illness “body chewing” and the Adangme, “body biting”—alluding to the extraordinarily painful nature of the affliction.



This slide shows some sickled cells under the microscope in Gregory Kato's lab. Red blood cells are typically smooth and round; their shape aids—or hinders—movement through blood vessels.

with renewed fervor.

"When I came, there [were] modest-sized, strong clinical programs ... but really no research in this space," Gladwin says. At the time, Novelli (Fel '01, Res '02) and his colleagues wanted to do more in the lab to help their 80-some patients, but he and the small staff were overwhelmed simply treating them.

"There's really a critical need for more hematologists doing research," Gladwin says, "but there's a national shortage. So part of this plan of building the VMI was to really enhance benign hematology research. So we're really thrilled now, six years later, that this plan is really coming together."

Gladwin brings a history of National Institutes of Health-backed pulmonary breakthroughs with him, primarily related to nitric oxide's role in blood vessel dilation and constriction. In translational studies, he showed that inhaled nitrite gas can reverse pulmonary hypertension, or high blood pressure in the lungs. Another of his studies showed that hemoglobin in SCD patients scavenges nitric oxide,

which narrows blood vessels. Gladwin spent his first three years at Pitt beefing up his own lab and supporting Novelli, assistant professor in hematology/oncology, in developing his.

"[Gladwin] has put sickle cell at the center of the institute," Novelli says. "With him being an expert in sickle cell ... he really had the clout to enact change within the institution. And so we've been able to secure funds now even from the Hemophilia Center for Western Pennsylvania and the Institute for Transfusion Medicine, to really boost our services."

In addition to crystallizing VMI's focus, Gladwin bulked up the institute's industry and community partnerships. (VMI collaborates with Ryan Clark's Cure League and has a partnership with Bayer.) UPMC's adult SCD program now has six doctors, two physician's assistants, two outpatient clinical nurses, and a senior clinician/social worker; together, they see more than 160 patients with sickle cell disease. (Children's Hospital of Pittsburgh of UPMC has another team of providers.) The VMI lays claim to a half-dozen labs pursuing

vascular research related to sickle cells.

These physicians and scientists hope to create an integrated benign hematology center in Shadyside.

Dominique Stevens-Young (Pitt MSW '89), the program's senior clinician and clinical social worker, specializes in sickle cell disease management. Stevens-Young has been with UPMC since 2000 and says the program has never looked better. She talks a mile a minute about the early Gladwin days: "I used to call Mark and say, *Mark, you promised you were gonna change things when you got here, and things are still the same, and what are you waiting for?*" At a retreat this last September, held just as the new VMI/UPMC team was assembling, Gladwin told her: "I was waiting for now."

This February, Johnson spent a couple of weeks in the hospital for double pneumonia. Nine days in, then less than 24 hours out, then seven more days in.

"That's happened several times before,"

Johnson says of the back-to-back hospitalizations. “There’s always something.”

A century ago, Noel attributed his lifelong shortness of breath to heavy smoking. Herrick suggested hookworm, syphilis, intestinal parasites, and malaria, never quite landing on the correct interpretation. Nowadays, doctors have the right diagnosis but still don’t understand the mechanisms of the disease.

“Most sickle cell patients do have some

it feels like a heart attack.”) It’s not unusual for sickle cell patients to end up with ACS while in the hospital. Ofori-Acquah wants to know precisely how it develops, and has created a mouse model of the condition that any researcher interested in ACS can use. In developing that model, he has identified possible triggers for the syndrome.

Acute hemolysis—a buildup of heme in the blood—may be one. When red blood

even remember,” she notes. “I’m sad to say that, but it is what it is.”

“Cognitive impairment is subtle but is there [in SCD patients], and there’s nothing we can do for it,” Novelli says.

“I’ve been really interested in this, and I thought it was natural to look at sickle cell with the same tools that we use for Alzheimer’s, dementia, and other diseases.” These studies, one of which Johnson participated in, are a

“We didn’t understand then why we couldn’t do a lot of the things that ‘normal’ kids could do.”

baseline lung dysfunction,” says Solomon Ofori-Acquah, one of three sickle cell all-stars Gladwin helped bring to Pittsburgh to expand the SCD team here.

Ofori-Acquah has a PhD in molecular genetics; he investigates the bases of SCD complications, specifically in the lung.

“Even when [patients] are clinically well, they may have slightly [lower oxygen levels in the blood],” he says.

Less oxygen means less energy—Johnson’s major symptom. Plus, hypoxemia often coincides with low levels of nitric oxide in SCD patients (one of Gladwin’s areas of study). The oxygen and nitric oxide molecules, only partially absorbed by hemoglobin and therefore red blood cells, bind together and stick to vessel walls, causing deficiency of these important gases.

As patients age, the compounding effects of lung complications and damage become permanent and debilitating. Pneumonia after a stint of traveling and a bath ultimately killed Noel at age 32. Johnson has pulmonary hypertension and asthma; she has had two blood clots in her lungs and sleeps with oxygen at night.

One common and especially devastating lung condition in SCD is acute chest syndrome (ACS). The number two reason for hospital admissions and the leading cause of death among adults with SCD, ACS ravages the lungs, resulting in inflammation and fluid buildup. No one knows exactly what leads to it. (Johnson doesn’t have ACS, but says lots of people in her support group do: “They say

cells break down, heme (and probably some iron) is released into the bloodstream. Since sickled cells die more quickly than healthy cells, a heme overload results. What signals this heme? What then causes ACS to progress so rapidly in mice and in humans? That’s one set of mysteries Ofori-Acquah’s NIH-funded lab hopes to crack.

His lab is also investigating the development of chronic lung injury and what might slow down its damage. When cells are stressed, they release enzymes to sweep up excess heme in the blood and halt damaging buildup. Ofori-Acquah thinks NrF-2, a transcription factor that induces those cytoprotective enzymes, might be a good target for future drug treatments. He wonders, *Is this the right pathway? Could drugs provoke the body’s protective response?*

“It’s almost like the cancer paradigm, where you are looking at a prognosis, and you take chemo to give you another 10 or 15 years,” Ofori-Acquah says of potential therapeutics that might come out of his lab. It wouldn’t be a cure, he says. But such a treatment could help patients “live a better quality of life with lungs that still function and that can still do a six-minute walk or jog.”

Throughout our conversation about her life and illness, Johnson struggled to remember exactly when her hospitalizations were. Perhaps that’s not surprising, as there’ve been quite a few; still, she says that her memory is “terrible.”

“There [are] people from school I don’t

new area of investigation for Novelli, as well as for SCD researchers generally. (Since he was a junior faculty member at Pitt, Novelli has focused much of his investigations on pulmonary hypertension and tissue pathways.) Physicians have long known that blockages in blood vessels affect organs and limbs, but not much, outside of anecdotes, is known about the effects on the brain.

Novelli says that, as a clinician, he sees how cognitive impairment makes it difficult for patients to adhere to plans for their care: “Sometimes we try and explain to patients, ‘You have to do this; you have to take this medication; this is what happens.’ And we think they understand. But then we realize that, indeed, their level of understanding and their memory are also very limited.”

These deficits, in conjunction with the need for high doses of pain medication, can set up patients for derision. Sometimes callous providers accuse sickle cell patients of looking for a high with prescription meds or not taking responsibility for their own care.

“You want to get along with your doctor,” Johnson says. “Dr. Novelli is very good at what he does. He’s very nice.” But she has encountered doctors elsewhere who didn’t treat her so kindly and accused her of exaggerating her pain.

And many with SCD have trouble getting to appointments in the first place, because of mobility problems or a lack of access to transportation. Stevens-Young says the burnout rate for her colleagues who work closely with SCD patients is about five years. (Regarding her own experiences, she says, “I’ve got a lot of stories,

but most of them are sad stories.”)

Though both Johnson and Stevens-Young sing the praises of those who’ve given long-standing care here, they’ve noticed the recent efforts to bolster the clinical team. “Never in the history of the program have I ever seen this much care and devotion towards our patients,” Stevens-Young says. “I’ve been telling the patients, just hold on, things are gonna get better. And now it’s here.”

Pitt’s Sruti Shiva, PhD assistant professor in pharmacology and chemical biology, and Novelli may have made the most intriguing SCD breakthrough at the VMI to date. With help from colleagues at Children’s Hospital of Pittsburgh of UPMC, they revealed that SCD patients exhibit mitochondrial dysfunction.

Their results, published in *Blood* this May, are noteworthy for a couple of reasons. First, no one had ever studied mitochondrial function in this patient population before. And second, the dysfunction they discovered is associated with increased platelet activation in the blood, which is, in turn, associated with increased red blood cell death, hemoglobin abnormalities, and pulmonary hypertension. The researchers think that this “bioenergetic aberrancy” may be caused by complex V—an important link in the chain of mitochondrial energy transfer that’s dysfunctional in SCD patients. All of this makes the mitochondrial issue a potential target for treatment.

And there’s more to look forward to. Aes-103—a drug in phase 2 trials that binds to hemoglobin and may block sickling altogether—has been shown in some patients to increase oxygen absorption and stabilize red blood cells, stopping the cells from dying. Pitt/UPMC’s new MD hire, Gregory Kato (pronounced kah-toe), led development of this prophylactic treatment as former director of the Sick Cell Vascular Disease Section at the NIH’s National Heart, Lung, and Blood Institute.

Also on Kato’s short list: a 2010 cover story in *Blood* about the role of placental growth factor in the development of pulmonary hypertension in SCD and an upcoming *Blood* article showing that excess iron from repeated blood

transfusions stimulates abnormal production of placental growth factor. He’s also building a sickle cell registry at UPMC.

Kato joins other 2013 all-star hires Ofori-Acquah and Laura De Castro, an MD and national leader in clinical sickle cell research from Duke University. De Castro runs the adult sickle cell clinical programs with Novelli and is director of clinical translational research for the UPMC Sickle Cell Disease Center of Excellence, as well as a clinical faculty member in Pitt’s Division of Hematology/Oncology.

De Castro focuses on mental health issues and end-organ damage in SCD, as well as finding novel treatments. She has been the principal investigator or coprincipal investigator on 20-plus NIH- and industry-sponsored clinical studies for hemoglobinopathies. Preliminary data from one recent study showed that 28 percent of SCD participants studied had indices of depression; further, De Castro found a “statistically significant association between the presence of depression and low scores for neurocognitive function domains,” she reports.

