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Rapid Advancements in Diagnostic Technology during the COVID Pandemic: Important and Difficult Tasks for Medical Laboratories

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Abstract: The acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes the illness COVID-19 first emerged throughout China in December 2019 and subsequently spread throughout the globe after the World Health Organization designated it a global outbreak in March 2020.We used the terms COVID-19, SARS-COV-2, Medical Laboratory Professionals,Diagnostic, and Importance, difficulties to search the databases of PubMed and Google Scholar for previously published material. Many molecular based diagnostic tests are applied in corona virus detection like Reverse Transcription Polymerase Chain Reaction, Multiplex Polymerase Chain Reaction, Droplet Digital polymerase Chain reaction, Loop-mediated Isothermal Amplification Test and more. Due to lack of availability of molecular and serologic tests that have been clinically validated or authorized by national or international regulatory bodies, Clinical laboratory experts are tackling threats to our global defense and wellness, including infectious diseases. The opportunity to express gratitude to the unsung medical laboratory heroes and COVID0-19 pandemic allies is now greater than ever. Each year, Medical Laboratory Professionals Week should honors those who contribute key diagnostic data that help save lives. This review article explore overall summary on testing methods including Important and Difficult Tasks for Medical Laboratories which will provide good message for better public health matter.

Keywords: coronavirus; COVID-19; diagnostic; epidemic; medical laboratory professionals; SARS-COV-2

1. Introduction

Coronavirus disease 2019 is caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which initially emerged in China in December 2019 and swiftly spread over the worldwide once the World Health Organization designated a worldwide outbreak in early March 2020 [1,2]. Acute severe respiratory syndrome coronavirus 2 is a positive-sense single-stranded beta-corona virus including an enveloped; coronavirus potentially affects all animals and human beings [2]. Approximately 30,000 sequences constitute viral SARS-CoV-2 genome, which codes for protein with both the structural components spikes (S), envelopes (E), membranes (M), hem agglutinin esterase (HE) and nucleocapsid (N). It has been found that the S proteins from both SARS viruses have submicromolar binding interactions for humans ACE2 [2-4].

Humans frequently contract coronaviruses like Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV), Sever Acute Respiratory Syndrome (SARS) and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that cause cold-like symptoms [2]. Coronaviruses are enclosed viruses with positive-sense ssRNA that have been identified using a variety of techniques. One of the coronaviruses, SARS-CoV-2 is linked to the coronaviruses found in bats and pangolins. Due to their high rate of transmission and fatality, such as the SARS-CoV outbreak in 2002–2003, which had a death rate of 9.56% coronaviruses are well recognized to be the source of worldwide

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pandemics [5]. In 2012, MERS-CoV began to spread over the Middle East. Late in 2019, the highly contagious Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus that eventually named as Coronavirus Diseases 2019 which caused viral respiratory distress and pneumonia in Wuhan, China. 350 million individuals will have tested positive for the virus globally by the end of January 2022, with an estimated 5.6 million fatalities [6].

Neurologic, gastroenterological, and respiratory symptoms can all be brought on by this virus [2,3]. In particular, fever, cough, and other respiratory problems are the most typical signs of early COVID-19 infections. While these are the primary signs of the disease, it is crucial to note that some individuals may still help spread the virus to new human hosts even when they do not report any symptoms of the sickness [4,5].

The predominant method of SARS-CoV-2 transmission in humans is through direct contact with an SARS-Cov-19 infected person who generates respiratory small tiny droplets or aerosols during coughing, sneezing, nearly to the distance of two meters. Since infected surfaces or objects can potentially disseminate the virus, the scientific community has identified airborne particle transmission as the main mode of infection. So at initial pandemic of coronavirus all concern public were encouraged for masking, sanitizing and too social distancing as a physical protective barrier for to prevention from direct contact of aerosols. Including all general protective measures appropriate use of personal protective equipment (PPE) for laboratory professionals is major key for the locking of transmission of corona virus during specimens collection, transportation and examination [2,3].

It is important to diagnose any corona virus disease cases with epidemiological information, clinical features, and symptoms of sickness in accordance with the WHO's recommended standards. Additionally, by spotting infected individuals early on, doctors can save patients from suffering serious consequences, halting the fatal pandemic's rapid spread. However, reliable and quick screening technologies that look for COVID-19 negative individuals will avoid needless quarantines and minimize the disease's detrimental effects on social life and the economy [1].

In this brief, thorough post, we'll go through the key techniques for diagnosing COVID-19, along with several key issues and difficulties facing lab workers during the epidemic.

2. Materials and Methods

During the period of May 2022 to July 2022 saw the review's execution by searching the major terms Coronavirus, Coronavirus diseases, Medical Laboratory Professionals, Diagnostic, Importance and difficulties towards COVID-testing from the databases of PubMed and Google Scholar for previously published relevant material. In order to find the pertinent material, a search for it was first undertaken on several journal websites from 2019 to the present. This search produced 22 references, of which 52 were used for analysis. A table and a summary of the data were used to convey the information after inconsistencies in each of the chosen articles were examined.

3. Review of SARS-COV-2 diagnostic methods

Numerous diagnostic techniques have received approval from both the US Food and Drug Administration (FDA) and the World Health Organization (WHO).Because of the virus's quick spread, the emergency use authorisation (EUA) has provided conditional permission to a number of additional techniques. Aside from the tools and procedures utilized the outcome also depends on collection of samples, laboratory solution use, internal hazards contamination, as well as specimen's storage capacity. All these variables should be taken into account when choosing any trustworthy and quick diagnostic procedure so that the right choice and prompt response to the public may be made [7,8].

