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Democracy Dies in Darkness

# Can dogs detect the novel coronavirus? The nose knows.

Canine studies aim to develop a quicker, more accurate test for the coronavirus

A dog works a scent wheel at Good Dog, a boarding and training facility in Greencastle, Pa.

By **Frances Stead Sellers**
Photos by Bonnie Jo Mount
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GREENCASTLE, Pa.— The black Labrador circled a giant horizontal metal wheel, sniffing the cans at the end of each spoke before stopping abruptly in front of one. Head up and ears pricked, Blaze froze, staring intently ahead.

"That's the grail!" exclaimed Cynthia Otto, director of the Penn Vet Working Dog Center at the University of Pennsylvania School of Veterinary Medicine.

"That's amazing! Just amazing!"

Kibble tumbled out of a dispenser, and Blaze bounded across the small training facility to devour it, tail-waggingly pleased with his reward but unaware of why his olfactory prowess so delighted the human onlookers.

Blaze is one of nine dogs enrolled in a University of Pennsylvania study into whether dogs can detect a distinct smell in people infected with the novel coronavirus. His triumph on that early July day — selecting a can containing urine from a hospitalized coronavirus-positive patient over an array of potentially confusing alternatives — is a key step in a training process that may one day allow dogs to pick out infected individuals, including those who are asymptomatic, in nursing homes, businesses and airports, potentially screening as many as 250 people an hour.

University of Pennsylvania professor Cindy Otto records a dog working a scent wheel during training in Greencastle, Pa.

New canisters for a scent wheel.

Blaze's success also marks an advance in the evolving field of olfactory disease detection — the concept that many human illnesses, including emerging diseases, are characterized by distinct "odorprints" that can be identified by both dogs and artificial noses, which could be quicker, less invasive and more accurate than current forms of clinical testing.

"This is a major field of research worldwide," said Kenneth Suslick, a professor of chemistry at the University of Illinois who invented an electronic nose for detecting toxic gases and explosives as well as diagnosing diseases, in much the way that a simple breathalyzer can identify the distinctive chemicals of alcohol.

"There have been substantial advances over the last decade in new technologies," he said.

Allie Caren/The Washington Post

As the coronavirus continues to ravage the world, those possibilities put the spotlight on research like this and a similarly rigorous study at the London School of Hygiene and Tropical Medicine. With demand high, scientists are emphasizing the need to proceed with caution.

"As eager as we are to put this out there, we want to make sure it is responsible, ethical, scientific and safe," Otto said, even as she admitted that seeing Blaze perform with such accuracy after just 10 weeks of training gave her chills. Moving from the controlled setting of the training facility to finding the scent on thousands of travelers in busy airports is a huge step.

"Done wrong, it could be more damaging than helpful," Otto said.

Perdita Barran, a professor of mass spectrometry at the University of Manchester who has worked with medical detection dogs in previous studies, has her doubts about using dogs to meet the world's pressing testing needs.

While dogs' sensitive snouts are very good at "proof of concept" — establishing whether infection with the virus actually produces a distinct odor — training each one is time-consuming and very expensive, Barran said, while the demand is widespread and urgent.

"It doesn't scale with the cost of dogs," she said.

The Penn team's research, funded largely by private donations, is based on two established principles: that changes in our health often alter the way we smell; and that dogs, with 50 times as many smell receptors as people, make great biosensors with a proven ability to detect not only drugs and explosives but some diseases, such as hidden cancers, the sudden shifts in blood sugar levels caused by diabetes, parasitic infections like malaria, and bacterial and viral infections including, potentially, the novel coronavirus, which causes the disease covid-19.

The work, which draws on disciplines including neuroscience, chemistry, nanotechnology and animal cognition, also reveals how much we still don't know about the way the sense of smell works.

"It's very poorly understood," said A.T. Charlie Johnson, a Penn physicist who was working with Otto before the pandemic to create an artificial nose that could sniff out early-stage ovarian cancer — a feat her dogs had already accomplished. Dogs play an ongoing role in the development of artificial noses, helping to identify key odors within a complex mix as scientists narrow down which molecules represent the disease. Johnson and Otto believe that electronic sensors could ultimately replace detection dogs, particularly in clinical settings where a hairy and enthusiastic four-legged tester might not be welcome.

Understanding just how the brain recognizes the specific aroma of, say, the novel coronavirus and distinguishes it from the scent of a rose or the stink of sewage, also promises to revolutionize other fields of research, including machine learning.

"There have been very exciting advances in demystifying how the brain codes odor," said Sridhar Raghavachari, program director of a National Science Foundation project aimed at "cracking the olfactory code." They have major implications for artificial intelligence, where technologies like facial recognition have relied so far on our understanding of visual rather than olfactory pattern recognition, he said.

