Ingenious e-Brain

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OPPORTUNITIES FOR COMPANIES WITH PRODUCTION CAPACITY TO COLLABORATE WITH INSTITUTES WITH READY KIT

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Contents

1. ABSTRACT

There are various big challenges that society has faced for a long time-such as infant mortality, natural disasters, hunger and nearly 100 other problems but the focus has shifted on a new, emerging global problem: the ongoing outbreak of the coronavirus disease [COVID-19]. Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus SARS-CoV-2. Most of the COVID-19 patients experience mild to moderate respiratory illness, fever, cough, and kidney failure.

Coronavirus pandemics could radically change the way people live, function, and use technology. Advanced industries are likely to see a shift in priorities as perceptions of employees and leaders begin to alter. Organizations that reinvent themselves will emerge far stronger than those that merely seek to regain their pre-COVID-19 status.

Major task during this crisis for Institutes is to develop affordable test for COVID-19 targeting large-scale deployment of kits

There are various Institution who have already developed their COVID-19 diagnostic kit, and some are still working on it. Institutes are collaborating with various firms for funds as well other services like towards support for production of already developed kit on large scale. As the world is struggling to contain the novel coronavirus (COVID-19) outbreak, healthcare infrastructure and testing capacity have emerged as major issues.

Diagnostic tests are now being done majorly by Reverse transcription polymerase Chain reaction and ELISA base techniques. However, there is a wide gap between number of test conducted to the number of cases reported due to unavailability of test kits for COVID19 or SARS-CoV-2 Due to increasing number of cases and unavailability of effective treatments, the pharmaceutical companies have big opportunities to explore.

While this situation unfolds, it is important to track the short-term and long-term impact on the economy. While at this time there is no guarantee as to when this epidemic will come to an end, it is fair to assume that the sector will continue to adapt and evolve to cope with current and possible crises.

2. INTRODUCTION

The coronavirus pandemic of 2019–2020 is caused by extreme acute respiratory coronavirus syndrome 2 (SARS-CoV-2). The virus is primarily spread between people in close contact with each other.

People with history of infection with COVID-19 must have an immunity to remove virus from their body due to the presence of antibody. So, these people can be considered as immune and will not be harmed by virus. So, at present there is need to develop the test that can recognize the presence of SARS-CoV-2 specific antibodies in patient's sample.

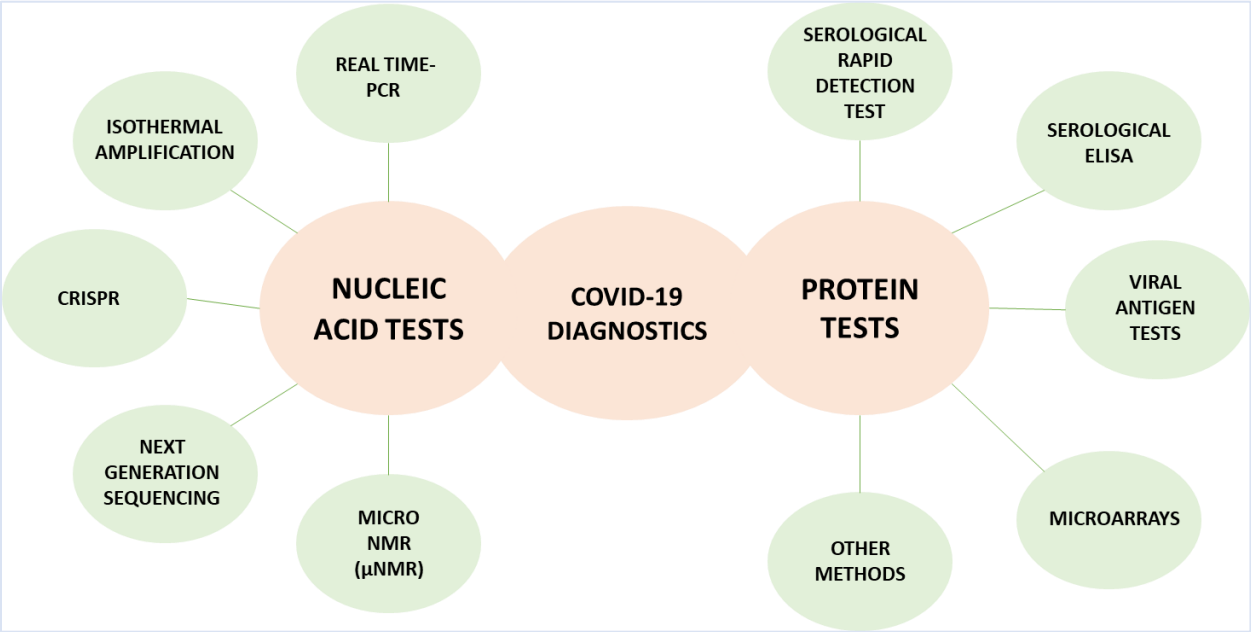
One of the most important thing that countries need to be doing to prevent the spread of SARS CoV-2 virus is diagnosis or testing of their citizens because community is relying on models and estimates of confirmed cases which in reality could be far more than the cases on records. It is very important to note that the number of confirmed cases is changing very quickly as tests are being conducted. At this moment, many countries expecting the situation under control could be in false dreams as it might be the situation that they have not conducted adequate testing of their citizens. Testing allows infected people to know that they are infected. This can help them receive the care they need, and it can help them take measures to reduce the probability of infecting others. Testing is also crucial for an appropriate response to the pandemic. It allows us to understand the spread of the disease and to take evidence-based measures to slow down the spread of the disease.

