### **GENERAL / HEALTH**

# *COVID-19 rapid tests can breed confusion – here's how to make sense of the results and what to do, according to 3 testing experts*

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As fall temperatures set in, cold and flu season gets into full swing and holiday travel picks up, people will undoubtedly have questions about COVID-19 testing. Is this the year people can finally return to large gatherings for traditional celebrations? What role does testing play when deciding whether to go out or stay home?

Adding to the confusion are personal accounts of people who are experiencing confusing or seemingly contradictory test results.

We are part of a team that has developed and tested SARS-CoV-2 tests since the early days of the pandemic. Additionally, some of us are infectious disease specialists with decades of experience.

Our insights from both the cutting edge of rapid testing research as well as our clinical perspectives from working directly with patients can help people figure out how to make the best use of rapid tests.

Multiple negative tests, then a positive - why?

SARS-CoV-2, the virus that causes COVID-19, takes time to build up in the body, like many other viruses and bacteria that cause respiratory illness. Typically it takes two to three days to test positive after exposure. Our research group has demonstrated this, as have others.

Rapid tests detect parts of the virus that are present in the sample collected from your nose or mouth. If the virus has not replicated to a high enough level in that part of your body, a test will be negative. Only when the amount of virus is high enough will a person's test become positive. For most omicron variants in circulation today, this is one to three days, depending on the initial amount of virus you get exposed to.

Why do some people test positive for extended periods of time?

It's important to clarify which type of test we're talking about in this situation. Studies have shown that some people can test positive for a month or more with a PCR test. The reason for this is twofold: PCR tests are capable of detecting extremely small amounts of genetic material, and fragments of the virus can remain in the respiratory system for a long time before being cleared.

When it comes to rapid tests, there are reports that some people test positive for an extended period of time with the current strains of the omicron variant compared with earlier variants. Several studies show that most people no longer test positive after five to seven days from their first positive test, but between 10% to 20% of people continue to test positive for 10 to 14 days.

But why it takes longer for some people to clear the virus than others is still unknown. Possible explanations include a person's vaccination status or the ability of one's immune system to clear the virus.

In addition, a small number of people who have been treated with the oral antiviral drug Paxlovid have tested negative on rapid antigen tests, with no symptoms, only to "rebound" seven to 14 days after their initial positive test. In these cases, people sometimes experience recurring or even occasionally worse symptoms than they had before, along with positive rapid test results. People who experience this should isolate again, as it has been shown that people with rebound cases can transmit the virus to others.

Why do I have COVID-19 symptoms but still test negative?

There are several possible explanations for why you might get negative rapid tests even when you have COVID-like symptoms. The most likely is that you have an infection of something other than SARS-CoV-2.

Many different viruses and bacteria can make us sick. Since mask mandates have been lifted in most settings, many viruses that didn't circulate widely during the pandemic, like influenza and Respiratory Syncytial Virus, or RSV, are becoming common once again and making people sick.

Second, a mild COVID-19 infection in a person that's been vaccinated and boosted may result in a viral level that's high enough to cause symptoms but too low to result in a positive rapid test.

Finally, the use of poor technique when sampling your nose or mouth may result in too little virus to yield a positive test. Many tests with nasal swabbing require you to swab for at least 15 seconds in each nostril. A failure to swab according to package instructions could result in a negative test.

Our previous studies show that if you are symptomatic and do two rapid antigen tests 48 hours apart rather than just one, you are more highly likely to test positive if you are infected with SARS-CoV-2.

Self-swabbing: It sounds kind of cringy, but it's really not so bad.

Do rapid tests work against the current strains of SARS-CoV-2?

Multiple studies have examined the performance of rapid tests against the omicron variant.

Fortunately, these studies show that all the rapid tests that have been authorized for emergency use by the U.S. Food and Drug Administration detect the current omicron variants just as well as previous variants such as alpha and delta. If a symptomatic person tests positive on a rapid test, they likely have COVID-19. If you are exposed to someone who has COVID-19, or have symptoms but receive a negative test, you should take another test in 48 hours. If you then test positive or if your symptoms get worse, contact your health care provider.

What's the best way to use and interpret rapid tests before gatherings?

regenerate. It can completely regrow itself even after two-thirds of its mass has been surgically removed. But damage from medications, alcohol abuse or obesity can eventually cause the liver to fail. Currently, the only effective treatment for end-stage liver disease is transplantation.

However, there is a dearth of organs available for transplantation. Patients may have to wait from 30 days to over five years to receive a liver for transplant in the U.S. Of the over 11,600 patients on the waiting list to receive a liver transplant in 2021, only a little over 9,200 received one.

But what if, instead of liver transplantation, there were a drug that could help the liver regenerate itself?

I am the founding director of the Pittsburgh Liver Research Center and run a lab studying liver regeneration and cancer. In our recently published research, my team and I found that activating a particular protein with a new medication can help accelerate regeneration and repair after severe liver injury or partial surgical removal in mice. Testing remains an important tool to identify infected people and limit the spread of the virus. It's still a good idea to take a rapid test before visiting people, especially older people and those with weakened immune systems.

If you believe you may be infected, the FDA recently updated their testing guidance largely based on data our lab collected. The testing regimen most likely to identify if you're infected is to take two tests 48 hours apart if you have symptoms. If you don't have symptoms, take three tests, one every 48 hours.