De Castro’s, Kato’s, and Novelli’s patient relationships should help inform the academic interests of the VMI labs and spur development of more effective treatments for SCD. Such collaborations are a bit like a relay race, with each party handing off a baton of knowledge to the next; with each revolution, the race distance gets shorter.

De Castro is quick to point out that Herrick’s study of SCD was published more than 100 years ago—it’s time to make strides toward better treatments, she says.

Ofori-Acquah will look toward Africa for insight. In his native Ghana, two of every 100 newborns have SCD, compared to one in every 5,000 in the United States generally and one of every 500 African Americans. This May, Pitt and the Kwame Nkrumah University of Science and Technology in Ghana signed a memorandum of understanding to help grow an international collaboration.

“There’s a very small number of eligible patients for clinical trials” in the United States, Ofori-Acquah says. “What we’re trying to do is develop collaborations in Ghana and elsewhere where there is a large patient popu-

lation of sickle cell disease so that if we find a potential therapeutic, the clinical trials will not be such a headache.”

It would mean the world to Johnson to have some of her energy back. Her passion is hair—twisting, curling, dyeing, cutting. Johnson trained as a stylist but doesn’t have the stamina needed for that work now. She’d like to open her own salon—maybe someday. She has to pace herself. For a friend’s wedding this June, Johnson did her aunt’s hair. “But it took everything out of me,” she says.

Johnson wants to build awareness about sickle cell disease. “There needs to be commercials, billboards, radio shows,” she says. “It’s not a nice disease. It needs to be more known.”

“We’re understanding the disease better; we’re figuring out how to study it,” Gladwin says. “The drugs are getting better, and companies are starting to focus on these diseases more and more. So this has become a kind of perfect storm here in Pittsburgh.”

Johnson has learned to understand her disease better, too. She tires easily, but she tries to be active—getting out to her sickle cell support group, visiting with family and friends. She listens to her body, takes her medications, aspires to eat right.

And after a childhood spent avoiding pools, Johnson gave swimming another shot in her mid-20s. “I was definitely nervous, because it affected us when we were little. But you take chances, you know? I just took a chance.”

At first, she just dipped her feet in. Then, she inched the rest of her body into the water, making sure it wasn’t too cold.

She didn’t get sick. “I can go swimming,” she says with a grin. “I don’t know why, but I can.”

“This illness will give you some curveballs. A lot of them. You cannot predict it at all. When you think, *Oh I got this in the bag. I know everything about it*—no! No, you don’t. I believe you can learn something until the day you die, because there’s always gonna be something new.

“There’s so much more to come about this disease.” ■

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WHAT \$100 MILLION, 600 TERABYTES,
AND A LOT OF CAREFUL THOUGHT WILL
DO FOR PITTSBURGH | INTERVIEWS AND
INTRODUCTION BY MICHAEL FITZGERALD

STITCHING THE PIECES TOGETHER

Some recent headline-making news:

- In November 2013, the FDA sent a letter asking 23andMe to stop assessing health risks for the genes it decodes.
- In March, Illumina (a biotechnology company) began shipping a machine that can sequence a human genome for less than \$1,000.
- The health exchanges mandated in the Affordable Care Act survived an infamously bumpy launch.

These events will play into or add texture to the issues surrounding the rollout of UPMC's five-year, \$100 million plan to bring personalized medicine into its clinics, announced in fall 2012. That effort, which will use patient data and analytics to develop and optimize treatments, will also guide and inform research at the University and beyond.

The academic medical center is in the midst of a massive effort to pull together and analyze its silos of patient data so that its doctors and scientists can customize treatments and care. The leaders of this effort talked with us about how that's going and the practical, ethical, and clinical questions that arise in the attempt to tailor medicine for individual patients.

ILLUSTRATIONS | CATHERINE LAZURE

As the undertaking entered its second year, *Pitt Med* put together a floating roundtable with some of the key people shaping this historic effort: Steven Shapiro, an MD who is chief medical and scientific officer for UPMC and professor of medicine at Pitt; Jeremy Berg, a PhD who is director of Pitt's Institute for Personalized Medicine, associate senior vice chancellor for science strategy and planning, health sciences, and Pittsburgh Foundation Professor of Personalized Medicine and of computational and systems biology; Adrian Lee, who directs the Women's Cancer Research Center (for the University of Pittsburgh Cancer Institute and the Magee-Womens Research Institute) and is a PhD professor of pharmacology and chemical biology; Lisa Parker, director of Pitt's Master of Arts in Bioethics program and a PhD associate professor of human genetics and of behavioral and community health sciences at the Graduate School of Public Health; and Lisa Khorey, who recently stepped down as UPMC's vice president of enterprise systems and data management. Their comments are condensed here.

We're more than a year into this five-year project. What's happened?

Khorey: The bulk of the work we've been doing in the last year is system implementation. We're building an information management factory.

[There's] a lot of digital data. It's 29 applications from three different vendors, 47 different servers, two hardware appliances (one for loading multimillions of records, one for real-time data integration). It took 11 months, but that's all done. Check the box.

Berg: Adrian [Lee] has used the term "data graveyards," because all that data takes up a lot of disk space, and nobody can figure out what to do with it. You have to decide which genomic data you actually collect—you don't want to collect it first and then sort it all out. The biggest things that I've been focusing on in the last year are data management and manipulation—and usability.

Shapiro: The data is starting to get moved, and we've done some small use cases. Our high-volume academic cardiologists were using thrombectomy catheters, for treating acute heart attacks, pretty routinely. Then a

big *New England Journal of Medicine* article came out saying there's no evidence that these catheters work. They looked at only one month's worth of data. We didn't see anything in one month either. But looking at the first three months of data at the end of last year, we found that mortality rates dropped from 15 percent to 10 percent, and the stenosis rate went from 15 percent to 5 percent. It's six months of data we want, but we're getting close to saying, *Hey, we should use this thing*. We think the *NEJM* study has it wrong. We think the analytics will give us the right answer.

What are the practical challenges of having all this data?

Berg: It's hard to manage. There are already more than a million files—six or seven hundred terabytes of data. [For comparison, the Library of Congress' Web archives take up about 525 terabytes.] It's a hugely complicated informatics and computer science challenge to store the data and track which version is which. We're involved with a project [a partnership between Pitt, UPMC, and the Pittsburgh Supercomputing Center], ... what's called the Pittsburgh Genome Resource Repository, to get all the data organized and



Berg



Lee



Parker



Shapiro

manageable. We want to get to a point where it's sort of like writing a Google request and getting the answer quickly, rather than having a year-long project to get the answer and then find out that you need to ask a different question.

Lee: Your genome has 3.2 billion base pairs, so in sequencing, an error rate of even 0.1 percent is a problem. Data governance, data control, data versioning become unbelievably important. Also, we're changing the way we share data and the way we work. My lab, which is a biology lab, now spends a lot of time working on the high performance computer. We need to increase our storage. Data transfer is a problem because we can't move these large data sets around. Our network wasn't built for that.

Khorey: In terms of loading data, we started with the last two years' worth. There are 250 million lab tests and about 38 million conditions [in our records]. So far we have incorporated data from 15 clinical systems. We need to make some decisions around what is the most valuable data versus our impulse to load all the data. The hungry man is starving and wants everything at the buffet, but that's wasteful.

What's next for UPMC?

Shapiro: In the thrombectomy catheter example, if the data show what we think [they] will, then the question is, *It costs \$900; do we really need it for everyone?* It looks like if you have it, your hospital stay is two days shorter;

so it's already cost effective. Then we can look and see if everyone needs it, or if it only works for some people. That's the concept. [In late winter, we were just] preparing for the data. We [started] moving the really large data in April.

Berg: There are close to 100 drugs for which there's reasonably good information about the genetic variations that are important in terms of how a patient will react to the drug. Different people respond to the same drug in different ways, in part due to genetic background. The question is, *How to get that into practice?* If the genetic information were already in the patient's chart, physicians would absolutely use it in prescribing drugs. If they have to order an additional test, that becomes a much different proposition. The challenge for the whole field is how to collect the relevant information for people who are likely to get specific drugs prescribed.

In the planning stages is a project being driven by David Whitcomb [MD/PhD chief of gastroenterology, hepatology, and nutrition. See story, p. 29.] He's working on a research study that would use genetic and other information to try to more accurately assess the risk of disease progression for patients who come in with pancreatitis. Many patients have one episode and never have another after that. Other patients develop recurring episodes and then chronic pancreatitis, with irreversible tissue damage. We're looking at kidney disease and other areas with different disease conditions that have a commonality to see if new tests may be relevant in a clinical setting.

Khorey: Our next six months will be spent refining operational processes involved in data movements, data interpretations, and analytics. We will prepare additional data source systems in collaboration with targeted user groups across UPMC, such as clinics, the health plan, and finance.

What are the ethical issues you've identified?



Shapiro: Jeremy and Lisa [Parker] are working on [various issues], from *Is it opt in or opt out when we sign patients up for genomic sequencing?* to *If we do sequencing, what needs to happen if we find something? [Like, what if the doctor learns that the patient has a risk for a disorder that wasn't the purpose of the visit?]*

There are many ethical issues around getting consent, incidental findings, and preparing patients for this.

Parker: There really are two issues with regard to privacy: hackers and risk of exposure. If the data is exposed, what's the risk? The

Genetic Information Nondiscrimination Act, passed in 2008 at the federal level, means health insurers cannot refuse to cover you because of a preexisting condition. And you can't be charged a higher premium in light of having a genetically based increased risk. Employers are not allowed to use genetic risk information. Life [insurers], long-term [care] insurance, and disability [insurers] could still make use of the information; they want to know the appropriate actuarial pool to put you into.

Berg: If you collect genetic information

to test for one condition, for some people you will see things that don't have anything to do with why you originally were doing the test. [Yet the genetic information the doctor uncovers may have] health consequences some people might want to know about.

The American College of Medical Genetics and Genomics issued a report [stating that doctors have] an ethical obligation to tell people [such information]. That goes against the grain of a lot of ethicists who place more emphasis on patient autonomy.

