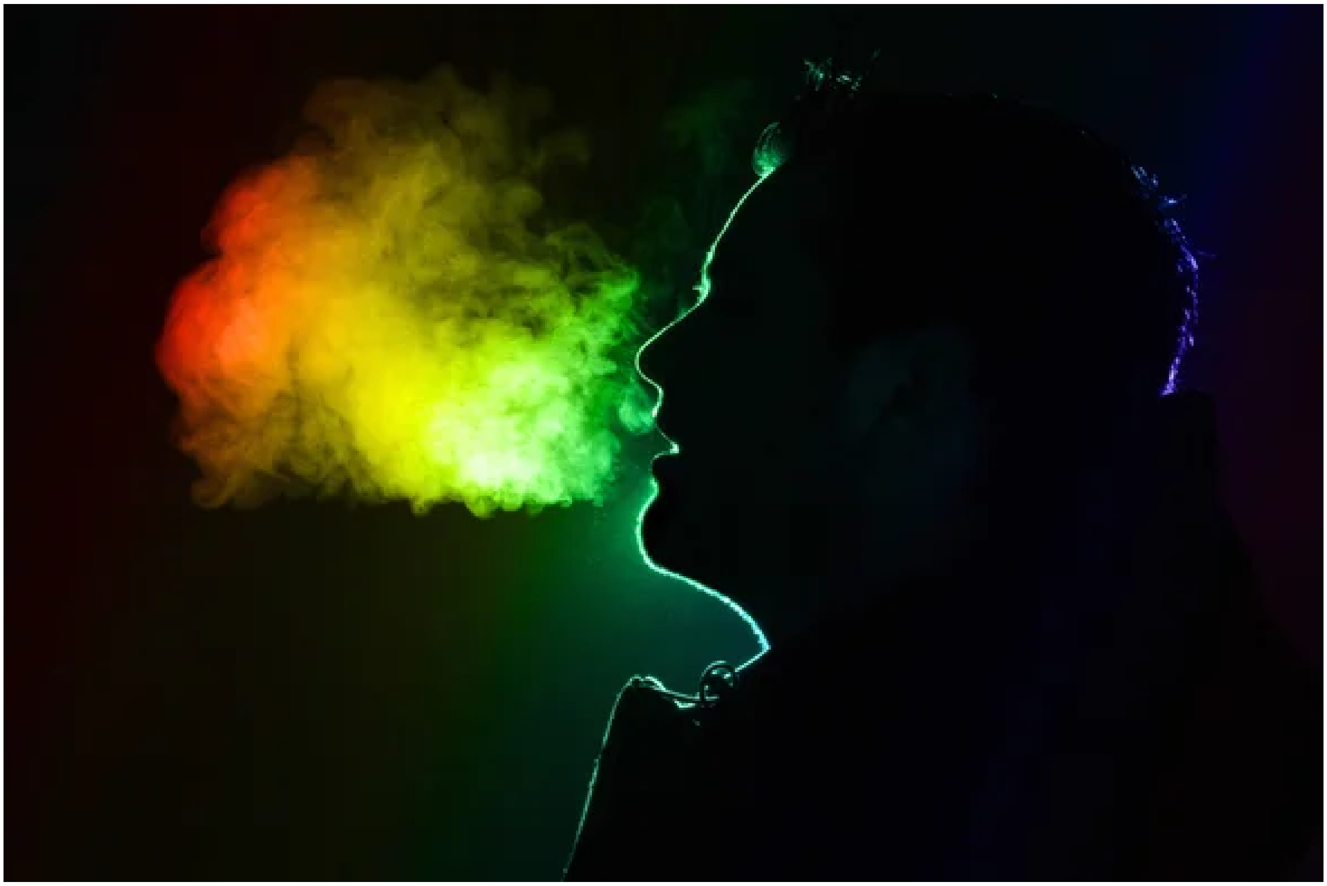
PUBLIC HEALTH

Astronomy Tool Can Now Detect COVID in Breath

Laser-based optical frequency combs, originally developed to time atomic clocks, can also perform fast, noninvasive tests for COVID—and potentially other diseases as well

By Starre Vartan on May 12, 2023



A versatile tool called an optical frequency comb can detect the signatures of diseases like COVID-19 in exhaled breath. Credit: Jasmina81/Getty Images

Astronomers and physicists have long used a laser-based sensor called an "optical frequency comb" to study the material makeup of the cosmos and to make timekeeping more accurate. But the COVID pandemic has pushed this versatile tool from the world of space and physics into health care.

Optical frequency combs are lasers that simultaneously shoot pulses of light at multiple frequencies. Because these superfast pulses are precisely spaced along the light spectrum—from infrared through the visible colors to ultraviolet—they form a series of peaks on a graph of the frequencies that look like the teeth of a comb. This "comb" can be used in a variety of ways. For instance, different types of molecules absorb different colors of light; by detecting which colors of light are absorbed near specific frequencies, the comb can identify specific molecules in an air sample. In a recent study, scientists proved this tool can detect COVID from Breathalyzer-type tests in which subjects simply blow into a tube—potentially paving the way for fast, noninvasive diagnostic tests for a multitude of diseases.

Every time humans exhale, we expel more than 1,000 kinds of trace molecules called volatile organic compounds, or VOCs. "Changes in VOC profiles can be linked to specific health conditions," says Cristina Davis, associate vice chancellor for interdisciplinary research and strategic initiatives at the University of California, Davis. Scholars have known for millennia that certain breath odors are associated with clinical diseases or disorders. References in ancient Greek and Chinese medical literature indicate that doctors used the nose as a diagnostic tool, Davis says. More recently, dogs have been trained to identify some diseases in humans—and laser comb detectors also need training, says physicist Jun Ye, co-author of the new study. "We are training our frequency comb nose using machine learning, and once it's trained, it becomes an electronic dog—with much greater sensitivity," Ye says.

