BACKGROUND PAPER

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Polymerase chain reaction (PCR) and Reverse transcription-polymerase chain reaction (RT-PCR) are widely considered the 'gold standard' for medical diagnostics. However, PCR and RT-PCR testing requires a fully functioning lab, a strong supply chain, long wait times, and trained technicians, which may be lacking in some resource-constrained testing locations. Rapid testing[1] has been studied as a quicker and easier diagnostic method for low-resource settings, especially for diseases with high transmission rates such as COVID-19. Tracking of infected individuals for early detection using Information & Communication Technologies (ICT) solutions, and lung ultrasound are increasingly used in resource-constrained settings.

Affordable Rapid Testing

A number of diagnostic techniques[2] have been developed and deployed for rapid testing. A broad division includes antibody tests that are based on the detection of the virus present in the human body and the antigen tests which are based on the detection of the immune response to the virus. The U.S CDC[2] has recognized viral tests[3] and antibody tests as two major types of diagnostic tests for COVID-19.[3] The U.S government[4] has issued guidelines for appropriate use of diagnostic testing and recommended actions according to the result of each test. Furthermore, rapid testing is still being evaluated in research settings and should not be used for clinical decision making as suggested by CDC. For example, in India, the Indian Council of Medical Research (ICMR) has issued a number of guidelines[5] in the country for setting up the labs, both private and government sponsored. Further, the ICMR has issued guidelines and protocols[6] for using a rapid antibody test only for surveillance purposes. As per the guidelines from U.S FDA, antibody tests should not be used to diagnose active infection. Further, antigen tests are very specific for the virus, but are not as sensitive as molecular PCR tests.[6,1] However, both the tests have an important role in patient management, and public health planning for effective control of COVID-19.

Antibody test

Antibody tests detect antibodies, immunoglobulin M (IgM) and immunoglobulin G (IgG), produced by the body's immune system to fight the virus.[7] IgM and IgG are the major antibodies found in patients that currently have COVID-19 or have recovered from the illness. The IgM is detectable after one week of initial infection and can be used to identify individuals with COVID-19. In contrast, IgG is detectable two weeks after the infection and continues to be produced in the body for over six months, making it possible to determine whether individuals were previously infected with COVID-19. The main advantage of the antibody test is that the results are available in 10-15 minutes and the testing procedure only requires blood testing without extra equipment.[8] However, the test only qualitative information (presence or not presence of antibodies) and possible false negative results have occurred (e.g., tests performed too early in the

infection process as antibodies have not yet been produced) and possible false positives (e.g., interaction with other diseases). The kits are being produced but are not widely tested, and, notably a wide use of kits in the future may incur shortages of reagents.[7]

Antigen test

Although not yet approved by the WHO,[9] antigen tests detect a protein fragment unique to coronaviruses from a nasal cavity sample collected with a cotton swab. On May 8, the U.S FDA authorized[10] the first antigen test[11] for use in the United States. Antigen tests can provide results in 15 minutes[12] but are 43.5%[12,1] less sensitive as compared to molecular PCR tests. As of April 2020, WHO recommends[9] negative antigen test results should be confirmed by viral testing before proceeding with treatment and antigen test to be used in research settings only. Further, if done properly, the technique is very sensitive and specific, however, if poorly executed, these tests run the risk of resulting in false negatives.

Using 3D Printed Swabs

The shortage of nasopharyngeal swabs needed to carry out PCR testing or antigen testing in conjunction with the widespread use of digital modeling and manufacturing technologies, have pushed hospitals to resort to locally and rapidly manufactured nasal swabs to supply the demand. To address this need, consortium of engineers, manufacturers, physicians, and regulators have developed 3D printed medical grade nasal swabs that are currently being rapidly manufactured at ISO13485 facilities.[13] Researchers from the University of California – San Diego have designed and tested the 3D printed swabs[12,2] which may overcome the possible shortages and thus reduce the rate of false negatives.

The U.S FDA provides guidance on technical considerations for additive manufactured medical devices.[14] The U.S NIH's 3D Print Exchange platform intended to share scientifically accurate or medically applicable models, has a COVID-19 supply chain response initiative that includes models for nasal and throat swabs for sample collection.[15]

Information and Communications Technologies (ICT) Solutions

Information and Communications Technologies (ICT), including big data and artificial intelligence (AI) allowing the use of research resources on global online platforms, can help companies develop diagnostic solutions faster and more efficiently. High-performance computing, big data, and AI algorithms have been shown to shorten the development process of diagnostic kits from several months to just two weeks.[16] AI algorithms self-calibrate by effectively learning how an expert technician interprets test results and analyzes automatically with derived knowledge, eliminating manual steps for patient testing.[17]