That's the tip of a big iceberg. I remember when the gene for Huntington's disease was identified. If you've got the bad form of it, you're very likely to develop Huntington's, an awful disease. I couldn't imagine not wanting to know that. The reality is that something like 80 percent of people don't want to know.

What about the risk of a class of genomic fortune tellers emerging?

Parker: You can't read genomes like tea leaves. Or maybe you can; tea leaves are not particularly reliable. The biggest risk of harm is that people themselves will, in some sense, misuse their own information. Or they'll get their genome on a chip at age 30, find out their risk, and not realize that this is an evolving science. That genome needs to be reinterpreted again at 35 and 40, because we're [continually] learning new things.

Otherwise, it's not obvious what we'd want to do with someone's genetic information. Maybe you could embarrass me, especially if I'm a celebrity or running for public office. People [might ask questions like], *Do we want a president who might become diabetic while in office?* But that's not so much [an issue of] the genetic information as it is the social structures.

Are we seeing personalized medicine yet?

Berg: You know, the first thing I did when I got here was try to find a better term than "personalized medicine." If I were a clinician I would find it insulting: "Wow, we're treating patients as individuals; wish we'd have thought of that 5,000 years ago." "Precision medicine" is the other term, but it's still a little bit presumptuous at this point.

It's in its infancy. There are some things for

which the genetics are relatively clear and the research is relatively strong and the information you get from the genetic test is actually pretty deterministic. For other things, there are literally hundreds of different genes that contribute to disease risks. And how they interact with each other is not really well understood. Medicine is always going to be stuck with these unpleasant probabilistic outcomes. Our percentages will be better, but there will still be uncertainty.

Lee: Pretty much every tumor is different. We have new tests that utilize these new technologies to screen for mutations so we can give targeted therapies specifically for genetic manipulation in that tumor. Unfortunately, cancer's pretty clever and most of the time finds its way around what we do to it. We have a long way to go.

Will it cut costs?

Shapiro: I would like to be able to tell you how we'll determine who's at risk for readmission, what makes someone need to come to the hospital so frequently. It's probably too early. [For example], we'd love to know what characteristics of breast cancer tell us [which] 25 percent of patients ... will do badly with minimal treatment.

How will patients respond to genomic/personalized medicine?

Berg: That's another area of research: Does genomic knowledge motivate people or not motivate people? If you find out that you have susceptibility to a disease, do you lose 20 pounds? Or do you say, *Oh well, it's in the genes. I'm going to have a donut.*

Lee: In our high-risk clinic, people often refuse genetic testing, and there's a lot to be said for that. It will take a while for it to become routine, as people become comfortable [with the idea] and insurance figures out what it wants to pay for. It's causing a revolution in diagnostics and therapies, and the system needs to adapt to that.

What will it mean for doctors?

Shapiro: Every day we're finding more and more genetic and genomic markers for

tumors. At some point we will use them clinically. When we do that, the average oncologist [won't] know what to do with this genetic information. The analytics themselves need to give them actionable information. The future is to allow the analytics to be a guide for clinicians as opposed to [telling them], *Hey, go read these articles.* It needs to be bedside.

Lee: We have huge capacity to create data but limited ability to turn the data into knowledge. You used to have your cholesterol and your height and weight [for a physician to assess]. Now, you've got 3.2 billion base pairs. If you walk in with your genome, what does the physician do with that? What about when people will come in and say, *Oh, I had it sequenced somewhere.* Do we accept that? Do we resequence? The current idea is it's so expensive to store this stuff, and so cheap to [sequence], we'd just redo it.

What does the future hold?

Berg: These things are going to take time. We have to be aggressively patient. Personalized medicine is going to be a major revolution in health care and society in general.

Shapiro: In the last five years we've doubled the amount of things we knew in medicine. The textbooks are large enough and medical school is long enough. In some ways, it'll be easier to teach students; there won't be as much need to memorize. As we get more information, I hope we'll simplify the pathways we're teaching. Research is starting to change. We're moving from an era where we have a specific hypothesis, a very reductionist approach of looking at a candidate gene and seeing what it does, to one where we say, *Let's generate hypotheses and let the data look at everything so we can come up with better things to ask.*

Lee: The human genome now takes roughly a day and \$1,000 to sequence. When people received the microscope and could see bacteria, that transformed medicine. The sequencer is like that microscope for the genome.

Shapiro: This is a long-term process. We are doing the hard work now without the glory. ... We don't have a lot of results now, but they're coming soon. With all the challenges in health care, we're seeing this as a big investment. Everyone needs to make it. ■



ONE SIZE DOES NOT FIT ALL,
BUT TAILORING
IS NOT SO SIMPLE
BY MICHAEL FITZGERALD

TRYING ON PERSONALIZED MEDICINE

The man in the exam room is in his early 40s. A salesman. He has two kids under 13 and metastatic melanoma that has spread to his lungs and his lymph nodes. Not long ago, his doctor, Ahmad Tarhini, would have had a grim conversation with him. There was little hope for a patient with stage 4 melanoma. Chemotherapy could shrink tumors but not prolong his life by much. Perhaps 10 percent of patients at this stage responded to a drug called interleukin 2, which sparks the immune system to fight off cancer. Some patients were helped by experimental drugs in clinical trials, yet there was no way to tell what drug would work for whom.

But it's now June 2014, and Tarhini can have a somewhat more upbeat conversation. He would not mention the word "cure" just yet to patients in this situation. But he does tell the man: "There are effective targeted and immune therapy options that are proven to prolong life and were recently approved by the FDA. Also, there are new medications and combinations of existing medications being tested in studies, and the preliminary data are very encouraging."

"The patients using them are still being followed by researchers, but we are seeing long-term survival."

Tarhini, an MD/PhD and associate professor of medicine in Pitt's Division of Hematology/Oncology, walks his patient through some options. He tells the patient his melanoma is driven by a mutation of the BRAF V600E gene. The same mutation is found in about 50 percent of melanoma cases. He could be given a drug that targets this mutation and shuts it down and effectively shrinks the tumors in a little more than half of the patients who have this kind of melanoma.

The trouble with these drugs, Tarhini explains, is that while they give patients a new lease on life, it's often brief—seven to nine months, on average. Then the cancer is back, and mutated again, into a more drug-resistant form.

Tarhini tells him about another option, a

drug called ipilimumab. Like interleukin 2, it's an immune therapy, meaning it elicits the man's own immune system to fight against the cancer. (Ipilimumab is approved as a monotherapy but is also available in combination with other drugs in clinical trials.) Those who respond well to ipilimumab have what Tarhini calls "durable" responses, living longer than patients who take existing targeted therapies. Some have lived for a decade. One catch: It only shrinks tumors, so far, in about 11 percent of patients; yet about 20 percent of patients have survived for years with it. Another catch: Some patients experience severe side effects with ipilimumab. Tarhini doesn't know how the salesman would do with this immune therapy. But his cancer is slow-moving, so it could be worth trying.

The salesman's case gives a glimpse of the

"If you have metastatic lung cancer, when you walk in the door, we're sequencing your tumor."

medical future for all of us: Once dread diseases leavened by hope. Treatments more tailored to our specific illness. Doctors becoming better informed about our diseases, about us, and the potential for cures.

Medicine starts with the person: Doctors have always treated individual patients, but the 1972 approval in the UK of tamoxifen as a counter to estrogen-fueled breast cancers eventuated in a push for more tailored treatments. In the decades since, clinical trials of tamoxifen (notably those led by Pitt's Bernard Fisher in the 1980s) and new technologies (like an immunohistochemistry assay made available in 1998) have helped doctors clarify who will respond to certain therapies.

Doctors now divide breast cancers into types and offer treatments based on those types. They dispense hormone therapies like tamoxifen for estrogen-receptor-positive tumors. They'll give trastuzumab for cancers that are estrogen-receptor-negative but have a receptor known as HER2. For tumors that are "triple-negative" (no estrogen or progesterone receptors, no HER2), which are among the most deadly, they are still looking for a

targeted therapy.

Since 1975, five-year survival rates for breast cancer in the United States have gone from 76 percent to 90 percent in 2007.

The sequencing of the entire human genome in 2003 created tantalizing potential for researchers to match treatments for any given disease to individuals. The National Cancer Institute started The Cancer Genome Atlas project in 2006, with the goal of sequencing the genomes of different cancers to establish the DNA aberrations that cause them. (By the way, Pittsburghers helped build this atlas; the University of Pittsburgh Cancer Institute is one of its largest contributors.)

UPMC expects a five-year, \$100 million investment in high-powered computing, data warehousing, and analytics will help its doctors and Pitt researchers evaluate treatments and develop new ones while bringing down the cost of care. (For more on how that massive undertaking is progressing, see p. 24.) In the meantime, a number of Pitt physician-scientists are

helping build a future for personalized care through other avenues, like the National Institutes of Health's SPORE, or Specialized Programs of Research Excellence (Pitt has three of these), as well as genomic and tissue databanks built by research consortia.

We can expect the history of personalized medicine to read like a Russian novel, revealing complex (biologic) interrelationships. This is just the first chapter in what's likely to be a tome.

Yet patients like the salesman already have more options.

Melanoma patients and their doctors started having more hopeful conversations after August 2011, when the FDA approved vemurafenib. Vemurafenib was a first-of-its-kind targeted therapy for late-stage (stage 4) melanoma in tumors with the BRAF V600E mutation. BRAF V600E causes a part of the protein pathway, the communications link from a cell's nucleus to its surface, to either be permanently on or off. Vemurafenib could flip that switch in cancer tumors, inhibiting growth and encouraging cancer cells to die off.

Oncologists now routinely sequence late-

stage melanoma tumors, looking for the BRAF mutation and others, says John Kirkwood, the Usher Professor of Medicine, Dermatology, and Translational Science and director of the melanoma and skin cancer program at Pitt. (He directs the skin SPORE, as well.)

BRAF and the other mutations account for about 70 percent of late-stage melanomas.

Kirkwood hopes we'll soon get a better harness on immunotherapies like ipilimumab, which spurs a specific part of the immune system's arsenal, cytotoxic T lymphocytes, to go after melanoma cells.

If you're the salesman, you also have to think about ipilimumab's side effects. For many patients it causes colitis, a swelling of the colon. Symptoms include diarrhea, sometimes so extreme patients die from it.

