The day after Christmas last year, as COVID-19 cases burgeoned at Cedars-Sinai Medical Center in Los Angeles, a colleague asked Eric Vail, MD, whether a virus variant first detected in the UK was fueling the surge. Vail, the hospital’s director of molecular pathology, didn’t know. So the colleague, whom Vail describes as a high-level person at the hospital, asked him to look into it.

Less than a week later, Vail was close to finding an answer. “The sequencer was loaded on New Year’s Eve at 11 PM,” he recalled in a recent interview.

The results of his team’s genomic sequencing study surprised them. Out of a random selection of 185 virus samples collected from patients between November 22 and December 28, none matched B.1.1.7, the so-called UK variant. The smaller of 2 main clusters was the predominant SARS-CoV-2 strain. But the larger cluster, making up 36% of the samples, was something different—a “new variant that is homegrown California,” Vail said.

The variant, now known as B.1.429, has 5 mutations, including 1 that has been associated with resistance to certain monoclonal antibody therapies. Functional studies are underway to define B.1.429’s clinical characteristics, including its ability to spread among people. But its quick ascent in California could argue for increased transmissibility. In Vail’s view, the variant likely contributed to the magnitude of Southern California’s peak around the holidays.

Vail said the serendipitous nature of his team’s findings, published online in JAMA on February 11, speaks to the sporadic way that virus variant detection has operated in the US for most of the COVID-19 pandemic.

Until late last fall, public health departments had no federal mandate or additional funding to sequence samples, although new variants were an inevitability, according to Kelly Wrobleswki, MPH, director of infectious diseases at the Association of Public Health Laboratories. Lacking that momentum of laboratories aimed at coordinating genomic sequencing and surveillance in the US, public health experts have called for improved variant surveillance since at least last summer, she noted in an interview.

In July, Phelan and collaborators authored a National Academies of Sciences, Engineering, and Medicine (NASEM) report that recommended the implementation of SARS-CoV-2 genomic sequencing on a national scale to address the US’s “passive” and “reactive” surveillance thus far.

Earlier that month, the CDC had launched SPHERES (SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance), a consortium of laboratories aimed at coordinating national scale to address the US’s “passive” and “reactive” surveillance thus far.

In February, President Joe Biden announced the CDC’s investment of nearly $200 million to “identify, track, and mitigate” emerging SARS-CoV-2 variants. “We’re quickly infusing targeted resources here because the time is critical when it comes to these fast-moving variants,” Carole Johnson, a member of the White House COVID-19 Response Team, said during a February 17 press briefing.

A $1.7 billion appropriation for genomic sequencing and surveillance in the American Rescue Plan Act will bolster the effort. Increasing genomic sequencing capacity won’t happen overnight, however, recently appointed CDC Director Rochelle Walensky, MD, MPH, cautioned in a JAMA livestream interview: “It’s going to be a dial, not a switch.”
national sequencing. Led by the CDC's Advanced Molecular Detection program, SPHERES involves about 170 institutions, including academic centers, industry, nongovernmental organizations, and public health agencies. But according to Wroblewski, the initiative in practice amounted to "a group of experts sharing information." Although the program has been valuable, she said, it suffered from the vacuum of federal guidance: "There weren't marching orders."

Without a national directive to conduct whole genome sequencing, cash- and time-strapped state and local public health departments, sometimes working with academic partners, took up the task on a case-by-case basis. "Many of them have been operating on a shoestring budget or had staff that are themselves depleted and exhausted over the past year," Hana Akselrod, MD, MPH, an assistant professor in the division of infectious diseases at the George Washington University School of Medicine and Health Sciences, said in a media briefing. The result: some states provided thousands of sequences, others none. "If you didn't have anybody in that state government saying surveillance for the evolution of the virus is a priority, then it didn't happen," Wroblewski said.

Meanwhile, with no monetary incentives to conduct sequencing, large diagnostic laboratories discarded positive SARS-CoV-2 samples without analyzing them, Gigi Kwik Gronvall, PhD, a senior scholar at the Johns Hopkins Bloomberg School of Public Health's Center for Health Security, said in an interview. "We were tracking variants as a way of disease control wasn't what we were doing." Georges C. Benjamin, MD, executive director of the American Public Health Association, said in an interview. "We were tracking variants as intellectual curiosity."

A more robust national genomic surveillance program almost certainly would have flagged B.1.429 sooner, Vail said. (His results were first posted to the preprint server medRxiv in January.) Searching through GISAID, his team discovered 1 infection with the variant virus in Los Angeles County in July 2020, and then 4 in Southern California last October. B.1.429, initially called CAL.20C, has been gaining ground rapidly since then. By January 22, it made up 35% of California's SARS-CoV-2 sequences uploaded to the database this year, and it had spread to 25 other states as well as to other countries.

