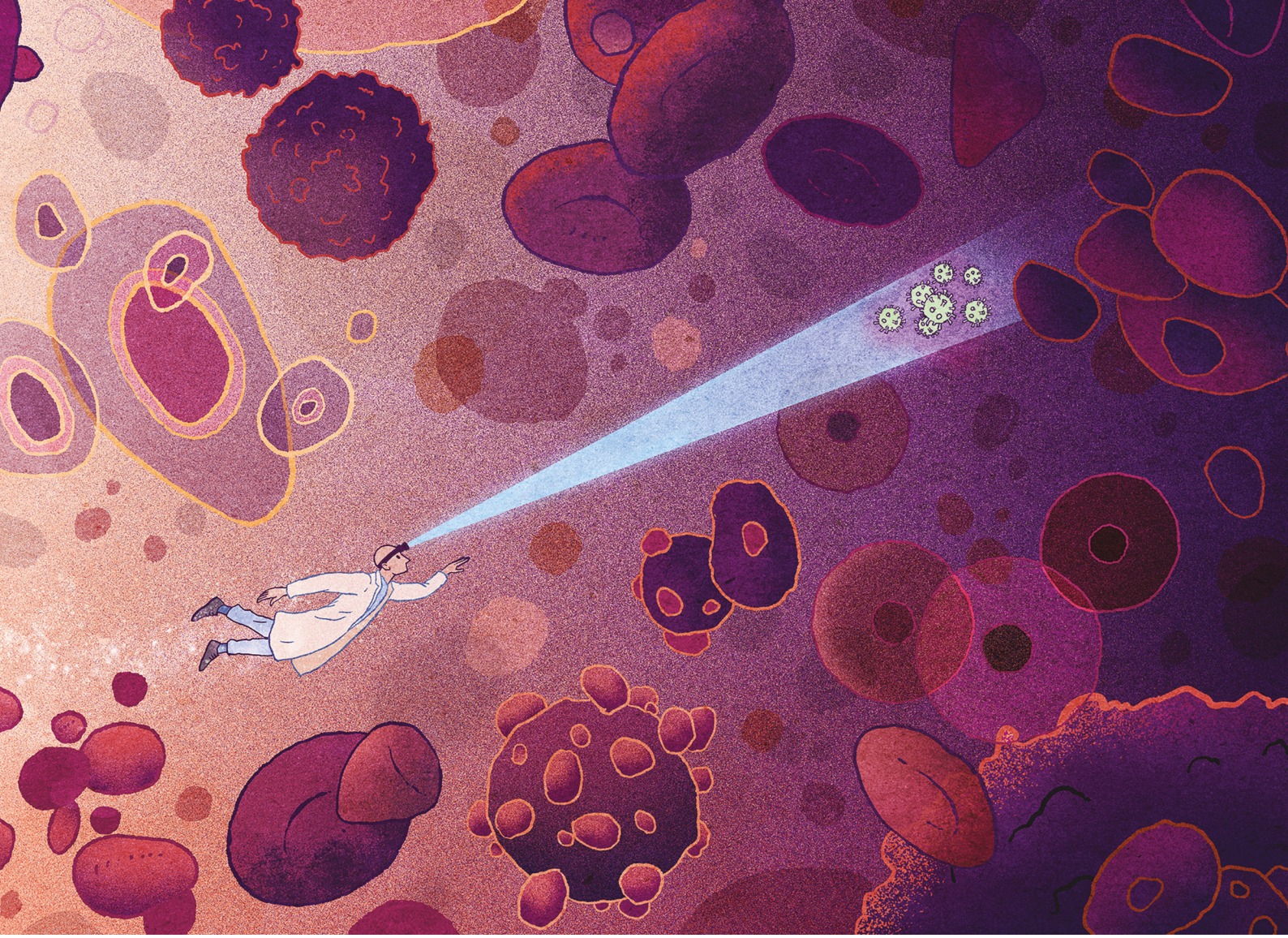

ANTOINE DORÉ

DIAGNOSTICS

A sticking point for rapid flu tests?