3. HOW IS DIAGNOSIS SITUATION WORLDWIDE?

Adequate testing capacity for SARS-CoV-2 is lacking worldwide due to which the virus is exposed to community spread. Community is relying on models and estimates of confirmed cases which could be far more than the cases on paper. Due to lacking resources for diagnostics and testing worldwide, it is becoming a pandemic situation for all and affecting healthcare services in countries worldwide. A wide range of diagnostic tests are commercially available for SARS-CoV-2, some of which have received authorizations for use by various national regulatory agencies. But companies are lacking in delivering these tests as per increasing demand.

4. TESTING FOR CORONAVIRUS

There are various methods for the detection of strain of coronavirus. Most of them are either molecular or serological tests.



4.1. NUCLEIC ACID TESTS (NATS, FOR VIRAL RNA)

Tests for nucleic acid amplification inform whether a patient is being deliberately contaminated with SARS-CoV-2. The presence of characteristic sequences of genetic material (RNA) from SARS-CoV-2 in patient respiratory samples is detected. Targets for nucleic acid tests are N1, N2 genes (single or multiple) and other emerging targets are E gene, S gene, Orf1ab gene, RDRP gene

4.1.1. Real time RT-PCR

Real time RT-PCR is a nuclear-derived method for detecting the presence of specific genetic material from any pathogen, including a virus.

This test is widely available, highly specific method. Main types of RT-PCR Detection methods used are Quantitative PCR (qPCR) which is highly sensitive, widely available, and current standard and Droplet digital PCR (ddPCR) which gives absolute quantification, 5-plex and reference is not needed. Disadvantages of RT-PCR based test kits are, it detects the virus only, not the antibodies so we cannot rely on this technique to determine the person who have already recovered from this disease.

It cannot provide information of other diseases or symptoms. It can only detect current cases. This test may only detect virus either on sputum or nasopharyngeal swab not essentially on both locations. So, if a person is infected this test may not detect virus at both locations simultaneously.

4.1.2. Isothermal amplification

Isothermal amplification (LAMP) combined with reverse transcription (RT-LAMP) allows the direct detection of Viral RNA. This system can be coupled with a pH indicator present in the reaction mix to allow readout of the amplification reaction by change in color.

It is Ultra-fast method that does not require thermal cycling. Potential for point-of-care (POC) use. Main types are loop mediated isothermal amplification (RT-LAMP) in which one-step amplification occurs at 60-65°C and is more sensitive than conventional RT-PCR.

Sequence specific LAMP which is more robust and specific compared to regular LAMP and rolling circle amplification (RCA) which uses a circular template and is simple and efficient. Nicking endonuclease amplification reaction (NEAR): ultra-fast (<10 min). Amplification occurs at 37-42 ° C and is as sensitive as qPCR

4.1.3. CRISPR

CRISPR technique can be used for the detection of COVID-19. Synthetic COVID-19 virus RNA fragments can be used to consistently detect COVID-19 target sequences. Tests may start with RNA purified from samples of patients.

