

# Coronavirus tests: researchers chase new diagnostics to fight the pandemic

*Nature* examines how viral diagnostic tests work, why testing has varied around the world and the CRISPR-based tests under development to fight COVID-19.

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Diagnostic tests for COVID-19 have loomed large in the ongoing coronavirus pandemic as an essential tool to track the spread of the disease.

The World Health Organization (WHO) has repeatedly urged health agencies to make testing for the novel coronavirus a top priority in their response to the pandemic, but the international response has been uneven. A combination of regulation and readiness has allowed some countries, such as South Korea and Singapore, to swiftly deploy hundreds of thousands of tests — but elsewhere, health agencies have struggled to get up to speed.

Meanwhile, in the United States, with hospitals backlogged, and corporate manufacturers weeks late to the game, university research labs had stepped in to develop their own diagnostics to meet the crushing need.

Here, *Nature* examines how viral diagnostic tests work, how some countries managed to ramp up testing while others stalled, and what new tests researchers want to develop to fight the pandemic, including those that use the gene-editing tool CRISPR.

## What's in a test

Most testing for COVID-19 is currently done on viral genetic material from nose and throat swabs, using a workhorse tool of molecular biology known as reverse transcription polymerase chain reaction (RT-PCR).

The test works by amplifying a specific genetic sequence in the virus. Short complementary sequences known as primers help to get the copying started. But PCR can only detect virus while it is present in a person. It doesn't reveal much about a resolved infection. It's also known to sometimes produce false positives if reagents in a lab become contaminated.

Labs worldwide have customized their PCR tests for SARS-CoV-2, using different primers targeting different sections of the virus's genetic sequence.

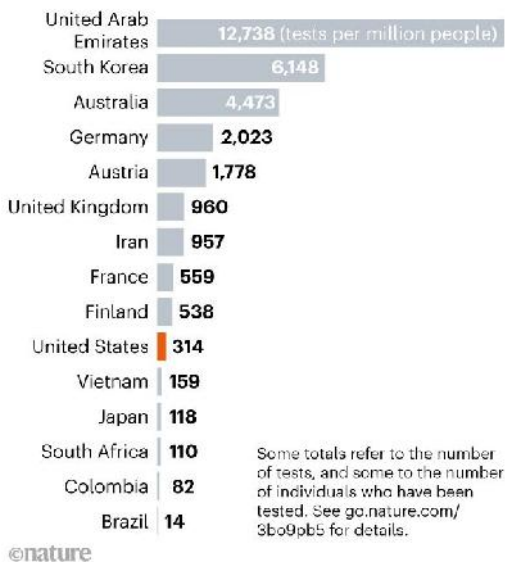
## Who got to it quickly?

Several countries have been able to test a huge number of people (see [Unequal testing](#)). South Korea [responded speedily](#) and effectively after the first cases emerged there in late January, deploying a combination of rapid testing and monitoring people who were in

contact with those who had tested positive. Regulations enacted after a 2015 outbreak of Middle East respiratory syndrome allowed for rapid approval of a version of the WHO's test, and four companies were scaling it up to test a total of 10,000 people a day, according to [reporting by the independent newsroom ProPublica](#).

### UNEQUAL TESTING

Some countries have been slow to scale up testing for the novel coronavirus that causes COVID-19. In estimates of tests provided per million people in the population, the United States has lagged far behind others.



Source: Our World in Data

As a result, says Angela Rasmussen, a virologist at Columbia University in New York City, authorities in South Korea were able to identify mildly ill and asymptomatic people and stop them from spreading the virus. “They haven’t had to do these social distancing measures in such a broad way,” she says.

Singapore developed a test even as the coronavirus was emerging in China, says Vernon Lee, director of Singapore’s Communicable Diseases Division at the Ministry of Health, and was early to look for cases. Hospital labs got the green light early on to use other approved PCR tests, with the provision that they validated their first cohort of results with a national lab. They also focused testing on the most essential cases — people with pneumonia, for example, or people who were at high risk in other ways.

Key logistics were put in place — including lab capacity, trained people, reagents and tools — after the 2003 outbreak of another coronavirus, known as SARS-CoV-1. “In Singapore we have been preparing and strengthening the entire system since SARS. This is not something we created because of COVID-19,” says Lee.

