Research on COVID-19

Subjects: Pathology

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As of March, most of the world is under the order of a “lockdown” or “restricted movement control” whereby world leaders and medical experts believe that social isolation is the best option at reducing the spread of the highly infectious and novel disease, that is Coronavirus Disease (COVID-19). While this preventive measure is in place, various diagnostic kits and treatment strategies are being researched daily to diagnose and curb this disease quickly. This report summarizes the characteristics of the SARS-CoV-2 virus and evaluates the diagnostic kits and treatment drugs as well as vaccines that are either currently being used (RT-PCR) or in the clinical pipeline for safety and efficacy testing, respectively. The sooner efficient diagnosis and treatment can be made, the greater the number of lives will be saved.

COVID-19 SARS-CoV-2 diagnostic kits antivirals

1. Introduction

Two months ago, the World Health Organization (WHO) had declared the Coronavirus Disease (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a Public Health Emergency of International Concern. Currently, health experts and world leaders have implemented social isolation as a preventive measure to control the spread of this disease, while researchers around the world discuss, experiment and develop effective diagnostic kits and treatment strategies. Within weeks from the first identified case of COVID-19 in Wuhan City, China, ample of research articles and reviews have been published with the majority published on Chinese journal platforms. As to date, research on COVID-19 and its virus have been focused on causes (38.5%), epidemiology (29.2%), prevention and control (18.5%) and clinical manifestations and diagnosis (13.8%) (Adhikari et al., 2020)[1], with newer articles emerging that evaluates possible treatment strategies. This report mainly discusses the available literature on the diagnosis and treatment strategies in place for COVID-19.

2. Characteristics and Transmission

The name Corona comes from Latin term *coronam* which means crown. Coronavirus has crown-like spikes on the external surface of the virus. The new Human Corona Virus (HCoV) which is isolated from a Covid-19 patient, has 89% nucleotide uniqueness with bat severe acute respiratory syndrome coronavirus (SARS)-like-CoVZXC21 and 82% of human SARS-CoV. As Covid-19 is a combination of SARS-like-CoVZXC21 and human SARS-CoV, it is named as SARS-CoV-2 (Chan et al., 2020)[2]. Its single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 amino acids. Coronaviruses are ranges from 65-125nm in diameter. This minute virus contains a

single-stranded RNA as a nucleic material ranging from 26 to 32kbs in length. The subgroups of coronaviruses family are alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus.

The basic source and mode of transmission of coronaviruses are assumed to be the similar characteristics possessed by SARS-CoV-2. A human can get infected only by α and β coronaviruses. Animals, which are used as a source of food, may get infected which could serve as a major cause of animal to human transmission (Cascella, Rajnik, Cuomo, Dulebohn, & Napoli, 2020)[3]. Human to human transmission is also possible (as in this case of COVID-19) if they are in close contact (about 1 meter) with an infected person, mainly through respiratory droplets (Cascella et al., 2020)[3]. Among the animal sources of this virus, bats are the most prominent one, which is suspected in the COVID-19 pandemic as well.

3. Available Diagnosis Methods

Highly infectious diseases like COVID-19 require a rapid biological diagnosis to be performed widely in suspected populations for efficient management of patients. Patients who meet any of the following three diagnosis criteria; recent travel history to COVID-19 documented areas, history of contact with COVID-19 positive person and presentation of COVID-19 symptoms, are required to get tested for the virus. Whilst the currently used gold-standard, and Centre for Disease Control (CDC) sanctioned diagnosis test, the Real-Time Reverse Transcriptase (RT-PCR) diagnostic kit manages to provide accurate results with high sensitivity and specificity, this diagnosis method, has a slow turnaround time (from sample collection to test results delivery) and is available in limited quantity within each country's CDC approved health care facilities and therefore mainly conducted on a person under investigation (PUI) cases who meet the aforementioned diagnosis criteria (Sheridan, 2020)[4]. Fortunately, these diagnostic criteria are currently being reviewed internationally to avoid "early in incubation" or asymptomatic cases to go unnoticed and contribute to the infection spread.

To overcome the limitation of supply in CDC RT-PCR, commercial manufacturers have replicated the viral assay diagnostic kit using the identified genome sequence of the virus that was publicly available on Genbank (Accession number: MN908947). With this, RT-PCR that detect unique regions of the viral genome or its nuclei acid was developed across different CDC approved laboratories (Amrane et al., 2020[5]; Chu et al., 2020[6]; Corman et al., 2020[7]) and sent to commercial manufacturers for mass production of assay kits (Binnicker, 2020)[8]. This allowed the diagnosis time to be shortened and supply to increase in hospitals. Unfortunately, many non-FDA (food and drug administration) but commercially approved diagnostics kits were being distributed to the anxious public and these commercially available diagnosis kits were warned by the FDA to provide inaccurate results, such as the rapid test kit (antibody-based assay which is non-specific to the virus) showing false positives or false negatives which could create serious public concerns and deter treatment strategies (Sheridan, 2020)[4]. While the FDA has declared an emergency use authorization (EUA) on several diagnostic kits (supplementary-Table 1) (David & Salzman, 2020)[9], they have urged the public to not purchase these kits, as it is only meant to be used in health care facilities with professional health care staffs present. Even though the '15 minute rapid test kit' that just recently been given the green light by the FDA sounds appealing, it is still strictly EUA and therefore the public should not be scammed into purchasing them by un-authorized bodies.

