Innovations

Review Article

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Toward the use of medical scent detection dogs for COVID-19 screening

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Abstract: Current testing for the presence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), which causes the novel coronavirus 2019 (COVID-19) infection, is typically reliant upon collection of nasal swab samples from subjects. These tests (reverse transcription polymerase chain reaction [RT-PCR] and antigen) are intrusive, can take significant time to process, and can give deleterious false negative and false positive results. Alternative methods for COVID-19 testing and screening are being studied, including the use of trained scent detection dogs to detect volatile organic compounds (VOCs) associated with the COVID virus. In August 2020 and October 2020, the first author (T.D.) searched MEDLINE/PubMed, Cochrane Library, Google Scholar, and additional news articles using keyword phrases including "COVID scent dogs," "COVID sniffer dogs," and "COVID detection dog," returning a total of 13 articles, nine of which were duplicates. Four remaining peer-reviewed studies dedicated to determining the feasibility and efficacy of detecting and screening individuals who may be infected by the COVID-19 virus with scent detection dogs were then examined. In this narrative review, the authors describe the methodologies and results of the remaining four studies, which demonstrated that the sensitivity, specificity, and overall success rates reported by the summarized scent detection studies are comparable to or better than the standard RT-PCR and antigen testing procedures, meaning that scent detection dogs can likely be effectively employed to nonintrusively screen and identify individuals infected with the COVID-19 virus in hospitals, senior care facilities, schools, universities, airports, and even large public gatherings for sporting events and concerts.

Keywords: coronavirus 2019; COVID-19; dogs; pandemic; scent detection; screening.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes novel coronavirus disease 2019 (COVID-19); the resulting worldwide pandemic has led to important research races for effective novel COVID-19 therapies and virus vaccines. However, a third critical need is for accurate and rapid screening of individuals who may be carriers, symptomatic or asymptotic, of the COVID-19 virus. Widespread screening with rapid reporting of results is important for slowing and limiting the spread of infection. In a recent *Science* article,[1] the author stated, "… a few public health experts say sending people back to work and school safely and identifying new outbreaks before they spread out of control could require testing much of the U.S. population of 330 million every day. Others suggest checking roughly 900,000 people per day would be enough."

Presently, most ongoing diagnostic COVID-19 testing involves nasopharyngeal swabs collected by trained personnel for the reverse transcription polymerase chain reaction test (RT-PCR) to identify the pathogen. (Nasopharyngeal swab sampling may be replaced by less contagious methods such as skin swab sampling from the neck or underarm.) The sensitivity and accuracy of this testing methodology was discussed by Wiersinga et al.,[2] who summarized modeling results using RT-PCR as follows: "… the sensitivity of testing varies with timing of testing relative to exposure. One modeling study estimated sensitivity at 33% four days after exposure, 62% on the day of symptom onset, and 80% three days after symptom onset. Factors contributing to false-negative test results include the adequacy of the specimen collection technique, time from exposure, and specimen source." The disadvantages of the RT-PCR method include intrusiveness to the subject, cost, current application to selected COVID-19 symptomatic patients, and delayed reporting of results.[2]

Alternative diagnostic COVID-19 antigen tests detect specific proteins on the surface of the virus. This relatively

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inexpensive method provides more rapidly analyzed results, but the antigen method has its own issues. According to the same report in *Science*,[1] most antigen tests have a sensitivity somewhere between 50 and 90%, potentially leaving up to half of infected people being informed that they are uninfected. That report also indicated that "Spanish health authorities returned thousands of COVID-19 antigen tests to the Chinese firm Shengzhen Bioeasy Biotechnology after finding the tests correctly identified infected people only 30% of the time according to a report by the Spanish newspaper *El Pais*."[1] Thus, there remains a need for alternative COVID-19 testing and screening methods that are non-intrusive, can provide rapid results, and can be performed randomly with a high degree of sensitivity, specificity, and accuracy for large numbers of individuals who may be at the earliest phase of exposure. One promising approach is to use medical scent detection dogs.

