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EDITORIAL

Spectroscopy as a tool for detection and monitoring of Coronavirus (COVID-19)

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Coronavirus was for the first time identified in 1960 as a cause of common cold. It is an enveloped RNA virus, single-stranded with a pleomorphic or spherical shape having projections of glycoprotein. It has various subtypes such as alpha, beta, gamma, and delta coronavirus along with serotypes of each subtype. The human coronavirus (OC43-like and 229E-like) can also be found in bats, pigs, birds, cats, dogs, mice, and whales. Coronavirus can be transmitted through airborne droplets and the replication of the virus occurs in the ciliated epithelium that causes cell damage and inflammatory reactions at the site of infection [1]. Consequently, the COVID-19 fatality rate (30–-90%) is observed to be higher in the older generation making them the most vulnerable group. The milder cases of COVID-19 can include nasal congestion, sore throat, difficulty in breathing, chest pains, chills, kidney failure, and pneumonia. This virus can infect several organs in the human body, such as respiratory, hepatic, central nervous, and gastrointestinal systems. The rate of the outbreak of this emerging coronavirus is increasing alarmingly and current methods of diagnosis such as polymerase chain reaction are not ideal as far as the cost-effectiveness, accuracy, and speed are concerned. Therefore, a faster and simpler method for the detection of viral infections in biofluids can become a front-line tool in order to tackle the spread of this deadly disease [2,3].

Real-time polymerase chain reaction (RT-PCR) is used for the detection of COVID-19, which is time-consuming as sample preparation is required prior to analysis.

RT-PCR is also known as quantitative PCR or qPCR, and therein, the amplification of DNA is detected in real time as PCR is in progress by the use of a fluorescent reporter. It detects nucleic acids either for their presence or absence or for their amount. PCR testing is a highly sensitive technique, 10 copies per reaction is the sensitivity that the researcher is relying upon, and false-negative tests can result in the failure of detection of COVID-19-infected patients [4]. Therefore, the correct procedure for PCR is crucial. According to WHO guidelines regarding COVID-19, laboratory testing is now available and research toward improved detection is desperately needed. The dynamics of the virus and subsequent immunological responses are significant in molecular testing. Thus, certain factors such as severity of disease in several populations, the relationship between the severity and viral concentration, duration of shedding, development of serological assays and their validation, monitoring of mutations that can affect molecular testing, and encouragement of sharing of data is significant in order to better manage the COVID-19 outbreak. The initiation and development of several other molecular techniques to detect the quick and easy prevention and diagnosis of the COVID-19 outbreak are crucial to develop countermeasures.

To date, the diagnostic kits developed by different countries for the detection of COVID-19 are based on nucleic acid assay that has been widely distributed in China. US Centers for Disease Control and Prevention (CDC) made CDC 2019-nCoV™ real-time reverse transcriptase PCR diagnostic panel that works on applied biosystems 7500 Fast Dx RT-PCR instrument with SDS-1.4™ software. University of Hong Kong developed two single-step quantitative RT reverse transcription PCR assays for *N* gene and *ORF1b* of sarbecovirus subgenus, Amoy Diagnostics (Xiamen, China), developed Coronavirus gene detection kit, whereas, Altona Diagnostics (Hamburg, Germany) made RT-PCR assay for the detection of coronavirus RNA from respiratory samples. Furthermore, BGI Group (Beijing) used Real-time fluorescent RT-PCR kit, BGI Group used Metagenomic sequencing kit for the monitoring of coronavirus mutations and developed nucleic acid detection kit using combinatorial probe-anchor synthesis method. Hong Kong University of Science and Technology developed On-site rapid molecular diagnostic system based on Shenzhen Shineway Technology, they used Integrated microfluidic PCR test with a silicon-based micro-heater module for rapid processing and heating of samples. Novacyt, Primerdesign ran a portable genesig16 RT-PCR instrument with test results being received within 2 hours. Thermo Fisher Scientific developed TaqMan 2019-nCoV Assay Kit, Qiagen (Hilden, Germany), one-hour delivery QIAstat-Dx Respiratory 2019-nCoV Panel test kit. A Biomeme COVID-19 Go-Strips were developed by Biomeme group on mobile handheld quantitative PCR device, Fortitude Kit 2.0 was developed by Agency for Science, Technology and Research (A*STAR), MiRXES (both Singapore), one-step PCR, SARS-CoV-2 E, RdRP or N gene CE-IVD 7 virus Respiratory Panel multiplex RT-PCR developed by TIB Molbiol (Berlin, Germany) also via Roche Diagnostics as given in Table 1 [4].

