Special COVID-19 Report

COURTESY UPMC

Insight on Variants

Pitt Med's **Paul Duprex** and **Kevin McCarthy** have helped scientists understand one way that new variants arise in the novel coronavirus. In a recurring pattern of evolution, SARS-CoV-2 evades immune responses by selectively deleting small bits of its genetic sequence.

When these deletions happen in a part of the sequence that encodes for the shape of the spike protein, the formerly neutralizing antibody can't grab hold of the virus, the researchers report in a Feb. 3 paper in Science. And because the molecular "proofreader" that usually catches errors during SARS-CoV-2 replication is "blind" to fixing deletions, they become cemented into the variant's genetic material.

"You can't fix what's not there," said study senior author Duprex, director of the Center for Vaccine Research at the University of Pittsburgh. "Once it's gone, it's gone."

Since the paper was first submitted as a preprint in November, the researchers watched this pattern play out as several variants of concern rapidly spread across the globe. The variants first identified in the United Kingdom (known as B.1.1.7) and South Africa (B.1.351) have sequence deletions.

Duprex's group first came across these neutralization-resistant deletions in a sample from an immunocompromised patient who was infected with SARS-CoV-2 for 74 days before ultimately dying from COVID-19. That's a long time for the virus and immune system to play "cat and mouse," and gives ample opportunity to initiate the co-evolutionary dance that results in the kinds of worrisome mutations in the viral genome that are occurring all over the world.

Lead author McCarthy, assistant professor of microbiology and molecular genetics at Pitt, who's an expert on influenza virus (which is a master of immune evasion), says: "How far these deletions erode [vaccine] protection is yet to be determined."

—Erin Hare

Speaking of variants: In the March 24 issue of Scientific American, Pitt evolutionary biologist Vaughn Cooper writes that SARS-CoV-2 may be settling in to a limited number of variations. The professor of microbiology and molecular genetics writes, "This may not be the multifront war that many are dreading." But only if we don't let down our guard. "These viral adaptations are already rewriting our biology textbooks . . . let's strive to limit new material."

Cooper proposes initiatives to help end this pandemic—as do Pitt Med's Kevin McCormick, Jana Jacobs (Public Health PhD '14) and John Mellors in a Science piece published that same week. Rapidly spreading variants are a cause for broad concern and action, the infectious disease faculty note: "Partial roll-out and incomplete immunization of individuals" could breed variants that render existing vaccines ineffective. The scientists advocate for increased surveillance of viral mutations and comprehensive inoculations; they suggest that vaccine boosters and antibodies are likely to help keep us protected from variants. *—Erica Lloyd*

Sources for this special section include Pitt and UPMC reports.

TOM ALTANY/UNIVERSITY OF PITTSBURGH

The Pitt team helping with the "60 Minutes" segment, from left: Will Hinson, Lindsey Robinson-McCarthy, Kevin McCarthy, Paul Duprex, Sham Nambulli, Ghady Haidar and Linda Murphy.