Dogs "view" the world to a large extent with their noses rather than their eyes.[3–6] Dogs are able to sense a broad range of molecules with extremely small concentrations – one part in a quadrillion compared with one part in one billion for humans, partially because of head shape (i.e., dogs, with a few breed exceptions, have more prominent noses).[4] They have 1,094 olfactory (smelling) receptor genes compared with 802 for humans.[4] These receptor genes sense volatile organic compounds (VOCs). VOCs are organic chemicals with high vapor pressure at room temperatures. VOC molecules thus evaporate or sublimate from liquid or solid compounds, becoming volatile.[6] Dogs' nasal area (called the olfactory epithelium), which is responsible for detecting odors, is over three times greater than humans'.[4] Dogs have two separate sets of inflow nostrils and outflow folds on the sides; humans inefficiently inhale and exhale through the same orifices (nostrils).[5] Dogs also smell in three dimensions, giving them smelling capability for depth perception.[5] Dogs have 125–300 million olfactory cells to only 5–6 million such cells for humans.[4] Finally, one-third of a dog's brain is dedicated to the interpretation of odors, compared to only 5% for humans.[4]

The science behind and efficacy of using dogs in detecting medical conditions and diseases such as cancers, diabetes, malaria, Parkinson's disease, and more has been documented.[3–9] Using inhaled air molecules and particulates, dogs can detect odorous human molecules that can originate from flaked off skin or hair cells, blood, breath, saliva, sweat, tears, nasal mucous, urine, semen, or feces.[6] More specifically, dogs can detect odors/volatile organic compounds (VOCs), which are produced by human tissues that evolve into particular pathologic states associated with specific diseases such as those listed above.[6] Dogs process and store this odorous information likely as patterns or smell 'images' in their brains for future reference.[5] Since smells linger, dogs even maintain a historical library of the smells of complex molecules.[5] This particular capability is used in search mode applications and for the identification of diseases with their individual chemistries and odors.[5,6] As an example, dogs have already been used to detect malaria, a parasitic disease caused by mosquitos.[6] They have also proven successful at sensing of a variety of cancers beyond those caused by viral or bacterial infections[6] Recently, trained beagles have been able to differentiate the odor of the blood serum of patients with lung cancer from the blood serum of healthy controls.[9]

To assess the potential for dogs trained in scent detection to have widespread application in COVID-19 testing and screening, we reviewed recent research employing trained and some previously untrained dogs for scent detection of VOCs associated with the COVID-19 virus.

Methods

In August 2020 and October 2020, the first author (T.D.) searched MEDLINE/PubMed, Cochrane Library, and Google Scholar using keyword phrases including "COVID scent dogs," "COVID sniffer dogs," and "COVID detection dog." The MEDLINE/PubMed search returned three articles. The first author (T.D.) reviewed the results to determine whether the research was peer reviewed and pertinent to COVID research with detection dogs. Articles were excluded if they were not peer reviewed or if they were devoted to unrelated themes. The Cochrane Library search returned two relevant articles and the Google Scholar search returned four relevant articles. Review of those articles followed the same inclusion criteria as those evaluated from the MEDLINE/PubMed search (Figure 1).

In a general internet search using the keyword phrases above, the first author (T.D.) discovered over 100 entries. However, research related to COVID-19 detection with scent dogs was found for only nine research teams through news stories and videos devoted to these same nine research programs. Descriptions of research from four of these programs were previously found in the aforementioned MEDLine/PubMed, Cochrane Library, and Google Scholar searches; those are summarized in this review. The first author then emailed lead investigators from the remaining five programs identified in the internet search, asking them to provide a list of references concerning their present and past relevant research on COVID-19 scent detection dogs or any relevant papers of which they were aware. Only two responded and neither was able to provide information. In summary, there were altogether nine duplicates across searches, leaving only four qualifying articles for inclusion in this review.

Grandjean et al.[10]

