A NON-INVASIVE METHOD FOR DETECTION OF COVID-19 VIRUS CAUSED BY CORONAVIRUS, SARS-CoV-2

SUMMARY

Deep Sensing Algorithms is introducing technology for a 2-minute COVID-19 diagnosis using exhaled breath sampling. With rapid testing, healthcare providers can perform SARS-CoV-2 testing outside the traditional four walls of a hospital in outbreak hotspots.

If distributed effectively, the test could help expand national testing capacities, better allowing public health experts to understand which populations are most at risk of infection and helping state and federal officials better to plan response strategies. As well as preventing lock-down situations when virus carriers can't be identified.

Such a test would also dramatically reduce testing backlog. The novel test approach could be a game changer in dealing with the outbreak and its second coming. When validated, the new test would give fast point of care in real time, and potentially be more accurate than the traditional molecular test modalities.

The clinical manifestations of a Covid-19 patient normally present as a combination of one or more of the following signs of infection: fever, tiredness, dry cough, shortness of breath, aches and pains, sore throat, diarrhea, runny nose and also a temporary loss of smell/taste – anosmia.

These representations of the SARS-CoV-2 virus infection follow from the oxidative stress, activation of the immune system, and the specific processes taking place as the Covid-19 infection progresses within the host. As a consequence, biomarkers that are generic to respiratory infections caused by seasonal flu and SARS viruses are generated together with the biomarkers that are specific to the SARS-CoV-2 manifestations in humans.

Deep Sensing Algorithms' novel Covid-19 Analyzer method and apparatus uses exhaled breath gas for identifying and monitoring. The method is non-invasive, fully integrated with the DSA VOC analyzer and realized as a full-born IoT device. 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.

The DSA Covid-19 Analyzer Health 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[1] gases measured by a set of nanostructured sensors.

[1] Volatile Organic Compounds – VOCs – are often associated with characteristic odors, although some volatiles may also be odorless.

1. BACKGROUND

SARS-CoV-2 VIRUS

The SARS-CoV-2 virus has been a nuisance for us for some months now, but already now we can determine where the virus came from and why it behaves in such a diabolical way. One of the few positive aspects of the crisis is that individual coronaviruses are easily destroyed. Each viral particle consists of a small number of genes enclosed into fatty lipid molecule spheres. The lipid shells of the spheres are easily ruptured by soap and a thorough hand wash for 20 seconds rinses the viruses into the sewer. Lipid shells are environmentally sensitive; research shows that the coronavirus, SARS-CoV-2, survives for only 24 hours on a cardboard and a couple of days on a steel or plastic surface. Viruses are not viable on their own, but they need their host - us.

Coronavirus is not yet well known. The preparations for the SARS epidemic of 2002 were seriously lacking, and with the SARS-CoV-2 virus now causing the global Covid-19 pandemic, research is finally gaining an effective boost.

For clarity: SARS-CoV-2 is not a flu. The virus causes a disease with many types of symptoms and spreads and kills more easily. It belongs to a special family of coronaviruses with only six other human infectious members. Four of these - OC43, HKU1, NL63 and 229E - have plagued people for more than a century, causing a third of common colds. The other two - MERS and SARS (or "classical SARS" as some virologists have started calling it) - cause far more serious illnesses. Why did this seventh coronavirus then become a pandemic?

SARS-CoV-2 VIRUS STRUCTURE

The structure of the virus explains its frighteningly efficient spread (Figure 2). The shape of the virus is mainly a spiny ball. The peaks recognize a protein called ACE2, which is found on the surface of the cell and adheres to it. This is the first step of the infection. The peak geometry of the SARS-CoV-2 virus allows efficient adhesion to ACE2, just like with the classic SARS virus, and it is likely that this particular feature of the virus helps it to efficiently transfer between humans. The tighter the virus binding, the less viruses are needed to start the infection.