This powerful artificial nose has the advantage of being able to sniff out disease in a way that's quick and noninvasive, says the study's lead author, Qizhong Liang, a graduate student at the University of Colorado Boulder. For maximum accuracy, Liang adds, positive results from the new technology's COVID tests should be followed up with a more reliable PCR test. But for quick screening at airports, concert venues or hospitals, it could beat other methods, such as body temperature scans, that are used to assess potential COVID infection without requiring an invasive nose swab.

Frequency combs can do more than identify molecules. They were originally developed in the 1990s to make more accurate optical atomic clocks, for which the inventors won the 2005 Nobel Prize in Physics. The combs can measure the natural oscillation of atoms so precisely that they have become an indispensable component of atomic clocks, which keep time incredibly well by counting these oscillations. In astronomy, researchers use optical frequency combs to measure the frequencies of light coming from distant stars; disruptions can indicate a star has an exoplanet. In atmospheric science, they have been used to study greenhouse gases. And in 2008 Ye and his colleagues at JILA (a joint institute of the National Institute of Standards and Technology and the University of Colorado Boulder) first proved that the technology could be used as a breath test for disease biomarkers. They set this finding aside, but global events suddenly gave them a very good reason to revive the work in

April 2020. "Using breath as a diagnostic tool has been around for a while," Davis says, "but I think it took a pandemic for research interest to really to really be moved forward."

Shortly after the COVID pandemic began, Ye got a call from his colleagues at the National Academies of Sciences, Engineering, and Medicine and the Air Force Office of Scientific Research. They wanted to know whether his early frequency comb "Breathalyzer" research might help develop a noninvasive COVID test.

Ye and his team started by updating their 2008 technology. The researchers extended the laser comb's frequency range from the near-infrared region of the spectrum into the mid-infrared part—where molecules absorb light two to three times more strongly. That signal boost allowed the researchers to improve the tool's detection sensitivity by 1,000-fold, letting them identify molecules at extremely low concentrations on the scale of hundreds of parts per trillion.

Next, Ye's team collected breath samples from 170 University of Colorado Boulder students and staff from May 2021 to January 2022. Each participant received conventional PCR nasal swab COVID tests, and about half were positive. The researchers then used the frequency comb to analyze light-absorption patterns among molecules in the participants' breath. Applying machine learning to the frequency comb data, combined with the already-known PCR data on who was positive or negative, they found six "discriminating molecules" that indicated COVID infection. The work was described in a paper published in April in the *Journal of Breath Research*.

Liang says AI was key to the project's success because of the vast amount of information the frequency comb gathers when analyzing breath. "Machine learning can analyze all of this data simultaneously and can automatically figure out the best way of utilizing all of that discriminating information to make a prediction model," he says.

Frequency combs aren't the only way to test human breath for COVID or other diseases. Other methods include gas chromatography/mass spectrometry systems such as the InspectIR test, which received emergency use authorization from the U.S. Food and Drug Administration in April 2022. In such chemistry-based techniques, the gas molecules to be analyzed are separated by an inert gas, broken down into fragments and then measured. Davis calls these types of tests the "gold standard," but they require time, specialized training and bulky equipment that limits their use to the lab. Davis has been working on a smaller, portable type of test, an ion mobility spectrometer, which identifies substances based on the mobility of their molecules in an electric field. Other options use chemicals that bind to VOCs to isolate and test them. "There are more than 15 companies working on a variety of these kinds of tests," Davis says.

The frequency comb technology is different, Liang says, because it uses laser spectroscopy and therefore “detects the molecules in breath in a nondestructive way.” By this he means the comb does not cause a sample to degrade or create any unwanted by-products, as breath tests that rely on chemical reactions can. Frequency comb technology also has the potential to be really, really fast: it could potentially eventually provide results in seconds, compared with minutes in other breath tests.

That said, you probably won’t see laser combs the next time you catch a flight. “Breath tests, in general, have not reached prime time yet,” says Wilbur Lam, a COVID test expert, pediatrician and biomedical engineer at Emory University and the Georgia Institute of Technology. With the frequency comb method, he says, “you get an optical signal, and whether that optical signal is truly indicative of a COVID infection really has to be proven. Right now, they’re showing some correlation. But how does it correlate with other types of conditions that could affect the breath?”

If frequency comb “Breathalyzers” do prove themselves in further research, they could make a huge difference in many clinical settings beyond rapid testing for COVID. Study co-author Kristen Bjorkman, director of interdisciplinary research at the BioFrontiers Institute, suggests this technology might one day be used to detect chronic obstructive pulmonary disease, kidney failure, lung and pancreatic cancers and even Alzheimer’s disease. Multiple early studies have provided preliminary evidence that the contents of exhaled breaths can be used for these diagnoses.

Breathalyzer-style tests could also be ideal for diagnosing children, and Ye says some pediatricians have already approached him about a frequency comb test for asthma in kids. When a child shows up sick at the emergency room, Ye explains, a lot of invasive tests are required to determine if the symptoms are caused by a bacterial or viral illness or asthma. He says one Denver-based pediatrician told him, “‘Imagine you can do a breath analysis on children, which is totally noninvasive. Kids won’t cry if they have to just donate a breath.’”

ABOUT THE AUTHOR(S)

Starre Vartan is a freelance writer with an unslaked curiosity about the natural world, which was sparked in an outdoors childhood spent in the tide pools of Sydney, Australia and the wetlands of New York's Hudson Valley. Starre was previously a columnist at *Audubon* and has written for *Newsweek*, Medium, *Slate*, NASA's Astrobiology magazine, and others about the intersection of geology, biology and technology. Follow Starre Vartan on Twitter

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