A team of collaborating researchers from France and Lebanon reported on their work to determine whether trained scent detection dogs can distinguish sweat odors produced by COVID-19 RCT-PCR positive individuals compared with sweat odors produced by COVID-19 negative individuals.10 It is important to note that the COVID-19 virus does not itself have a smell. However, the researchers hypothesized that the resulting infection generates metabolic changes, which cause the release of a distinctive type of sweat odor (VOCs) that can be detected by a dog. More specifically, the authors[10] assumed that the cellular actions of the COVID-19 virus generate specific metabolites and catabolites that can be excreted by the apocrine sudoriferous glands and generate VOCs identifiable to dogs. Eighteen dogs were initially selected for the study; these included 16 Belgian Malinois, one German Shepherd, and one Jack Russell Terrier.[10] The eight dogs used for the proof of concept study, which included 368 trials, had previously been trained to detect explosives and colon cancer. The research team collected sweat samples from 198 human armpits of patients in different hospitals, since sweat provides the key odor used for search and rescue or tracking dogs.[5] The research team placed these samples of human armpit-derived sweat soaked in cotton and wool gauzes into cylinders, placed in a line. The dogs were trained to only sit in front of a COVID-19-positive sample contained in a box with a sample canister. A “trial” consisted of one dog detecting the presence of the COVID-19 positive sample in one box out of three, four, six, or seven presented boxes. Trials were conducted independently and the positive sample was moved randomly. Special measures were taken to avoid olfactive contamination or interaction, and dogs and handlers were isolated in a separate room without access to the testing room between trials. After only four days of training using COVID-19 samples, the success rate for the dogs ranged between 83 and 100%. True failures were apparently caused by distractive external smells or movements by a TV filming crew. One of the dogs was thought to have pointed in error to two samples that were supposed to be negative, thus receiving a failing grade. However, a week later, those sample donors were admitted to a hospital with the COVID-19 infection. This research provides experimental evidence that trained scent dogs are capable of detecting the presence of the COVID-19 virus.

Jendrny et al.[3]

A research team in Germany also conducted a randomized, double-blinded, controlled pilot study to determine whether previously-trained scent dogs could successfully detect the presence of the COVID-19 virus.[3] Eight scent detection dogs were trained for one week to detect the COVID-19 virus in samples of saliva or tracheobronchial secretions collected from the infected patients. Two different hospitals were used as sources for the virus samples, thus minimizing possible biases associated with distinctive hospital smells. Because the research team felt, based on research by Sit et al., that the dogs might be susceptible to the COVID-19 virus, samples from COVID-19 positive patients were inactivated using beta propiolactone (BPL) to prevent possible infection of the dogs and their handlers. Samples were presented in a randomized, automated manner with no trainer interference. The dog, its handler, and a person observing the study were blindfolded. The number and duration of each dog's “nose dips” into the scent holes, along with the location of the positive and negative samples, were automatically recorded and verified using time-stamped video analysis. The results derived from 1,012 automated sample presentations showed an overall average detection rate of 94% (standard deviation, +/−3.4%): 157 correct indications of positive, 792 correct rejections of negative, 33 false positive, and 30 false negative indications. The test sensitivity (ability to detect a true positive) ranged from 67.9 to 95.2% and the specificity (ability to detect a true negative) ranged from 92.4 to 98.9%. The team reported no notable difference in detection ability between the use of sample saliva and sample tracheal secretion. The team concluded from their preliminary research that trained scent detection dogs with only one week of specialized training could identify samples from COVID-19 infected individuals with a high success rate. The team also acknowledged several major limitations to their pilot study, including the need for more sampling, and reported that additional research would be necessary before implementation. In particular, the authors noted that their positive samples came only from severely affected, hospitalized COVID-19 patients. Their negative samples were from healthy individuals with no indications of respiratory infections. They suggested that future studies could be used to determine whether dogs can detect different disease phenotypes and phases of expression with a goal of identifying asymptomatic, presymptomatic, and mild to severe COVID-19 cases.

Vesga et al.[12]