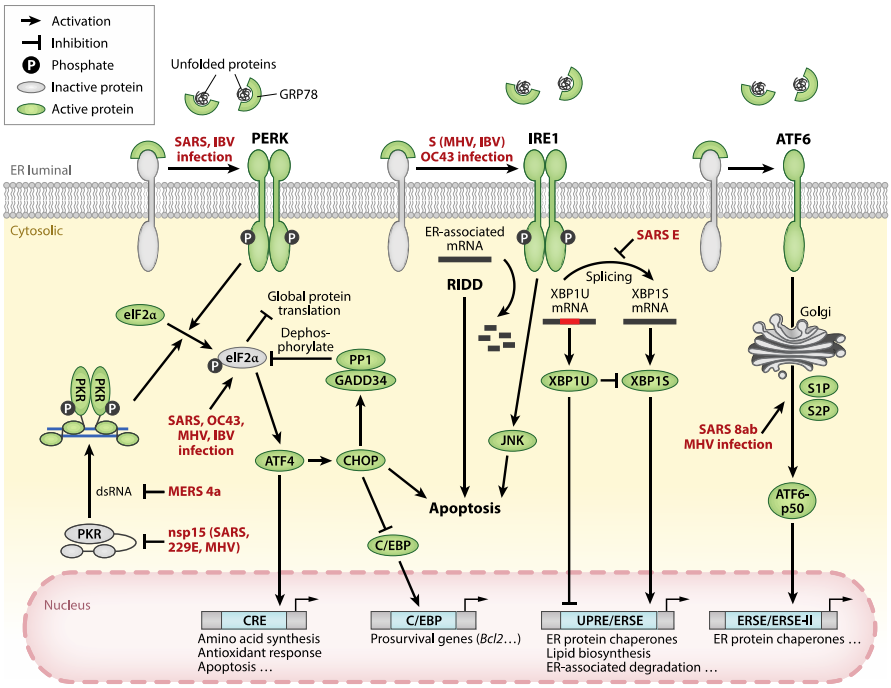

Figure 1: *Induction and modulation of unfolded protein response by HCoV infection. Schematic diagram showing the three branches of UPR signaling pathway activated and regulated by HCoV infection. Viruses and viral components modulating the pathway are bolded in red. Abbreviations: ATF6, activating transcription factor 6; C/EBP, CCAAT enhancer binding protein; CHOP, C/EBP-homologous protein; CRE, cAMP response element; eIF2α, eukaryotic initiation factor 2 subunit α; ERSE, ER stress response element; GADD34, growth arrest and DNA damage–inducible 34; GRP78, glucose-regulated protein, 78 kDa; HCoV, human coronavirus; IBV, infectious bronchitis virus; IRE1, inositol-requiring enzyme 1; c-Jun N-terminal kinase; MERS, Middle East respiratory syndrome; MHV, mouse hepatitis virus; PERK, PKR-like ER protein kinase; PKR, protein kinase RNA-activated; PP1, protein phosphatase 1; RIDD, IRE1-dependent mRNA decay; SARS, severe acute respiratory syndrome; UPR, unfolded protein response; UPRE, unfolded protein response element; XBP, X-box-binding protein.*

Another key feature of the virus is its structure: the coronavirus peaks consist of two interconnected halves, and the peak is activated when its halves are separated - only then can the virus enter the host cell. In the classical SARS virus, the virus halves are only slightly different, but in SARS-CoV-2, the bridge connecting the halves is easily broken by an enzyme called furin. Human cells produce high levels of furin, which is found in many of our tissues. This has proven to be a key factor in the spread of the SARS-CoV-2 virus.

SYMPTOMS OF COVID-19

Most respiratory viruses tend to infect either the upper ***or*** lower respiratory tract. Generally, upper respiratory tract infections are easier to spread but less severe, while lower respiratory tract infections are most difficult to spread but more severe. SARS-CoV-2 appears to contaminate ***both*** upper and lower respiratory tract probably because of the abundance of furin. This double wax can also explain why the virus can spread between people before symptoms appear - a feature that has made it difficult to control. The virus appears to be still limited to the upper respiratory tract before heading deeper and causing severe symptoms. However, the model is still hypothetical; the virus was only discovered in January and most of its biology remains to be determined.

FROM THE SARS-COV-2 VIRUS ORIGIN

The new virus effectively infects humans regardless of their animal origin. The closest wild relative of the SARS-CoV-2 virus is found in bats, suggesting that the virus was transmitted to humans either directly or through another species.[2] When the classic SARS virus made a leap to humans, a short mutation time was required to identify ACE2. The SARS-CoV-2 virus was able to do it from the beginning. It had already found its best way to penetrate the human…

The virus's ability to spread to humans has encouraged conspiracy theorists: How is it possible that a random bat virus had exactly the right qualities to infect an unbelieving person? The explanation is trivial for biological evolution: there are billions of viruses, and this highly unlikely human transmission will inevitably occur over time.