In an email, a California Department of Public Health spokesperson said the state is working with the CDC, local public health departments, and genomic sequencing laboratory partners to learn more about this and other variants, "including if they have any differences in how easily they spread or any implications on potential difference in response to treatment or vaccination."

B.1.429 is a "variant of interest" to the CDC, Vail said, but 3 others have risen to the level of "variants of concern." In addition to B.1.1.7, these include B.1.351, originally discovered in South Africa, and P1, first detected in travelers from Brazil. By March 16, the CDC had reported 4686 B.1.1.7 cases in 50 US jurisdictions, 142 B.1.351 cases in 25 states, and 27 P1 cases in 12 states. But the counts are based on a still-small sample. They therefore may not reflect the true proportion of variants in the overall circulating virus—a major surveillance goal—according to Wroblewski.

Contact tracing revealed that individuals who did not wear masks and who attended in-person gatherings contributed to the variants' spread, Walensky said during a February 3 press briefing. Cases of B.1.1.7—which is 30% to 80% more contagious than the dominant strain—are doubling every 10 days, according to research posted on February 7 to medRxiv, which has not been peer-reviewed. Modeling by the study's researchers and the CDC suggest that the variant will likely have become the predominant strain in the US by late March.

Research from the UK suggests that the B.1.1.7 variant may carry an increased risk of death. Additionally, in a small number of UK cases, the variant has acquired the spike protein mutation E484K. This genetic change, also found in the 2 other variants of concern, could reduce vaccine efficacy and is considered among the most important SARS-CoV-2 mutations. The first case of B.1.1.7 with E484K has been detected in the US, Walensky told the press in February.

Ramping Up

As surveillance expands in the weeks and months ahead, the picture of virus variants—including new homegrown strains—should begin to take shape. In November 2020 the CDC launched the National SARS-CoV-2 Strain Surveillance (NS3) program to increase sequencing volume and representativeness. At the time, the expectation was that by January, each state would provide 10 samples to the CDC for sequencing every 2 weeks, amounting to an average 250 weekly sequences.

In late January, the CDC scaled up to receive about 750 samples per week from public health laboratories, with each state's individual responsibility determined by its population size. "I think once we have more sequencing,... we'll have a better idea as to how many variants there are and what proportion are out there," Walensky said during a February 8 press briefing.

To ensure that monitoring is nationally representative, the CDC says the specimens should capture a variety of demographic and clinical characteristics and geographic locations. States also have been instructed to notify the agency about B.1.1.7 cases, and each state can send up to 20 specimens every week from confirmed B.1.351 and P1 variant cases, other variants, or "vaccine breakthrough" infections for further characterization.

In addition, the CDC has contracted with large commercial laboratories to sequence at least 6000 samples every week, and 7 academic institutions are receiving funding to assist public health departments in their
efforts. To increase their in-house sequencing capacity, the departments themselves received $15 million in December that Wroblewski characterized as a small but welcome amount.

Phelan said the increased focus on sequencing may not have happened without the rise of concerning variants. “I’m not sure we’d have the same attention, even with a very good new administration, unless we also had this public health urgency that is occurring,” she said.

But now that variant surveillance is in the spotlight, experts say that increasing local sequencing capacity is a critical priority. “We really need to bolster this capability in order to meet the challenges from new variants of the virus,” Akselrod said.

“Right now it’s 2- to 3-plus weeks for us to get sequencing results back” from the CDC, a state health department epidemiologist who did not want to be identified, told JAMA. “There’s no window for meaningful public health action to control potential clusters or transmission.”

Walensky acknowledged in the February JAMA livestream that “we’re not where we need to be” with surveillance. According to the CDC’s National Genomic Surveillance Dashboard, more than 174,000 US sequences have been submitted to GISAID. There’s no consensus on what number of sequences is ideal. Modeling by genomic sequencing company Illumina Inc, suggests that 5% of tests positive for SARS-CoV-2 must be sequenced to detect a new variant early on, before it causes more than 1% of cases. Some US experts are arguing for more volume—even up to 30% of cases.

The recent federal funding boost should increase US sequencing capacity from about 7000 to about 25,000 samples every week. Analyzing all the data will present a considerable challenge. To that end, Walensky and Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, recently unveiled a new coordinated effort to rapidly characterize variants of concern and their effects on diagnostic, therapeutic, and vaccine effectiveness. The SARS-CoV-2 Interagency Group includes the CDC, the National Institutes of Health, and the US Food and Drug Administration, among other federal bodies.

As Gronvall put it, “It’s really just a matter of putting political will behind it and getting it done.”

That will has long been missing in the US, Benjamin said: “We’re juggling resources all the time. Our surveillance systems are outmoded and our data-reporting systems are truly out of date.”

The lack of prioritization for strain surveillance thus far, he said, is “just a manifestation of the level of disrepair of our overall public health system.”

Note: Source references are available through embedded hyperlinks in the article text online.