Like qRT-PCR assays and can be read out in less than an hour using a dipstick without requiring detailed instrumentation. Different methods (CAS12a or CAS13a) are currently in development for POC use. It is a simple readout (lateral flow detection) test and is very rapid (<1 hr.) and specific

4.1.4. Next generation sequencing (NGS)

This technique enables research for complete genome sequencing and study of virus responsible for the COVID-19 (SARS-COV-2). This technique is highly specific and give accurate results within a day. Components required for the technique are universal coronavirus primers, high fidelity master mix, amplified genomic segments and DNA amplicons. The range of amplicons required in this technique: 125-275 base pair.

NGS is primarily used to track transmission routes globally, population management, viral mutation, and discovery of targets for therapy.

Advantage of NGS based tests are they have less detection time i.e. 2.5 hrs. These tests are highly accurate with high success rate as it can detect even the sample that contain low viral loads.

NGS based tests are less cost-effective for sequencing low numbers of targets (1–20 targets) and time-consuming for sequencing low numbers of targets (1–20 targets). These are the major disadvantages.

4.1.5. Micro NMR (μ NMR)

NMR metabolic profile can easily distinguish between healthy (control) and COVID-19 (disease) patients. NMR metabolic profile of a healthy person and then for COVID-19 infected person is compared.

Specific & potential biomarkers that show remarkable changes is searched in metabolite profiling during infection. Multivariate statistics (PCA, PLS-DA and OPLS-DA model) techniques can be combined with 1H NMR to distinguish between healthy and COVID-19. Micro NMR uses magnetic assays to detect PCR products and it does not require lengthy sample purification.

4.2. PROTEIN TESTS (IMMUNOGLOBULINS, VIRAL ANTIGENS)

Protein tests detects the spike protein (S-protein) and nucleocapsid protein (N-protein) that is encoded by all coronaviruses, including the coronavirus (COVID-19). Most common targets for protein tests are human IgG, human IgM; IL-6 and other interleukins and Viral antigens: nucleocapsid (N) protein and spike (S) protein and key reagents are antiviral IgG, IgM; recombinant N and S proteins

4.2.1. Serological rapid detection test (RDT)

Serologic test detects SARS-CoV-2 antibodies in serum, which is a component of blood. These tests use live virus and a specific SARS-CoV-2 protein, the spike antigen. It detects SARS-CoV-2 IgG/IgM in blood using lateral flow assay (LFA). It is a rapid test that gives result in <20 min and it is qualitative, equipment-free test. It is a colorimetric read out (gold nanoparticles) test.

4.2.2. Serological ELISA

Serological ELISA test detects SARS-CoV-2 IgG/IgM on a plate coated with capture agents. It gives high throughput, quantitative result with, multiple formats (ECLIA, EIA, FIA, ECS). Its Signal amplification allows low detection limit (~pM). Serological ELISA test uses blood samples

4.2.3. Viral antigen tests (VAT)

Viral antigen tests quickly detect fragments of proteins found on or within the virus by testing samples. It detects viral nucleocapsid N or S proteins using capture antibodies via LFA or ELISA. Viral antigen tests can be used for respiratory tract samples

4.2.4. Microarrays

Antibody Microarray is a serological disease screening test developed to screen for infection specific to COVID-19. Discovery of IgG/IgM targets at the epitope level. In this technique peptide-coated chips are used to capture IgG/IgM. Microarrays finds its major applications in diagnostics, vaccine research

4.2.5. Other methods

Other methods include Virus neutralization test (VNT) that detects presence of active antibodies, Western blots (WB) that detects viral proteins and Immunofluorescence microscopy (IFM) that shows antibody interaction with virus proteins

4.3. ARTIFICIAL INTELLIGENCE:

As the number of people infected with COVID-19 are increasing, companies are approaching towards artificial intelligence to control the pandemic. Artificial intelligence is an emerging technique to control COVID-19.

Earlier an AI based triage was prepared that give continuous monitoring of the spread of virus. Israeli Healthcare system launched a 'Diagnostic Robotics' for digital risk assessment and monitoring of COVID-19. This analyses the symptoms, health status and generates AI based risk profile for COVID-19.