As of Feb 2020, a chest CT scan was proposed to be conducted as a diagnostic measurement to confirm and evaluate these RT-PCR results as well as to reduce the interval time of the shift from initial negative to later positive results and vice versa (Ai et al., 2020[10]; Bai et al., 2020[11]; Yuhui Wang et al., 2020[12]). However, both these diagnosis tests increase the risk of nosocomial transmission as they require the presence of the suspected person at the hospital for testing and specimen collection, which may expose them to a COVID-19 positive environment. Thus, some countries have implicated specimen collection via “drive-thru” diagnosis, while others proposing home self-diagnostic collection tools such as nasopharyngeal swab made available to homes and then safely posting the specimens to nearby diagnostic labs for RT-PCR, which altogether reduces the potential exposure risk to COVID-19. The self-diagnostic method benefits the wider population (older and disabled people, caregivers with children and people with no transportations in rural areas) and would be cost-effective in terms of staff and primary care setups. Ideally, the better option is providing the complete self-diagnosis (sample collection and testing) with improved sensitivity immunoassays and protein-based tests to be available to the public, similar to a home pregnancy kit, therefore reducing the load at diagnostic laboratories, but novel viruses such as SARS-CoV-2 is still fairly under-researched and therefore its sensitivity is debatable in a home setting without a professional clinician present to provide diagnostic advice. Hopefully, one of the FDA approved diagnostic assays in Table 1 or those being developed and seeking FDA approval as in Table 2 (supplementary) would overcome the limitations of the current RT-PCR and be used outside of the EUA constraints.

Table 1. In Vitro Diagnostics for SARS-CoV-2 sanctioned by FDA as EUA (U.S. Food and Drug Administration, 2020)[13].

Date EUA Issued	Manufacturer	Diagnostic (Letter of Authorization)
03/27/2020	Luminex Molecular Diagnostics, Inc.	NxTAG CoV Extended Panel Assay
03/27/2020	Abbott Diagnostics Scarborough, Inc.	ID NOW COVID-19
03/26/2020	BGI Genomics Co. Ltd	Real-Time Fluorescent RT-PCR Kit for Detecting SARS-2019-nCoV
03/25/2020	Avellino Lab USA, Inc.	AvellinoCoV2 test

Date EUA Issued	Manufacturer	Diagnostic (Letter of Authorization)
03/24/2020	PerkinElmer, Inc.	PerkinElmer New Coronavirus Nucleic Acid Detection Kit
03/23/2020	Mesa Biotech Inc.	Accula SARS-Cov-2 Test
03/23/2020	BioFire Defense, LLC	BioFire COVID-19 Test
03/20/2020	Cepheid	Xpert Xpress SARS-CoV-2 test
03/20/2020	Primerdesign Ltd.	Primerdesign Ltd COVID-19 genesig Real-Time PCR assay
03/19/2020	GenMark Diagnostics, Inc.	ePlex SARS-CoV-2 Test
03/19/2020	DiaSorin Molecular LLC	Simplexa COVID-19 Direct assay
03/18/2020	Abbott Molecular	Abbott RealTime SARS-CoV-2 assay
03/17/2020	Quest Diagnostics Infectious Disease, Inc.	Quest SARS-CoV-2 rRT-PCR
03/17/2020	Quidel Corporation	Lyra SARS-CoV-2 Assay

Date EUA Issued	Manufacturer	Diagnostic (Letter of Authorization)
03/16/2020	Laboratory Corporation of America (LabCorp)	COVID-19 RT-PCR Test
03/16/2020	Hologic, Inc.	Panther Fusion SARS-CoV-2
03/13/2020	Thermo Fisher Scientific, Inc.	TaqPath COVID-19 Combo Kit
03/12/2020	Roche Molecular Systems, Inc. (RMS)	cobas SARS-CoV-2
02/29/2020	Wadsworth Center, New York State Department of Public Health's (CDC)	New York SARS-CoV-2 Real-time Reverse Transcriptase (RT)-PCR Diagnostic Panel
02/04/2020	Centers for Disease Control and Prevention's (CDC)	CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel (CDC)

Table 2. Selected Commercial Rapid Tests For Sars-Cov-2 as of 23rd March 2020.