Rapid molecular tests for influenza are as quick as older on-the-spot tests and much more accurate. But that might not be enough to drive widespread adoption.

BY ELIZABETH SVOBODA

It begins like many other tests at the doctor's surgery: a quick swipe inside the nostrils with what looks like a giant cotton bud, which is then plunged into medium designed to keep the sample fresh.

But it is what happens next that makes the Xpert Xpress molecular influenza test different. A technician places the sample into the machine, which then makes copies of any genetic information it contains. Fluorescence detectors scan for the presence of specific genes. In less than half an hour, the doctor knows with near certainty which influenza virus — if any — is present in the patient's respiratory tract.

The developer of the Xpert Xpress, Cepheid based in Sunnyvale, California, thinks that rapid molecular tests like this will transform flu diagnosis. And other pharmaceutical companies such as Abbott, based in Chicago, Illinois, and Roche of Basel, Switzerland, have created similar diagnostic tools. Since these tests were launched in the United States several years ago, medical providers have raved about their speed and accuracy, which they say makes treatment decisions easy and reduces the burden of disease. But a few problems, including high costs and the risk of sample contamination, make it hard to predict whether these tests will become the standard diagnostic tool.

INCONSISTENT RESULTS

Influenza cuts a seasonal swath of destruction around the world, leading to more than 200,000 hospitalizations and 30,000 deaths each year in the United States alone. The virus is highly contagious but treatable, so it is important to identify it as quickly and as accurately as possible. Today, many people who visit a clinic with flu symptoms receive a rapid influenza diagnostic test (RIDT). Unlike molecular tests, such as the Xpert Xpress, RIDTs contain an antibody that sticks

to an antigen protein on the flu virus, typically changing colour to show a positive result.

The main advantage of RIDTs is their speed — they produce a result in less than 30 minutes. But they sometimes deliver poor results. "You need a lot of flu to be there, and if there's not enough, you'll get a negative result," says Neil Anderson, who studies infectious diseases at the Washington University School of Medicine in St Louis, Missouri. Children tend to shed a lot of virus particles, he adds, but some adults do not produce enough to give a positive test result even if they have severe symptoms.

False-negative results are therefore a big problem. In one clinical study[1] involving 600 people, 77% of those with influenza initially received an incorrect negative result from a RIDT. Newer RIDTs have been developed to address such accuracy issues but several researchers say that even these are still not sensitive enough to be reliable. Another type of quick influenza test known as an immunofluorescence assay has similar reliability problems.

Rapid molecular tests, however, use a different approach. Rather than relying on finding sufficient quantities of antigen, they instead copy long stretches of viral genetic code contained in the sample. Flu viruses have RNA so the tests first immerse the sample in lab-made nucleotides, creating a matching strand of DNA. Multiple rounds of heating and cooling then create many more strands of DNA. This process, called amplification, makes it easy to detect even small quantities of virus. Abbott's rapid molecular test, called ID Now, amplifies the DNA at a constant temperature.

After amplification, fluorescence detectors test whether the genetic sequences match those of known flu viruses. In Cepheid's test, much of this sample processing takes place inside a maze of plastic channels no wider than a poker chip. Within 20–30 minutes, the machine reveals not just whether a person has flu, but which strain and subtype of the influenza virus is causing the illness.

A DEFINITIVE RESULT

There is widespread consensus that rapid molecular tests for influenza are much more accurate than RIDTs. A 2017 meta-analysis[2] that pitted RIDTs against rapid molecular tests found that both were more than 98% accurate in identifying people who did not have flu; the big difference was in people who did. Using RIDTs, more than 45% of people with flu received false negatives, compared with just 8% using rapid molecular tests.

Greater accuracy also improves the speed of diagnosis because it eliminates the need for further lab tests, says Esther Babady, a microbiologist at the Memorial Sloan Kettering Cancer Center in New York City. A negative result from an RIDT is treated as merely advisory, she says: "They would still send the sample to the clinical lab." The molecular tests change that protocol. "With the molecular tests it's done," she says. "It doesn't require additional testing."

