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EDITORIAL

Breathomics – the Way Forward Towards a Mask Free World

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As the world braces to open up from a hiatus of nearly two years as an aftermath of the COVID-19 pandemic, scientists & medical practitioners need to accelerate the pace at which research in "*Breathomics"* (the science of analysing the breath as a sample for diagnostics) is occurring globally for the diagnosis of COVID-19. As governments are debating over relaxing COVID protocols due to mass protests in various countries by public, the need for a rapid non-invasive testing for COVID 19 is a global imperative.

Globally, governments are readying to open transcontinental travel, schools, colleges, gymnasiums, theatres etc. There could not be a better time to come up with a Point of Care Testing device which would aid in segregating masses with COVID-19 for the purpose of isolating the infected. In third world countries, were large swathes of population who do not have access to the conventional methods of testing and vaccination for COVID-19, a hand held POCT device for diagnosis of COVID-19 may prove to be a boon to curb the spread of COVID-19.

The current testing methodologies being employed at airports during international & domestic travel is RT- PCR or Rapid Antigen Testing both of which give false positive results even after the patient is non-infectious i.e. five to seven days after being symptomatic since these testing methodologies detect sequence of the SARS-CoV2 virus even after patient is non-infectious, sometimes even after 04–06 weeks of infection. This is presently posing immense logistical problems to international travellers.

VOCs (Volatile organic compounds) are liberated in the breath by various metabolic & pathological processes occurring in the alveoli and also by microbes colonising the alveoli. They give a snapshot of the interaction between microbiota colonising the alveoli and the alveolar mileu. The signature profile of VOCs being liberated in COVID- 19 pneumonia has been identified by Chen et al. [1]. They studied patients with COVID Pneumonia, non COVID Pneumonia, lung cancer patients, healthy health care workers & healthy controls and identified VOCs by Gas Chromatography coupled with Ion mobility spectrometer. Such profiles require to be validated by multicentric consortia globally. These VOCs are metabolised by the body rapidly hence the issue of false positive test even beyond the infective timeline of the patient will be obviated.

Breath being a non-invasive sample has a huge potential which requires to be explored. Presently the sample known to give best yield of COVID-19 is BAL (Bronchoalveolar lavage) which has an issue of being obtained by an invasive procedure which requires skill hence cannot be done at peripheral centres. There is also an issue of dilution of biomarkers present in minute quantities in BAL. Breath does not have such issues. Amylase which is the major constituent of saliva has not been detected from breath samples thereby also indicating that breath sample is not likely to get contaminated by salivary proteins and will thus give an accurate snapshot of alveolar metabolic dynamics. Nasopharyngeal and throat swabs which are currently in vogue, are minimally invasive which cause considerable discomfort. Add to this the rigour of RNA extraction and thereafter RT-PCR.

Although, Breathomics has been studied there have been major barriers to its implementation from bench to the bedside. Methods of sampling have not been standardised which can lead to loss of precious analytes sometimes present in the concentration of ppb or ppm (parts per billion or million). Broadly online and offline methods of sample collection are being practised. Online modes entail direct analysis of the breath sample and in the offline mode samples must be collected in containers /bags for analysis in Labs at a convenient time. Most POCT methods employ online methods of sampling. The TAT (turnaround time) of some of these POCT tests is a few minutes [2] which makes these tests ideal for mass screening. The collection in bags which are disposable also add a layer of safety to the collection of infectious samples. The TAT of RT PCR reports is 24–48 h

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hence after collection of nasopharyngeal and throat samples, individual must be isolated till reports are available. Tests with shorter TAT will thus save numerous manhours.

Various analytical technologies are being tried for analysis of breath ranging from GC-MS (Gas Chromatography-Mass Spectrometry), LC-MS (Liquid Chromatography- Mass spectrometry), Nano sensors with cloud based Artificial Intelligence, FAIMS (Field asymmetric Ion mobility spectrometry) etc. for the detection of VOC s & SARS- COV-2 in the breath.

Some of these tests which use Mass Spectrometry and Artificial Intelligence (Worlds Protect Kiosk) cost around 0.5$ and hence will be a much more cost-effective option compared to a PCR [3]. In the kiosk, a person has to breath into a copper inlet with a disposable straw. In between two tests the copper pipe is heated to disinfect. This employs mass spectrometry. The US Air Force & A& M Texas University have already sampled 800 breath samples and they are in the process of getting Emergency Use Authorisation by FDA. The E nose which is essentially an array of biosensors which use Artificial intelligence for identification of signatures of breath analytes are hand held devices which do not require skill for operation. Therefore, these will be of immense value in rural settings and for fast segregation based on rapid TAT. These breath-based test will also cut down the cost of testing by obviating recurring costs of consumables required for conventional testing by RT-PCR.

Thomas et al. who have a veritable body of work on breath analysis in COPD and Bronchial Asthma, are exploring the Diagnosis of COVID-19 using VOCs in the proprietary test aptly named Breath Biopsy by Owlstone Medicals [4][5]. It uses another approach of capturing viral particles from respiratory droplets collected in disposable collecting devices and then it's subsequent analysis by RTPCR.

It's time that the attention of breath researchers from the academia, corporate and regulatory bodies be galvanised so that concerted global efforts by an international organization like the World Health Organisation constitute a Breath Taskforce for COVID-19 which can quickly validate these individual isolated efforts so breath prints of SARS-Cov-2 can be launched into mainstream diagnostics.

As a learning point from the present pandemic, research groups across the world should proactively validate breath prints of Viruses with respiratory symptoms during future pandemics so that large scale isolation can be practised. During the present pandemic due to the absence of rapid, robust methods of detection of the Virus, governments across the world were forced to take harsh measures like lockdowns. Such steps have brought untold economic loss and misery to the masses especially in the third world developing nations which have pushed millions of families below the poverty line.

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