Blaze and eight other dogs — seven more young labs and a more experienced Belgian Malinois — are learning their coronavirus-sniffing skills at the Good Dog boarding and training facility on the Pennsylvania/Maryland border, where Otto transferred her project after the pandemic temporarily shut down the Working Dog Center on Penn's Philadelphia campus. Pat Nolan, who trains dogs for elite military teams, and his wife and fellow trainer, Connie Cleveland-Nolan, imprinted the new scent on the dogs by offering them several smells and rewarding them when they sniffed a coronavirus-positive sample.

Good Dog training facility in Greencastle, Pa.

Trainer Pat Nolan walks Jake.

Labrador retriever Dixie is one of the pups in the University of Pennsylvania study.

"We find the thing that makes them want to work," Cleveland-Nolan said, as she held a leashed dog in one hand and a trigger in the other that would automatically release kibble when the dog performed the behavior she was hoping for.

The trainers keep a record not only of each dog's performance but the time of day, the air temperature and the humidity, which, as every hunter knows, can affect the dispersal of scent molecules. They wipe down the sample cans with alcohol between dogs. And they monitor their own body language to avoid one of the infamous traps of animal cognition research, the Clever Hans Effect.

In the early 20th century, Der Kluge Hans, a German horse, appeared to answer advanced math problems by tapping his hoof on the ground. Researchers discovered that the animal was providing the correct answers by responding to involuntary cues given by his trainer.

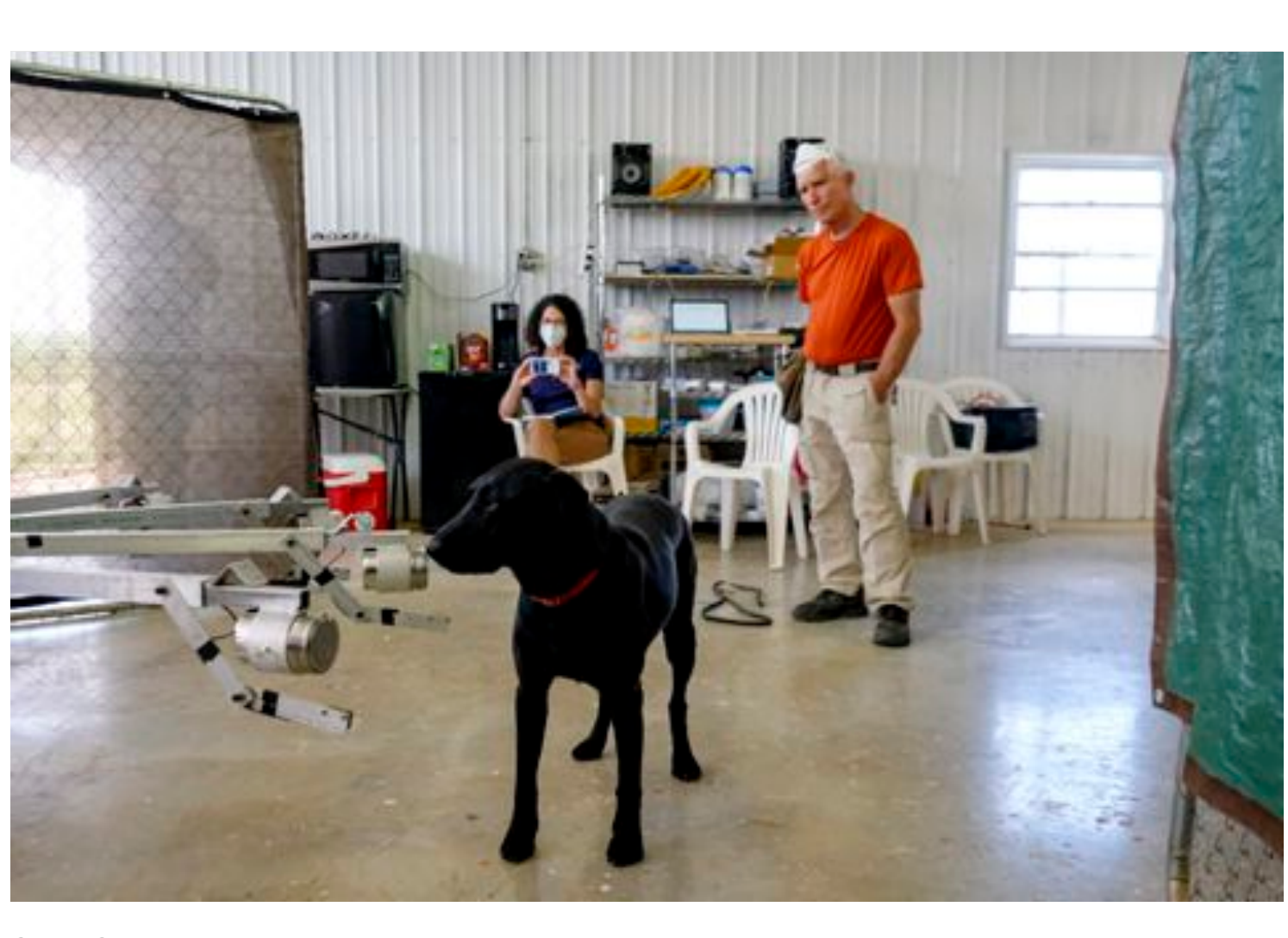
"We're very careful," said Nolan, standing quietly aside as the dogs took turns circling four different scent wheels, where the control options included coronavirus-negative urine, the chemical detergent used to deactivate the virus, and cake batter.