Does a positive test mean you can spread COVID to others?

The Centers for Disease Control and Prevention recommends that if you test positive for COVID-19, you should stay home for at least five days from the date of your positive test and isolate from others. People are likely to be most infectious during these first five days. After you end isolation and feel better, consider taking a rapid test again.

If you have two negative tests 48 hours apart, you are most likely no longer infectious. If your rapid tests are positive, you may still be infectious, even if you are past day 10 after your positive test. If possible, you should wear a mask. Multiple studies have shown a correlation between the time an individual tests positive on a rapid test and when live virus can be collected from a person, which is a common way to determine if someone is infectious.

Testing is still an important tool to keep people safe from COVID-19 and to avoid spreading it to others. Knowing your status and deciding to test is a decision that individuals make based on their own tolerance for risk around contracting COVID-19.

People who are older or at higher risk of severe disease may want to test frequently after an exposure or if they have symptoms. Some people may also be worried about having COVID-19 and transmitting it to others who may be at higher risk for hospitalization. When combined with other measures such as vaccination and staying home when you're sick, testing can reduce the impact of COVID-19 on all of our lives in the coming months. (The CONVERSATION)

to zone 1, significantly limiting the liver's overall function. This finding suggests that liver cells experience an ongoing push and pull in gene activation that can modify their functions, and Wnt is the master regulator of this process.

Eliminating the two Wnt genes from endothelial cells also completely stopped liver cell division, and thus regeneration, after partial surgical removal of the liver.

Liver regeneration after Tylenol overdose

We then decided to test whether a new drug could help recover liver zonation and regeneration. This drug, an antibody called FL6.13, shares similar functions with Wnt proteins, including activating liver regeneration.

Over the course of two days, we gave this drug to mice that were genetically engineered to lack Wnt2 and Wnt9b in their liver endothelial cells. We found that the drug was able to nearly completely recover liver cell division and repair functions.

## Helping the liver regenerate itself could give patients with end-stage liver disease a treatment option besides waiting for a transplant

Satdarshan (Paul) Singh Monga Professor of Pathology and Medicine, University of Pittsburgh Health Sciences The liver is known for its ability to



# DOWN PAYMENT ASSISTANCE



Key players in liver regeneration

The liver performs over 500 key functions in your body, including producing proteins that carry fat through the body, converting excess glucose into glycogen for storage and breaking down toxins like ammonia, among others.

Liver cells, or hepatocytes, take on these many tasks by a divide-and-conquer strategy, also called zonation. This separates the liver into three zones with different tasks, and cells are directed to perform specialized functions by turning on specific genes active in each zone. However, exactly what controls the expression of these genes has been poorly understood.

Over the past two decades, my team and other labs have identified one group of 19 proteins called Whts that play an important role in controlling liver function and regeneration. While researchers know that Wht proteins help activate the repair process in damaged liver cells, which ones actually control zonation and regeneration, as well as their exact location in the liver, have been a mystery.

To identify these proteins and where they came from, my team and I used a new technology called molecular cartography to identify how strongly and where 100 liver function genes are active. We found that only two of 19 Wnt genes, Wnt2 and Wnt9b, were functionally present in the liver. We also found that Wnt2 and Wnt9b were located in the endothelial cells lining the blood vessels in zone 3 of the liver, an area that plays a role in a number of metabolic functions.

To our surprise, eliminating these two Wnt genes resulted in all liver cells expressing only genes typically limited

#### Berke: from front

2017, defeating three challengers.

While mayor, Berke reshaped Chattanooga's city government, adding a Department of Transportation and overhauling the pension plan for the city's police and fire pension funds, cutting \$227 Lastly, we wanted to test how well this drug worked to repair the liver after Tylenol overdose. Tylenol, or acetaminophen, is an over-the-counter medication commonly used to treat fever and pain. However, an overdose of Tylenol can cause severe liver damage. Without immediate medical attention, it can lead to liver failure and death. Tylenol poisoning is one of the most common causes of severe liver injury requiring liver transplantation in the U.S. Despite this, there is currently only one medication available to treat it, and it is only able to prevent liver damage if taken shortly after overdose.

We tested our new drug on mice with liver damage from toxic doses of Tylenol. We found that one dose was able to decrease liver injury biomarkers – proteins the liver releases when injured – in the blood and reduce liver tissue death. These findings indicate that liver cell repair and tissue regeneration are occurring.

Reducing the need for transplantation

One way to address liver transplantation shortages is to improve treatments for liver diseases. While current medications can effectively cure hepatitis C, a viral infection that causes liver inflammation, other liver diseases haven't seen the same progress. Because very few effective treatments are available for illnesses like nonalcoholic fatty liver disease and alcoholic liver disease, many patients worsen and end up needing a liver transplant.

My team and I believe that improving the liver's ability to repair itself could help circumvent the need for transplantation. Further study of drugs that promote liver regeneration may help curb the burden of liver disease worldwide.

million in expenses. He also established a first-of-its-kind program to expand free high-speed internet service to families with children receiving free or reduced lunch at school. In addition, his administration launched efforts to reduce poverty, improve aging infrastructure and increase the use of clean energy.