In June, Tarhini presented preliminary results from an ipilimumab trial in which 60 percent of patients taking the medication suffered some form of colitis in response. Fourteen percent had grade 3 or higher colitis, with more than eight bowel movements a day.

The patients did not have a history of colitis, inflammatory bowel, or autoimmune diseases. In Tarhini's preliminary results, 86 percent of the patients who experienced any grade of colitis (18 of 21) had a mutation in one gene.

Tarhini says the study suggests that genetic



profiling that may predict which patients are likely to benefit from ipilimumab.

A lot of money needs to be raised for a larger trial. Being part of the NIH SPORE helps, but does not cover all the costs.

Interpreting data is already a huge part of his work, but Tarhini expects the new UPMC data analytics initiative, in combination with new technology, will make sequencing faster and significantly cheaper.

The salesman decides to start with immunotherapy and see how it goes.

He'll join an NIH-funded national study, led by Tarhini, that tests ipilimumab in combination with interferon-alpha. Samples collected on this study will allow the validation of Tarhini's preliminary biomarker findings.

Pitt's Timothy Burns, an MD/PhD and assistant professor of medicine, investigates targeted therapies for lung cancer. Lung cancer is by far the biggest killer among cancers in the United States. (Burns lost both his parents to lung cancer before he was 16.)

several targeted treatments have been developed, notably gefitinib and erlotinib. Similarly, crizotinib was approved after a phase 1 clinical trial produced a 70 percent success rate in patients suffering from lung cancer driven by a genetic alteration called ALK-translocation. Patients who have mutations for which targeted treatments are available can sometimes live years with their disease, as opposed to 12 months or less for patients without these targetable mutations.

Such improvements in outcomes led 16 cancer centers, including the University of Pittsburgh Cancer Institute, to form the Lung Cancer Mutation Consortium, an industry-funded group researching treatments for 14 common genetic alterations in lung cancer. Burns' own ongoing research has focused on KRAS, a mutation responsible for 25 percent of all lung cancers but so far resistant to treatments.

Burns thinks the sorts of analytics tools being deployed at UPMC may lead to innovations in care, like helping to identify the right

There's a 20 percent reduction in mortality for patients who have a CT screen, but, "It's not economically feasible to screen everybody who's 55 to 75 with the equivalent of 30 years of smoking," Burns says.

markers exist for patients who might suffer side effects from ipilimumab. The drug costs \$30,000 a dose; a course of treatment is four doses. No one wants to give it to a patient who might suffer a potentially fatal reaction. Yet Tarhini needs to see data from many more patients for a statistically valid conclusion about what he considers culprit genes.

His other recent gene-expression profiling study, of the melanoma microenvironment, had 34 patients and cost \$22,000. In April, he reported on a preliminary gene expression signature based on the microenvironment

Lung cancer treatment is also being transformed by genomics. Burns' office in the Hillman Cancer Center is crammed with papers on the subject. Knowing what mutations lung cancer patients have completely changes how they can be treated—about 60 percent of lung cancers have driver "oncogenes" that are identifiable, says Burns.

"If you have metastatic lung cancer, when you walk in the door, we're sequencing your tumor," he says.

One driver linked to a mutation is EGFR (epidermal growth factor receptor), for which

patients to screen for lung cancer. There's a 20 percent reduction in mortality for patients who have a CT screen, but, "It's not economically feasible to screen everybody who's 55 to 75 with the equivalent of 30 years of smoking," Burns says.

Cancer treatments represent one part of personalized medicine; chronic disease therapies another. The two will require very different approaches, notes Jeremy Berg, director of Pitt's Institute for Personalized Medicine, associate senior vice chancellor for science strategy and planning, the Pittsburgh Foundation

Professor of Personalized Medicine, and a professor of computational and systems biology. Many cancers are driven by one or two genetic factors, which can be isolated and attacked, at least until the cancer mutates again. Genomic factors may also tell us who might be better off without certain therapies.

Chronic diseases are another country altogether. They play out across a spectrum of risk, where specific factors do not necessarily lead to disease.

For such chronic diseases, “the genomic stuff is not going to work the way we thought. They’re too complicated,” Berg says. Chronic diseases stem from complicated interactions between multiple environmental and genetic sources. (This is where the entanglements in that Russian novel get really hard to follow.)

nal factors, unlike, say, the lung or kidney.

Here’s the thing. The organ’s anatomy might be straightforward, yet in terms of what Whitcomb and other GI specialists know at the moment, nothing about figuring out who will get diseases of the pancreas seems “very simple.”

Five to 10 percent of people in the general population have pancreatic divisum, in which the two ducts that are supposed to merge to form the bile duct instead stay separated. This group faces a higher risk for chronic pancreatitis; yet the majority of people with pancreas divisum never suffer from anything. Some suffer severe pancreatic reactions as a result of passing gallstones, smoking cigarettes, or drinking alcohol—the pancreas becomes inflamed and scars. Others drink

goal is to combine clinical information with genetic information from 1,000 patients with pancreatic diseases for clues regarding what phenotypic or genomic characteristics lead to specific diseases. Included in the plan are detailed medical histories, as well as tissue and blood samples. Whitcomb’s team will then look for patterns in the data. This information will inform follow-up studies for devising new types of treatment.

Whitcomb has done small studies to see how the analytics program will work. One prepilot study looked at how to manage genetic information. Researchers sequenced the genomes of 70 pancreas patients and 70 liver patients and moved that information into a database. They wanted to figure out how best to format the data; see how easy it

If the research yields answers, Slivka might be able to recommend certain patients have their pancreas removed immediately, rather than enduring years of procedures that ultimately do little for them.

Pitt’s David Whitcomb thinks medical scientists should be looking to the pancreas as a guide to tackling chronic conditions. He is. The organ looks complicated; it’s both an endocrine and exocrine gland, meaning it produces hormones like insulin that go straight into the bloodstream and digestive enzymes secreted via ducts.

“It turns out that the pancreas is the best organ to work on for developing new models of personalized medicine because it is very simple,” says Whitcomb, an MD/PhD, chief of Pitt’s Division of Gastroenterology, Hepatology, and Nutrition, Giant Eagle Professor of Cancer Genetics, and professor of medicine, of cell biology, and of human genetics. His own work looks at the exocrine part of the pancreas, which has only two classes of cells—acinar cells, which make enzymes, and duct cells, which squirt them out. These cells do only one thing, says Whitcomb, “and we know from a molecular standpoint exactly how each works.”

That means when a person has a pancreatic disease, it can be linked to one of two sources. The pancreas is also largely isolated from exter-

or smoke heavily and suffer no pancreatic disorders. Some have extreme pain in reaction to even mild scarring, others have little pain. Whitcomb says a pancreatic disease can have multiple factors involved, none of which is enough to cause the disease on its own.

Whitcomb thinks answers will come through computer modeling and simulations and applied analytics. “This is what every other science has gone to except for medicine,” he says. By using big data sets and information on individual patients, Whitcomb believes scientists can help identify people who are likely to suffer from severe pancreatitis or severe pain, diabetes, or fibrosis. Because the number of potential variations is so large, tens of thousands of patients will need to agree to participate in research studies to help identify causes. Yet (thanks to efforts Whitcomb has helped lead), scientists have some genetic markers; the challenge now is to figure out how to apply knowledge of these markers in clinical settings.

To advance that cause, Whitcomb has proposed the Genomic Resources to Enhance Available Therapy (GREAT) study. Its main

was to get it into and out of the database; and demonstrate they could protect patient privacy. For the GREAT study to become reality, Whitcomb has to get past the Institutional Review Board, which approves all patient research. He is hopeful that will happen soon.

In July, Whitcomb and colleagues published a study in *PLOS Genetics* that he says will offer new clues for treating some of his patients. Whitcomb’s group showed that many people with idiopathic pancreatitis have an alternate form of cystic fibrosis. “We would love to steal treatments designed for classic cystic fibrosis to help our pancreatitis patients,” he says. “*This* is personalized medicine.”

On a summer day, after flying into Pittsburgh at 12:30 a.m. from a conference in Israel, Whitcomb made time for a lunch meeting with this reporter. Over a Pittsburgh Salad at the University Club, he drove home his main point: He sees the GREAT study as a template that researchers and clinicians can use to mesh data and care.

“You want to know outcomes for your patient and start making some predictions about what treatment is going to be effective.”

Prediction demands description, says Adam Slivka, who is an MD/PhD, associate chief of clinical services in the Division of Gastroenterology, Hepatology, and Nutrition, and a bear of a man. He's voluble and excited about the potential of personalized medicine; he also thinks about the challenges. Consider how you might describe pain.

Pain, he says, can be a characteristic, an intensity, a frequency. "Is it chronic, intermittent? Sharp and stabbing? Dull? Is it neuropathic? Is it visceral? Is it musculoskeletal?" Slivka ticks the terms off rapid-fire.

Somehow, these different definitions of pain, of a feeling, need to end up as a quantitative searchable item in a database for studies like GREAT that will lead to more individualized care. "It's not all computer-science, flat-file database type of input," Slivka says. And correlating qualitative phenotypic data, like pain measures, with genotypes "is really hard."

In his homey office in UPMC Presbyterian, with its three small fish tanks and loads of family mementos, Slivka says the term "personalized medicine" suffers the same issue as "pain."

"Ask 20 people what it means, and you'll get 10 different answers," he says.

Yet assessing pain in a way that is consistent across physicians and can be made searchable in a database is something Slivka and Whitcomb intend to do.

"People don't appreciate what it takes to make a history meaningful for a database so that we can get to the point where we can [determine] how genetic variables correlate with what the patient's telling you," says Slivka.

He points out that doctors will need to ask questions that aren't part of their routine right now. The GREAT study initially proposed an 11-page form for each patient visit. Slivka might see 25 patients on a typical day. Those 11-page piles are above and beyond the normal documentation doctors have to do just to get paid; and Slivka says they would have probably doubled the time spent entering records. Whitcomb says he's significantly shortened the form now and put it into UPMC's electronic health record. "It can take as little as 2 minutes," Whitcomb promises.

Slivka is on board with Whitcomb's GREAT study because he believes it will yield new insights into what causes pancreatic conditions and how to treat them more effectively.

