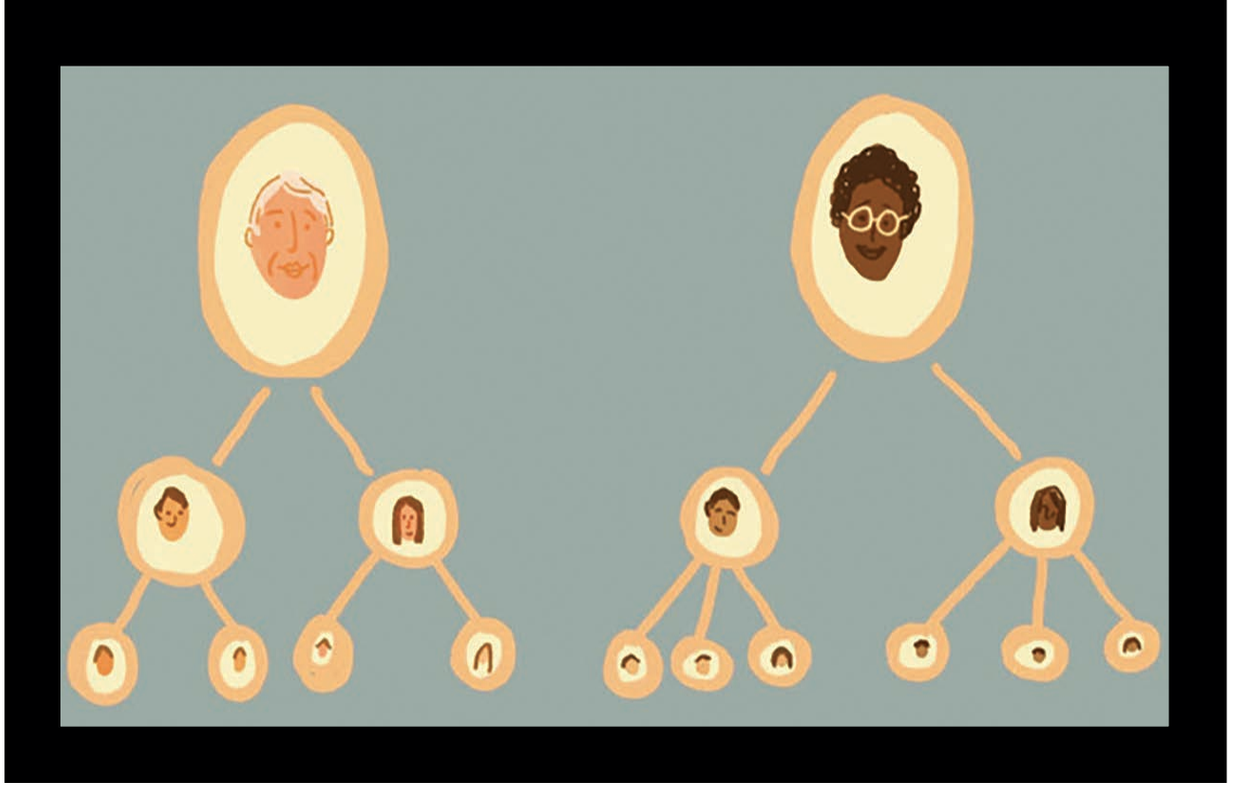


REPRESENT

TO MAKE PRECISION MEDICINE A REALITY, RESEARCH ITSELF MUST CHANGE

BY ELAINE VITONE

ILLUSTRATIONS COURTESY THE NATIONAL INSTITUTES OF HEALTH



In August 1825, in a home near London's Finsbury Square, a woman lay dying of postpartum hemorrhage, in spite of the usual remedies of the day—blankets and brandy, mostly. In a last-ditch effort, the team turned to an experimental and as yet controversial treatment; they drew several ounces of blood from her husband's arm into a tumbler, then cautiously injected the still-warm fluid into the patient's vein. Within hours, she "rallied considerably," her doctor, Charles Waller, later wrote in defense of this "operation" and his now-famous colleague who developed it, James Blundell.

In the early days of human blood transfusion, not every patient was so lucky. Doctors didn't know their type As from their Bs, Os, or ABs until 1902, and Rh-negative blood types weren't discovered until World War II. In the meantime, people figured blood was blood. One patient's cure could potentially become another's fatal reaction.

The complexity and variety of the human form, as well as the diseases that ail it, continue to challenge scientists. We now know that a given cancer—or any other disease or injury, for that matter—will not look the same in one person as it does in another, nor will responses to a given treatment. And so the new drugs keep coming, because, about half the time, the medicine misses the mark. Either it doesn't work as hoped, or there are side effects that might outweigh the benefits.