Mutations in the SARS-COV-2 virus

Since the beginning of the pandemic, the virus has not changed in any significant way. It mutated like viruses in general. Of the more than hundreds of mutations already documented, nothing has proven to be dominant. The virus has thus been extremely stable, given its prevalence. From the biological evolution point of view, this makes sense because the virus has no evolutionary pressure to better communicate. It's already powerful enough to spread everywhere…

There is one possible exception. A few SARS-CoV-2 viruses isolated from Covid-19 patients in Singapore lack a gene defect that also disappeared from the classical SARS virus in the late stages of the epidemic. This change was thought to make the original virus less virulent, but it is too early to know if the same applies to SARS-CoV-2. Why some coronaviruses are deadly, and others not is a mystery. It is not understood why SARS or SARS-CoV-2 are so bad, but the OC43, for example, does little damage.

SARS-COV-2 Virus Infection Method

A preliminary description of how the coronavirus works is as follows: Once in the body, the virus is likely to attack ACE2-containing cells on our respiratory tract. Dead cells are wiped out, filling the airways and transporting the virus deeper into the body down toward the lungs. As the infection progresses, the lungs become clogged with dead cells and fluid, making breathing difficult.[3]

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[2] Coronavirus in wild pangolins also resembles SARS-CoV-2, but only a small part of its peak, which recognizes ACE2. The two viruses are otherwise similar, and the pangolins are unlikely to be the original carriers of the new virus.

[3] The virus may also infect cells containing ACE2 in other organs, including the intestine and blood vessels.

The immune system is activated and attacks the virus; this causes inflammation and fever. In extreme cases, the immune system goes into overdrive, causing more damage than the virus itself. An example of this is the blood vessels that may open to release cells of the immune system into the infected area. If the blood vessels become too tight, the lungs are filled with more fluid. These deleterious overreactions are called cytokine storms. They were the cause of many deaths during the 1918 influenza pandemic, the outbreaks of H5N1 avian influenza and the 2003 SARS outbreak. They are probably the cause for the most serious Covid-19 cases. These viruses take time to adapt to the human host. As they grasp, they do not yet know how to proceed, but soon learn - through trial and error - how to attack our cells.

During a cytokine storm, the immune system operates randomly without destroying the right targets. When this happens, people are more susceptible to infectious bacteria. Storms can affect other organs besides the lungs, especially in people with chronic illnesses. This may explain why some Covid-19 patients have complications such as heart problems and secondary infections.

THE CONSEQUENCES OF COVID-19 VIRUS INFECTION

But why do some Covid-19 patients become seriously ill while others survive with mild or nonexistent symptoms? Age is a factor. Elderly people are at risk for more serious infections, possibly because their immune systems are unable to respond effectively. Children suffer less because their immune systems are not yet exposed to the cytokine storm. Genetic inheritance, immune system function, viral load, and body microbes all have their own influence on the progress of infection. Within the same age group, SARS-CoV-2 virus can cause serious or very mild illness - the reason for is not explained.

Coronaviruses, such as influenza, are usually winter viruses. In cold and dry air, the thin layers of fluid covering the lungs and airways become even thinner, and in these layers the hair tends to evict viruses and other foreign particles. Dry air also appears to dampen the immune response to trapped viruses. In summer heat and humidity, respiratory viruses struggle to gain a foothold. Unfortunately, this may not play a role in the Covid-19 pandemic. The new virus spreads easily among others in Singapore (which is in the tropics) and Australia (where it's still summer). A recent model study concluded that "SARS-CoV-2 can spread at any time of the year".

It is not even known how many people get normal coronavirus infection each year. There are no coronavirus surveillance networks, as has been built for the flu. We do not know the seasonality of their occurrence or where they go in winter, and we do not know how these viruses mutate from year to year. So far, research has been slow. Ironically, the three-yearly conference where world coronavirus experts would have met in a small Dutch village in May has been postponed due to the coronavirus pandemic.

2. DETECTION OF COVID-19 VIRUS INFECTION

DETECTING SARS-COV-2 VIRUS

Table 1 summarizes the laboratories currently developing Covid-19 tests.

The real-time reverse transcriptase polymerase chain reaction (rRT-PCR)[4] can be performed on samples from the respiratory tract, e.g. nasopharynx swab sputum sample.[5] Results are available within a few hours to a few days.[6] Molecular methods utilize polymerase chain reaction (PCR)[7] in combination with nucleic acid tests and other analytical techniques to detect viral genetic material in the reverse transcriptase-polymerase chain reaction.