Researchers based in Colombia have tested trained scent dogs to develop a screening method for detecting COVID-19 in individuals who may be asymptomatic, presymptomatic, or symptomatic.[12] Their work was motivated in part by concern for countries with economies particularly susceptible to poverty, malnutrition, and potential social unrest. The researchers were interested in using scent detection dogs to control infection rates through early, accurate screening, thereby reducing periods of quarantine related to COVID-19. They contended that, if successfully applied, these screening methods could hasten economic recovery. The research team developed a device to safely expose scent-trained dogs to VOC samples collected from respiratory secretions of COVID-19-positive patients. Their dogs included three female Belgian Malinois aged 6, 25, and 36 months; one male Belgian Malinois aged 31 months; a first-generation female Alaskan Malamute-Siberian mix, aged 36 months; and a male American Pit Bull Terrier, age unknown. The latter dog was a rescue that had been previously mistreated. It was originally aggressive and required rehabilitation. The research program had three phases. Phase 1 was devoted to training and experimental design. Dogs were trained using rewards of treats, play, or clicker sounds. This phase involved 28 days of training of six dogs to identify COVID-19 from human respiratory secretions (half with active virus and half with inactive virus). The negative control samples were made of sterile 0.9% solution. During Phase 1, 3,200 samples were tested. Phase 2 required an additional 21 days of training of the same six dogs. The Phase 2 experiment utilized saliva from individuals with active COVID-19 virus, as well as saliva from healthy individuals as the distractors. The Phase 2 experimental configuration consisted of 100 samples spaced 2 m apart in a field with the number of randomly placed positive COVID-19 samples varying between 1 and 10 per 100 total samples. A total of 6,000 samples were tested. The Phase 2 results showed dog performances with 95.5% sensitivity and 99.6% specificity. For the Phase 3 research, the team is utilizing direct smelling of humans to screen for COVID-19. They are also presently doing work to evaluate the limits of COVID-19 detection, including presymptomatic and asymptomatic testing. The researchers have proposed that virtually any breed or mixed breed of dog may be trained for COVID-19 screening and they envision implementation in a variety of venues including airports, ships, trains, factories, hospitals, and stadiums.

Jones et al.[13]

In a perspective article from August 2020, a research team from the United Kingdom gave a preliminary description of their intended research focused on the goal of using biodetection dogs for limiting the spread of COVID-19 by travelers.[13] Their plan of action involves the use of more than 300 asymptomatic and mildly symptomatic participants, and is divided into three phases. The first phase would be intended to show that medical detection dogs can be trained to identify samples of asymptomatic or mildly symptomatic COVID-19 infections with high sensitivity and specificity. The second phase would assess the capability of the trained scent dogs to detect individuals who are asymptomatic or mildly symptomatic with COVID-19; in that phase, the authors would test sensitivity and specificity of the dogs' performances as they sniff volunteers who are waiting to donate swab samples for diagnosis. The final phase would involve deployment of the trained dogs at United Kingdom ports of entry as part of the COVID-19 screening process.

Discussion

While the results of recently reported and ongoing research are encouraging, there remain challenges to be considered before broad-scale implementation of scent detecting dogs to identify and screen for COVID-19. Specifically, two related virus transmittal questions must be addressed. First, can medical detection dogs contract and become ill with the COVID-19 virus? Second, can dogs pass COVID-19 to humans? These questions have been addressed in diverse ways. As mentioned earlier, some researchers are taking precautions to protect the safety of their scent dogs and handlers from exposure to the COVID-19 virus. A recent paper by Damas et al.[14] described a comparative genomics approach to study the conservation of the angiotensin I converting enzyme 2 (ACE2). ACE2 is the main receptor of COVID-19, and was used to investigate possible routes of transmission and sensitivity in different species. The key results were summarized with a 5-category ranking score based on the conservation properties of 25 amino acids. These selected amino acids were considered to be important for the binding between receptor and virus. The rankings for individual species were ranked from very high to very low risk. Example species in the high-risk category were primates, cats were in the medium risk category, and dogs were in the low risk category. This work supports the argument that dogs are not likely transmitters of COVID-19. In addition, Shi et al.[15] have stated, "Dogs appeared not to support viral replication well and had low susceptibility to the virus, and pigs, chickens, and ducks were not susceptible to SARS-CoV-2." However, Sit et al.,[11] Leroy et al.,[16] and Almendros[17] have described a few cases of dogs infected with COVID-19. Sit et al.[11] commented, "It is unclear whether infected dogs can transmit the virus to other animals or back to humans." Almendros[17] concluded, "The consensus remains at this time that there is no evidence that infected pets are a source of infection for people or other pets." With the obvious importance of these issues, national health organizations have issued relevant statements. In particular, the U.S. Centers for Disease Control and Prevention (CDC) stated, "At this time (August 1, 2020), there is no evidence that animals play a significant role in spreading the virus that causes COVID-19. Based on the limited information available to date, the risk of animals spreading COVID-19 to people is considered to be low. A small number of pets have been reported to be infected with the virus that causes COVID-19, mostly after contact with people with COVID-19."[18,19] On the international level, according to Grandjean et al.,[10] "the ANSES (Agence Nationale de Sécurité Environnementale et Sanitaire) in France agrees with the US CDC that there is absolutely no evidence that pet animals, and especially dogs, play any significant role in the transmission or in spreading the virus that causes COVID-19, and the risk is considered as close to zero." In addition, the World Organization for Animal Health has made recommendations that are consistent with those of the CDC, stating that, "Currently, there is no justification in taking measures against companion animals which may compromise their welfare."[20] This is supported by the American Veterinary Medical Association (AVMA), which explained that the chances of COVID-19 exchange between dogs and humans is quite low because this virus does not tend to live on surfaces like dog hair, which is porous and fibrous.[21] In terms of future widespread COVID-19 scent dog use, sweat sniffing would be the likely choice, as it would be non-intrusive and there is little chance of transmission of the COVID-19 virus by this means.