In many ways, the subtypes of diseases and disorders are blind spots. We still don't know our As from our Bs.

Waller once said it was impossible to prove whether the full recovery of his historic patient was "produced by nature or by the remedy." The past two centuries of clinical research history seem in answer to that, with tomes of papers full of comparisons between Treatment X and none at all. Blind, placebo-controlled trials are the reason why we've come such a long way from the days of blankets and brandy.

But now, we have a new problem: How do all these drugs compare against one another? For example, there are dozens of drugs approved for hypertension alone. Which one, if any, is right for *you*, given your genetics, environment, and exposures? To find these answers, clinical research itself must change.

In 2015, the National Institutes of Health (NIH) launched the Precision Medicine Initiative. Its centerpiece: a patient registry of 1 million volunteers from across the country, aptly named All of Us.

This historic recruitment effort began in May 2017 with volunteer number one, at site number one, the University of Pittsburgh and its clinical partner, UPMC. Why here? When the NIH reviewed proposals for the first sites to launch, the Pittsburgh team got the top score nationwide. Total funding is expected to exceed $67 million.

On a recent chilly Tuesday afternoon, a small black screen on Steven Reis's desk flashes a number in red. As of this moment, it tells him, 2,223 Pennsylvanians have signed up (and, as we go to print, 3,047). These volunteers amount to about 25 percent of all enrollees nationally, he says, adding that the enrollment effort is still in its beta phase—the national launch is expected to begin this spring.

Several new enrollment sites across the state are in the works, as well as a partnership with Giant Eagle to bring their pharmacists and technicians in on the game. Meanwhile, All of Us Pennsylvania is busily signing people up through community events, visits to public libraries (sponsored by a $4.5 million grant from the National Network of Libraries of Medicine), e-mails to Pitt and UPMC staff, and letters to individual physicians. For practices in the Pittsburgh area, the program sends trained Pitt



students to pitch the program to patients in the waiting room. "We've been talking to providers throughout the region, and there's a lot of enthusiasm," says Reis.

When volunteers enroll, he explains, they come in for a brief visit for baseline measurements—weight, blood pressure, height, and the like—as well as blood and urine samples for genetic and other testing. Volunteers also complete a brief online questionnaire about their health, as well as a not-so-brief consent process. It takes so long, in part, because of what may be the most crucial part of the project: sharing their electronic health record information with the All of Us registry. All of the information is de-identified and secured using the latest and greatest cybersecurity technologies, notes Reis.

These data, along with periodic online surveys, and perhaps eventually metrics from wearable devices, will combine to create the largest and richest biomedical dataset ever assembled. Academic and industry researchers—and, to a lesser degree, citizen scientists, including high school students—will be able to request free access to these data. "You don't know who's going to come up with a discovery," says Reis, who, as founding director of Pitt's Clinical and Translational Science Institute (CTSI), has promoted a cross-disciplinary culture here, bringing design theorists, engineers, and others together with biomedical scientists to spark innovations. "People look at data differently depending on their background and skills."

One of the main goals of this NIH initiative—and of the field of precision medicine itself—is to close gaps in care, says Mylynda Massart, an MD/PhD assistant professor of family medicine at Pitt who practices primary care at Matilda H. Theiss Health Center, a UPMC family medicine practice in Oak Hill that serves a diverse and underserved population. Take, for example, Massart's own familial high cholesterol. The literature says statins can lower cholesterol and reduce mortality—but those conclusions are based on studies of middle-age Caucasian men. "So I don't know what that data means for me. And I don't know what that data means for an African American male sitting across from me in my office."

Massart is a member of the national All of Us special populations committee, which is leading the charge in an ambitious goal: to enroll at least 51 percent of its 1 million participants from groups underrepresented in biomedical research. This includes racial and ethnic minorities, sexual and gender minorities, and participants across the gamut of socioeconomic status and geography (rural, urban, and suburban areas). A range of ages will also be important; though the registry is currently open only to adults 18 and older, eventually, children and teens will be recruited, as well. A large-scale pediatric study is getting off the ground in Pittsburgh sooner—see "Tending to Children," below.

Here in Pittsburgh, Massart cochairs All of Us PA's stakeholder advisory board with Father Paul Abernathy, director of FOCUS Pittsburgh, a Hill District–based nonprofit that provides food, counseling, transportation, job training, and other services. Also on the board is Esther Bush, president and CEO of the Urban League of Greater Pittsburgh, a comprehensive social service/civil rights organization focused on serving African Americans and other groups. The Urban League has partnered with Pitt's CTSI for more than a decade. Together, members of the advisory board will gather feedback from the community and incorporate it into the study.