Behind the Scenes

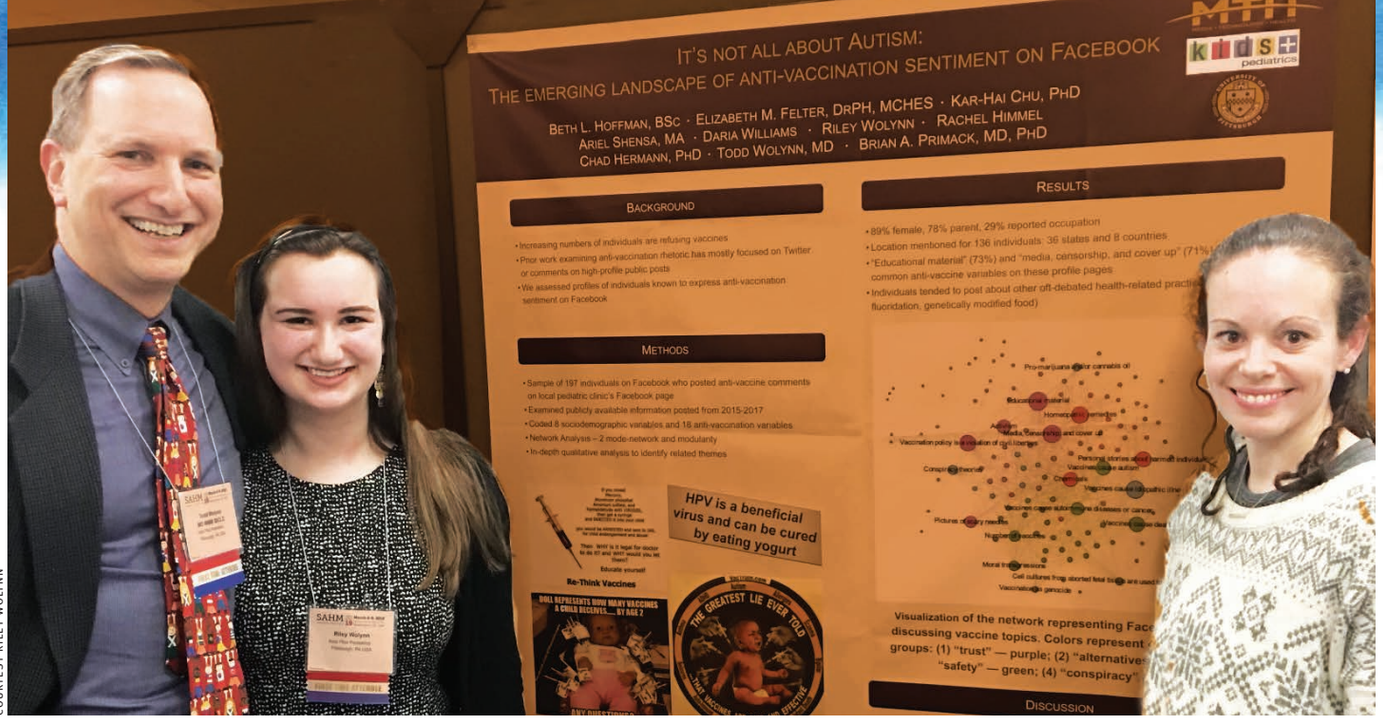
Researchers with Pitt's Center for Vaccine Research were featured on CBS's "60 Minutes" on March 14. To help explain and visualize variants to the novel coronavirus, center director Paul Duprex used a nearly 5-inch-tall 3D model of the coronavirus spike protein—a precise representation, though blown up 800 times from what would actually be found on the surface of the virus. (See photos above.) The bright-red model was made by Will Hinson of Pitt's Center for Teaching and Learning. Hinson received a request to print the model of the coronavirus spike on a Monday. By that Saturday, he had completed it, working well into the night to hand-paint the finishing touches on the model that took more than 70 hours to print. "It was one of the most fun projects I've worked on," says Hinson. *—Anastasia Gorelova*

AIMEE OBIDZINSKI/UNIVERSITY OF PITTSBURGH

Vaccine Venue

The University partnered with Allegheny County to offer its facilities and staffing for Allegheny County COVID-19 vaccine clinics this spring. As of April 6, the partnership had provided 12,000 doses at the Petersen Events Center (shown here) and elsewhere, with many more to come. "We will continue to work to provide vaccinations to our University community and community partners as vaccine is available," says Melissa McGivney, associate dean for community partnerships at the School of Pharmacy, who is leading the effort. Through the first week of April, the partnership had held 17 clinics with help from more than 700 volunteers from Pitt. Seven second-dose clinics were planned for later in the month.

—Gavin Jenkins



COURTESY RILEY WOLYNN

Dad and daughter duo, Todd and Riley Wolynn, team up with Beth Hoffman (right) and Jaime Sidani (not shown) against misinformation online.

