COVID-19 detection by dogs: from physiology to field application—a review article

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ABSTRACT

For years, the dog, man's best friend, was the most widely employed scent-detector tool for civilian and military purposes. Recently, many studies highlighted the role of canine olfactory ability in the medical field, specifically in detecting different infectious, metabolic and neoplastic conditions. The objective of this literature review is to clarify the rationale behind dog's ability to detect diseases, to assess the possible application for COVID-19 detection and to discuss the evidence available on the matter. Available evidence shows that properly trained disease-detector dogs are an efficient tool for identification of specific disease-associated volatile organic compounds marker profiles for a particular disease. And since COVID-19 positive persons have a specific volatilome different from non-infected persons, they can be recognised by the dogs, by sniffing different body fluids consequently aiding in the diagnosis of COVID-19. Possible applications of dogs as COVID-19 detectors will be an easy real-time mobile diagnostic aid with low cost and good performance. More evidence is needed to be able to describe standardised measures concerning the best fluid to test, testing procedure, time of possible detection according to disease evolution, risks associated with the dog exposure and to translate the good results in study setting into the real-life operational one.

INTRODUCTION

COVID-19 pandemic is one of the most challenging medical problems of the century. The infection was first reported in December 2019 in Wuhan, a city in the Hubei province of China[1]; it has spread widely since then and was declared a global pandemic by the WHO in February 2020. By the time this article is written, infection by the SARS-CoV-2 virus has led to more than 40 million cases of COVID-19 worldwide.[2] Efforts aiming to control this pandemic have been deployed all over the world. While successful containment has been achieved in some countries with exhaustive testing and case isolation, other countries continue to struggle . Testing for SARS-CoV-2 was considered the key for a successful national strategy. However, finding the most efficient testing regimen and balancing the performance of the test with its cost and availability are difficult to achieve task.[3] The need for rapid, cheap and efficient tests in the real life settings has been pointed out by Mina *et al* in their article published in the new England journal of medicine: 'Measuring the sensitivity of a testing regimen or filter requires us to consider a test in context: how often it is used, to whom it is applied, when in the course of an infection it works, and whether its results are returned in time to prevent spread'.[3]

Dogs' ability to detect diseases by sniffing has been described for various infectious, metabolic and neoplastic conditions. Reports on using canine olfactory ability for COVID-19 detection have been published in scientific literature while others have been circulated on media. Detecting COVID-19 using dog's ability to smell could offer a valuable opportunity for universal testing strategies. We performed this literature review to clarify the rationale behind dog's ability to detect diseases, to assess the possible application for COVID-19 detection and to discuss the evidence available on the matter.

SMELL AS DISEASE DETECTOR

Human sense of smell has been used as a diagnostic tool since the era of ancient medicine. Ever since the times of Hippocrates, regarded as the father of medicine, medical practitioners relied on their olfaction to detect diseases. The most renowned examples, among others, still used in modern medicine being the strong musty breath smell of fetor hepaticus indicating advanced liver disease, and the fruity smell of ketones in exhaled breath indicating diabetic ketoacidosis.[4] Infectious diseases have been labelled by their odour long time before appropriate diagnostic and identification tools were available. For instance, *Clostridium perfringens*, the bacteria responsible of a severe soft tissue and skin infection, was described since the middle ages as producing a typical foul smell of gas gangrene.[5] During the First and Second World War, physicians relied specifically on their senses, particularly smell, since no other diagnostic tools were available, to diagnose *Pseudomonas aeruginosa* infection as a fruity odour emanating from wound infections.[4]

From a physiological point of view, the sense of smell relies on the capacity of specific sensory cells of the nose to perceive volatile organic compounds (VOCs). The olfactory epithelium contains bipolar sensory neurons with dendrites extending from the apical surface of the epithelium into the mucus lining the nasal cavity. As airborne molecules are inhaled through the nose, they pass over the olfactory epithelium and dissolve into the mucus. The odorant molecules bind to proteins that keep them dissolved in the mucus and help transport them to the olfactory sensors.[6]

Olfaction is the dogs' most developed sense, the canine capacity for odour detection being around

10 000–100 000 times that of an average human being.[7] The improved knowledge about animal smelling capacities has led toward exploring the use of these, most notably dogs, in the detection of disease and other types of health problems in humans.[8] The dog (*Canis familiaris*) is the most widely employed scent-detector tool for civilian and military purposes.[9] This advanced olfactory sense and the ability to learn by conditioning were exploited by humans to help in the discovery of a huge scope of elusive targets, including explosives, opiates, missing people.