This technique works with the help of test message simple questions are asked to the clients. Then with the help of remote screening process results are analyzed. Proper information of the virus spreading rate can be determined.

5. COMPARISON OF RESULTS FROM DIFFERENT TEST TYPES

TYPE	TARGET	ASSAY TIME	LIMIT OF DETECTION	ASSIGNEE
Polymerase Chain Reaction	VIRAL RNA	2-8 H; >12h	10 Copies/µl	Roche, LabCorp, Biomerieux, Qiagen, PE, BD, Luminex, Thermo Fisher
PCR Point of Care	VIRAL RNA	<1 H	10 Copies/µl	Cepheid, Mesa, Credo, Atila
Digital Droplet PCR	VIRAL RNA	2-4 H	0.02-0.1 Copies/µl	Bio-Rad
Nicking Endonuclease Amplification Reaction	VIRAL RNA	15 Min	0.125 Copies/µl	Abbott
Rolling Circle Amplification	VIRAL RNA	2 H	100 Copies	
Specific High-Sensitivity Enzymatic Reporter	VIRAL RNA	1.5 H	10-100 Copies/µl	Sherlock Biosciences
DNA Endonuclease-Targeted CRISPR Trans reporter	VIRAL RNA	1 H	10 Copies/µl	Mammoth Biosciences
Next Generation Sequencing	VIRAL RNA		0.1 Copies/µl	Vision, Idbydna, Illumina
Micro Nuclear Magnetic Resonance	VIRAL RNA	2 H	10 Copies/µl	T2 Biosystems
Lateral Flow Assay	IGG, IGM	15 Min	Variable	Cellex, Pharmact, Sugentech, Innovita, Chembio
Enzyme Linked Immunosorbent Assay	IGG, IGM	2-4 H	10 Pg/Ml	Snibe, Zhejiang Orient, Calbiotech, Creative Dx, Biorad, Mount Sinai, Ortho-Clinical
Chemiluminescence Immunoassay	IGG, IGM	30 Min		Abbott
Enzyme Immunoassay	IGG, IGM			Biorad
Electrochemiluminescence Immunoassay	IGG, IGM	20 Min		Roche

Electrochemical Sensing	IGG, CYTOKINE	1 H	5-50 Pg/ML	Accure Health
Viral Antigen Test	VIRAL ANTIGEN	20 Min	113 TCID50/Ml	Quidel, Sona NT, Ray biotech, SD Biosensors, Bioeasy
Microarrays	IG EPITOPES	1.5 H	0.2-2 Pg/ML	Ray biotech, Pepperprint
Immunofluorescence Microscopy	VIRAL PROTEIN	3 H	Variable	
Western Blot	IGG, IGM; VIRAL PROTEIN	4 H	>100 Ng/ML	

6. TESTS THAT CAN POTENTIALLY BE USED FOR SCREENING

Multiple diagnostic test manufacturers have developed and started selling fast and easy-to-use products to promote testing outside of laboratory settings in response to the increasing COVID-19 pandemic and shortages of laboratory-based test kits.

However, tests must be validated in the correct populations and environments before such methods could be recommended. Inadequate tests can exclude patients with active infection, or incorrectly categorize patients as having the disease if they do not, further preventing efforts to control disease.

At-Home test will help to prevent clinician from any risk of spreading. Major advantages of this test are this test is very simple to perform. Patient administered test is widely available and will improve efficiency. Protects healthcare workers by minimizing the risk of spreading. No use of personal protective equipment such as gloves, face masks etc. This test is both practical as well as sensible. However, this test is incomplete and still needs verification.

Saliva-based test for COVID-19 have already received authorization from U.S. Food and Drug Administration gave emergency use developed by researchers at RUCDR Infinite Biologics, a Rutgers University-backed group.

Saliva COVID test has number of advantages over nasal swab test:

- This test requires fewer materials so it will help to overcome the problem of supply chain.
- Large number of options are available for collecting the sample no problem of shortage will be there.
- Less requirement of wearing protective equipment when taking the sample.
- It could easily be adapted for rapid home testing.

7. CHALLENGES FACED DURING DEVELOPMENT OF COVID-19 DIAGNOSTIC KIT

There is still a long way to go and there is simply no way for any country to win against COVID-19 without extensive testing. The effects on the country's COVID-19 plans suggest a far greater concern with how the Countries coordinated their pandemic response. The industry facing numerous obstacles.