Hence, timely detection along with clinical validation of sensitivity and specificity of technique is important to overcome the diagnostic challenges; such as implementation of test, personnel training, quick detection timing, and

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Table 1. Detection methods used for COVID-19 (Sheridan et al. [4]).

No.	Detection test	Test developer
1	Nucleic acid assay	Chinese national institute for viral disease control and prevention
2	CDC 2019-nCoV™ real-time reverse transcriptase PCR diagnostic panel	US Centers for disease control and prevention (CDC)
3	Real -time reverse transcriptase PCR assays	University of Hong Kong
4	Coronavirus gene detection kit	Amoy Diagnostics (Xiamen, China)
5	Real Time-PCR assay	Altona Diagnostics (Hamburg, Germany)
6	Real-time fluorescent RT-PCR kit	BGI Group (Beijing)
7	Nucleic acid detection kit	BGI Group
8	On-site rapid molecular diagnostic system based on Shenzhen Shineway Technology	Hong Kong University of Science and Technology
9	Novel coronavirus strain	Novacyt, Primerdesign
10	TaqMan 2019-nCoV Assay Kit	Thermo Fisher Scientific
11	QIAstat-Dx Respiratory 2019-nCoV Panel test kit	Qiagen (Hilden, Germany)
12	COVID-19 Go-Strips	Biomeme
13	Fortitude Kit 2.0	Agency for Science, Technology and Research (A*STAR), MiRXES (both Singapore)
14	SARS-CoV-2 E, RdRP or N gene CE-IVD 7 virus Respiratory Panel multiplex RT-PCR	TIB Molbiol (Berlin, Germany) also via Roche Diagnostics

availability of primers and probes. The definite need for better techniques and portable technology can benefit researchers and clinicians. Spectroscopy can offer a promising detection approach through the potential disease molecular/chemical biomarkers [4].

Spectroscopy with its advances in technology is central to novel applications in bioengineering, natural sciences, and now in the medical field. Both Raman (RS) and infrared (IR) spectroscopies can help in the diagnosis of infections at the point of care [5,6]. Spectroscopic techniques have attracted growing interest as biomedical tools for the early diagnosis and monitoring of human disease. The need to study bacteria and viruses has seen a renewed interest with recent technologies capable of providing snapshot information about the overall composition of biological species [7,8]. As a result, complex biological samples such as urine, CVF, blood, saliva, breast milk, etc., can now be assessed with unparalleled efficiency and resolution using techniques such as proton nuclear magnetic resonance (1 H-NMR), RS, and IR [9–11].

These analytical techniques are vibrational spectroscopic techniques that look at the molecular vibrations of the chemical structure of molecules. The viral proteins or antibody proteins from the immune system response can be detected in the vibrational spectrum [12]. Wood et al. emphasized the need for better methods of diagnosis and reported on the detection of viruses through infrared spectroscopy claiming that it offers significant economic and social benefits to the community [13]. Recently, we successfully separated different types of bacteria by both FTIR and Raman spectroscopy and the data (to be published) provides compelling evidence. This is encouraging, as we strongly believe that both the techniques can be used for detecting viruses, as glycoprotein and nucleic acids of these species can be analyzed ultimately paving the way for rapid and accurate diagnosis and continuous monitoring.