For instance, for pancreatic pain, he has seen studies that show giving people pancreatic enzyme supplements doesn't help them. Yet Slivka says that some patients seem to respond well to such enzymes. The studies lumped together different types of pain and pancreatic dysfunction. He hopes that using genetic information will show that certain types of patients do benefit from enzyme supplements.

He also hopes there will be a clear genetic reason why some people develop pancreatitis so severe that the organ eventually has to be removed. Right now, there's no way to tell who will respond to preventive procedures and who won't.

If the research yields answers, Slivka might be able to recommend that certain patients have their pancreas removed immediately, rather than enduring years of procedures that ultimately do little for them.

In Slivka's clinic in the UPMC Digestive Disorders Center, standard-issue talismans of hope fill the walls of a patient room: efficient-looking medical instruments, an optimistic print of a flower, a chart mapping out an organ system. Inside this particular room sits a mother and a patient (not yet 20) who has suffered from intestinal pain her entire life. She has been referred from another doctor, who suspects a gallbladder ailment.

In an ideal world of personalized medicine, Slivka would know the young patient's genetic makeup. Slivka would also have access to records showing whether procedures like endoscopies and CT scans had been performed, and what they found, even if those patients were not part of the UPMC system (which digitized its medical records years ago). But we have not reached that world yet. In this room, there is no genetic code in the patient's chart, and no history except comments Slivka must elicit from mother and patient.

To question after question, the patient says, "Sometimes." How does that get entered into a database in a way that is meaningful? What about the vague memories of what previous procedures revealed?

Slivka also says ethical issues are bound to come up in patient care. At conferences he gets into debates with doctors about doing a disservice to patients if he sequences their genomes. Some argue he will cause them to be discriminated against by insurers. (A federal act prohibits health insurers from discriminating based on genetic data. See p. 24 for a discussion of such issues.) Slivka says a long-term problem for personalized medicine research is how to take data that's been blinded and open it up, so that when a clinical study concludes, doctors can go back and help patients who were part of it. Whitcomb hopes to show how to do this in his GREAT study.

Slivka also predicts that personalized medicine will be difficult to reconcile with medical insurance practices. Insurers, he says, "want efficiency, mass scale. Personalized medicine is almost the antithesis of that." He knows that personalized medicine should save money by avoiding unnecessary tests and procedures. "But the onus is going to be on us doctors to prove it," he says.

Still, he thinks the future will be better for patients like the one he's just seen. He can say that she does not have a gallbladder problem. But he can't say what the issue is. He can't even say whether genetic sequencing will yield a treatment for her. But "it may help us stop unnecessary testing. Look what that patient's been through," he says, "CT scans, five scopes," and he gestures with his fingers going down his throat.

Such patients are black boxes, he says. "You don't know what's wrong with them. You're hunting for answers to try different treatments that might help them. But if I'm going to do an ERCP [endoscopic retrograde cholangiopancreatography, the scope he referred to above] on you, cut open your sphincter, or put a stent in your pancreas, all those things [can] have complications."

He hopes that analytics will give him a better way to see what ails them. Getting there will take longer than he or anyone else would like.

When considering the complexity of the human system and the challenges of tailoring care, Berg, of Pitt's Institute for Personalized Medicine, notes, "I'm feeling very humble." ■

MATCH RESULTS

CLASS OF 2014

ANESTHESIOLOGY

Jenabi, Isaac
UCLA Medical Center, Calif.
King, Chih
Brigham & Women's Hospital/
Harvard University, Mass.
Kiyatkin, Michael
NewYork-Presbyterian Hospital/
Columbia University Medical Center
Koh, Duane
University of California, Irvine Medical Center
Michaelsen, Kaarin
UPMC/University of Pittsburgh, Pa.
Paoletti, Gabrielle
Massachusetts General Hospital/Harvard University
Russino, Hanzi
UCLA Medical Center, Calif.
Tomlin, Brett
University of Wisconsin Hospital and Clinics

DERMATOLOGY

Collins, Mary Katharine
UPMC/University of Pittsburgh, Pa.
Durkin, John
Hahnemann University Hospital/Drexel University, Pa.
Moreau, Jacqueline
Massachusetts General Hospital/Harvard University

EMERGENCY MEDICINE

Adams, Carson
UPMC/University of Pittsburgh, Pa.
Deng, William
George Washington University, Washington, D.C.
Jones, Amy
UPMC/University of Pittsburgh, Pa.
Li, Annabel
George Washington University, Washington, D.C.
Li, Simiao
McGaw Medical Center/Northwestern University, Ill.
Marino, Ryan
UPMC/University of Pittsburgh, Pa.
Miller, Thomas
University of Wisconsin Hospital and Clinics
Nambu, Hiroya
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Nega, Mahlet
Boston University Medical Center, Mass.
Sanders, Jason
Brigham & Women's Hospital/
Harvard University, Mass.
Schram, Carly
Detroit Medical Center/Wayne State University, Mich.
Shine, Kristy
Hospital of the University of Pennsylvania
Stokes, Timothy
University of Michigan Hospitals

FAMILY MEDICINE

Akiona, Ka'ohimau
Hilo Medical Center, Hawaii
Gentile, Natalie
Mayo Clinic/Mayo School of Graduate Medical
Education, Minn.
Goldring, Sandra
UPMC St. Margaret/University of Pittsburgh, Pa.
Kowalski, Adam
Carl R. Darnall Army Medical Center, Tex.
McAnaney, Cara
Greater Lawrence Family Health Center, Mass.

Thorson, Sara
Family Medicine of Southwest Washington/
University of Washington
Walton, Allison
Washington Hospital Healthcare System, Pa.

INTERNAL MEDICINE

An, Amy
Strong Memorial Hospital/
University of Rochester, N.Y.
Badlani, Jayshiv
Jackson Memorial Hospital/University of Miami, Fla.
Cabello, Ricardo
Beth Israel Medical Center/
Albert Einstein College of Medicine, N.Y.
Chen, Hui Wei
UPMC/University of Pittsburgh, Pa.
Dave, Shravan
University of California, San Francisco
Doamekpor, Frederick
Morehouse School of Medicine, Ga.
Gary, Brittany
Montefiore Medical Center/
Albert Einstein College of Medicine, N.Y.
Hu, An Qi
Tufts Medical Center, Mass.
Joel, Ian
UCLA Medical Center, Calif.
Koenitzer, Jeffrey
Barnes-Jewish Hospital/Washington University, Mo.
Laderian, Bahar
Jackson Memorial Hospital/University of Miami, Fla.
Lee, Elizabeth
Johns Hopkins Hospital, Md.
Lin, Jean
Yale-New Haven Hospital, Conn.
Mah, Jennifer
University of California, Irvine Medical Center
Mendez, Juan
North Shore-LIJ Health System, N.Y.
Michaelidis, Constantinos
Brigham & Women's Hospital/
Harvard University, Mass.
Miller, David
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Miller, Weldon
University of Maryland Medical Center
Mohanty, Sudipta
University of California, Riverside
Morton, Jessica
Oregon Health & Science University
Parikh, Sneha
University of Utah Affiliated Hospitals
Parris, James
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Parris, Ritika
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Patel, Agam
NewYork-Presbyterian Hospital/
Weill Cornell Medical Center
Patel, Divyang
Duke University Medical Center, N.C.
Patel, Kunal
NewYork-Presbyterian Hospital/
Columbia University Medical Center
Siebert, Paul
Emory University, Ga.

Thuppal, Niranjani
University Hospitals Case Medical Center/
Case Western Reserve University, Ohio
Yecies, Emmanuelle
UPMC/University of Pittsburgh, Pa.

INTERNAL MEDICINE— PEDIATRICS

Hartog, Rebecca
UPMC/University of Pittsburgh, Pa.
Milutinovic, Pavle
Duke University Medical Center, N.C.

INTERNAL MEDICINE— PRIMARY

Gelman, Amanda
University of Colorado
Insetta, Emily
Johns Hopkins Bayview Medical Center, Md.

INTERNAL MEDICINE— WOMEN'S HEALTH

Lu, Amy
UPMC/University of Pittsburgh, Pa.
Rossiter, Brianna
UPMC/University of Pittsburgh, Pa.
Zupetic, Jill
UPMC/University of Pittsburgh, Pa.

MAXILLOFACIAL SURGERY

Clark, Jev
UPMC/University of Pittsburgh, Pa.
Perrone, Joseph
UPMC/University of Pittsburgh, Pa.

NEUROLOGICAL SURGERY

Chivukula, Srinivas
UCLA Medical Center, Calif.
Tonetti, Daniel
UPMC/University of Pittsburgh, Pa.
Voronovich, Zoya
University of New Mexico Health Sciences Center

NEUROLOGY

Ebdlahad, Sommer
Duke University Medical Center, N.C.
Joshi, Aditya
Stanford University Programs, Calif.
Lin, Kathie
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Manners, Jody
UPMC/University of Pittsburgh, Pa.
Soneji, Deepak
UPMC/University of Pittsburgh, Pa.

OBSTETRICS/GYNECOLOGY

Horowitz, Max
UPMC/University of Pittsburgh, Pa.
Luiza, John
Geisinger Health System, Pa.
Martin, Sarah
Temple University Hospital, Pa.
Rosenbaum, Alan
Ohio State University Medical Center
Soriano, Alex
University Hospitals Case Medical Center/
Case Western Reserve University, Ohio
Werner, Carly
UPMC/University of Pittsburgh, Pa.



Institutions that snagged the most members of the Class of 2014 for their house staffs were UPMC, Harvard, UCLA, and Johns Hopkins. **LEFT:** A big family hug for Kaarin Michaelsen, with husband, Kenny Mai, daughter, Emily, and son, Alex; Michaelsen will stay in Pittsburgh. (See p. 16 for her story.) **CENTER:** Someone's mom was inspired by the portraits of pale men on the walls and decided to take this girl-power shot. **RIGHT:** Jill Zupetic (with fiancé, Bob Johnson, following) matches in internal medicine with UPMC.