One of the early PCR tests was developed at Charité in Berlin in January 2020 using the rRT-PCR method; The WHO distributed 250,000 test kits based on the method.[8]

South Korea's Kogenebiotech developed a clinical PCR-based SARS-CoV-2 test kit (PowerChek Coronavirus) on January 28, 2020.[9] The test locates a common beta-coronavirus"E" gene, as well as the "RdRp" gene specific for SARS-CoV-2.[10] In February 2020, Korean companies Solgent and Seegene developed the DiaPlexQ and Allplex 2019-nCoV Assay clinical test kits.

In China, the BGI team was the first to receive an emergency use license from the Chinese National Medicines Agency for the PCR-based SARS-CoV-2 test kit.[11]

In the United States, the Centers for Disease Control and Prevention (CDC) distributes the Covid-19 RT-PCR real-time diagnostic panel to public health laboratories through an international reagent resource.[12] One of the three versions of the gene tester did not work due to faulty reagents and caused test problems at the Atlanta CDC. As a result, only fewer than 100 samples were processed per day during February of the current year. Tests using two components were only found to be reliable until February 28, 2020, when state and local

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4 "2019 Novel Coronavirus (2019-nCoV) Situation Summary". Centers for Disease Control and Prevention. 30 January 2020. Archived from the original on 26 January 2020. Retrieved 30 January 2020.

5 "Real-Time RT-PCR Panel for Detection 2019-nCoV". *Centers for Disease Control and Prevention*. 29 January 2020. Archived from the original on 30 January 2020. Retrieved 1 February 2020.

6 "Curetis Group Company Ares Genetics and BGI Group Collaborate to Offer Next-Generation Sequencing and PCR-based Coronavirus (2019-nCoV) Testing in Europe". GlobeNewswire News Room. 30 January 2020. Archived from the original on 31 January 2020. Retrieved 1 February 2020.

7 Thermal cycle, usually called the PCR-engine.

8 Sheridan, Cormac (19 February 2020). "Coronavirus and the race to distribute reliable diagnostics". Nature Biotechnology. doi:10.1038/d41587-020-00002-2.

9 *"KogeneBiotech (Homepage)". Kogene.co.kr. Retrieved 16 March2020; Jeong, Sei-im (28 February 2020). "Korea approves 2 more COVID-19 detection kits for urgent use - Korea Biomedical Review".*

10 *"ABOUT US | NEWS".*

11 "BGI Sequencer, Coronavirus Molecular Assays Granted Emergency Use Approval in China". *GenomeWeb*. Retrieved 9 March 2020.

12 "International Reagent Resource > Home". www.internationalreagentresource.org.

laboratories were allowed to begin testing.[13] The test was approved by the Food and Drug Administration with an emergency license.

US commercial laboratories began testing in early March this year, and as of March 5, 2020, LabCorp announced that it would be ready to deliver Covid-19 tests based on RT-PCR.[14] Quest Diagnostics released its nationwide Covid-19 test on March 9, 2020.[15] No limits were specified; the collection and processing of samples shall be in accordance with CDC requirements. In Russia, the Covid-19 test was developed and produced by the state research center for virology and biotechnology VECTOR. The test was registered by the Federal Health Service on February 11, 2020.[16]
The Mayo Clinic test series was reported on March 12, 2020.[17]

On March 13, 2020, Roche Diagnostics received FDA approval for its test, which could be performed within 3 hours and 30 minutes, with one device processing 4,128 tests within 24 hours.[18]

On March 19, 2020, the Abbott Laboratories authorized Abbott Laboratories to use the Abbott m2000 system; The FDA had previously granted similar authorizations to Hologic, LabCorp and Thermo Fisher Scientific.[19] Similarly, on March 21, 2020, Cepheid Inc received the EUA's FDA for a test that will be completed in about 45 minutes.[20]

A test using a monoclonal antibody that specifically binds to the new coronavirus nucleocapsid protein (N protein) is being developed in Taiwan; the goal is to get results in 15 to 20 minutes, just like a rapid flu test.[21]