Unfortunately, Massart says, there are reasons why underrepresented groups, especially African Americans, have historically been wary of medical research, the Tuskegee syphilis study being the most infamous example.

"We have to have open discussions about what happened historically," she says, "and what things have been put into place to prevent that from ever happening again." Sadly, she adds, those tragic episodes have contributed to health disparities within research. "We need to overcome that and reverse that process. That requires building trust and dialogue and relationships, and so the community advisory board is helping us with that."

Erricka Hager, a 29-year-old from Pittsburgh, first learned about All of Us when she came to work with the Urban League as a health advocate seven months ago. She decided to enroll, motivated by her grandmother, who, four years ago, was diagnosed with breast cancer—the first known case in their family tree.

"My son and my grandmother have a very strong bond," says Hager. "It hit him hard."

When she signed up, she did it for both generations. It was a way to honor her grandmother, Hager says, and to help ensure that there will be better detection and treatments available in case her two children are at risk for the disease.

At the Urban League, Hager works primarily with elderly African Americans, providing health education and advocacy, as well as recruiting for clinical studies. As she pitches All of Us and its merits, people might hesitate at first but warm to the idea when she explains her own reasons for joining. She reassures them: The registry is entirely voluntary and anonymous. Ask questions and learn as you go. If at any point you feel uncomfortable, you can opt out and elect to be removed from any studies going forward.

But if the volunteers stay—and All of Us hopes they will, for at least a decade—they will help seed a new era of scientific discovery.

"This is my way of taking hold of my health," says Hager, "of being involved, and being at the forefront of the decisions that I want to be made for my future, as well as my children's future." ■

TENDING TO CHILDREN

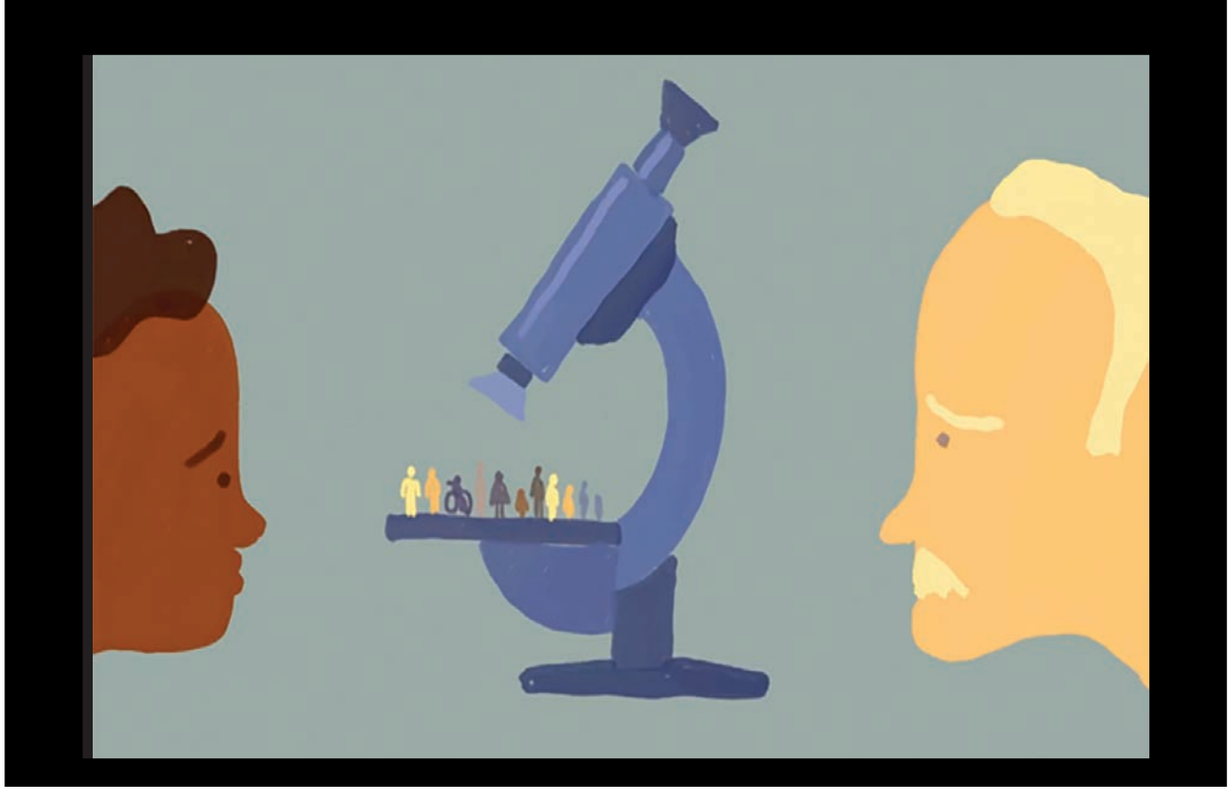
What are the ingredients of a healthy childhood? What correlates with a young person graduating from high school, steady and ready to roll along the path to adulthood? These are essential questions, says the University of Pittsburgh's Terence Dermody, who holds the Vira I. Heinz Chair of Pediatrics and is the physician-in-chief at Children's Hospital of Pittsburgh of UPMC. He says Pitt and Children's are uniquely poised to find the answers.