OPHTHALMOLOGY

Bodily, Lance
UPMC/University of Pittsburgh, Pa.
Ling, Jennifer
University of California, Davis Medical Center

ORTHOPAEDIC SURGERY

Ashley, Blair
Hospital of the University of Pennsylvania
Christensen, Tyson
Mayo Clinic/Mayo School of Graduate Medical Education, Minn.
Gande, Abhiram
University of California, Irvine Medical Center
Hempfen, Eric
McGaw Medical Center/Northwestern University, Ill.
Johnson, Paul
University of New Mexico Health Sciences Center
Lee, Hannah
UPMC/University of Pittsburgh, Pa.
Neral, Mithun
University Hospitals Case Medical Center/
Case Western Reserve University, Ohio
Nwasike, Chinedu
UPMC/University of Pittsburgh, Pa.
St. Louis, Kwesi
UPMC/University of Pittsburgh, Pa.
Wolf, Megan
University of Connecticut Health Center

OTOLARYNGOLOGY

Greenberg, Jesse
UPMC/University of Pittsburgh, Pa.
Kolia, Nadeem
Strong Memorial Hospital/
University of Rochester, N.Y.
Leonardis, Rachel
UPMC/University of Pittsburgh, Pa.
Lord, Christopher
Vanderbilt University Medical Center, Tenn.
Stephenson, Ryan
UCLA Medical Center, Calif.

PATHOLOGY

Yoest, Jennifer
UPMC/University of Pittsburgh, Pa.

PEDIATRICS

Asencio, Jessica
Miami Children's Hospital/
Florida International University
Janofsky, Stephen
Yale-New Haven Hospital, Conn.
John, Liny
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
LaRossa, Peter
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.

Levine, Alison
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Lu, Annie
University of Michigan Hospitals
Raghu, Vikram
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Ross, Anthony
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Svilar, David
St. Louis Children's Hospital/
Washington University, Mo.
West, Laura
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Yang, Cheryl
Children's Hospital Colorado/University of Colorado

PEDIATRICS/PSYCHIATRY/ CHILD PSYCHIATRY

Whelan, Rachel
Tulane University, La.

PHYSICAL MEDICINE & REHABILITATION

Kinback, Nicholas
Temple University Hospital, Pa.

PLASTIC SURGERY

Dreifuss, Stephanie
UPMC/University of Pittsburgh, Pa.
Emelife, Patrick
Louisiana State University, New Orleans

PSYCHIATRY

Khandai, Abhisek
McGaw Medical Center/Northwestern University, Ill.
Phelps-Tschang, Jane
UPMC/University of Pittsburgh, Pa.

RADIATION ONCOLOGY

Berhane, Hebist
UPMC/University of Pittsburgh, Pa.
Thompson, Marcher
Icahn School of Medicine at Mount Sinai, N.Y.

RADIOLOGY—DIAGNOSTIC

Kwon, Carolyn
UPMC/University of Pittsburgh, Pa.
Ludwig, Daniel
Barnes-Jewish Hospital/Washington University, Mo.
Luo, Jing
University of Washington Affiliated Hospitals
McGovern, Jonathan
UPMC/University of Pittsburgh, Pa.
Nuffer, Zachary
Strong Memorial Hospital/University of Rochester, N.Y.

Patel, Vivek
Stanford University Programs, Calif.
Van Roekel, Daniel
Georgetown University Medical Center,
Washington, D.C.
Wo, Sean
University of Washington Affiliated Hospitals

SURGERY—GENERAL

Abegglen, Ryan
UPMC Mercy/University of Pittsburgh, Pa.
Afrazi, Amin
University of Wisconsin Hospital and Clinics
Byrne, Raphael
Oregon Health & Science University
Flynn, Sean
University of California, San Diego Medical Center
Jackson, Kyle
Johns Hopkins Hospital, Md.
Kauffman, Jeremy
PinnacleHealth Hospitals, Pa.
Lee, Michael
Rutgers University, N.J.
Li, Shen
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Nag, Uttara
Duke University Medical Center, N.C.
Riera, Katherine
Vanderbilt University Medical Center, Tenn.
Van Hal, Michele
Baystate Medical Center/Tufts University, Mass.
Weis, Joshua
University of Texas Southwestern Medical Center
Zaldana, Michelle
University of California, San Diego Medical Center

TRANSITIONAL MEDICINE

Cheng, Michelle
UPMC/University of Pittsburgh, Pa.

UROLOGY

Bartels, Christian
University of Connecticut Affiliates
Farber, Nicholas
Rutgers University, N.J.
Schwen, Zeyad
Johns Hopkins Hospital, Md.
Toussi, Amir
Mayo Clinic/Mayo School of Graduate Medical Education, Minn.
Yecies, Todd
UPMC/University of Pittsburgh, Pa.

VASCULAR SURGERY

Go, Catherine
UPMC/University of Pittsburgh, Pa.



CLASS NOTES

'60s

John A. Paar (MD '60) has been a frequent visitor to Nicaragua since 1984. The following year, the (now-retired) cardiologist organized what would become a series of dozens of medical mission trips to León, Nicaragua. The effort, which organized formally as Project Health for León in 1995, has since provided care to thousands of patients. It has also provided medical equipment and education for health care professionals in León.

It's all thanks to some 200 doctors, nurses, dentists, technicians, and others who have volunteered, he says—and more volunteers are always welcome. In particular, patients in León are in dire need of open-heart surgical teams, says Paar; rheumatic fever—which causes heart-valve damage—is rampant in the region. For more information, visit projecthealthforleon.org.

'70s

To hear **Marc Drezner** (MD '70) tell it, he chose his particular path as a researcher just to make those presentations—and dreaded Q&As—easier back when he was an endocrinology fellow at Duke. "I took the easy route. Nobody knew a lot about bones." In his second-ever paper (*New England Journal of Medicine*, 1973), he discovered a new disease, pseudohypoparathyroidism type II—and that was just the start of a fruitful career in translational research on genetic diseases of bone and mineral metabolism. Last year, his work on X-linked hypophosphatemia, the most common form of familial rickets, culminated in a proof of concept for a potential curative therapy for this currently incurable disease (*Journal of Bone and Mineral Research*). In addition to his own ongoing work as an investigator, he

now shepherds the bench-to-clinic research flock at the University of Wisconsin School of Medicine and Public Health as senior associate dean for clinical and translational research, as well as executive director of its Institute for Clinical and Translational Research.

'80s

A longtime professor of medicine at the Uniformed Services University of the Health Sciences, **Gregory Argyros** (MD '87) spent three years as a U.S. Army medical researcher and three as chief of medicine at Walter Reed Army Medical Center. Starting in 2005, he helped oversee the consolidation of Walter Reed and the Bethesda Naval Hospital as part of Base Realignment and Closure legislation. Argyros was charged with leading the effort to integrate the two hospitals' training and teaching capabilities—allocating upward of \$100 million in grants and research money, along with nearly 1,500 teaching positions. The colonel retired to civilian life in 2012 to work at MedStar Washington Hospital Center, where he now serves as interim vice president of medical affairs and chief medical officer. He was elected a master of the American College of Physicians in 2012.

Following an ear infection or other illness that affects the vestibular system—which, along with vision, helps maintain spatial orientation—dizziness can set in. Often, this off-kilter feeling lingers even after the initial illness is over. Mayo Clinic's associate professor of psychiatry **Jeffrey Staab** (MD '88) and colleagues study this mysterious condition, dubbed chronic subjective dizziness (CSD). Up next: identifying those who may be at risk and improving diagnostic strategies. Last winter, while on sabbatical at the Imperial College London, Staab developed what he hopes will be a novel method for investigating how visual stimuli affect CSD patients.

John Flynn (MD '89), associate chief of orthopaedic surgery and associate trauma director at Children's Hospital of Philadelphia and professor of orthopaedic

surgery at Penn, recently finished a term as president of the Pediatric Orthopaedic Society of North America (POSNA). He was first inspired "to give back" and become a teacher by former Pitt professor and orthoped, Ed Hanley. Flynn also codirects the International Pediatric Orthopaedic Symposium, a joint professional education effort between the American Academy of Orthopaedic Surgeons (where Flynn chairs its Educational Courses Committee) and POSNA. For Flynn, it doesn't matter whether it's seeing patients or teaching students and fellow doctors, he says. "It's all just payback."

'90s

As chief of the Obstetric and Pediatric Pharmacology and Therapeutics Branch of the National Institutes of Health, **Anne Zajicek** (née Glynn, MD '95) oversees regulatory efforts and clinical trials related to the Best Pharmaceuticals for Children Act (BPCA). Signed into law in 2002, the BPCA supports investigations of the effects of prescription drugs in children—at the time, an area of study with an alarming dearth of research.

After helping with the law's initial rollout, Zajicek went on to become involved in the creation of the Pediatric Trials Network, which she also oversees. The PTN has streamlined the pediatric clinical trials process significantly.

In February 2013, when orthopaedist **Gloria Beim** (Sports Medicine Fellow '96) learned she was going to Sochi as Team U.S.A.'s chief medical officer for the 2014 Olympics, she was so excited, she immediately bought language-instruction audio tapes and began practicing Russian on the drive to her clinic in rural Colorado. The homework paid off when she was able to network with local administrators in Sochi.

In addition to treating American athletes, Beim managed more than 70 medical staffers. Their patients sustained garden-variety bumps and bruises but were otherwise healthy. This left time to enjoy the U.S.A. v. Russia hockey game from the stands—and use her language skills to swap friendly jibes.

Beim hopes to be invited to Rio in 2016 and will be ready if the call comes. "I've already ordered my audio tapes."

'00s

When a patient has a lung infection, it's not always clear what's going on—microbiology results can take days. Physicians feel pressure to prescribe antibiotics quickly, even though, in the event the infection turns out to be viral, these meds are moot—and potentially harmful from the long view, given the growing problem of antibiotic resistance.

This summer, **David Huang** (Critical Care Medicine Fellow '03), associate professor of critical care medicine and emergency medicine at Pitt, will launch a five-year, multicenter National Institutes of Health (NIH)-funded trial he hopes will ultimately help emergency physicians who are caught between this particular rock and a hard case. The trial will test whether high levels of procalcitonin—one of the many mysterious amino-acid chains that crop up in inflammation—could be used clinically as a biomarker for bacterial infection in the lower respiratory tract. (It has previously been shown to be potentially effective



Beim in Sochi

and safe in studies based in Switzerland, he notes.)

