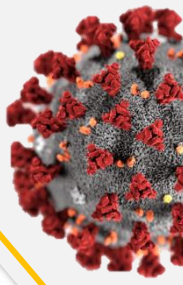
COVID-19 BREATHANALYSER SCREENING TOOLS



PURPOSE

To provide scientific evidence on the effectiveness, safety and cost-effectiveness of breathanalyser tests for the detection of COVID-19.

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged rapidly and caused a great mortality. As of November 9, 2021, there have been 250,154,972 confirmed cases of COVID-19 worldwide, with 5,054,267 deaths.[1] The molecular tests Real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) technology is the recognised method by the World Health Organization (WHO), US Center for Disease Control (CDC) and Ministry of Health Malaysia for confirmation of COVID-19 case but this method require a swab sample, trained staff with time consuming laboratory procedure.[2] As a result, there is a delay of hours to many days between when tests are taken, and results are obtained. Thus, finding fast and portable test for screening people who may have increase risk of pathogen contact is important.

This different approach in diagnosing coronavirus is a diagnostic medical device enabling the user to test the presence of COVID-19 in an exhaled breath. There are several countries that has attempted to develop the COVID-19 breathanalyser such as Singapore, England, Israel, United states, Indonesia, Finland and China. The development of COVID-19 breathanalyser is to develop a highly accurate and affordable screening tool that can be used anywhere and deliver result in real time. The technology may allow mass screenings in the high human traffic facility such as airports and public events.

EVIDENCE/INFORMATION SUMMARY

A pre-print systematic review and meta-analysis was conducted to study the diagnostic performance of volatile organic compounds (VOC)-based breath analysis for diagnosing SARS-CoV-2 infection. Six studies were included with a total of 4,093 samples from various settings.[3] The included studies utilised various products of breathanalyser as the index test and RT-PCR as the reference standard. Cumulative results were calculated from pooled outcomes of six included studies. Sensitivity value is reported to be at 98.2% (97.5% CI; 93.1%-99.6%) and specificity of 74.3% (97.5% CI; 66.4% - 80.9%). Subgroup analysis on chemical analysis (GC-MS) and pattern recognition (eNose) revealed higher sensitivity in the eNose group. This high sensitivity value supports the potential of breathanalysis screening method to identify more people with COVID-19 as COVID-19 patients showed a distinct pattern of VOCs.[3]

A company from the National University of Singapore (NUS) called Breathonix Pte Ltd have developed a COVID-19 breathanalyser called The BreFence™ Go.[4] It is a real-time, non-invasive COVID-19 breath test system intended for the qualitative detection of VOCs in the human breath.[5] The exhaled breath collected will be fed into a cutting-edge mass spectrometer for measurement.[4] A machine learning software analyses the VOC profile and generates the result in less than a minute.[5] Disposable mouthpiece with a one-way valve and a saliva trap is used to prevent inhalation and any saliva from entering the breathalyser platform and avoid cross-contamination.[5] This breathanalyser use a non-AI algorithm with an accuracy of 85% sensitivity and 97% specificity. The National University of Singapore conducted a pilot clinical research including 180 patients to evaluate the breathanalyser using breathonix technology, and the developer stated that more than 90% accuracy was obtained, with sensitivity of 93% and specificity of 95%.[5] No further information on the study in terms of comparator used was obtained. Currently, another trials are being conducted at Nadd Al Hamar, Dubai primary health care centre with 2500 patients. This breath test system has attained provisional authorisation from Singapore's Health Science Authority (HSA) in May 2021.[6] According to the developer, the tests would be sold for between S$5-S$20 (MYR 15.42-61.68; 1 SGD=MYR 3.08) each, depending on the number purchased.[6] This breath test is more affordable than a PCR swab test and does not require a trained healthcare professional to operate.[7]

Figure 1: BreFence™ Go COVID-19 Breath Test System[5]

Besides that, a team led by Professor Hossam Haick and Dr. Yoav Broza of the Technion Faculty of Chemical Engineering and Russell Berrie Nanotechnology Institute, in collaboration with researchers from Wuhan, China, has developed a novel breath analyser test that can rapidly detect COVID-19 from specific VOCs in exhaled breath.[8] The rationale behind approach of

nanomaterial-based sensor array for detection of COVID-19 in exhaled breath relies on findings that viral agents and/or their microenvironment emit VOCs that can reach the exhaled breath. The sensors are composed of different gold nanoparticles linked to organic ligands, creating a diverse sensing layer that can swell or shrink upon exposure to VOC, causing changes in electric resistance. During exposure, VOCs diffuse into the sensing layer or fall on the sensing surface and reacts with the organic segment or the functional groups capping the inorganic nanomaterials. The interactions cause a volume change (swelling/ shrinkage) in the nanomaterial film. As a result, the contacts among the inorganic nanomaterial block the change (higher/lower) with an increase/decrease of conductivity. The nanomaterial layer exposure to VOCs causes a swift charge transfer to/from the inorganic nanomaterial, producing variations in the measured conductivity even when no steric changes occur within the sensing layer.[8]