A rapid, accurate diagnosis allows doctors to prescribe treatment faster, which brings noticeable benefits to patients. In a study[3] of more than 1,400 people with flu, those who took antiviral medication within 12 hours of the onset of fever had three fewer sick days than those who started medication after 48 hours. "Getting treatment earlier is going to lessen symptoms," Anderson says.

A 2019 study[4] compared the outcomes of pregnant women with flu-like symptoms at two time points: before rapid molecular flu tests were introduced and afterwards. In women with flu, hospitalization rates were 83% before the tests were introduced but only 38% in those given the rapid molecular tests, largely because these women were given effective treatment sooner. Women given the new tests also received fewer than half as many antibiotic prescriptions as those who did not, because there is no benefit in prescribing antibiotics for viral diseases such as flu once they are diagnosed.

As well as streamlining treatment, rapid molecular tests could also reduce the rate of flu transmission, says Ritu Banerjee, who studies antimicrobial drugs at the Mayo Clinic in Rochester, Minnesota. "If patients are diagnosed with influenza quickly using an accurate test, they will spend less time in health-care settings waiting for test results," Banerjee says, reducing the opportunity for the virus to spread in busy waiting rooms. People given a quick, definitive diagnosis might also be more likely to avoid going to work or school, she adds, lowering the odds of transmission even further.

SLOW UPTAKE

Despite the benefits of rapid molecular tests, hospitals and health systems have been slow to buy them. In 2016, the World Health Organization found that only 15% of hospitals were using rapid molecular tests to diagnose flu. One of the biggest problems is the cost, Babady says. Whereas RIDTs cost about US$15 per test, rapid molecular tests can cost up to $45 — a financial burden that many health-care providers, both public and private, would struggle to bear. Rapid molecular testing also requires a hefty initial investment in a testing platform, such as Cepheid's GeneXpert Xpress or Abbott's ID Now. "Right now, everyone has to make the case to their hospital system because of the added costs," Anderson says.

"With the molecular tests it's done. It doesn't require additional testing."

Some researchers argue that the cost of rapid molecular testing would be paid for by reductions in flu complications and the resulting unnecessary treatments. A team at Newcastle University, UK, concluded[5] that adopting rapid molecular tests would save the UK National Health Service about £240,000 ($295,000) each year for every 1,000 people with flu-like symptoms, largely because patients who are quickly and correctly diagnosed consume fewer hospital resources. When improved patient outcomes and reduced resource use are considered, "the cost savings almost come to the point of balancing out", Anderson says, and could result in a cost benefit over time.

ABBOTT LABORATORIES

Rapid molecular tests, such as Abbott's ID Now, quickly and accurately identify viruses in a sample.

Another problem that has slowed the adoption of rapid molecular testing is the risk of contamination. Rapid molecular tests are designed to detect and magnify snippets of viral RNA but their high sensitivity means they can post an inaccurate result if a lab technician has flu, for example, or if a sample is mishandled. "Monitoring that is something we do consistently in the clinical lab," Babady says. "In a busy emergency room, it becomes much more complicated."

Babady is not sure whether rapid molecular tests will ever become commonplace. But Anderson thinks that early institutional adopters — such as his own medical centre at Washington University — could encourage other health providers to try the tests, as they pile up more and more data illustrating how the test results affect patient outcomes and hospitals' bottom lines.

And conventional health systems are not the only potential customers. As the tests become more widely accepted, Anderson says, "you're going to see them used outside hospital settings — at pharmacies, potentially even at a nurse's room in a high school."

The unpredictability of the influenza virus's evolution could ultimately be what nudges fine-tuned rapid diagnostics into routine use. If a virulent flu strain lays waste to schools and workplaces in a few years, a nearly instant test that offers accurate results might just be too compelling a prospect to ignore. ■

Elizabeth Svoboda *is a science writer in San Jose, California.*

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