[13] Transcript for the CDC Telebriefing Update on COVID-19, Feb 28. 2020.
[14] "LabCorp Launches Test for Coronavirus Disease 2019 (COVID-19)".
[15] Covid19 : COVID-19". *www.questdiagnostics.com*.
[16] В России зарегистрирована отечественная тест-система для определения коронавируса.
[17] Plumbo, Ginger. "Mayo Clinic develops test to detect COVID-19 infection". Mayo Clinic. Retrieved 13 March 2020
[18] www.ETHealthworld.com. "US regulators approve Roche's new and faster COVID-19 test - ET HealthWorld". ETHealthworld.com. Retrieved 14 March 2020
[19] "FDA Approves Abbott Laboratories Coronavirus Test, Company To Ship 150,000 Kits". IBTimes.com. 19 March 2020. Archived from the original on 20 March 2020
[20] "Sunnyvale company wins FDA approval for first rapid coronavirus test with 45-minute detection time". EastBayTimes.com. 21 March 2020. Archived from the original on 22 March 2020.
[21] *"中央研究院網站". www.sinica.edu.tw. Sinca. Retrieved 12 March2020.*

Table 1: *A list of laboratories currently developing SARS-CoV-2 tests according to WHO (6.3.2020).*

COUNTRY	INSTITUTION	GENES
China	China CDC	ORF1ab ja Nucleoprotein (N)
Germany	Charité	RdRP, E, N,
Hong Kong	HKU	ORF1b-nsp14, N
Japan	National Institute of Contagious Diseases, Dept. of Virology III	Pancorona etc., Spike-protein (Peplomer)
Thailand	NAtional Institute of Health	N
U.S.	US CDC	3 N-protein related targets
France	Pasteur Institute	2 RdRP-protein related targets

Chest CT scans

In X-ray and CT imaging, Covid-19 is identified as a disease-specific feature[22] that appears to be enhanced as the disease develops[23]. Comparison of the PCR test with CT scanning in Wuhan[24] concluded that CT scanning was significantly more ***sensitive*** but less ***specific*** than PCR testing. The results of CT imaging are often confused with those of other pneumonia-causing diseases.[25]

Chinese radiologists report 72-94% sensitivity and 24-94% specificity to distinguish Covid-19 from other types of viral pneumonia in CT imaging.[26] Convolutional neural networks based on Deep Computing techniques have been used to identify the symptoms caused by the SARS-CoV-2 virus on X-ray and CT imaging[27].

The CDC recommends that the PCR test be used for Covid-19 screening because of its specificity.

Detection of antibodies

The immune response to infection produces a number of antibodies such as IgM and IgG. Antibodies can be used to detect infections, determine the state of immunity, and monitor the population for one week after the onset of symptoms.
Tests are performed in Central Laboratory (CLT) or Treatment Point (PoCT) tests. Automated systems in clinical laboratories are capable of passing tests, but their effectiveness varies. One peripheral blood sample is commonly used with CLT, although serial samples can be used to monitor the immune response. For PoCT, a single blood sample is usually obtained from the skin. Unlike PCR methods, the extraction step is not required prior to the assay. In the United States, the aim is to make the nursing exam available by March 30.[28]

A blood test for the detection of antibodies is underway on March 9, 2020. A rapid test at the clinic can be used to assess whether a person has been infected in the past; the test works

[22] Salehi, Sana; Abedi, Aidin; Balakrishnan, Sudheer; Gholamrezanezhad, Ali (14 March 2020). "Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients". American Journal of Roentgenology: 1–7. doi:10.2214/AJR.20.23034. ISSN 0361-803X. PMID 32174129.
[23] Lee, Elaine Y. P.; Ng, Ming-Yen; Khong, Pek-Lan (24 February 2020). "COVID-19 pneumonia: what has CT taught us?". The Lancet Infectious Diseases. **0**. doi:10.1016/S1473-3099(20)30134-1. ISSN 1473-3099. PMID 32105641. Retrieved 13 March 2020.
[24] The original epicenter of the current pandemia.
[25] Ai, Tao; Yang, Zhenlu (26 February 2020). "Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases". *Radiology*. Radiological Society of North America: 200642. doi:10.1148/radiol.2020200642. PMID 32101510
[26] Bai, Harrison X.; Hsieh, Ben; Xiong, Zeng; Halsey, Kasey; Choi, Ji Whae; Tran, Thi My Linh; Pan, Ian; Shi, Lin-Bo; Wang, Dong-Cui; Mei, Ji; Jiang, Xiao-Long; Zeng, Qiu-Hua; Egglin, Thomas K.; Hu, Ping-Feng; Agarwal, Saurabh; Xie, Fangfang; Li, Sha; Healey, Terrance; Atalay, Michael K.; Liao, Wei-Hua (10 March 2020). "Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT". *Radiology*: 200823. doi:10.1148/radiol.2020200823. ISSN 0033-8419. PMID 32155105
[27] Heaven, Will Douglas. "A neural network can help spot Covid-19 in chest x-rays". *MIT Technology Review*. Retrieved 27 March 2020.
[28] Commissioner, Office of the (21 March 2020). "Coronavirus (COVID-19) Update: FDA Issues first Emergency Use Authorization for Point of Care Diagnostic". FDA. Retrieved 23 March 2020.