With startup funding from the Shear Family Foundation, the Pittsburgh Children's Study recently began recruiting infants and children for a longitudinal epidemiological assessment that could make its official launch as early as January 2019. The sponsor team includes two Pitt ob/gyn profs—Janet Catov (who oversees the Magee Obstetric Medical and Infant Database) and Yoel Sadovsky (who directs the Magee-Womens Research Institute)—as well as George Gittes (professor of surgery and of pediatrics at Pitt and surgeon-in-chief at Children's) and Steven Reis (Distinguished Service Professor of Medicine and director of the Clinical and Translational Science Institute, among other titles). The team hopes to enroll about 5,000 children in the study each year.

In addition to genetic and other biological data, the study will eventually encompass detailed interviews through periodic visits to schools and homes, conducted by personnel trained to answer questions and offer referrals as needed.

"That process itself may improve the health of kids in the community," says Dermody, "and we're excited about that." *—EV*





PRECISION VISION

THINKING OF YOU

The right treatment, at the right time, for the right person. Precision medicine—also known as personalized medicine—has been a focus at Pitt for a few years now. In the past year alone, big data and machine-learning projects here have begun to help doctors confirm when patients are suffering from acute kidney injury, they've helped identify which pancreatic cysts will progress to cancer (see "Cancer Detective," p. 3), and they're predicting who is likely to benefit from a new therapy for treatment-resistant COPD. Also, a smartphone app for pregnant women considers each user's risk factors and barriers to care, helping them prevent preterm birth.

What else is on the horizon?

NICU NEWS: Preemies often have a long road home from the hospital, not to mention a costly one. The average stay at the neonatal intensive care unit (NICU) is 17 days and costs about $220,000. But recent computational modeling suggests many could be discharged sooner if their underlying conditions were identified through genome sequencing at birth and treated right out of the gate. To test this hypothesis, Jerry Vockley, an MD/PhD, chief of medical genetics at Children's Hospital of Pittsburgh of UPMC, and professor of pediatrics at Pitt, recently secured a five-year, multicenter grant of more than $10 million from the National Center for Advancing Translational Sciences. The clinical trial is expected to launch this year.

BLOCK TALK: When a patient has a blockage in the heart, a cardiologist is likely to put in a stent, then head off any further trouble with antiplatelet agents—usually, a drug called clopidogrel (Plavix). But as the School of Pharmacy's Philip Empey, a PharmD/PhD, and colleagues reported in *JACC: Cardiovascular Interventions*, if you happen to carry a certain gene variant, you may metabolize the drug more slowly, and it may not work as expected. Such was the case for about a third of the patients Empey and his team studied, and those patients had worse outcomes: higher rates of death, stroke, or repeat heart attacks. Two years ago, UPMC Presbyterian implemented a protocol to identify patients who carry this allele as part of its standard of care.

GENE SCREEN: The field of pharmacogenomics—how your genetics influence your response to drugs—is growing rapidly. To date, nearly 200 drugs come with genetic-variant-related warnings, ranging from a heads-up about minor side effects to graver cautions. "The issue is, we've not had the genetic testing [results] to drive [prescribing] decisions," says Empey. This spring, Pitt/UPMC researchers will begin providing that testing, inviting patients to volunteer for a study evaluating a panel of nearly 5,000 genes. The data will then be linked with the participant's UPMC health record. "So when [a doctor] goes to prescribe a certain medication, there might be a pop-up saying, based on this person's pharmacogenomics analysis, this drug may be less effective than another drug, for instance," says Steven Reis, Distinguished Service Professor of Medicine, associate vice chancellor for clinical research, and director of Pitt's Clinical and Translational Science Institute. —*Elaine Vitone* ■