Hijacked on Social

Coauthor a journal paper with your dad? Pitt undergrad Riley Wolynn has.

Wolynn, a sophomore health sciences major, and her father, Todd Wolynn (MD '92), a pediatrician and CEO of Kids Plus Pediatrics, both contributed to a paper published April 13, 2021, in Vaccine. The study analyzes tweets that use the hashtag #DoctorsSpeakUp, which was originally a pro-vaccine hashtag until anti-vaccine activists co-opted it. In a coordinated attack, the activists employed the hashtag in tweets citing bogus studies and spreading misinformation and fear.

"Replace all #Vaccines with #Vitamin shots. #DoctorsSpeakUp," writes one Twitter user. The original intention of the hashtag was more along the lines of: "#DoctorsSpeakUp about how vaccines save lives."

This wasn't Wolynn's first time studying the anti-vaccine movement; nor was it her first research project with her dad. As a junior in high school, she became involved in a study of an anti-vaccine Facebook attack against her father's practice.

Beth Hoffman, a Public Health PhD student in behavioral and community health sciences, oversaw Wolynn's work on the Facebook study and was more than happy to have her as a research assistant once she started her first year at Pitt. "We'd been really pleased with her work on that first vaccine paper," says Hoffman, an MPH who is with Pitt's Center for Behavioral Health, Media and Technology.

After the Facebook attack, Todd Wolynn created the nonprofit Shots Heard Round the World, which encourages doctors to respond to vaccine misinformation on social media. Shots Heard went on to collaborate with physician and internet personality Zubin Damania, who organized a social media event around #DoctorsSpeakUp.

Hoffman and Riley Wolynn were at the ready to study the activity around the event. "We learned some really constructive lessons" from the anti-vaccine response, says Hoffman. Their takeaways (see pi.tt-co-opted) were published in the April 13 paper. Hoffman was the lead author on that paper with Jaime Sidani, assistant professor of medicine and a core faculty member in the center, as the senior author.

Wolynn hopes to attend the accelerated program at Pitt Public Health on the Behavioral and Community Health Sciences track and continue working on topics involving media and health.

—Sarah Stager

Support to Stop the Spread

Even before the first COVID-19 vaccine candidates were approved and administered, false information was spreading on social media sites about the vaccines.

"We saw some national surveys indicating many people were hesitant to get the COVID-19 vaccine, even before a vaccine candidate became available, and that was increasing over time with each subsequent survey. But they didn't really explain why or how," says Jaime Sidani, assistant professor of medicine.

"We're using social network analysis to see how messages spread among groups and into other groups," says Sidani, "but also to learn more about the reasons for hesitancy and develop educational messaging to counter that."

In October 2020, the researchers received a $117,000 grant from the Richard King Mellon Foundation to support their efforts.

"A vaccine that is scientifically proven to be 95% effective still will be ineffective if it is distrusted and shunned by significant percentages of the population," says Sam Reiman, director of the Richard King Mellon Foundation.

Another group passionate about inoculations is getting a boost(er), so to speak. The Influenzers, a new interdisciplinary science policy student group at Pitt, was awarded a Research!America Civic Engagement Microgrant. The Influenzers work to educate the Pittsburgh community about facts and myths surrounding immunizations. The students are also exploring the feasibility of making dentists eligible to administer vaccines.

Shreyaa Nagajothi, a first-year neuroscience student and member of the Influenzers, told the Pitt News that during the pandemic, "We all feel a bit helpless." Yet: "Being part of an organization that is encouraging people to get the vaccine, encouraging people to stay healthy and taking active roles in health policy is truly the best thing that anyone can do to help out during this time."

Poison Center Pinch Hits

When the pandemic hit, the Allegheny County Health Department was suddenly flooded with hundreds of calls a day: Could I have COVID? Where can I get tested? What does "quarantine" really mean?