Training dogs to recognise specific targets relies on dog's ability to detect specific markers of the disease and generate a discriminant response like barking specifically when exposed to these markers. This type of training is named 'operant discriminant training' since it relies on reinforcing the response to samples known to be positive for the disease by rewarding the dog while not reinforcing it for negative samples.[10] It is a strenuous effort and relies on two major capacities: generalisation and discrimination. Generalisation is the ability to generalise response to targets slightly different from the one used for recognition during training like responding in a similar way to all viruses from the same family or to different mixtures of explosives, while discrimination is the ability to treat different stimuli by generating different responses leading to better detection of slight differences between different viruses from the same family or differentiating different types of explosives. Olfactory generalisation relies on both characteristic elements of the smells and behavioural and intellectual variables identified with present and experience. Balancing dogs' ability between generalisation and discrimination will have a great impact on the risk of false negative and false positive results when dogs are used to detect diseases in real life thus affecting the sensitivity and specificity of the testing procedure. Correspondingly, dogs have been used to distinguish sickness biomarkers in people, including malignancy and bacterial diseases.[11] Translating the dog ability to detect the disease marker to operational setting is secured by progressive reduction of the reinforcement from a systematic reward to every correct detection at the beginning of the training to intermittent reward with reduced frequency to get the dog ready for operation in real life.[10] This approach was suggested to subside a big difficulty in current practice where samples collected from individuals or contaminated environments are subsequently transported to the laboratory to perform testing method and detect the pathogen of interest. This results in a significant delay in response time and containment efforts.[11] Consequently, the abilities of trained dogs to identify odours are suggested as an easy real-time mobile pathogen sensing technology.[11]

Diagnostic techniques using instrumentation in one operational situation are affected by factors like the absence of neatness, impedance via air particulates, nearness of non-target detectable compounds created by different substances in nature and continually evolving factors, for example, temperature, moistness, wind and thermal plumes.[11] These can be partly resolved by the utilisation of prepared finder canines as they were demonstrated to be effective as a portable innovation in numerous harsh situations on the planet during military, police, salvage and different activities because of the generalisation ability. Despite canines being more effective than instruments to detect target substances, many of the factors listed as affecting instruments also influence canine detection but the highly sensitive canine olfactory sensory system can detect some target substances at concentrations as low as parts per trillion.[7] This is three orders of magnitude more sensitive than today's available instruments, which can reliably identify substances at concentrations as low as parts per million (ppm) or billion (ppb).[12] Canine has a huge olfactory sensitivity as Angel C. explains in his article published in 2016: 'a dog could detect the equivalent of one drop of a liquid in 20 Olympic-size (2500 ft3) swimming pools'.[12]

Canine detection systems are mobile and can trace an odour to its source. For a detection system to be comparable to the detection ability of dogs, it should be extraordinarily sensitive, mobile and able to move toward a target source. No currently available system meets those criteria.[11] Thus, efficient scanning of large areas is a tremendous advantage offered by dogs. In other words, dogs offer a highly sensitive, real-time sensory system on an intelligent mobile platform without the need to collect, process or analyse samples, which gives them significant advantages over machines in operational environments.[12]