Given the steady decline in NIH funding, the venture-capital route is a viable way for universities to create “self-sustaining ecosystems” of research and development, says **Amanda Christini** (MD ’08). An assistant professor of medicine at Penn and director of strategic initiatives for Penn Medicine’s Center for Healthcare Innovation, Christini works to attract investors to research projects undertaken by faculty and staff. This March, the center held its first Entrepreneurs’ Forum, with more than 600 researchers and investors coming together to pitch one another.

In the event of a heart attack, damage control can start on the Life Flight, says **Christian Martin-Gill** (Emergency Medicine Resident ’08, Emergency Medicine Fellow ’10), assistant professor of emergency medicine at Pitt. In 2010, a *Lancet* paper from an international team showed that a simple procedure called remote ischemic conditioning (RIC)—in which an ordinary blood pressure cuff is applied and inflated for four, 5-minute cycles with 5-minute intervals in between—reduced the size of infarcts in patients with STEMI (ST-elevation myocardial infarction). So, the Class of 2016’s **Max Wayne** worked with Martin-Gill and colleagues to complete a four-month pilot study of RIC for STEMI patients, the first ever in an air-transport setting; their abstract was published in *Prehospital Emergency Care* earlier this year. Having found that RIC is indeed safe, well-tolerated, and workable in this setting, the group has launched a new quality-improvement measure with UPMC. Next, they’ll follow long-term outcomes, study the underlying mechanisms of RIC’s benefits, fine-tune the procedure, and determine which patients could benefit from it most. —Zach Nichols and Elaine Vitone

R. SCOTT BRAITHWAITE

MODELER SPEAKS, W.H.O. LISTENS

In low-resource settings where HIV is on the rise, it’s hard to know where to spend the precious few health care dollars that are available. Randomized controlled trials can’t address such questions, says physician **R. Scott Braithwaite** (MSc Clinical Research ’04), director of the comparative effectiveness and decision science division at New York University and president of the Society for Medical Decision Making.

“It seemed to me that using a lot of the methods commonly used in, say, industrial engineering or operations research, could really improve the efficiency of public health endeavors. That realization was very motivating,” says Braithwaite, who studied physics as an undergrad at MIT before earning his MD from the State University of New York at Stony Brook. After practicing internal medicine for two years, he came to Pitt for an MSc in clinical research, eager to put his quantitative skills to good use. He has since modeled issues as wide ranging as expanding the role of nurse practitioners and making end-of-life decisions.

For example, in a 2011 *Journal of the International AIDS Society* paper, Braithwaite and collaborators—including Pitt’s Mark Roberts, MD/MPP professor and chair of health policy and management in Pitt’s Graduate School of Public Health and professor of medicine, of industrial engineering, and of clinical and translational science—focused on the East African population, which is second only



Braithwaite

MAA SAYS, “YOU’RE WELCOME”

What has your **MAA** (Medical Alumni Association) done for you lately, Pitt med progeny? Probably more than you even realize. MAA’s funds, most of which are generously donated by Pitt med alumni, support all manner of student expenses, from their first white coats to their graduation garb, and plenty in between. (And we’re not just talking about the free coffee brewed daily in MAA’s Scaife Hall offices, though that’s certainly a popular perk.)

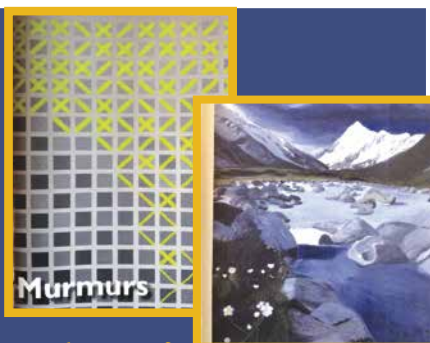
MAA funds \$70,000–\$100,000 in tuition scholarships each year (with help from the Dean’s Office). MAA also covers travel expenses for clinical and research trips abroad, as well as for domestic travel to conferences and poster presentations. MAA even has an Emergency Loan Fund—because, stuff happens.

MAA is also a patron of the arts, supporting *Murmurs*, Pitt’s med-student-run arts and literary journal; PalPITTations, the School of Medicine’s *a cappella* group; and Scope and Scalpel Society, Pitt med’s comedic musical theatre ensemble. Founded in 1955, it’s probably the longest running theatrical production in the Pittsburgh area (not to mention gut-bustingly funny).

MAA routinely covers some or all of the check for various meet, greet, and eats throughout students’ four years here—Black Bag Ball, Senior Class Picnic, and Graduation Luncheon. And for alumni, it organizes Medical Alumni Reunion Weekend events in the spring and several alumni receptions and lectures throughout the year (see p. 40 1/2, inside our back cover, for this season’s calendar).

To keep the Pitt med community connected after commencement and beyond, MAA prints and distributes the annual yearbook. Last but not least, the MAA makes sure you get the fine publication in your hands.

For more information or to volunteer or make a donation for any of the above, contact **Pat Carver**, MAA director, at cpat@pitt.edu. To join the MAA’s Executive Committee, contact **Jan Madison** (MD ’85), the new president, at jwmadisonmd@gmail.com. —Zach Nichols and Elaine Vitone



TOP: The cover of *Murmurs* by Christopher Hong (Class of 2017) RIGHT: The painting, “Escape,” by Divya Keerthy (Class of 2016)

to southern Africa in HIV prevalence. The team examined guidelines on HIV monitoring and antiretroviral therapy, asking which would have the greatest impact on the epidemic overall: monitoring treatment efficacy in existing cases more carefully or starting more people on therapy sooner?

The team used what’s known as a “Monte Carlo” approach (a technique that involves running simulations over and over to find a distribution of possible outcomes) to calculate the trade-offs associated with the typical causes of treatment failure—genotypic resistance, nonadherence, or intolerance to treatment.

They found that starting more patients on treatment earlier would ultimately save more lives than investing in more frequent blood tests on existing cases—a “very robust result,” says Braithwaite. Ultimately, the study influenced the World Health Organization’s 2013 guidelines for treating adolescents and adults.

—Brett Murphy and Elaine Vitone

JOHN A. BARRANGER

AUG. 5, 1945–MAY 25, 2014

John Barranger, an MD/PhD, was in the vanguard in the understanding and treatment of genetic metabolic disorders. During his fellowship at the National Institutes of Health, he helped develop the first enzyme treatment for Gaucher's disease, a genetic disorder that causes lipids to accumulate in cells and organs. The treatment has since become standard of care, notes W. Allen Hogge, who holds the Milton Lawrence McCall Chair and leads the Department of Obstetrics, Gynecology, and Reproductive Science and whom Barranger helped recruit to the University of Pittsburgh.

Barranger died in his Pittsburgh home May 25.

He came to Pitt in 1992, holding appointments in the Graduate School of Public Health's Department of Human Genetics and in the School of Medicine's Departments of Molecular Genetics and Biochemistry and of Pediatrics—most recently as a professor.

Hogge describes Barranger as an easygoing teacher and “superb investigator” who saw beyond current paradigms. He was among the first to develop animal models for genetic diseases and to treat genetic diseases prenatally. He advocated for monetizing research before entrepreneurship was part of the medical research community.

As director of the Center for the Study and Treatment of Jewish Genetic Diseases, Barranger developed screening methods for a number of genetic maladies with above-average incidence in Jewish communities. He left Pitt in 2005 to start the Lysosomal Storage Disease Clinical Care Network. The University community and friends are invited to a September memorial service. For information: johnbarranger.memorialservice@gmail.com. —ZN



Barranger

ROBERT PONTIUS

NOV. 11, 1923–APRIL 12, 2014

When open-heart surgery was in its infancy, the mortality rate in children was so high that only a few institutions dared attempt these procedures, which used a new machine called a pump-oxygenator for cardiopulmonary bypass. In 1958, Robert Pontius performed the first successful of these procedures at Children's Hospital of Pittsburgh of UPMC—and then nine more, consecutively. His continued success with increasingly complicated cases led to a Buhl Foundation grant that established what would become a world-renowned pediatric cardiac program.

Pontius, a former assistant professor of surgery and clinical assistant professor of surgery at Pitt, died in April.



Pontius (left) and Parenzan

In the 1960s, he'd helped his mentee, **Lucio Parenzan** (Pediatric Surgery Resident '59), who also died earlier this year (see In Memoriam), in bringing pediatric cardiac surgery to Italy. For these efforts, Pontius was awarded the Bronze Medal by Italy's University of Padua. (Before Pitt, Parenzan had planned on blowing his life savings on a sports car—he bought a pump-oxygenator instead. Parenzan would go on to perform Italy's first neonatal transplant and to found Fondazione di Bergamo per la Formazione Medica Continua, also known as the International Heart School.)

Though Pontius resigned to devote his time to private practice in 1976, he attended grand rounds and weekly conferences at Children's for some 30 years. He's warmly remembered for his knowledge of medical history and detailed memory of clinical anecdotes, notes Lee Beerman (MD '74, Cardiology Fellow '79), professor of pediatrics at Pitt.

“He was a role model for his dedication,” Beerman adds. Pontius maintained ties with many of his child patients into adulthood,

sending Christmas cards and attending at least one former patient's wedding.

Pontius moved to Shadyside late in life, for the joy of being near Oakland campuses and students, recalls his daughter, Joan Pontius, who, as a bioinformatics scientist, was highly influenced by him. “He always enjoyed thinking, always playing games and word puzzles,” she says. Her father's favorite paper, she adds, was his last one, which reported 10 cases of surgeons closing the wrong artery because of an optical illusion created by a rare anatomical variant.

“Those were the kinds of things he got really excited about. You think you see one thing, but you're seeing something else.” —EV

ISAMU SANDO

OCT. 28, 1928–APRIL 12, 2014



Sando

Isamu Sando, professor emeritus of otolaryngology, loomed large among scientists who study the microscopic anatomy and pathology of the inner and middle ear. A native of Japan, Sando began teaching in 1976 at Pitt's School of Medicine, where he remained until his retirement in 2001.

Sando died in April, five months after becoming a naturalized U.S. citizen.

Pitt professor Barry Hirsch (Otolaryngology Resident '82, Neurotology Fellow '85), a mentee and colleague of Sando's, remembers the former director of the Elizabeth McCullough Knowles Otopathology Laboratory as calm and soft spoken, with “masterful” powers of description—his explanations of complex anatomical relationships were “like walking up stairs.” He'd fill you in step by step, and before you knew it, you had a clear view of the anatomy, Hirsch says.