As an example of how AI can quickly recognize and analyze big data and enable more accurate decision-making, it was confirmed that a specific pattern appeared on the chest 3 to 5 days after infected by COVID-19.[18] An AI technology was applied to lung ultrasound to detect specific patterns and diagnose within seconds through image analysis.[19] This technology is still low in accuracy and in the development stage, and there are many researchers working on better AI algorithms[20] to detect COVID-19 and proposing for standardizations of the use of lung ultrasound for patients with COVID-19.[21]

The European Union[22] and Korean government[23] provide guidelines for technologies that can be self-diagnostic through mobile applications. Mobile applications can be designed to monitor symptoms of individuals and provide appropriate medical advice. Many countries, including United States,[24] have

initiated COVID-19 telehealth programs that enable healthcare providers to consult with patients remotely in their homes.

Since COVID-19 is a disease that is spread between individuals through droplets and contact transmission, digital contact tracing tools are one solution to understanding and reducing the spread of the virus. Contact tracing[25] is the process of identifying, evaluating and managing people who have been exposed to the disease to prevent transmission. Through contact tracing, health care workers can prioritize individual testing. International and national organizations such as WHO, U.S CDC and Africa CDC have published guidelines of contact tracing for contact tracing. U.S CDC provides specific training plans about COVID-19 contact tracing to contact tracers,[26] case investigators,[27] and supervisors[28] for better planning. In South Korea, ICT solutions were introduced to trace the rapidly increasing the number of confirmed COVID-19 cases. Officials in South Korea used data such as mobile information, GPS and credit-card transaction history to conduct a spatial-temporal analysis to track viral spread. As another example, the National Informatics Centre[29] of India has developed a digital service, primarily a mobile app (Aarogya Setu[30]), for contact tracing, syndromic mapping and self-assessment under the Ministry of Electronics and Information Technology (MeitY).

External Reference Links:

[1] https://www.who.int/diagnostics_laboratory/faq/simple_rapid_tests/en/
[2] https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html
[3] https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html
[4] https://www.whitehouse.gov/wp-content/uploads/2020/05/Testing-Guidance.pdf
[5] ICMR Guidelines on setting up testing labs
[6] ICMR Protocols on using Rapid Antibody Test
[6.1] Coronavirus (COVID-19) Update: FDA Authorizes First Antigen Test to Help in the Rapid Detection of the Virus that Causes COVID-19 in Patients
[7] https://www.finddx.org/wp-content/uploads/2020/05/FIND_COVID-19_RDTs_18.05.2020.pdf
[8] https://www.clinisciences.com/en/read/newsletter-26/sars-cov-2-covid-19-diagnosis-by-2264.html
[9] https://www.who.int/docs/default-source/coronaviruse/sb-2020-1-poc-immunodiagnostics-2020-04-08-e.pdf?sfvrsn=4c26ac39_2
[10] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-antigen-test-help-rapid-detection-virus-causes
[11] https://www.fda.gov/media/137886/download
[12] https://www.quidel.com/immunoassays/rapid-sars-tests/sofia-2-sars-antigen-fia
[12.1] https://pubmed.ncbi.nlm.nih.gov/19477042/
[12.2] https://www.med-technews.com/news/3d-printed-swabs-show-better-covid-19-detection-rates/
[13] https://printedswabs.org/
[14] https://www.fda.gov/media/97633/download
[15] https://3dprint.nih.gov/collections/covid-19-response
[16] http://www.korea.kr/common/download.do?fileId=190536078&tblKey=GMN
[17] https://www.diagnostics.ai/
[18] https://pubs.rsna.org/doi/full/10.1148/radiol.2020200463
[19] https://www.nature.com/articles/s41591-020-0931-3
[20] https://pubs.rsna.org/doi/full/10.1148/radiol.2020200905
[21] https://onlinelibrary.wiley.com/doi/full/10.1002/jum.15285
[22] https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1587141168991&uri=CELEX:52020XC0417(08)
[23] http://ncov.mohw.go.kr/en/baroView.do?brdId=11&brdGubun=111&dataGubun=&ncvContSeq=&contSeq=&board_id=&gubun=
[24] https://www.fcc.gov/covid-19-telehealth-program

[25] https://www.who.int/publications/i/item/contact-tracing-in-the-context-of-covid-19
[26] https://www.cdc.gov/coronavirus/2019-ncov/downloads/php/contact-tracer-sample-training-plan.pdf
[27] https://www.cdc.gov/coronavirus/2019-ncov/downloads/php/case-investigator-sample-training-plan.pdf
[28] https://www.cdc.gov/coronavirus/2019-ncov/downloads/php/contact-tracing-training.pdf
[29] https://www.nic.in/
[30] https://www.mygov.in/aarogya-setu-app/