The training of scent dogs for COVID-19 work was similar among the research groups whose work is described in this paper and similar to previous medical scent dog training applications; it generally involves

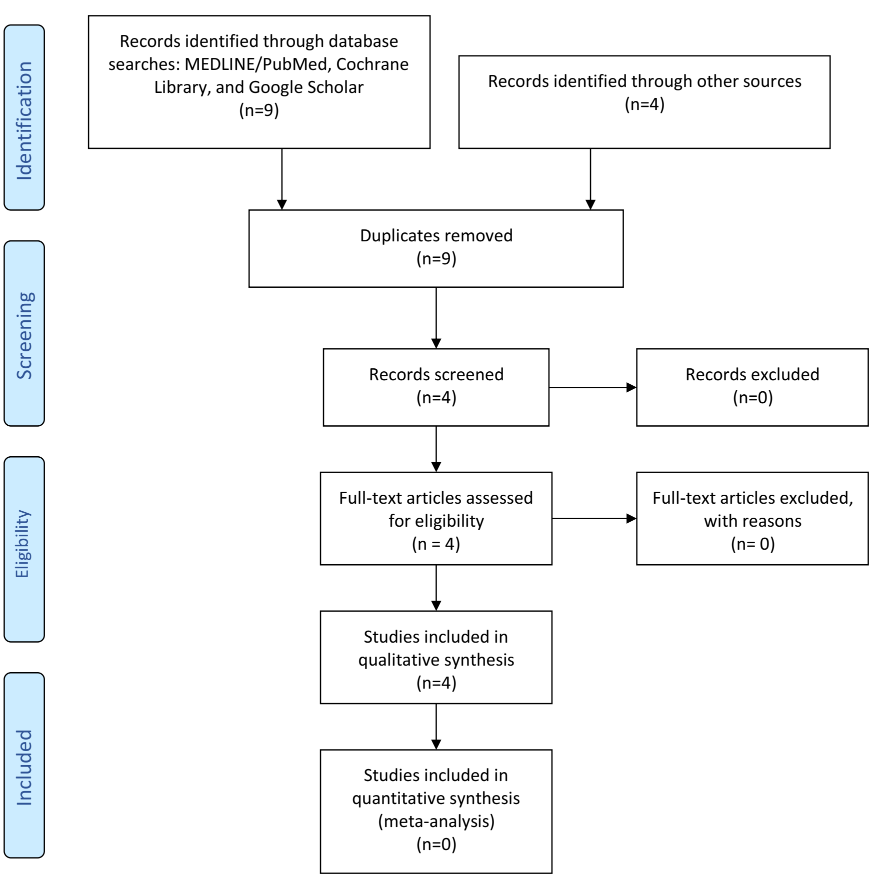

Figure 1: Preferred reporting items for systematic reviews and meta analyses (PRISMA) flow diagram documenting the literature search process conducted for this narrative review.