Sando's eye for detail made his collection of slides, which showcased the hard-to-see parts of the temporal bone, an attraction for researchers from around the world.

In 2007, he was awarded the Order of the Sacred Treasures from the Emperor of Japan.

This honor came in part from his longstanding research relationships with Japanese ENTs, but also from his dedication to instructing otolaryngology fellows from his homeland. As Hirsch describes it, Sando's fellows “would go back to Japan and end up being chairmen of their departments” with impressive consistency. —ZN

IN MEMORIAM

'50s

HAROLD E. CICCARELLI
MD '54
MAY 15, 2014

THOMAS E. MCCARTHY
MD '55
APRIL 22, 2014

LUCIO PARENZAN
RES '59
JAN. 28, 2014

'60s

WILLIAM J. STEPT
MD '60
MAY 16, 2014

WALTER B. HARTNER
MD '62
MAY 28, 2014

ROY D. JOHNSTON
MD '69
JUNE 16, 2013

FACULTY
EDUARDO FIGALLO
APRIL 15, 2014

CAROLYN SUFRIN IN CLINIC FOR THE INCARCERATED

BY AMY WHIPPLE

Like many new ob/gyns before her, Carolyn Sufrin (Res '07) was shocked to find out that, unless laws specifically ban the practice, shackling pregnant women is the system's default during transport from a jail to a hospital, during a hospital visit, and—in some states—even during labor and delivery.

Suddenly, Sufrin had a host of questions and concerns: What if a patient needed an emergency C-section? What if she required repositioning during delivery?

Sufrin, who's now an assistant professor at University of California, San Francisco, would learn that she wasn't the only one who hadn't really thought about family planning for incarcerated women—even though two-thirds of those women have children under the age of 18. Very few people, it seemed, were doing research in that area.

Although San Francisco County Jail already had a nurse practitioner on staff, when incarcerated women needed care outside of an NP's scope, they had to be transported to San Francisco General Hospital. Since both SFGH, where she was an attending and family planning fellow, and Jail Health Services were under the umbrella of the Department of Public Health, she opened a referral-level clinic at the jail—staffed through a residency rotation she created. The onsite clinic allows women to receive important care for issues that wouldn't otherwise be prioritized for transport by the jail, such as chronic pelvic pain or follow up for an abnormal pap smear.

"For some women, this is the only time they're going to have access to health care," says Sufrin. Because jail is temporary and temporally unplanned (an important distinc-

tion from prison), follow-up care proves difficult. In addition to routine needs like pap smears, incarcerated women nationwide face far more complications to their reproductive health. Nearly 40 percent have irregular periods. As many as 50 percent are survivors of abuse. The rate of chlamydia—a curable infection with serious health consequences if left untreated—is upward of 13 percent among female inmates, about two times higher than that of the general population. And, primarily because of a lack of access to birth control, some 50 percent of these women at some point in their lives have an unintended pregnancy that ends in abortion. (It's striking, says Sufrin, how similar incarcerated women are to women who seek to terminate their pregnancies: They are all feeling stigma and shame from society at large, and they express surprise when they're treated with respect and dignity by their physicians.)

In May, Sufrin received her PhD in medical anthropology from UCSF/UC Berkeley. For her dissertation, she followed pregnant women, deputies, and medical staff, her entry point being the paradox that prisoners are the only people who have a constitutional right to health care. "Jail has become an integral part of our society's medical safety net, especially with the urban poor," she says. Sufrin examined how these ideas play out—for example, incarcerated women are legally entitled to

abortions, though they are often led to believe they're not. She's also interested in paradoxical day-to-day interactions, such as how correctional officers both punish and care for the women they oversee.

When Sufrin arrived in California, it was illegal to restrain women during labor and delivery—but it was allowed for the duration of pregnancy. Citing the risks this practice poses—including increased risk of falling and inability to break a fall, which can lead to abdominal injuries ending in placental separation and maternal hemorrhage, among other complications—Sufrin advocated for legislative change. In 2012, Governor Brown signed a bill that nearly eliminates restraint during pregnancy and makes sure that, should restraints become absolutely necessary for safety, the least restrictive means are used.

Sufrin says she noticed "how much power [doctors'] voices have, how much our voices are valued, for better or for worse." In April, UCSF honored her with the Edison T. Uno Award for Public Service—a warm sendoff as she begins a new chapter. Sufrin joins the faculty at her MD alma mater, Johns Hopkins, in the fall. It will be a new experience, as medical services for Baltimore's jails are privatized, but Sufrin looks forward to the challenge.

"Things are not always as they seem," she says. "It's important to dig deep into people's experiences to get people's reality." ■

PHOTO BY SARI GOODFRIEND/PHOTO EXTENSION BY TIM GROEN



Sufrin set up a women's health clinic at San Francisco County Jail.



OF BREAD AND BACTERIA

First off, this bread is good. It's pungent, substantial, with a no-nonsense, hint-of-cheese taste. When toasted and slathered with butter, this bread could take those airy artisanal loaves with one hand tied behind its back.

"We often sell out," says Jenny Bardwell, owner of Rising Creek Bakery, in Mt. Morris, Pa. She is referring to the misleadingly named "salt-rising bread," which her bakers make using a 19th-century Appalachian recipe. The dough contains no yeast and very little, or no, salt. (One theory of the moniker's origins has frontier families traveling while their starter dough warmed in the sun in salt barrels atop their wagons.) What's the secret ingredient helping 700 loaves rise each week in Bardwell's kitchen? The bacterium *Clostridium perfringens*.

Think of it as the organism's community service.

Bruce McClane, a PhD professor of microbiology and molecular genetics at the University of Pittsburgh School of Medicine, has been studying *C. perfringens* for more than 30 years. Some strains are toxic, making the bacterium "the second most common cause of food poisoning," he says.

Bardwell consulted McClane while researching the bread's science and continues to contact him for tips to improve the baking process. There's no historical record or scientific evidence linking the bread to illness, yet she asked McClane to evaluate dozens of starter samples to be sure. He found no toxin-producing strains. Plus: "When they bake the bread, the heat kills a lot of *C. perfringens*," says McClane.

"It's a natural fermentation with what most people think of as a pathogen," says Bardwell. The starter stage can take up to 12 hours to ferment and requires careful monitoring of temperature and bacterial activity.

McClane is hoping to find a therapeutic for the aggressive strains of *C. perfringens*. Perhaps he should have a look at Bardwell's bread once again:

"People often comment on how it soothes their stomachs," she says.

—Michele D. Baum, Photo by Rising Creek Bakery

CALENDAR

FOR ALUMNI & FRIENDS

WHITE COAT CEREMONY AUGUST 10

3 p.m.
Scaife Hall, Auditoriums 5 and 6
Reception to follow
Petersen Events Center lobby
For information:
Jen Moritz at 412-648-9059
jlm337@pitt.edu

HEALTH SCIENCES ALUMNI RECEPTION OCTOBER 9

6 p.m.
Clift Hotel
San Francisco, Calif.
For information:
Rachel Edman at 412-864-1957
rge6@pitt.edu

MEDICAL ALUMNI ASSOCIATION SCHOOL OF MEDICINE SCHOLARSHIP LUNCHEON OCTOBER 24

12 p.m.
Pittsburgh Athletic Association
For information:
Jen Moritz, jlm337@pitt.edu

MEDICAL ALUMNI ASSOCIATION WILLIAM S. MCELLROY AWARD PRESENTATION NOVEMBER 5

3 p.m.
Lecture
Recipient—David Geller, MD
For information:
Jen Moritz at 412-648-9059
jlm337@pitt.edu

HEALTH SCIENCES ALUMNI RECEPTIONS FLORIDA MARCH 11, 2015

Palm Beach Winter Academy
For information:
Pat Carver, 412-648-9741, cpat@pitt.edu

MARCH 13, 2015

Naples Winter Academy
For information:
Pat Carver, 412-648-9741, cpat@pitt.edu

To find out what else is happening at the medical school, visit www.health.pitt.edu and maa.pitt.edu.

ALEX BELOMLINSKY/GETTY IMAGES



FOR REAL! TWEEN SCIENCE

Can someone own the alphabet? How about a word, or a string of letters in a code? If you decipher the code, do you get to own what it stands for? Now think about DNA. Your DNA code is really an incredibly long series of symbols (made up of a four-letter alphabet); this code translates into instructions for the building and operating of you. But 99.9 percent of your DNA code is exactly the same as everyone else's all over the planet.

DNA is a powerful substance; it is essentially a code for life. Genes are small bits of DNA that code for traits like blue eyes, curly hair, and how tall you will be. Sometimes genes mutate, or change, just a little bit. Usually that's no big deal. But sometimes a little change makes a big difference. Some mutations make people more likely to get diseases like diabetes or Alzheimer's.

Imagine that scientists at a private company have identified a mutated gene that predicts whether a person is likely to get a certain disease. Since they invested a lot of time and money into identifying the gene, should the company have exclusive rights to using the gene to develop tests for the disease? In other words, should it be allowed to own a patent on that gene? It's a tricky question, and one that went all the way to the U.S. Supreme Court last year. If you were a Supreme Court justice, what would you decide? (File a brief brief with us: medmag@pitt.edu.)

—Jennifer Lienau Thompson

To find out what happened with the Supreme Court decision, go to the For Real! link on our site: www.pittmed.health.pitt.edu/summer-2014

Pitt bioethicist Lisa Parker helped us think about this quandary. For more kids' stuff see www.howscienceworks.pitt.edu.

KIDS' STUFF!



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THE GIFT THAT GIVES BACK

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To learn more, contact:

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Forbes Tower, Suite 8084
3600 Forbes Ave.
Pittsburgh, PA 15213
412-647-0515
slisa@pitt.edu
www.pitt.planyourlegacy.org

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

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AGE	RATE	YEARLY INCOME	ESTIMATED DEDUCTION
55	4.0	\$400	\$2,654
60	4.4	\$440	\$2,908
65	4.7	\$470	\$3,489
70	5.1	\$510	\$4,099
75	5.8	\$580	\$4,577
80	6.8	\$680	\$5,020
85	7.8	\$780	\$5,659
90	9.0	\$900	\$6,294