COVID-19 diagnostic tests go through a cycle of development, approvals, and deployment with challenges along each part of the value chain.

7.1. Shortage of raw material

Making matters more complicated, many countries, including the UK and the US, have had problems getting enough supplies for testing. It is not so much a matter of lacking the raw materials but making sure they are pure and mixed in the right amounts. Each brand of test has their own unique blend of about 20 chemicals. Each set requires its own unique packaging.

7.2. Testing capacity:

Difficulties with the availability of sufficient test kits and the necessary equipment significantly hinder test speed and scalability. This causes production difficulties in addition to the supply chain bottlenecks and the necessary regulatory approvals and dramatically reduces the test capacity

7.3. Economic impact

The cost of research and the scale of the expenditure needed to carry it out puts a great deal of pressure on government budgets. More confirmed cases also have an impact on business continuity resulting in further economic challenges, particularly in the early stages of the outbreak, when its transmission mechanisms and gravity are not fully understood.

7.4. Compliance & safety

Policies for diagnostic testing and social distancing will clash at times including in testing locations that can lack efficient and healthy crowd control measures. Combined with insufficient knowledge, this can influence adoption by the public.

7.5. Policy lag

Amid rapidly evolving circumstances, the rapid development of the pandemic and its volatile

existence, policy and intervention are lagging with the lack of concrete and appropriate data on the effects of the interventions. This often renders under-informed and rapidly outdated strategies. It also makes it difficult to determine strategies and rapidly turn gears to alternative strategies when appropriate.

8. LIST OF INSTITUTES ALREADY DEVELOPED KITS

COMPANY	KIT	OVERALL	PRINCIPLE	TARGET DETECTED	SENSITIVITY / DETECTION TIME	REGULATORY STATUS	REGION
WADSWORTH CENTER	Ny Sars-Cov	MOLECULAR ASSAY	PCR		24-72 Hr	FDA, EUA	USA
McMaster University	COVID-19 Test kit				20 MIN	RUO	USA
National Institutes of Health/Handout	COVID-19 Test kit					RUO	USA
Stanford University	COVID-19 Test kit	MOLECULAR ASSAY	RT-PCR		12 to 24 hours	RUO	USA
University of Boston	COVID-19 Test kit					RUO	USA
Sakarya University	COVID-19 testing kits					RUO	Turkey
University of East Anglia	Throat Swab Test kit	MOLECULAR ASSAY	RT-PCR		~50 MIN	RUO	EUROPE
DAAN GENE OF UNIV SUN YAT-SEN	NOVEL CORONAVIRUS (2019-NCOV) REAL TIME MULTIPLEX RT-PCR KIT	MOLECULAR ASSAY	RT-PCR	ORF1ab/N Gene		China FDA, EUA	APAC
ACADEMIA SINICA	SARS-COV-2 NUCLEOCAPSID PROTEIN RAPID DETECTION KIT	MOLECULAR ASSAY	RT-PCR	RdRp, E genes	*15 To 20 Minutes*	RUO	APAC
ACADEMIA SINICA	ANTI-SARS-COV-2 NUCLEOCAPSID PROTEIN HUMAN IGM/IGG RAPID DETECTION KIT	IMMUNOASSAYS	ELISA	IgG, IgM		RUO	APAC
Bangabandhu Sheikh Mujib Medical University (BSMMU)	Detection kit for 2019 Novel Coronavirus (2019-nCoV) RNA (PCR Fluorescence Probing)					RUO	APAC
Chulalongkorn University	Chula COVID-19 Strip Test	IMMUNOASSAY	ELISA	IgG, IgM	10-15 minutes	RUO	APAC
Da A Gene Co. Ltd. of Sun Yat-sen University	COVID-19 Test kit	MOLECULAR ASSAY	RT-PCR			RUO	APAC
Fuzhou University	COVID-19 Test kit			NUCLEIC ACID DETECTION	5-6 hours	RUO	APAC
Iranian university	COVID-19 Test kit				20 MIN	RUO	APAC
Makerere University hospital	Genelyzer KIT				5 MIN	RUO	APAC
Nankai University	Novel Coronavirus (2019-nCoV) IgM/IgG antibody detection kit				15 minutes	RUO	APAC
National AIDS Research Institute	COVID-19 Test kit	IMMUNOASSAY	ELISA			RUO	APAC