rewards and, in some cases, clicker training. The collection and analyses of data were somewhat different amongst the studies, but appear to be consistent and suitable for comparisons with prevalent nasal swab testing (i.e., RT-PCR). A variety of breeds of dogs and mixed-breed dogs were used for the studies described here. Many of these dogs had been previously trained to do scent work for various purposes; however, some had no previous scent work training at all. Regardless, they were all able to be trained for COVID-19 detection over relatively short periods of time (weeks or less). This is important because widespread use of COVID-19 detection dogs would require a large number of trained dogs. Grandjean et al.[10] and Vesga et al. suggested that many different canine breeds and mixed breed dogs could be successful COVID-19 detectors. Today, there is a shortage of scent detection dogs and time investment will be needed to train new COVID-19 scent dogs. Estimates for the time to train a medical scent dog range from as little as a week for a pretrained scent dog to over a year for juveniles, depending on several factors such as breed, age, and previous scent detection experience. A host of organizations and private companies utilizing appropriate breeds and mixed breeds in addition to those described here would be needed. Transmission of the COVID-19 virus to or from dogs remains a research topic, as discussed; further, there still could be issues of liability. Implementation of COVID-19 scent detection dog programs will necessarily require frequent COVID-19 testing of both the scent detection dogs and their handlers as precautionary measures to protect handlers, dogs, and the public. To be safe, dogs used near humans will need to be able to detect the virus at a distance, so sweat VOCs associated with the COVID-19 virus, with their low transmission properties, would be ideal biomarkers. In this general context, dogs have already demonstrated their efficacy in airport security and numerous other applications.

In 1914, Alexander Graham Bell stated, "If you are ambitious to find a new science, measure smell".[22] Within the past two decades, there have been major advances in the quest to measure smells. They have led to the further development of electronic noses (i.e., e-noses, ENoses, odor sensors, artificial noses).[23] These biosensors have many different applications and were largely inspired by the goal of simulating and analyzing smells and learning about the human smelling sense. In the medical field, researchers have attempted to identify the VOCs associated with cancers and diseases using biosensors.[23,24] To this end, the remarkably well-developed olfactory senses of dogs are being utilized. In particular, cancer-sniffing dogs are being utilized to create e-noses, since dogs are capable of detecting patterns in complex VOC mixtures. Using the dogs' responses to cancer samples, the goal is to identify the chemical signature of a cancer for input into the e-nose or biosensor. In principle, this new technology can be applied for different diseases, miniaturized, and mass-produced. The future uses of e-nose-based biosensors are unlimited and could be used for rapid and efficient screening of large populations during pandemics such as the current COVID-19 pandemic.[13]

There are several limitations in addition to those mentioned above that should be considered when interpreting this existing research. For example, the studies described here have used a limited number of dogs and samples; larger sample sizes with greater numbers of COVID-19-uninfected samples should be used in future studies to reduce the possibility of dogs memorizing the samples rather than the VOCs of the virus. Also, the samples used during training should not be the same used for testing. There may be some systematic effects such as dogs remembering the odors of individuals or environments opposed to the target odor associated with COVID-19. Evaluations without the presence of a trainer are also very important to obviate inadvertent body language cues; trainers should be behind a screen, or better, in another room. Also, some of the research was done with individuals with clinical symptoms.[3,10,12] The identification of asymptomatic individuals is a major goal, but success in this aspect remains anecdotal. Dogs may be distracted, hungry, bored, or fatigued, have limited attention spans, or like humans, may simply have bad days. How long the dogs can perform their duties is likely quite individual and the dogs will require their trainers' and handlers' undivided attention. Biosensors/e-noses developed in conjunction with dogs would obviate many of these limitations.

Conclusion

The research described here, which presented recent information and perspectives on the potential for broad application of trained scent dogs for screening of COVID-19-infected individuals, can be used to assist in development of future studies and implementation of screening programs to more broadly benefit preventative medical research. Remaining research challenges include conducting more research into potential human-dog-human COVID-19 transmissions, optimal training methods for large numbers of scent dogs, and infrastructure supporting COVID-19 scent dog deployments. However, the research summarized here has demonstrated the potential for using scent detection dogs for COVID-19 screening. Trained scent detection dogs could, in principle, be used to non-intrusively screen and identify individuals with various stages of COVID-19 infections in hospitals, senior care facilities, schools, universities, transportation centers like airports and train station, and even large public gatherings for sporting events and concerts. Further, mandatory quarantines of international travelers could be reduced. The economic benefits from such screening would be great. The sensitivity, specificity, and overall success rates reported by the early COVID-19 scent dog detection studies appear to be comparable to or better than the standard RT-PCR and antigen testing procedures. Importantly, the waiting time for COVID-19 scent dog detection results is seconds opposed to hours or days for the RT-PCR test. Finally, this line of research will be valuable for the development of new biosensors for detection and screening of other infectious diseases using dogs' abilities to sense low concentrations of infectious VOCs.

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