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

Recently, the outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged rapidly and caused a great mortality. In the past week, over 3.3 million new cases have been reported globally. As of 26th of November, there have been 59,481,313 confirmed cases of COVID-19, including 1,404,542 deaths have been reported globally.[17]

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.[18] 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.

There are several countries that has attempted to develop the COVID-19 breathanalyser such as China, United States, Finland, Israel, England, Australia and Germany.The goal of 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.[2]

A team led by Academic Chair 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 volatile organic compounds (VOCs) in exhaled breath.[11]

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.[13] It was discovered that the human exhaled breath is a complex mixture containing over 3,000 VOCs.[1] VOCs in human breath for detection could prove to detect diseases before the onset of symptoms, earlier than any of the current methods, easy to administer, and it does not require specially-trained staff or laboratory processing. A person only needs to blow into a disposable mouthpiece connected to a high-precision breath sampler.

Thus, the emergence of VOC in exhaled breath may serve as immediate detection of COVID-19. 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. The inorganic nanomaterials are responsible for the electric conductivity, with the organic film element providing sites for the adsorption of VOCs. 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. [13]

A registered company in United States named Canary health Technologies is also developing a breathanalyser with disposable nanosensors using Artificial Intelligence-powered cloud-based analysis and utilizing targeted VOC. The clinical study is expected to start this month and aim to map the COVID-19 signature bio-pattern longitudinally, evaluating disease progression in COVID-19 positive patients using a novel breath-based rapid diagnosis.[1]

In Finland, there are collaboration with Finnish Software Firm Deep Sensing Algorithms, funded by the Helsinki-Uusimaa Regional Council in developing the COVID-19 breath analyser. The concept is both ideally sensitive and selective real time method of identifying the Covid-19 infection caused by the SARS-CoV-2 virus. The Covid-19 ‘breathprint’ of a person is reconstructed on the basis of the metabolites extracted from the samples of exhaled breath. The approach yields excellent sensitivity and specificity for the prediction based on a set of VOC. The gases will be measured by a set of nanostructured sensors. The VOCs targeted by the DSA Analyzer are derivatives of the biomarkers such as: Cardiac Troponins, C-reactive proteins, Cystatin C, D-dimer, Myoglobin, NT-proBNP, Procalcitonin, Human Serum Amyloid A, or Albumin.[7]

Deep Sensing Algorithms (DSA) company have started to manufacture the DSA Analyzer and are preparing for mass production. Currently, the analyser is available in limited volumes. The DSA Analyser is a handheld breathanalyser that consist of configured nanosensors.[6] Meanwhile in Australia, the concept of breathanalyser is still in the early stages of development.[7]

Besides that, there are another company from the National University of Singapore (NUS) called Breathonix Pte Ltd developed a breath test to detect COVID-19. A person only needs to blow into a disposable mouthpiece connected to a high-precision breath sampler. The exhaled breath is collected and fed into a cutting-edge mass spectrometer for measurement. A machine learning software analyses the VOC profile and generates the result in less than a minute.[10] Disposable mouthpiece with a one-way valve and a saliva trap is used to prevent inhalation and any saliva from entering the Breathonix breathalyser platform and avoid cross-contamination.

Figure 1: Breathonix breathanalyser

On the other hand, India and Israel are jointly developing 30-second COVID-19 breathanalyser test based on terahertz waves. The team of researchers are currently conducting trials using a large number of samples. The test is expected to be less costly and will be able to deliver results on-site which eliminate logistics as well as the cost involved for sending samples to the laboratory.[9]

EVIDENCE/INFORMATION SUMMARY

The efficacy of the reported nanotechnology was evaluated via a case-control clinical study conducted during March 2020 on 140 participants by Shan et al using multiplexed nanomaterial-based sensor array. Participants were selected based on three distinct groups of COVID-19 patients, healthy controls and non-COVID-19 lung infection controls. Discriminant analysis of the obtained signals from the nanomaterial-based sensors achieved very good test discriminations between the different groups (COVID-19, healthy controls and lung infections). Results showed an area under the curve (AUC) of 0.81 [95% CI; 0.70, 0.89] in patients with COVID-19 when compared with controls, 0.97 [95% CI; 0.92, 0.99] in COVID-19 vs other lung infection/conditions, and 0.87 [95% CI; 0.67, 1.00] in COVID-19 first sample vs COVID-19 second sample. Significant results ($P<0.001$) was obtained for the comparisons of the training set for each of the binary classifications. The main comparison between COVID-19 and healthy controls group give 100% sensitivity and specificity.[13]

