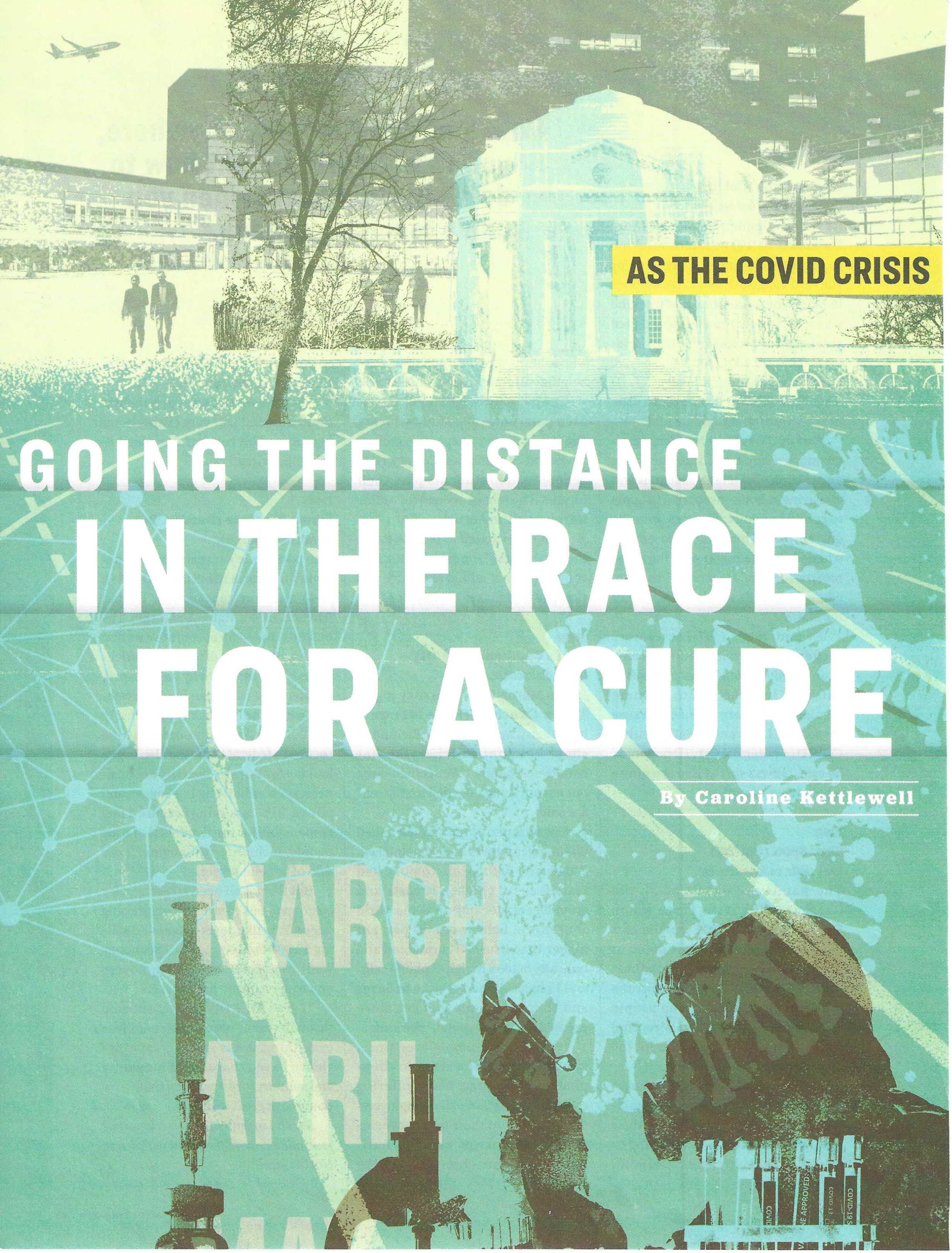
AS THE COVID CRISIS

GOING THE DISTANCE IN THE RACE FOR A CURE

By Caroline Kettlewell



PERSISTS, SO DOES UVA'S RESEARCH EFFORT

Nearly a year into a global pandemic that has led to more than 1 million deaths, infected tens of millions more and upended daily life around the world, the scientific community is attempting to do the seemingly impossible: conquer a deadly virus not in years, but in months. In the race to achieve such an unprecedented victory, researchers across Grounds joined the effort—even as the world plunged abruptly into a new reality of shutdowns and social distancing—bringing their expertise together to understand the virus and prevent and treat infection.