DISEASES AND VOCS

In recent years, advances in analytical chemistry led to the ability to quantify and compare VOCs of cellular origin.[12] VOCs are low molecular weight compounds that easily evaporate at normal temperatures and pressure.[13] They may be associated with an odour, and may provide the continuous signal needed for real-time detection.[14] All odorants are VOC, and advancements in VOC analysis have led to new beginning, it is not difficult anymore to understand what dogs are detecting in regard to biological targets.[12] All organs produce cellular VOC, a metabolic product. VOC is simultaneously produced in millions of cells and released extracellularly on a detectable scale. After entering the blood stream, these VOCs are released into the air around a human, through breath, saliva, urine, faeces, skin emanations and blood.[15] Once in the environment, the VOC—the unique individual volatilome—surrounds the body allowing the dog to detect any biological target. The volatilome reflects the unique metabolic state of an organism,[12] it is the entire set of VOCs produced by an organism. Hence, the volatilome is the accumulation of VOCs in an organism.[12] VOCs are released in concentrations of ppb to ppt in human breath, and ppm to ppb in human blood and urine. They are constantly emitted from the human body.[16] Indeed, N-amyl acetate was detected by dogs in the ppt range,[16] indicating that most of the VOC in the volatilome are within a dog's capabilities of detection.[12]More precisely, the expression of specific HLA sequences results in a fingerprint VOC odour or an 'odour print': formation of a unique VOC pattern. This may be used for reliable detection by a well and properly trained canine.[17] Pathogen-specific odour that can be detected by dogs is composed of specific patterns of VOC and non-volatile molecules: exhaled breath condensate and aerosols.[18] VOCs are released by infected body cells as a result of metabolic host processes.[15 18 19] Therefore, dogs sniffing abilities are important for detecting pathogens in large herds of animals, in crowds of people, on or in objects (eg, ships, airplanes, buildings), or around areas of land[12]

Recent research demonstrated that the volatilome could be used to detect diseases, pathogens, and many other unique aspects of an organism. Besa *et al* stated in the study published in February 2015, that various inflammatory and metabolic processes, either physiological or disease related, may produce VOC.[20] These compounds are extremely variable between individuals and their concentrations depend on multiple factors, such as metabolism or systemic physiologies.[20] Moreover, Schmidt and Podmore concluded from their article published in 2015 that many uncontrolled variables, such as genetic differences, environmental settings; diet, drug ingestion and smoking affect VOC patterns, thus, leading to its variation between individuals.[16]

Therefore, VOC profile is influenced by many different physiological and pathological processes; in other words, not all VOCs released from the body are related to human metabolism, they can be related to the commensal microbiota or from microbial infections. Other VOC may be from foods, drinks, medications, polluants. Consequently, the new VOC produced or the VOC which expression pattern is altered by a disease or an infection may serve as a biomarker for the assessment or recognition of diseases by dogs.[16] If the nature, ratio and strength of VOC emitted from an organism are affected by a pathological processes, such as neoplasia, infections and metabolic disorders, then unique VOC patterns may create a specific signature odour for the dog to detect.[21] For instance, many studies showed that VOC patterns might be specific to diseases and infections because of their unique expression, such as cancer, asthma, cystic fibrosis, diabetes, tuberculosis, chronic obstructive pulmonary disease, heart allograph rejection and irritable bowel syndrome. The first description of an animal capacity to recognise a disease was a case of melanoma.[4] Later on, bladder cancer was the main disease for which animal scent detection was analysed as a diagnostic tool. In one study, dogs were trained to perceive bladder malignancy in urine tests; the resulting formal assessment study indicated a symptomatic achievement pace of 41%.[22] In one of the biggest animal scent detection studies to date, lung malignancy was recognised with a sensitivity of 71% and a specificity of 93%, independently of chronic obstructive pulmonary disease COPD or tobacco smoke.[23] Another study demonstrated that canine scent detection of lung cancer after sniffing exhaled breath samples with a sensitivity and a specificity of 0.99.[24] A study conducted by Sonada *et al* showed that a trained dog sensitivity and specificity to detect colon cancer in samples of exhaled breath and watery stool were respectively: 0.91 and 0.99 in breath samples and 0.97 and 0.99 in stool.[25] In addition, dogs could detect cervical cancer-specific VOC contained in adsorbent material samples and fresh cervical smear, with an overall high sensitivity and specificity of 90% with a very high success rate of differentiating odours.[26] Many other studies reported that trained sniffing dogs had high sensitivity and specificity in detecting bovine viral diarrhoea viruses[11] and *Clostridium difficile* in human stool samples.[27] A trained dog was able to detect *C. difficile* with high estimated sensitivity and specificity, in stool samples of hospital patients infected with *C. difficile*. It would seem dogs could also detect *C. difficile* in the air surrounding patients. This also has been shown in recognising diabetic ketoacidosis[4] and hypoglycaemic[8] through exhaled breath. In addition, urinary tract infections due to *Escherichia coli*, *Enterococcus, Klebsiella* and *Staphylococcus aureus*[28] were accurately detected by trained dogs with overall sensitivity at or near 100%, and specificity above 90%.