"They just couldn't keep up," says **Amanda Korenoski** (PharmD '12), shown left, managing director of the Pittsburgh Poison Center of UPMC. "So they reached out to us. We, of course, were willing to help. We already had the infrastructure." Since then, all of the county's medical-related COVID-19 calls have been routed to the center.

The center is a natural fit for this: staffed 24/7 by a team of 14 RNs, each of whom has years of experience in emergency medicine or critical care. They're seasoned in the delicate art of guiding people over the phone through moments of utter panic—and calming callers enough to answer questions that will be crucial to their care. Without the benefit of vital signs or even facial cues, the nurses assess callers, triage them and connect them with whatever they need: maybe an ambulance, maybe just management at home.

The center, whose medical director is **Michael Lynch** (MD '04, Res '07, Fel '09), has continued to evolve with each new wave of needs. SOS calls for necessities like rent and food prompted a partnership with 211, the United Way's community services helpline.

The addition of a backdoor line to arrange COVID-19 testing for emergency responders solved another problem: "Police, fire and EMS were getting exposed in their day-to-day work," says Korenoski, "which was keeping them away from work when we really needed them."

And as the first crop of laypeople received their vaccines, UPMC created a dedicated poison center line for questions about side effects. "Vaccines are very safe," Korenoski stresses. "Usually, it's just reassuring them that their body aches and fatigue are OK. But we're 24/7. If someone wakes up in the middle of the night and starts to feel not so great, they can call and talk to a health care professional."

Throughout the pandemic, the center team continues its original day job: serving as a round-the-clock emergency call center for poisoning queries in 44 counties across western and central Pennsylvania—from the western border of PA to just about the Susquehanna River.

Like its 54 sister centers across the United States, the Pittsburgh Poison Center is staffed by health care pros who've completed stringent training in toxicology. The poison control number, 1-800-222-1222, is the same throughout the country and routes to the nearest poison control center. *—Elaine Vitone*

Hear the origin story of these centers and Mr. Yuk, the poster child of accidental poisoning, on Pitt Medcast at pi.tt/pittmedcast.

THE MR. YUK LOGO IS A REGISTERED TRADEMARK OF CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC. USED WITH PERMISSION

Big Stakes, Big Stats

By Sharon Tregaskis

When we hear about clinical trials, we might picture doctors and patients partnering to test new therapies. What we might not think about are the teams of other professionals and scholars who make those studies happen and figure out what the results mean.

In the search for new and better treatments, those roles are critical in normal times. In a pandemic, the work becomes all the more urgent.

Take, for instance, **Maria Mori Brooks**. In the three decades since she earned her PhD in statistics, the Pitt professor of epidemiology and biostatistics has proved her mettle, making sense of the numbers generated by multicenter research collaborations. As codirector of the Graduate School of Public Health's Epidemiology Data Center, she's helped dozens of National Institutes of Health–funded scientists design and optimize data collection and management, as well as formulate computing and statistical methods for clinical studies. She also serves as principal investigator for the data coordinating centers of three multicenter investigations.

Still, nothing quite prepared Brooks and her colleagues for their roles since June with ACTIV-4 Antithrombotics, a set of clinical trials funded through Operation Warp Speed. The study is part of the U.S. government's public-private partnership Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). ACTIV-4 Antithrombotics evaluates how well blood thinners (anticoagulants) work in treating COVID-19 patients.

The trials consortium will yield outcomes from three distinct COVID-19 patient populations—inpatient, outpatient and post-discharge.

Many COVID-19 deaths are caused by microscopic blood clots.

Before this pandemic, doctors often gave patients low-dose blood thinners during extended hospitalizations to prevent clots that might form because of reduced physical activity. Given that COVID-19 clotting can cause lung damage, strokes and heart attacks, higher-dose blood thinners seemed like a good idea for people with COVID-19.

Yet, that was just a hunch. Or a hope. The treatment had not been vetted in clinical trials, so physicians didn't have any evidence to guide their practice.