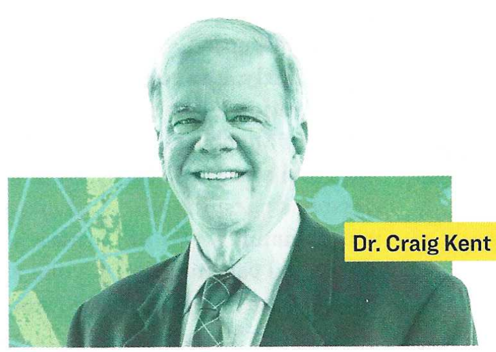
Dr. Craig Kent, executive vice president for health affairs for UVA Health, says that UVA's research community brings two particular strengths to this fight. The first is nationally recognized expertise in infectious diseases and epidemiology. And the second is a dedication to collaboration that UVA and its research community made a priority well before the COVID-19 outbreak.

"I have never seen the level of collaboration I have experienced here at UVA," Kent says. "Everybody is at the table, and everybody is working together."

PREVENTION

As early hope of containing COVID-19 outbreaks faded, focus turned to a vaccine as the path to gaining control over the pandemic. And although a handful of front-runners quickly moved into advanced clinical trials in the U.S. and elsewhere, it's unlikely that any will prove a "magic bullet" for rapidly combating the virus. UVA researchers have several projects in early development.

To address a growing concern about waning COVID-19 immunity, professor of surgery **Dr. Craig Slingluff (Col '80, Med '84)**

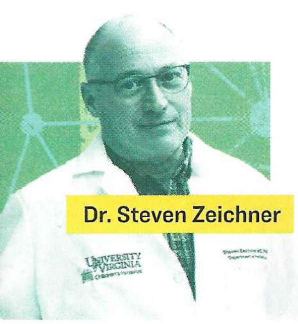


Dr. Craig Kent

LEFT: CLARE NICHOLAS; RIGHT: SANJAY SUCHAK

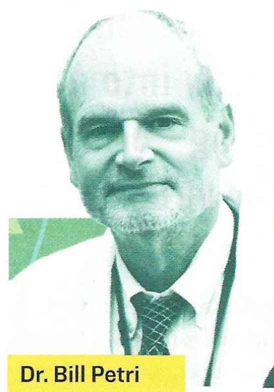
Researchers Vignesh Rajasekaran (Col '19) (left) and Hanna Yu are part of a team working on a vaccine that would use existing technologies to ease production.

and his team are developing a vaccine with a "prime-and-boost" approach, likely with two different shots that would be administered several weeks apart. "Some of the emerging evidence suggests that immunity against the coronavirus is not as strong or long-lasting as we would like," Slingluff says. "So what we anticipate is that there will be subsets of people who get the first vaccine who don't get a very good immune response and aren't protected, and that others may get an immune response but it wears off over time. We hope that this approach will create a stronger, more durable response."

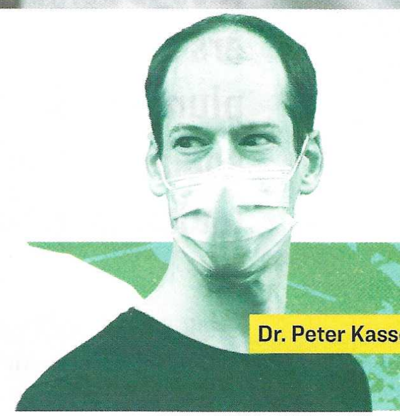


Dr. Steven Zeichner

Similarly, a vaccine collaboration led by the School of Medicine's Dr. Bill Petri and Dr. Peter Kasson is pursuing sustained immunity with an intranasal vaccine that would target the first site of infection and include an added ingredient to stimulate a stronger immune response.