The researchers have been changing the positive samples they are using as the work evolves. In early July, they were working with chemically deactivated urine provided by the Hospital of the University of Pennsylvania and Children's Hospital of Philadelphia. The dogs were later presented with heat-treated urine, as well as other bodily secretions such as saliva and the oily substance on skin known as sebum, which is collected from T-shirts worn by a variety of recently tested people, some of whom have the coronavirus but are not sick enough to be hospitalized, potentially allowing greater understanding of presymptomatic and asymptomatic infection.

There's nothing new about the notion that diseases smell. In his aphorisms, written in 400 B.C., Hippocrates, the "father of modern medicine," recognized a "heavy smell" in the sputa and urine of people suffering from certain illnesses. Physicians continued to rely on their noses to make some diagnoses — recognizing the putrid sweat of vitamin C deficiency or scurvy and the fruity-scented urine of diabetics. A sudden change in the way our breath or urine smells remains a reason to check in with the doctor.

If you've been tested for covid, or are about to be tested, you can take part in the T-shirt study.

That's because human bodies constantly give off a cocktail of chemicals known as volatile organic compounds, or VOCs, in sweat, saliva, urine, breath and sebum that change when cells grow, as in the case of cancer, or when they die after being infected, for example, by a virus.



Cindy Otto and Pat Nolan watch as a dog works a scent wheel.

"With covid detection, you are not recognizing the virus," Suslick said. "You are recognizing the volatile byproducts of cells dying because they have been infected with the virus."

Some VOCs have such strong smells that people have been able to detect them even without recognizing what the odor means. More than a decade before her husband was diagnosed with Parkinson's disease, a Scottish woman noticed a change in the way he smelled. He had developed a "sort of woody, musky odor," Joy Milne told a London newspaper — a telltale smell she was later able to recognize on T-shirts worn by other people with the disease.

With gas spectrometry, which is used in explosives and drug detection as well as in the food and perfume industries to identify specific molecules within a sample, Barran, the University of Manchester professor, was able to analyze the Parkinson's disease markers. For a condition in which diagnosis typically relies on identifying an array of physical symptoms (many of which can be confused with signs of aging), the possibility of presymptomatic diagnosis (and early treatment) is exciting.

Milne's nose did for Parkinson's research much the same thing as Otto's dogs are now attempting — establishing that a diagnostic odorprint exists.

"The dogs are acting like Joy [Milne] did for us," Barran said. There is an added mystique associated with canine detectors, she added, particularly in an era when distrust of expertise is prevalent. Dogs have no ulterior motives.

"People love the idea of dogs doing things, and they are mistrustful of scientists," Barran said.

Electronic noses have numerous advantages over canine noses. They don't need trained handlers; they can work 24/7; and their own health is not of concern, particularly when detecting a zoonotic disease like the novel coronavirus, which has already transferred from humans to some other mammals including dogs, cats and mink.

Electronic noses, which have been around in simpler forms for decades, have had to overcome some of the same shortcomings as dogs. Both can be fooled by confounding factors such as using coffee to hide the smell of explosives or by the strong smell of what a person recently ate masking other odors on their breath.

But recent advances in nanotechnology, biomolecular science and robotics, which can help scale the process, give electronic noses a promising future allowing for greater sensitivity and specificity in testing, according to Johnson, the Penn physicist.

"I am thinking this is a time we can break through," he said.

Still, several mysteries hover over the work at the Good Dog training facility in Greencastle.

"We don't know what the dogs are finding, what the common denominator is," Otto said, as she observed each dog thrusting its nose at the metal cans.

Despite some distractions, including visiting journalists and a loose dog in a neighboring area, the canine trainees performed with stunning accuracy until one Labrador suddenly froze, head up and ears pricked, in front of can containing a urine sample from a hospitalized patient who had tested negative for the virus.

It was one of the few mistakes of the day. Unless it wasn't a mistake after all.

Clinical tests give more than 10 percent false negative results, raising the possibility that the urine could actually have come from a coronavirus-positive patient and that the dog may not have been wrong after all.

"The challenge is, the dogs may be better than the tests," Nolan said.

That appeared to be true a few weeks later, when the dogs all alerted on a sample from a patient who had recently tested negative. They were so insistent — and consistent — that Otto went back to the hospital to learn more about the person's history. It turned out the patient had previously tested positive, suggesting there may have been some lingering odor from the earlier infection.

"There's a phrase in dog training," Otto said: "Trust your dog."

Trainer Connie Cleveland-Nolan takes a break with dogs that are training to detect the coronavirus.

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