"Some people are treating their patients with anticoagulants and some aren't," **Alison Morris**, Pitt's division chief for pulmonary, allergy and critical care medicine, noted in January. But now, ACTIV-4 Antithrombotics inpatient arm has given doctors some answers.

The trial randomized participants, with a goal of enrolling 2,000, to receive either high-dose heparin or the standard anticoagulant regimen used as a preventive among hospitalized people.

ACTIV-4 Antithrombotics inpatient arm is one of three collaborating multicenter studies of hospitalized patients—the others are based in the U.K. and Canada—that together span 300 hospitals on four continents, all working in parallel on the blood thinner question.

A typical multicenter clinical trial team spends years detailing proto-

GETTY IMAGES

cols and enrollment plans, garnering approval from institutional review boards and vetting contracts. Patient recruitment, data collection, analytics and the publication of findings often span multiple five-year grant cycles. With ACTIV-4 Antithrombotics, everyone involved has hustled like never before, says epidemiologist **Steve Wisniewski** (PhD '94), who leads coordination of the entire ACTIV-4 Antithrombotics effort.

"The train tracks were being put down as the train was coming down the path," says Wisniewski, who is Pitt vice provost for budget and analytics and codirector with Brooks of the Epidemiology Data Center. The EDC team works with Berry Consultants, a private firm that analyzes multicenter clinical trial data and has aggregated all of the data from ACTIV-4 Antithrombotics and its partners abroad.

Brooks is lead statistician for the outpatient protocol, which was initiated in September 2020. For the inpatient protocol, which launched first, she was responsible for presenting preliminary results to the ACTIV-4 Antithrombotics data safety monitoring board (DSMB). DSMBs evaluate issues like study integrity and safety for participants, explains Brooks from behind the closed door of her home office. (Like many families, hers has been schooling and working remotely since March 2020.)

She's served on a number of external DSMBs in the past two decades. For the conventional clinical trial, such reviews might occur every six months.

For the inpatient population, Brooks presented monthly, yielding two major announcements in a matter of months:

In late January, the NIH announced some good news. Among those hospitalized with moderately severe infections, full-dose heparin reduced their need for mechanical ventilation and other life support. The results were convincing enough to close enrollment for the inpatient arm.

This was after the DSMB closed recruitment of critically ill patients in late December; interim analysis suggested that it was futile to give full-dose heparin to these patients—the treatment could even worsen their condition.

Pitt physicians have taken major roles with ACTIV-4 Antithrombotics, as well: **Matthew Neal**, the Roberta G. Simmons Associate Professor of Surgery, cochairs the ACTIV-4 Antithrombotics inpatient study; **Frank Sciurba**, a professor of medicine and education, cochairs the outpatient study; and Morris cochairs the ACTIV-4 Antithrombotics post-discharge study.

Says Morris: "Despite the hopefulness around the vaccine, people are still getting sick and dying. We still really need studies like this to figure out how to treat patients."

Wheels Up

The conventional way to organize clinical trials compares a single treatment to placebo and takes years to generate results. All of the study infrastructure—enrollment protocols, electronic records and analytics—serves that single comparison. It's as though each airplane flying into a region had its own control tower and airport, and those airports were torn down after passengers disembarked.

ACTIV-4 Antithrombotics, which evaluates the effectiveness and safety of treating COVID-19 patients with varying types of blood thinners, is a multiplatform adaptive trial. This is the new, high-powered and, frankly, more sensible, way to get answers about treatments. In tandem with the Pitt co-led international REMAP-CAP platform (which has pivoted from pneumonia studies to COVID-19 trials), it uses a single, overarching experimental infrastructure to briskly collect a wide range of clinical and laboratory data. Think of it as an international airport of randomized clinical trials, serving passengers of existing airlines, as well as those still to be founded.

As additional questions arise regarding blood thinners, ACTIV-4 Antithrombotics will tackle those, too. *—SRT*