National Institute of Cholera and Enteric Diseases	COVID-19 Test kit					RUO	APAC
National Institute of Pathology	COVID-19 Test kit					RUO	APAC
National Institute of Virology	COVID-19 Test kit	IMMUNOASSAY	ELISA			RUO	APAC
PIMSR	COVID-19 Test kit	MOLECULAR ASSAY	PCR			RUO	APAC
SHANXI MEDICAL UNIVERSITY	SARS-COV-2 IgM/IgG antibody test (Colloidal Gold)	IMMUNOASSAYS	ELISA	IgG, IgM		RUO	APAC
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECH	GeneLAMP-N	MOLECULAR ASSAY	RT-PCR	N gene		RUO	APAC
Tsinghua University and West China Hospital of Sichuan University	COVID-19 Test kit					RUO	APAC
University of Macau	COVID-19 Test kit				< 30 MIN	RUO	APAC

9. LIST OF COMPANIES WIH GOOD PRODUCTION CAPACITY

Company Name	Company Size	Region	Headquarter	MOLECULAR ASSAY	ELISA	NEXT GENERATION SEQENCING	OTHERS
Qvella	Big player	USA	Canada	✓			
Natera	Big player	USA	USA	✓	✓	✓	
AltheaDx	Big player	USA	USA	✓		✓	
genefluidics	Big player	USA	USA	✓			
Arbor Vita	Big player	USA	USA		✓		
ImaginAb	Big player	USA	USA		✓		
Intrinsic Life sciences	Big player	USA	USA		✓		
AESKU.GROUP	Big player	USA	USA		✓		
Clovis Oncology	Big player	USA	USA		✓		
Pacific Bioscience	Big player	USA	USA			✓	
CareDx	Big player	USA	USA			✓	
Banyan Biomarkers	Big player	USA	USA				✓
Agendia	Big player	USA	USA				✓
Anpac Bio	Big player	USA	USA				✓
Bioauxilium	Emerging player	USA	Canada		✓		
EntroGen	Emerging player	USA	USA	✓		✓	
Novodiax	Emerging player	USA	USA		✓		
OmniSeq	Emerging player	USA	USA			✓	
Cellgen Diagnostics	Emerging player	USA	USA				✓

ViennaLab Diagnostics	Big player	Europe	Austria	✓			
ALK Abello	Big player	Europe	Denmark		✓		
Genomic Vision	Big player	Europe	France	✓			
Advanced Accelerator Applications	Big player	Europe	France				✓
PROGEN	Big player	Europe	Germany		✓		
Orgentec Diagnostics	Big player	Europe	Germany		✓		
DeltaGene	Emerging player	Europe	Hungary	✓			
Breathomix	Emerging player	Europe	Netherlands				
Universal Biosensors	Big player	APAC	Australia				✓
BioReliance	Big player	APAC	USA	✓			

10. ROADMAP IEBS RECOMMENDATION

Research institutes around the world are involved in developing the testing kit. Institutes are developing low cost kits and receiving approval from authorities. This was when the world stopped using the Chinese rapid test kit for coronavirus testing due to the huge difference in test results, which made the challenge of controlling the pandemic more complicated. Institutes are developing the testing kits that has the advantage of the testing large number of samples within few hours, so healthcare professionals can quickly take the necessary follow-up steps.

The institute's current goal is to deploy the toolkit on a large scale "at the fastest price" and with suitable industrial partners at an affordable price.

As major problem that companies are facing is false results, test kits developed by institutes can help overcome this challenge as test kits developed could be used in large numbers with specific and high throughput testing. In addition, the test kits develop by companies take large detection time while kits produce by institutes can solve this problem by testing large number of samples in just few hours. Another challenge that companies are facing is expensive test kits while institutes can provide affordable low-cost diagnostics.

Collaboration between company and institutes can solve the problem of both sectors solving the problem of company of false results and helping institutes to use their testing kits at a large scale. There is no need to invest in RND, the company only needs to produce the kit. In addition, locally produced test kits will reduce transportation costs and minimize the risk of disease transmission

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