Consequently, because of their outstanding mobility and their high sensory capacity, dogs are disease sensors, more precisely pathogen sensors. However, one of the main challenges is how to engage the appropriately trained canines for the task. This needs highly professional trainers and intensive dog training programmes in order to properly detect the target pathogen, even in the presence of multiple distractors.[12] In addition, dogs are quick and efficient: patients in a hospital ward can be screened for the presence of *C. difficile* infection in less than 10 min.[27]

Properly trained disease-detector dogs are an efficient tool for identification of specific disease-associated VOC marker profiles for a particular disease. It is foreseeable that dogs can help in clinical practice in detecting diseases. Could these diseases include COVID-19?

SARS-COV-2 AND VOLATILOME PRODUCTION

SARS-CoV-2, the causal virus of COVID-19, is an enveloped positive-stranded RNA virus belonging to the Coronaviridae family, Betacoronavirus genus. Full-genome sequencing and phylogenic analysis have indicated that the novel virus shares genetic material with the bat coronavirus, SARS-CoV and is more distantly related to Middle east respiratory syndrome-coronavirus MERS-CoV.[29,30] Similar to SARS-CoV, SARS-CoV-2 mainly operates through its spike S-protein that binds to the human ACE II receptors found in the lower respiratory tract cells, inducing endocytosis.[31,32] This fusion is accompanied by a decrease of pH in the endosome that results in uncoating of viral particles and the release of the viral genome in the cytoplasm for protein synthesis. Genome translation produces two large replicase polyproteins, pp1a and pp1ab which are subjected to autoproteolytic processes resulting into the formation of non-structural proteins that ultimately together with recruited host cell proteins, form membrane-associated replication and transcription complexes.[18,33] Replication and transcription result in the formation of a set of subgenomic RNAs which encode accessory and structural proteins. Newly formed genomic RNA, nucleocapsid proteins and envelope glycoprotein are assembled in the endoplasmic reticulum and the Golgi apparatus and form the viral particle buds that will be released outside the cell into the airways.[31,34]

This whole process of protein synthesis involves many signal transduction and protein expression pathways with the production and the use of multiple small molecules (cofactors, reactants and side products) that can cross the cell membrane and can possibly be detected in the exhaled breath.[18] Furthermore, since SARS-CoV-2 has a different viral entry receptor than those of influenza or rhinovirus it is thought that it can generate specific VOCs and thus be differentiated from other viruses.[18]

On the other hand, SARS-CoV-2 antigens are presented by the dendritic cells in order to induce humoral and cellular immunity, and form virus-specific B-cells and T-cells.[31] Since HLA gene expression profiles exhibit unique VOCs as an immunological fingerprint based on exposure to a specific antigen, it is expected to have unique and specific VOCs when exposed to SARS-CoV-2.[35,36]

Finally, in the unfortunate event of a cytokine storm, an overproduction of inflammatory cytokines with a wide range of biological activity is triggered by a variety of tissues and cells. These cytokines exert a positive feedback on other immune cells to secrete additional inflammatory products. They also serve to attract more immune cells to the site of inflammation inducing an exponential growth of inflammation and organ damage. The main cytokines involved are interleukins (IL), such as IL-1β, IL-6, IL-12, interferons (IFN), mainly IFN-γ, tumour necrosis factor, colony stimulating factors, the chemokine family, growth factors, and others.[37] This cascade of inflammatory processes in reaction to SARS-CoV-2 infection will lead to a lung injury due to destruction of the cellular structure through oxidative stress and lipid peroxidation and will liberate additional distinctive VOCs that could reflect the severity of the damage, mainly organic lipid peroxidation markers.[15,18] In point of fact, two previous studies examining volatile markers in exhaled air found higher n-pentane levels and lower isoprene concentration in acute respiratory distress syndrome ARDS patients compared with baseline measurements in healthy individuals.[38,39] Consequently, specific VOCs in this case could both play a diagnostic and prognostic role.