Dr. Bill Petri



Dr. Peter Kasson

Professor of pediatrics Dr. Steven Zeichner's team began their vaccine project with the end in mind, recognizing that a truly successful vaccine for a global pandemic will have to be rapidly producible using existing industrial capacity, affordable for the world's poorest nations and easily administered in countries that lack advanced health infrastructures. Their preliminary research is focusing on developing a vaccine that comes from a part of the virus that appears stable across the different variants that have been sequenced and would provoke an effective immune response without precipitating a more intense inflammatory reaction. And "because the vaccine production technology would involve growing E. coli bacteria and then inactivating them," Zeichner explains, "the vaccine should be able to be produced in large quantities for a low price using existing technologies and factories around the world that are used to make other vaccines."

DIAGNOSIS AND TREATMENT

As we continue to live with the virus for now, however, one of the most confounding aspects is "the tremendous heterogeneity in patients," Petri points out. Some experience no to mild symptoms,

DAN ADDISON; SANJAY SUCHAK

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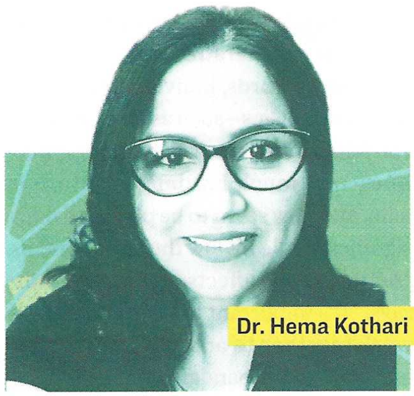
while others develop the life-threatening or fatal effects. Multiple teams at UVA are researching diagnostic tools to identify who is most at risk for severe illness, as well as therapeutic interventions that could prevent or treat those complications.

Because a runaway immune response is believed to play an important role in the most severe illness, Dr. Jeffrey Sturek, an assistant professor and pulmonary and critical care physician, and Dr. Eli Zunder, an assistant professor of biomedical engineering, are leading one of several projects looking for specific "biomarkers" in patient samples that might serve as predictors for illness severity.

Dr. Hema Kothari, a research assistant professor in cardiovascular medicine, is conducting a study of the immune response, using blood samples from patients enrolled in the remdesivir drug trial at UVA to see whether it's possible to determine not only who is at risk of severe illness but also which patients are most likely to respond to medication.

Drawing on plasma samples collected from COVID-19 patients admitted to the UVA Medical Center, researchers in Petri's lab determined that patients who developed severe enough symptoms to require being put on a ventilator showed an immune system response with qualities similar to asthma. Now working in a mouse model of COVID-19 developed at UVA, researchers have found initial indications that inhibiting immune system proteins associated with that response seems to help partially protect the mice from the disease. If a therapy could be developed to do the same for patients,



Dr. Hema Kothari

it could potentially help protect people "from the most feared complication of the disease, which is respiratory failure," Petri says.

To assess patients for that complication, a project led by cardiologist Dr. Randall Moorman, who holds appointments in the schools of medicine and engineering, will use artificial intelligence to analyze massive volumes of physiological monitoring data collected from COVID-19 patients treated at UVA, looking for patterns that could serve as a kind of early warning system to signal which patients are at risk for deteriorating. Based on similar "predictive diagnostics" tools Moorman has successfully developed for neonatal sepsis and adult intensive-care patients, the algorithms can detect complex patterns in huge volumes of data.

Moorman and School of Medicine assistant professor Dr. Shrirang Gadrey are also working on a project that would use small, wearable sensor devices for remote monitoring and assessment of labored breathing, an important indicator of respiratory distress that is normally visually assessed at bedside. The researchers will look for whether there might be a predictive pattern unique to those patients who develop the most severe disease. But also, by allowing remote assessment, these sensors would help protect health care workers from the risks of exposure from bedside evaluations.

Finally, other researchers are trying to determine what might be helping most people recover from COVID-19 without getting seriously ill, and what interventions might prevent worsening illness in those at risk. Two of these projects will examine immune system T-cells from blood donated by recovered patients to try to determine whether it would be possible to "arm" T-cells from healthy donors to target the virus in sick patients, a therapy based on similar work already being conducted at UVA for treatment against cancer. Dr. Lawrence Lum, a specialist in hematology/oncology who is helping lead one of the projects, says his team's concept "is grounded in work we did and patented over 10 years ago using convalescent immune plasma from people who recovered from cytomegalovirus. So you never know how your work is going to cross-fertilize and be leverageable for the next thing."