However, Shan et al was concerned that the case-control design could overestimate sensitivity and specificity, so a larger cohort study is required to validate the results. The results presented apply only to a prediagnosed patient population in China, for which disease duration may vary; further studies for asymptomatic or presymptomatic persons are required in different settings and breath measured is composed of respiratory gases, VOCs, and humidity; humidity changes in breath might influence the way sensors work and could have caused relatively low specificity. [13]

In a pilot clinical trial done to test the breathanalyser with breathtonix technology by the National University of Singapore involving 180 patients, it was mentioned by the developer that more than 90 per cent accuracy was achieved, with sensitivity of 93%, and specificity of 95%. No further info on the study in term of comparator used was obtained. According to the developer, more trials will be required to improve and validate the accuracy of the technology. The clinical trial is ongoing, and more tests are required to further improve the accuracy of the breathonix technology.[10]

The DSA Covid-19 Analyzer Health developed by research team in Finland is using a nanotechnology-based gas sensor system for detecting and analyzing biomarkers of the gaseous exhaled breath air samples. 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 for evaluating the performance of the DSA Analyzer, its sensitivity and specificity against Covid-19 infection based on exhaled gas samples.[7] However, no further info on the result of the clinical test could be obtained.

The DSA Covid-19 breathanalyser specification is as table belows:

Analysis medium	Exhaled Breath Gas
Sampling Time	30 sec
Dimensions	60 x 60 x 190 mm
Weight	250 g
Operating Temperature	0 - 55 Celsius
Ambient humidity	10 - 80% non-condensing
Input Voltage	Nominal 10 - 24 VDC
Input Current	0.5 - 1.5 A; voltage dependent
Battery (option)	Li_Ion / Li-Poly / 2 AA
Daily power consumption	35 Wh
Voltage	7.2 V (2 Li cells in series)
IP-class	IP20
IoT	WLAN 2.4 GHz / 4G
VOC Sensors	9 analog / digital nanosensors on separate sensor module
Environmental Sensors	T [C], RH[%], P[mbar]
Compatibility	EMC (2014/53/EU)
Software	Over-the-air (OTA) updates, sensor regulation and calibration
Covid-19 recognition	Deep Computing Algorithms

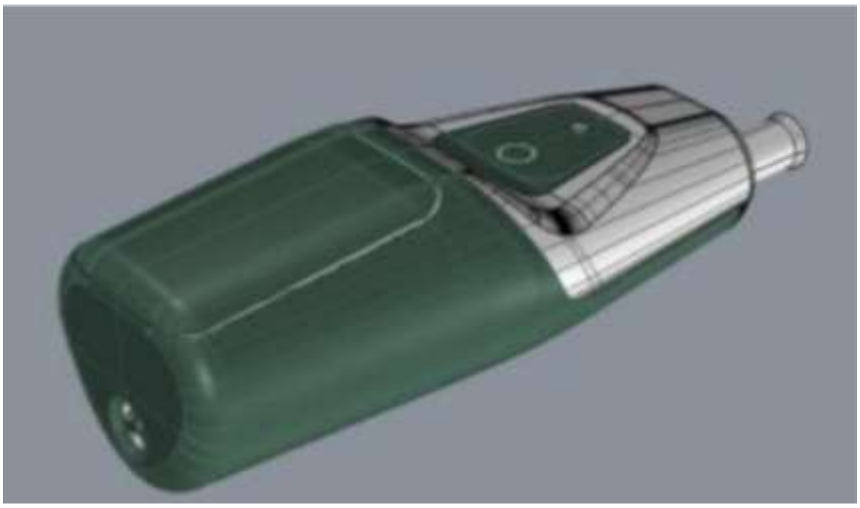

Figure 2: The DSA COVID-19 Analyser. The breath samples are given through a replaceable mouth piece (upper right hand corner), the outgoing air is filtered by a HEPA filter module (lower left hand corner). The device uses a local data network for communicating with the cloud applications.

CONCLUSION

In conclusion, there are several COVID-19 breathanalysers that are currently being developed by different groups in several countries. 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.

Limited study showed good specificity and sensitivity of the tests to discriminate and screen COVID-19 and lung infection, COVID-19 and healthy controls simultaneously as well as confirming COVID 19. However, further evaluation,validation and verification process with larger sample size is required to ascertain its effectiveness and safety.

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Based on available evidence up to 26th Nov 2020

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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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