A registered company in United States named Canary health Technologies is also developing a breathanalyser called ASU Detect CV-19™.[9] The breathanalyser uses a disposable nanosensors with artificial intelligence-powered cloud-based analysis and utilises targeted VOC. A clinical trial was conducted at the end of 2020 but no further information on the clinical trials and update obtained from the developer.[9]

In Finland, there are collaboration with Finnish Software Firm Deep Sensing Algorithms (DSA), funded by the Helsinki-Uusimaa Regional Council in developing the COVID-19 breathanalyser. The DSA BreathPass™ uses a non-invasive method for detection of COVID-19 caused by the SARS-CoV-2 coronavirus.[10] The device measures the exhaled breath for 15 to 30 seconds, characterizes the VOCs within breath samples, produces predictions for different health conditions based on Deep Computing algorithms and generates results in few seconds. The DSA BreathPass™ can be used through the Mobile Application and Web-UI.[10]

Figure 2: DSA BreathPass™

A clinical test of the DSA COVID-19 Analyzer is carried out in June 2020 in collaboration with DSA and City of Helsinki Health Department to evaluate the performance of the DSA Analyzer, its sensitivity and specificity against Covid-19 infection based on exhaled gas samples. However, no further information on the results or updates of the clinical test could be obtained.[11]

On the other hand, India and Israel are jointly developing a 30-second COVID-19 breathanalyser test based on terahertz waves. Currently the company is carrying out a comprehensive validation experiment, which includes large number of subjects at the Shamir Medical Center in Israel. As part of the test development, this trial is aimed at challenging the technology in order to make it operational as soon as possible. From preliminary evaluations of the results, the test showed over 90% accurate in detecting coronavirus-positive patients.[12] The company has started preparing for

device approval application to the FDA and initiated an additional study using the same technology to test the efficacy of the vaccine in patients. In addition to the clinical trials, the company is in the process of merging with the shell company BioMed NextGen (TASE:NXGN) in Israel.[12]

Exhalation Technology Ltd (ETL) in Cambridge announced their clinical trial for its CoronaCheck™ breath test for Covid-19 earlier this year.[13] Professor Anoop Chauhan led the clinical trial programme for CoronaCheck™, which involved a cohort of 150 patients being tested in clinical trial at the Respiratory Medicine, Queen Alexandra Hospital in Portsmouth. CoronaCheck™ offers a non-invasive, fully automated test for SARS-CoV-2 in Exhaled Breath Condensate (EBC). The sensor offers high specificity and sensitivity, test results in less than 5 minutes and a cost per test which is aimed to be under £8 (MYR 45.05; 1 GBP=MYR 5.63). CoronaCheck™ builds on the CE-marked Inflammacheck® device, the only device on the market that collects EBC and tests for its constituents right at the point of care (PoC).[13]

Figure 3: CoronaCheck™ breathanalyser[13]

Recently, researchers at Ohio State University managed to develop a breath test for COVID-19. This novel breathanalyser technology uses nanosensors to identify and measure specific biomarkers such as specific combination of oxygen, nitric oxide, and ammonia in the breath. The research on this device was approved by the Ohio State University Biomedical Sciences Institutional Research Board (IRB) and Institutional Biosafety Committee (IBC).[14] A total sample size of 39 patients admitted to the intensive care unit (ICU) requiring mechanical ventilation were recruited. Patients with early COVID-19 infection (within 72 hours of beginning of respiratory failure) had the typical omega pattern, according to the breath detector analysis.[14] Overall, 14 (88%) of the 16 individuals who tested positive for COVID-19 on research day 1 had the omega pattern ($p<0.0001$). The breathanalyser had negative predictive value of 90%.[14] The two patients who had false negative breathanalyser results were both relative remote from onset of COVID symptoms (8 and 20 days respectively) when they had respiratory compromise and diagnosed with bacterial pneumonia, implying that their respiratory failure was not caused by the virus. The four patients who had false positive breathanalyser tests were admitted to the hospital for a variety of reasons (stroke, pneumonia, and cirrhosis).[14] Given that two of the patients had cirrhosis, increased ammonia from their underlying cirrhosis could have caused the false positive result. Overall, the amplitude of the omega pattern was associated with days from clinical onset of COVID-19 pneumonia among all COVID-19 patients ($R^2 = 0.12$, $p = 0.037$). However this study have several limitations such as small sample size, no documentation of the signal pattern of other coronavirus and no study done on the signal pattern at baseline level after COVID-19 infection.[14]

CONCLUSION

In conclusion, there are several COVID-19 breathanalysers that are currently being developed by different groups in several countries. Some of the breathanalyser have successfully being marketed. This innovative noninvasive nanomaterial based hybrid sensor may have potential for early detection of novel coronavirus for rapid large population screening in a short period of time, active-case searching in the community and affordable point-of-care diagnostic tool.

Several studies have shown that VOC-based breath analysis has a high sensitivity and negative predictive value, as well as a quick and easy technique, indicating that it has a strong potential for COVID-19 screening in public settings. However, further evaluation,validation and verification process with larger sample size in our community setting is required to ascertain its effectiveness and safety.

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Based on available evidence up to 9th Nov 2021

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Disclaimer: This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

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