TRACKING, MODELING AND CONTAINING

A global pandemic is a dynamic crisis, and a number of UVA researchers have continued to work at understanding, modeling, or projecting the pandemic and its impacts. Locally, an initiative led by Vice President for Research Melur (Ram) Ramasubramanian produced a saliva screening test to allow rapid testing of UVA students—part of a multipronged strategy for monitoring and containing the virus in the University community.

More globally, a COVID-19 surveillance dashboard (covid19.biocomplexity.virginia.edu) has been the ongoing work of a large team based at UVA's Biocomplexity Institute, which provides tools for users to visualize global surveillance data on the pandemic. The main goal of the dashboard is to achieve "situational awareness," explains Dr. Bryan Lewis, a computational epidemiologist and research associate professor in the Biocomplexity Institute, who tracks outbreaks of communicable diseases around the globe. "You have to know where the disease is, and you need to know the dynamics of how it is changing over time to offer any kind of educated guess as to what the future might be."

And what is that future? Lewis and Dr. Madhav Marathe, another member of the dashboard team and director of the Network Systems Science and Advanced Computing (NSSAC) Division of the Institute, used anonymized, aggregated data from digital devices to track how human mobility patterns have correlated with the pandemic. Their team's analysis affirmed that the lockdowns of early spring effectively reduced the virus's spread. The researchers' analysis found that even a one-week delay would have doubled the number of U.S. cases seen by the end of July.

However, as people became increasingly active after Memorial Day, mobility patterns proved less predictive. "We think that this is due to important changes people have made in how they interact and as they follow rules of safe interactions," Marathe explains.

In other words, individual behaviors and local policies—such as mask-wearing and adhering to social distancing guidelines—are much harder to capture in data, and now seem to be playing a more significant role in how the virus spreads. "Action by one affects others," Marathe says. "It's important that we collectively work together to address the problem and control the pandemic."

In a paper published in April, co-authors Dr. Anton Korinek, associate professor in the Darden School of Business and in the economics department, and Dr. Zach Bethune, assistant professor in the economics department, sought to put an actual number on those actions, analyzing the economic cost of lockdown versus the benefits of mitigating the spread of the pandemic. The economists said they were surprised to find that greatest benefit came not just from flattening the curve of infections but from

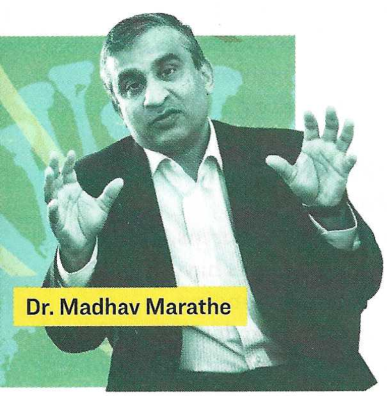
working to suppress the virus to the point at which a "smart containment policy" of test, trace and isolate would be fully effective, Korinek explains. "That is the strategy that not only saves the most lives but also hurts the economy the least," he says, "because once you are in control of the virus, people can go back to a normal life again." And analyzing the cost of a self-interest approach—doing what you want regardless of the potential negative effects on others—versus collective commitment to a smart containment strategy, the researchers determined that "the difference between the two strategies would amount to an extra loss of $10 trillion for the U.S. economy," Korinek says.

THE LONG FIGHT

What the final toll of this pandemic will be—in lives lost and social and economic costs—remains unknown, and overcoming it will demand a sustained and multifaceted effort. At the same time, by marshaling the exponential strength of their collective expertise, UVA researchers are contributing both to the fight against a devastating outbreak and to a large and rapidly expanding global reserve of knowledge, one that not only will help curb this pandemic but also may help arm the world against future threats.

"When you see something that threatens humanity," researcher Zeichner says, "and you think you might have some insights or techniques that could potentially address that, you are almost beholden to take a deep breath and jump in and see if you can help out."

Caroline Kettlewell is a science writer and editor based in Richmond, Virginia.



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