EVIDENCE ON COVID-19 DETECTION BY DOGS

The above set of information lead to the conclusion that canine detection of VOC specific to SARS-CoV-2 in body secretions is feasible and can have diagnostic and prognostic applications. In numerous countries, dogs are being trained to detect COVID-19. Some trials were completed and have shown promising results, while many are still ongoing.

In their proof-of-concept study that was conducted on three sites (two in France and one in Lebanon) following the same protocol, Grandjean *et al* started with the assumption that COVID-19 positive persons have a different armpit sweat odour than COVID-19 negative persons.[40] And, assuming that dogs can be used to detect the difference and consequently lead to the diagnosis of COVID-19. Eighteen dogs were trained then were tested for their capacity to identify positive cases, but only eight were able to adapt properly and complete the trial. During training, samples were placed in a glass jar connected to a cone of olfaction. Dogs would then sniff different samples at a time through the cone of olfaction and are taught by their trainers to sit in front of the positive one. Training was based on positive reinforcement, and the time needed for a dog to acquire COVID-19 specific sweat odour varied between one and 4 hours, with a total of positive samples sniffed between 4 and 10. A total of 198 samples were collected from different hospitals, of which 101 belonged to patients with COVID-19 positive and 97 belonged to patients with COVID-19 negative. Samples were considered positive if patients had clinical symptoms of COVID-19 with a positive PCR test and did not receive medical treatment for more than 36 hours as this may interfere with sweat composition. Samples were considered negative if patients had no symptoms of COVID-19 and tested negative on PCR. During the trial, a total of 368 attempts (each including one positive and several negative samples) were made over a period of 21 days. As a result, the capacity of trained dogs to detect positive samples (or success rates) ranged from 83% to 100%. These results were significantly different form success rates obtained by chance alone proving that dogs did not choose positive samples randomly. To note, some cases were detected by dogs before having positive PCRs. The authors related two negative samples that were detected as positive by dogs. This led the researchers to retest the patients and their second PCR tests came back positive. On the other hand, the authors reported a false-positive case marked by two dogs, and were attributed to the female sexual pheromones, as the patient was sampled during her fertile period.

Additionally, as the pandemic continued to spread widely, Jendrny *et al* thought of a need for a COVID-19 detection method that would be less time consuming and less costly than PCR.[41] The research was conducted in Germany. For this, the researchers collected samples from seven hospitalised patients with COVID-19 positive (two tracheobronchial and five saliva samples) and seven healthy individuals. A sample was considered positive if the person showed symptoms of COVID-19 with a positive PCR, and negative if the person had no previous history of COVID-19, showed no current symptoms along with a negative PCR. They inactivated all infectious samples because some cases showed human-to-animal transmission and consequently risk of infecting the dogs along with the risk of infecting the handlers.[42 43] Eight detection dogs were trained on a total of 10388 sample presentations and over a period of 7 days using the Detection Dog Training System, a system that allows sample presentation in an automated and randomised way, without the interference of the trainer. Furthermore, during each trial, the study observer along with the dogs and their handlers were always blinded. During the actual study, 1012 double-blinded, randomised and automated sample presentations were done. The average detection rate was 94% with a sensitivity ranging from 67.9% to 95.2% (with an average of 82.63%) and a specificity ranging from 92.4% to 98.9% (with an average of 96.35%). With this high detection rate, the authors concluded that dogs can be trained over a short period of time to detect patients infected with COVID-19. Specificity for all dogs was high with a small range of variation indicating low risk of false positive. Conversely, sensitivity was lower with a wide range of variation indicating high risk of false negative; this could be due to the short training period and dogs' training backgrounds. Also, positive samples were collected from severely ill patients and not from presymptomatic or asymptomatic individuals, and this could have affected the results.