regardless of whether the person has symptoms or not.[29] The test results are intended to be used within 15 minutes for both IgM and IgG antibodies.[30]

3. NON-INVASIVE COVID-19 TESTING

Covid-19 Breath Metabolites

A non-invasive approach in identifying the Corona virus carrying individuals is here proposed based on the analysis of exhaled volatile organic compounds (VOC). In adults, several studies have independently shown that VOC can differentiate between patients with asthma, patients with chronic obstructive pulmonary disease and healthy controls[31]. In children with established asthma, volatile biomarker analysis enabled prediction of subsequent exacerbations[32]. A recent study[33] showed that children with preschool wheeze have different VOC when compared with their healthy counterparts. These results are likely to be driven by the association of VOC with inflammatory markers such as eosinophilia [34]. This raises the possibility that a prolonged inflammatory response associated with Corona-induced wheeze could be detected by VOC analysis.

The DSA Analyzer allows probabilistic analysis and classification of subjects but is not intended to identify individual exhaled molecular constituents. The exact origins of the VOC differentiating symptomatic and asymptomatic individuals are unknown, but most likely result from a combination of airway obstruction, an increase in oxidative stress, changes in the microcirculation and the hosts immune response. These compounds are likely to have both pulmonary and systemic origins. The Corona virus-associated VOCs are likely to be dependent on pathogen–host interactions.

It is likely that the DSA Analyzer can be used as a noninvasive measure of the host response to viral infection both during acute symptoms and thereafter. These expectations are in line with recent findings showing that exhaled biomarkers correlate with inflammatory sub-phenotype (sputum eosinophils) in asthma[35].

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[29] "Coronavirus Disease 2019 (COVID-19)". Centers for Disease Control and Prevention. 11 February 2020. Retrieved 20 March 2020.

[30] Li, Z.; Yi, Y.; Luo, X.; Xiong, N.; Liu, Y.; Li, S.; Sun, R.; Wang, Y.; Hu, B.; Chen, W.; Zhang, Y.; Wang, J.; Huang, B.; Lin, Y.; Yang, J.; Cai, W.; Wang, X.; Cheng, J.; Chen, Z.; Sun, K.; Pan, W.; Zhan, Z.; Chen, L.; Ye, F. (2020). "Development and Clinical Application of a Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis". Journal of Medical Virology. doi:10.1002/jmv.25727. PMID 32104917.

[31] S. Dragonieri, R. Schot, B.J. Mertens, et al., *An electronic nose in the discrimination of patients with asthma and controls,* J Allergy Clin Immunol 120(2007)856–862; N. Fens, A.C. Roldaan, M.P. van der Schee, et al., *External validation of exhaled breath profiling using an electronic nose in the discrimination of asthma with fixed airways obstruction and chronic obstructive pulmonary disease,* Clin Exp Allergy 41(2011)1371–1378.

[32] C.M. Robroeks, J.J. van Berkel, Q. Jöbsis, et al. *Exhaled volatile organic compounds predict exacerbations of childhood asthma in a 1-year prospective study,* Eur Respir J 42(2013)98–106.

[33] K.D.G. Van de Kant KDG, J.J. van Berkel, Q. Jöbsis, et al., *Exhaled breath profiling in diagnosing wheezy preschool childre,.* Eur Respir J 41(2013)183–188.

[34] B. Ibrahim, M. Basanta, P. Cadden, et al., *Non-invasive phenotyping using exhaled volatile organic compounds in asthma,* Thorax 66(2011)804–809; M.P. Van der Schee, R. Palmay, J.O. Cowan, et al., *Predicting steroid responsiveness in patients with asthma using exhaled breath profiling,* Clin Exp Allergy 43(2013)1217–1225.