## Who responded slowly?

Health experts have slammed the United States for its slow response to the pandemic, particularly the poor availability and speed of testing, which specialists say has allowed the virus to spread undetected, and required strict social distancing measures to contain it.

US health officials acknowledged the gap. At a congressional hearing on 12 March, National Institute of Allergy and Infectious Diseases director [Anthony Fauci said](#) that the country was “failing” in its ability to test people, and explained that the United States was not set up to offer tests at the pace currently needed.

Kenneth Bernard, who has advised former US presidents on biodefence, says that a White House pandemic response coordinator or office might have eased communications across agencies and developed a plan to scale up testing. But the person in that role [left](#) President Donald Trump’s National Security Council in May 2018. “In this case, it was the scaling that was the big problem — it’s one thing to make a reference lab test at [the Centers for Disease Control and Prevention (CDC)], it’s another thing to make millions of lab tests,” Bernard says.

Rigid regulations for new diagnostics were a further hurdle — initially, the only approved US test was created by the CDC and found to be flawed. And only state-run health departments were allowed to use it. The US Food and Drug Administration (FDA) didn’t loosen those rules until the end of February, and didn’t approve commercial labs to run tests until mid-March. Only on 21 March did US regulators approve a rapid test that can be completed without having to send samples to a lab, which they expect will be ready by the end of this month.

As the federal response lagged, virology research labs at the University of Washington in Seattle emerged as the [first major US testing operation](#), where researchers adapted the WHO protocol to work with reagents and platforms they had to hand. Dozens of other labs and research consortia have now followed suit.

“The administration made a decision to significantly limit the access [to tests] in the beginning,” says Joshua Sharfstein, former principal deputy commissioner at the FDA. “If you could go back in time and tell the FDA in mid-January that you really are going to need a million tests pretty quickly, they would have picked a different strategy.”

## **What about a serological test?**

A big goal is to develop a serological test — one that can detect past viral infections by looking for antibodies someone has produced to fight the virus.

Such a test could show the extent of viral spread in a community and provide useful public-health information.

“Right now it’s clear we’re only seeing the tip of the iceberg: people who are so sick they need hospitalization or intensive care,” says Robert Garry, a virologist at Tulane University School of Medicine in New Orleans, Louisiana. “What’s concerning is the notion that there’s a lot of [inapparent or mild disease](#) out there.”

Several groups, including Garry’s, are working towards such a test. A group including researchers at Icahn School of Medicine at Mount Sinai in New York City [described another](#) in a non-peer-reviewed preprint posted on the medRxiv server on 18 March. “We don’t expect any hurdles to making these assays — just some tinkering to do,” says Garry.

A group in Singapore used serological tests to aid in contact tracing, but at the time the test had not been broadly validated for clinical use. “We believe this is the first time in the world where these particular tests have been used in this context,” said Danielle Anderson, a virologist at the Duke-NUS Medical School in Singapore, in a February press conference.

## **What other tests are on the horizon?**

There’s still room for innovation. Groups led by two of the biggest names in CRISPR are each working on tests that take advantage of the popular gene-editing technique to improve testing.

At the University of Washington School of Medicine, virologist Keith Jerome’s group is validating and optimizing the [SHERLOCK](#) test co-developed by CRISPR pioneer Feng Zhang at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. Zhang says he has sent some 1,600 kits to a dozen labs around the world.

And Mammoth Biosciences, a biotechnology company in South San Francisco, California, co-founded by CRISPR pioneer Jennifer Doudna at the University of California, Berkeley, is working to validate a CRISPR-based approach called [DETECTR](#) for coronavirus.

The techniques use the CRISPR machinery’s ability to recognize specific genetic sequences and cut them. In the process, it also cuts a ‘reporter’ molecule added to the reaction, which reveals the presence of viral genetic material relatively quickly.

“Every single time we have an outbreak, we’re one step behind in that we don’t have a rapid diagnostic to detect that new organism,” says Charles Chiu, an infectious-diseases physician at the University of California, San Francisco, who is working with Mammoth Biosciences. “The key advantage is that a CRISPR reaction is incredibly specific and can be done in 5–10 minutes.”

Garry, at Tulane, is hopeful about such advances. “It’s a powerful technique. I’ve seen it work in Zika and a few other viruses,” he says. “If anyone can come up with a way to blunt the impact of this, let’s make it happen.”