Similar studies to the ones noted above are taking place in several countries, all with the same purpose: detect COVID-19 early in the course of the disease. In the USA, eight dogs are being trained to detect odours samples of COVID-19 infected persons. The study is being conducted at the Working Dog Center (University of Pennsylvania School of Veterinary Medicine) with hopes to have good results. In the UK, six dogs are also being trained on odour samples (later on urine and saliva samples) at the London School of Hygiene and Tropical Medicine in the aim of becoming able to screen everyone and even detect the asymptomatic.[44] In Chile, four dogs are being trained on sweat samples of infected and healthy individuals, with the aim in case of success to use dogs as biodetectors of COVID-19.[45] A pilot study that was conducted in Finland at the University Of Helsinky also seems promising. Trained dogs were able just in few weeks to distinguish between urine samples of infected and healthy individuals. Given this, the Finnish researchers are now preparing a double-blinded and randomised study.[46] In addition, trials were conducted by UAE's Ministry of Interior using K9 police sniffer dogs trained to detect armpits of infected persons. Results were favourable with a 92% accuracy rate.[47] For this, the UAE has recently implemented this detection method with trained dogs stationed across its airports; it is believed to be the first in the world to do so.[48]

DISCUSSION

This review showed that trained dogs can detect COVID-19 cases by smelling body fluids secretions. Available evidence shows promising results in terms of sensitivity and specificity of the test. The main concern when discussing the data is the external validity. External validity relates to the reproducibility of the study results when implemented in the real-life operational setting. Edwards *et al* described in their article a multitude of factors that could affect the performance of the dogs as disease detectors when not in the experimental setting.[10] First, the negative and positive samples used to train the dog must be comparable on every point except for the disease marker. Several confounding factors may interfere in creating unwanted associations like getting the dog associate the tobacco with samples from patients with lung cancer because of the high frequency of smokers in these samples. This would result in negating the presence of cancer for all non-smokers. Usual matching factors like age, sex and ethnicity may not be sufficient when choosing positive and negative samples for dog training and additional factors must be considered to avoid confusion. Second, the preparation of the samples when done in different locations or time may lead to false association of the dog response with VOCs specific to the location, the time or season of preparation of the samples rather than to volatiles specific to the disease. The attempts to avoid contamination between positive and negative samples used to train the dogs by strict separation in place and time of preparation may lead to systematic differences between the samples that are not specific to the disease. The dogs would perform well during training sessions, but the learning would not translate into disease detection ability outside the study samples used. Third, using different samples from different fluids of the same person or from a limited number of persons may lead to false associations with volatiles specific to the source person of these samples and not to the disease impeding on the generalisation ability of the dogs to detect the disease in different types of samples and settings. This raises also the importance of samples preparation and choice to tune the generalisation and discrimination of dogs,thus avoiding excessive generalisation leading to positive response in presence of other coronavirus or even other viruses like influenza. Fourth, the trainer blindness to the positivity of samples is an important factor because the dog ability to detect cues in the trainer behaviour may increase the correct answers rate in presence of the unblinded trainer while this cuing effect will not be present in operational setting. Fifth, the training samples should be set for a prevalence of positive samples that will reproduce the prevalence in the target population. The prevalence of positive samples is shown to be inversely correlated with the rate of miss errors.[10]

For screening tests in an epidemic context, test sensitivity is most important to avoid keeping false negative cases with potential risk of disease transmission. The test has sensitivity above 80% in most cases with the important note that this sensitivity is easier to reproduce in real life setting than PCR study results if training rules cited above are respected. PCR sensitivity is compromised by the time lost between sampling and result declaration in addition to the possible gap between technical performance of study investigators and real-life performers of the sampling procedure. Specificity is also above 90% meaning that the test would generate a small number of false positive results making additional tests and anxiety inducing measures for persons a minor problem if managed by professionals. This approach could have prognostic implications in detecting cytokine storm by specific volatilome recognition and this would be another possible advantage. However, more evidence is needed to be able to describe standardised measures concerning the best use of this method according to disease evolution as available evidence have shown slightly better results for patients in the presymptomatic or at the beginning of their symptomatic phase rather than those in severe state or those who already received treatments. This emphasises the potential role of this method in screening and detection in outpatient and ambulatory setting.