[35] B. Ibrahim, M. Basanta, P. Cadden, et al., *Non-invasive phenotyping using exhaled volatile organic compounds in asthma,* Thorax 66(2011)804–809; M.P. Van der Schee, R. Palmay, J.O. Cowan, et al., *Predicting steroid responsiveness in patients with asthma using exhaled breath profiling,* Clin Exp Allergy 43(2013)1217–1225.

VOC FINGERPRINTING

Exhaled breath air-based non-invasive detection of Covid-19 viral disease is based on volatile organic compound (VOC) analysis.[36] Studies in adults have previously shown that VOC analysis can differentiate between asthma patients, patients with chronic obstructive pulmonary disease, and healthy controls.[37] Analysis of VOC biomarkers in children with established asthma predicted disease progression.[38] A recent study[39] showed that in pre-school children with asthma, the VOC biomarker population differs from healthy children. VOC biomarker gases are likely to be associated with inflammatory markers such as eosinophilia.[40] This suggests that the response to long-term inflammation induced by coronavirus could be detected by VOC analysis.

SAMPLE COLLECTION

DS Deep Sensing Algorithms Oy (hereafter DSA) has developed a new VOC analyzer for exhalation analysis. Patients blow into a sampling tube connected to a DSA analyzer, and the breath sample is analyzed for 30 seconds on nano-sensors that interact with the VOC mixture non-selectively. The analyzer produces a "fingerprint" of the tested person based on the VOC composition of the exhaled gas. The sensor data is wirelessly transferred to a secure database on the server.

DATA ANALYSIS

Exhaled breath gas analysis is based on Deep Computing algorithms developed by DSA.

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[36] The human integument is coated with a thin layer comprising *sebum*, sweat, corneocyte debris and natural moisturizing factors. Whilst generically referred to as sebum, the mixture is more accurately referred to as "residual skin surface components" or RSSC. Changes in the molecular composition of RSSC may arise as a result of local and/or systemic disease states. Indeed, clinical conditions such as acne are associated with changes in both the secretion rate and the composition of sebum. In addition, perturbations in the rate of sebum secretion have also been reported for hypothyroidism, Turner syndrome, Behçet's syndrome, Parkinson's disease and rheumatoid arthritis. Thus, the detection and quantification of disease-specific molecules present on the skin surface offer potential for the development of non-invasive diagnostic and prognostic techniques (for further reading see: www.nature.com/scientific reports | 7: *8999* | DOI:10.1038/s41598-017-09014-6. DS Deep Sensing Algorithms Oy is in the process of introducing an analysis method and apparatus that uses RSSC for health monitoring.

[37] S. Dragonieri, R. Schot, B.J. Mertens, et al., *An electronic nose in the discrimination of patients with asthma and controls*, J Allergy Clin Immunol 120(2007)856–862; N. Fens, A.C. Roldaan, M.P. van der Schee, et al., *External validation of exhaled breath profiling using an electronic nose in the discrimination of asthma with fixed airways obstruction and chronic obstructive pulmonary disease*, Clin Exp Allergy 41(2011)1371–1378.

[38] C.M. Robroeks, J.J. van Berkel, Q. Jöbsis, et al. *Exhaled volatile organic compounds predict exacerbations of childhood asthma in a 1-year prospective study*, Eur Respir J 42(2013)98–106.

[39] K.D.G. Van de Kant KDG, J.J. van Berkel, Q. Jöbsis, et al., *Exhaled breath profiling in diagnosing wheezy preschool childre,*. Eur Respir J 41(2013)183–188.

[40] B. Ibrahim, M. Basanta, P. Cadden, et al., *Non-invasive phenotyping using exhaled volatile organic compounds in asthma*, Thorax 66(2011)804–809; M.P. Van der Schee, R. Palmay, J.O. Cowan, et al., *Predicting steroid responsiveness in patients with asthma using exhaled breath profiling*, Clin Exp Allergy 43(2013)1217–1225.

DSA-analyzer

The DSA analyzer calculates a prediction for the tested individual to have contracted the SARS-CoV-2 virus infection; it is not intended to identify the molecular level of individual exhalation gases. The exact metabolic origin of VOCs that distinguish between symptomatic and asymptomatic individuals is unknown but is most likely due to a combination of airway obstruction, increased oxidative stress, changes in the microcirculation, and the immune response of the subject. VOCs are likely to have both pulmonary and systemic origins. VOC gases associated with SARS-CoV-2 are likely to be dependent on pathogen-host interactions.