Developer	Test	Description	Status
Guangzhou Wondfo Biotech (Guangzhou, China)	Wondfo SARS-CoV-2 antibody test	Lateral flow 15-minute immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	National Medical Products Administration EUA in

			China; CE mark in Europe
Innovita Biological Technology	SARS-CoV-2 antibody assay	Lateral flow 15-minute immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	National Medical Products Administration EUA in China
Jiangsu Medomics Medical Technologies (Nanjing, China)	SARS-CoV-2 rapid combined IgM/IgG antibody test kit	Lateral flow 15-minute immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	Shipping
Mammoth Biosciences	SARS-CoV-2 DETECTR	30-minute lateral flow assay	In validation studies
Pharmact (Berlin)	SARS-COV-2 Rapid Test	POC 20-minute test for detecting SARS-CoV-2 exposure through identification of IgG and IgM antibodies	CE-marked and shipping
Snibe Diagnostic (Shenzhen, China)	MAGLUMI 2019-nCoV IgM/IgG kit	Automated central laboratory rapid test that runs on MAGLUMI chemiluminescence immunoassay system	CE mark received 19 February 2020
Sona Nanotech (Halifax, Nova Scotia)	Rapid SARS-CoV-2 antigen detection test	Lateral flow screening test for S1 domain of SARS-CoV-2 S1 protein	Assay development and testing with GE Healthcare Life Sciences underway
Sherlock Biosciences, Cepheid	Rapid CRISPR-based tests for SARS-CoV-2 and other pathogens	Combines SHERLOCK Cas12 and Cas13 enzymes for nucleic acid detection with Cepheid’s	Intended as proof of concept for a broad product development

		GeneXpert test-processing instruments	alliance in infectious disease
Zhejiang Orient Gene Biotech (Zhejiang, China)	COVID-19 IgG/IgM Rapid Test	Solid-phase immunochromatographic assay	Aytu Bioscience has sublicensed US distribution rights from L.B. Resources (Hong Kong) and plans to obtain EUA; already has CE mark
Biomerica	Rapid POC IgM/IgG antibody test	$10 lateral flow immunoassay	Commenced shipping samples; seeking FDA EUA approval
Caspr Biotech	Ultrasensitive, rapid, and portable coronavirus SARS-CoV-2 sequence detection	Based on CRISPR-Cas12	Proof of principle evaluation
Sugentech (Daejeon, South Korea)	SGTi-flex COVID-19 IgM/IgG	Ten-minute lateral flow immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	CE Mark
Cepheid	Xpert Xpress SARS-CoV-2	Rapid PCR test that runs on GenXpert benchtop system – delivers result in two hours from sample collection to delivery of result	Received FDA emergency use authorization
Xiamen AmonMed Biotechnology (Fujian, China),	COVID-19 IgM/IgG test kit (Colloidal gold)	Ten-minute lateral flow immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	CE Mark

EUA, emergency use approval.

Sources: Company websites, PubMed (Sheridan, 2020)[4].

4. Possible Treatments

As of now, there is no effective treatment or vaccine available for COVID-19. Hospitals are currently treating the moderate to severe symptoms presented by COVID-19 patients as well as providing oxygen therapy to them (Adhikari et al., 2020[1]; Hassan, Sheikh, Jamal, Ezeh, & Akhtar, 2020[14]). Unfortunately, this floods the threshold of occupancy and staff care capacity in hospitals that are limited in resources. Moreover, due to the increasing number of deaths and intensive care patients among the elderly and vulnerable, nations are scurrying to find a drug that could reduce these numbers exponentially.

WHO and big corporate companies have been assessing candidate therapies since January 2020, as reviewed by (Pang et al., 2020)[15] and recently announced the four drug candidates with most potential under their SOLIDARITY project (Science, 2020)[16], which involves safety and efficacy drug testing on COVID-19 positive patients at different locations around the world. Experts believe that a possible treatment drug will be available to the public within a couple of months once the safety and efficacy of the proposed drug have been determined. The four-drug candidates include: 1) Remdesivir (Science, 2020[16]; Wang, Wang, Chen, & Qin, 2020[17]), an intravenous drug that inhibits SARS-CoV-2 viral replication but can only be given in moderate to severely symptomatic cases, 2) Chloroquine (Vincent et al., 2005)[18] and hydroxychloroquine (Science, 2020)[16], once antimalarial drugs, were claimed by the Chinese researchers to have benefitted their severe patients but these claims could not be verified for both these highly toxic drugs which furthermore are required in large doses to inhibit viral attachment to body cells, 3) Ritonavir/lopinavir combination drug (Science, 2020[16]; Yixuan Wang et al., 2020)[12], an approved HIV infection treatment drug that can break down coronaviruses protease and therefore eradicating the virus but the lack of significant results to date in clinical setting has halted its progress in the project, 4) Ritonavir/lopinavir combination drug with interferon beta (Science, 2020)[16], is the newest candidate in the project where the interferon beta is meant to regulate inflammation and thereby controlling the symptoms of the virus while the combination drug kills it but experts believe this drug combination is highly timeframe dependent and if given at late stages could be detrimental to the patients.

Despite the insufficient results and potentially risky nature of rushing these drugs through the drug discovery process, these four antiviral candidates are the most promising according to WHO as for now but new drugs such as favipiravir (Japan)(Science, 2020)[16] may be added with time and evident results. As for vaccines, mRNA-1273, a vaccine by Moderna, USA, was claimed to be ready for human testing and may be available to the public once safety and efficacy are proven significant (Yixuan Wang et al., 2020)[12] in the coming weeks. Besides that, the

FDA is also considering convalescent plasma from COVID-19 survivors as a strong treatment option for the critically ill COVID-19 patients.

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