Some details need to find answers in future research like the best fluid to test, the time of possible detection according to disease evolution, risks associated with the dog exposure and the performance of the test in operational settings. The operational procedures need also detailing especially on topics related to the dog ability to detect the disease over time and possible extinction effect. The validation of dogs' training is another point to develop to standardise the testing capacity and train dogs with the best generalisation to discrimination ratio according to the intended application of the test. Finally, the mean of interaction between the tested person and the dog needs to be standardised and diversified, taking into consideration that some school aged children or adults may have difficulty or fear of getting in close contact with dogs.

Fighting the COVID-19 pandemic is a matter of balance between saving lives and preserving economic activity.[49] Lockdown measures are no doubt the most effective measure to flatten the curves but the economic impact is unaffordable for most countries.[50] Households with poor income face the double edged risk of getting infected with SARS-CoV-2 or suffering from reduced income especially in developing countries and every country with limited social support.[51] Smart strategies are developed to find the good balance between keeping the best possible economic activity while keeping the epidemic under control.[50] Universal testing has been suggested by several experts as a good mean to screen, detect and isolate cases in a massive and repetitive way.[52] Romer suggests a rate of 7.5% daily screening of the US population in order to achieve a safe and successful reopening based on simulation studies.[53] A number hardly achievable for most countries with cost, production capacity and field implementation barriers. Universal testing approach requires to adopt according to Cherif and Hasanov an epidemiological rather than a clinical method.[52] This implies accepting screening methods with less performance in terms of sensitivity and specificity in favour of lower cost applicability and easiness of performance. This will allow to achieve a higher screening rate with the possibility to perform a sustained screening effort during the pandemic period.

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Self assessment questions

1. Dogs' have the ability to detect different infectious, metabolic and other diseases by sniffing.
2. The smelling capacities of dogs is similar to those of human olfactory abilities.
3. The volatile organic compounds produced in human cells are detectable by dogs.
4. The volatile organic compounds are not variable between individuals and are produced in the same concentrations.
5. The COVID-19 positive persons have a different armpit sweat odour than COVID-19 negative persons.

Conventional screening and diagnostic tests adopted for COVID-19 have been used worldwide. Production of these tests is limited by human and non-human factors.[54] Reverse transcriptase PCR rt-PCR testing has been the reference test for detection of the virus RNA. Other tests aiming to detect the viral antigen have been developed with different levels of sensitivity and specificity for detection. All the abovementioned tests need proper sampling and manipulation techniques to give the best performance. Antibody detection has been also suggested as an adjunct for diagnostic purposes.[55] It will usually test positive few days after the onset of disease needing a blood sample. All these tests require huge increments in production to make them available on a local and global scale to subside to the increasing needs of scaling up testing. When testing regularly and extensively, patient acceptance and comfort with the testing procedure is another player. For example, performing repetitive and large-scale PCR for students after school opening may be a source of disturbance for school aged persons. Cost is also a major barrier to universal testing application especially in developing countries and countries with economic difficulties.

For all what has been stated, we think that fighting COVID-19 pandemic while keeping the economy alive needs a smart strategy, applying universal screening using tests with good performance, low cost and easy application for large-scale use. Possible applications of dogs as COVID-19 detectors are schools reopening, airway passengers screening, religious gatherings and any other situation where rapidly performed, efficient, noninvasive tests are needed with point of care possibility to get immediate results.

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Contributors MZ conceived and designed the study. RS, CG, CR, VL, and RR performed the literature search. RS, CG, CR, VL, RR, and MZ drafted the manuscript. RS, CG, CR, VL, RR, MZ, and CH critically revised the manuscript. All authors read the manuscript, revised it for intellectual content, and approved the final version.

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Answers

1. True
2. False
3. True
4. False
5. True