Spectroscopy coupled with a multivariate analysis approach could be a powerful tool to explore biomolecules. Artificial intelligence, having the potential to customize deep neural networks that have the ability to learn the spectra, could, after training, make instant predictions regarding spectra. Additional studies should investigate the diagnostic capability of spectroscopy and machine learning [14]. The effectiveness, sensitivity, and specificity of these methods, although significant, could still be further improved. This pandemic situation around the globe calls for the sharing of data among countries with anonymized samples, so that researchers are able to explore diagnostic opportunities and so that a rapid development of point of care testing methodology can be developed, strengthening the global fightback against the spread of COVID-19. A Spectroscopic device based on either IR or/and RS for the detection of viruses and bacteria can be developed by analyzing proteins and nucleic acid structure in a multiplexed fashion. Spectroscopic techniques have immense potential in diagnosing human diseases including bacterial and viral infections, inflammatory conditions, and various cancers as demonstrated in a schematic diagram in Figure 1. Currently, although PCR can aid in the diagnosis of viral diseases, the process is time-consuming and sample preparation intensive. Proposed spectroscopic techniques can be of immense value for rapid, accurate, and relatively cost-effective methods of not only detecting infections but also monitoring. The monitoring aspect is even more crucial, as viruses are known to change their RNA in relation to the surrounding environment making it more difficult to find a cure. The use of RS and IR combined with artificial intelligence and machine learning will allow the monitoring of the chemical pathway to the progression of the disease and identify any changes in the chemical structure of the viruses (and bacteria) that may occur. In addition, due to the ability to precisely determine the chemical structural changes by spectroscopy, it should be possible to detect the concentration of various infections in saliva, urine, blood, or serum.

The aim should be to develop a spectroscopic test methodology by employing Infrared and Raman spectroscopies as diagnostic techniques to analyze COVID-19 samples and compare spectral results with the current PCR method that is routinely used. Vibrational spectroscopy will help in understanding the process of viral infection, not only it is rapid and accurate detection but also monitoring, which could lead to understanding its mutation and drug development for COVID-19 as well.

A complete spectroscopic detection system can be a next diagnostic tool going through different stages of spectral data acquisition, defining a test methodology, statistical process control, and spectral data mining and hence, developing a rapid diagnostic system.

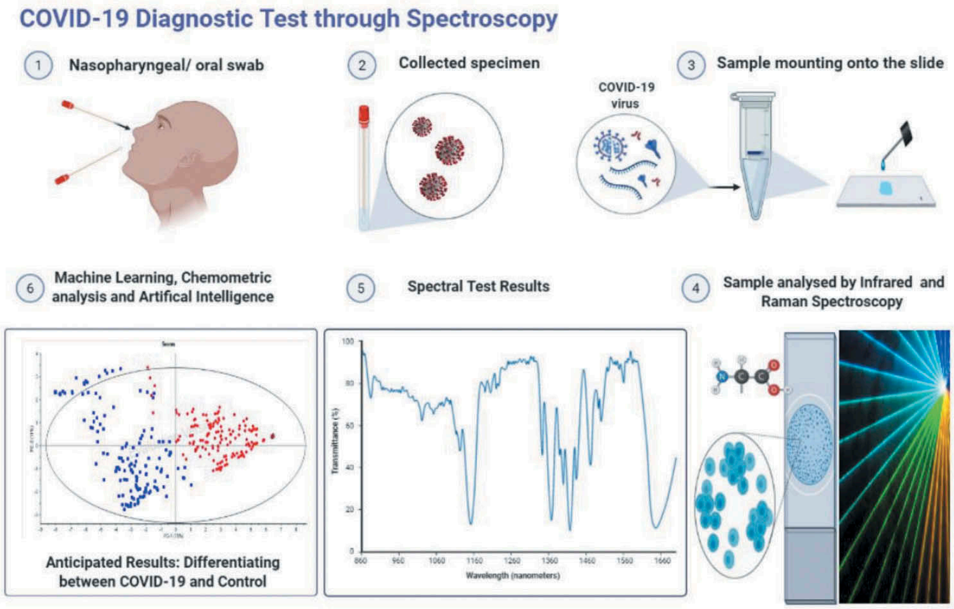

Figure 1. A schematic diagram for vibrational spectroscopy for SARS-COV-2, COVID-19.

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