It is likely that the DSA analyzer can be used as a non-invasive analyzer for the host response to viral infection, both during and after acute symptoms of Covid-19. These expectations are consistent with recent findings showing that exhaled biomarkers correlate with the sub-phenotype of asthma inflammation (eosinophils of sputum).[41]

The DSA Analyzer

The DSA analyzer (Figure 2) is a nanotechnology-based gas sensor system for detecting and analyzing biomarkers of the gaseous exhaled breath air samples.

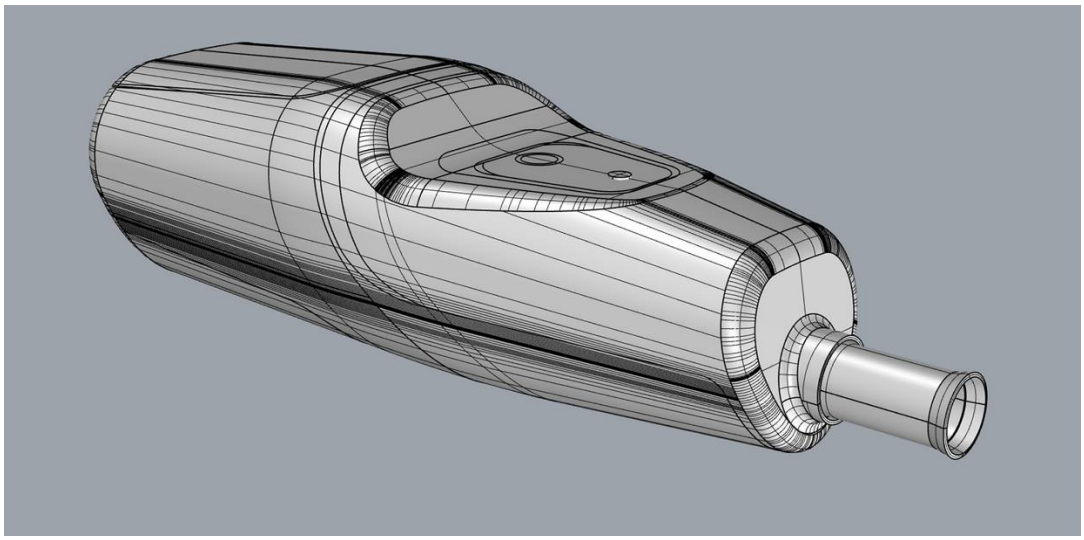

Figure 2: *An illustration of the DSA Analyzer*

The analyzer produces predictions for different health conditions based on Deep Computing algorithms. Deep Learning algorithms are trained based on the samples provided by a group of test subjects and tested by a second set of test subjects.

The analyzer includes processor and sensor modules (PCBA).

[41] B. Ibrahim, M. Basanta, P. Cadden, et al., *Non-invasive phenotyping using exhaled volatile organic compounds in asthma,* Thorax 66(2011)804–809; M.P. Van der Schee, R. Palmay, J.O. Cowan, et al., *Predicting steroid responsiveness in patients with asthma using exhaled breath profiling,* Clin Exp Allergy 43(2013)1217–1225.

The analyzer communicates with cloud applications over a cellular network using the NB-IoT protocol in either the NB1 or LTE-M1 class. The device also has a low-power Bluetooth (BLE) interface that can be used to communicate locally with a mobile device.

The practically speaking real-time Covid-19 test has the potential to play a significant role in accelerating the speed at which health care providers make crucial decisions about identifying and isolating people infected with coronavirus. It would provide a tremendous opportunity for front-line caregivers, those having to diagnose a lot of infections, to close the gap with the present testing modalities. A clinic would be able to produce the result in real time.

Shortening wait times for tests is also a crucial tool for policymakers and public health officials - quicker diagnoses should help the government and health care system have a more accurate assessment of how many cases are actually popping up in real time - and assist them in understanding whether measures to prevent Covid-19's spread are working.

PROJECT

The Covid-19 project has been done in collaboration with the Helsinki University Hospital with other international Universities to joint to validate the development of the Internet-of-Things (IoT) platform for real-time health monitoring. The primary objective was to validate the DSA analyzer concept for rapid identification of SARS CoV-2 infection based on exhaled gas samples.

The continuation of the project will see development of additional diagnosis algorithms for early diagnosis of lung cancer, colon cancer and the likes.