Virological cell culture assay is an universal standard laboratory test for virus characteristics identification, virulence research study, and policy assessment, however COVID-19's appearance has changed this. For rapid testing needed, molecular base study polymerse chain reaction (PCR) has become the gold standard procedure globally. Genomic sequencing employs sophisticated methods to monitor the pandemic and support the creation of vaccines. Severe acute resperiatory syndrome-Coronavirus-2 depends heavily on viral RNA analysis [3]. Within these approaches include RT-PCR,

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which has become largest popular method of detecting viral Proteins.Both papers on marketed, government-authorized assays and articles describing non-commercially approved procedures are examples of RT-PCR. Increasment of advances technology on laboratory various methods like Gene Xpert Xpress ,Loop-mediated Isothermal Amplification (LAMP), Multiplex PCR, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), Aided Amplification (RAA), Droplet Digital PCR (ddPCR), Recombinase Polymerase Amplification (RPA), and many more others techniques are applied which is shown in Table 1 as an techniques which are applied in Covid-19 infection diagnosis [3,8,9,10].

Table 1. Overall diagnostic methods and techniques applied in covid-19 infection diagnosis [11-14].

OVERALL DIAGNOSTIC METHODS AND TECHNIQES APPLIED IN COVID-19 INFECTION DIAGNOSIS		
S.N	**Methods**	**Test Techniques with Parameters**
1.	Serological Screening	A. Rapid Diagnostic Test (RDT) ❖ Antigens (S and N Proteins) ❖ Antibodies (IgG and IgM)
2.	Immunological	A. Antigen (Immunochromatographic Assay) B. Antibodies (IgG,IgM and IgA) ❖ Enzyme Immuno Assay (ELISA) ❖ Immunofluorescence (IF) ❖ Chemiluminescent Immuo-Assay (CLIA) ❖ Lateral Flow Immuno-Assay (LFIA)
3.	Biosensors	A. Bio-molecular B. Transducer ❖ Filed effect transistors (FET) ❖ Localized surface plasmon resonance (LSPR) ❖ Cell based potentiometric biosensor(CBPB) ❖ Cell-Based Potentiometric Biosensor (CBPB)
4.	Gene Sequencing	A. Nano Pore Target B. Amplicon Sequencing C. Hybird Capture based sequencing
5.	Neutralization & Virus Culture	A. Virus Neutralization Test (VNT) B. Pseudo virus Neutralization Test (PVNT)
6.	Nucleic acid Testing & Amplification	A. Polymerase chain reaction (PCR) ❖ Real Time (RT) Quantification PCR (qRT-PCR) ❖ Nest Real Time (RT)-PCR ❖ Droplet digital PCR ❖ Loop mediated isothermal amplication test (LAMP) ❖ Gene Xpert Xpress test ❖ Multiple Cross Displacement Amplification (MCDA) ❖ Recombinase polymerse amplification test (RPA) ❖ Nanoparticle Amplification ❖ Pulse controlled amplification test (PCA) ❖ Recombinase aided amplification test (RAA)c
7.	Radiological Testing	A.Imaging ❖ X.Ray ❖ Computed Tomography Scan (CT) ❖ Magnetic Resonance Imaging (MRI)

4. Review of Important and Challenges in the Medical Laboratory Field

One of the most important jobs in clinical laboratories is unquestionably achieving and maintaining quality. Clinical laboratories that lack adequate standards are inherently dangerous for patients. Poor quality findings can lead to mistrust between laboratories and end users, which jeopardizes the practice of evidence-based medicine and prevents productive collaborations between

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physicians and laboratories. Furthermore, substandard clinical laboratories might obstruct international efforts to combat infectious illnesses and outbreaks [15].

Some studies emphasized the significance role of the medical laboratory in human health issues including efficient, reliable, correct and early identification of diseases for regular inspection of individuals' medication outcomes and suitable care. Relevant study shows that nearly around 70% of patient admission and discharge decisions are based on information from the medical laboratory [16]. Tasks like medical laboratory equipment installation, validation and restitution in medical laboratory professionals provide instructions and guidelines for medical healthcare professionals for selecting the appropriate laboratory tests and ensuring adequate sample collection. In healthcare laboratories, medical laboratory services also provide equipment installation, validation, and reimbursement. Always early monitoring duty applied by medical laboratory technologist for emerging human infectious illness like tuberculosis, influenza, Acquired immunodeficiency syndrome, Ebola and recently on SARS-CoV-2 is crucial. Besides this skills and tasks performance, technologist aimed high quality improvement which enables quality assurance of a health professional sectors and community health [17,18].

Numerous investigations have revealed the following as the primary duties of medical laboratories during the COVID-19 epidemic [15,17,18].

- ✓ Setting up adequate, reliable, and long-lasting diagnostic testing capabilities to meet COVID-19 response requirements.
- ✓ Ensuring surge capacity to handle a significant number of specimens to meet COVID-19 epidemiological response demands.
- ✓ Carrying out regional, national, international, local, and virological surveillance of the pandemic.
- ✓ Ensuring the timely publication of laboratory results and connecting results with surveillance data to support public health decision-making and intervention efforts.
- ✓ Monitoring the genetic development of COVID-19 and using viral characterisation to assist in vaccine research and development.

Distance between testing and collecting sites and the associated technicalities may affect the early detection and reporting of COVID-19 cases [15]. Additionally, there is a lack of availability of molecular and serologic tests that have been clinically validated or authorized by national or international regulatory bodies, whether through the WHO network, commercial manufacturers, or national regulators. Large diagnostic kit shortages and challenges with importation exist in the nation as COVID-19 causes stress over the globe. On COVID-19, research and understanding are lacking. The quantity of tests may differ depending on the season in addition to technical issues with the COVID-19 testing [17,19,20]. Some of the problems and solutions related to providing COVID-19 medical laboratory services are shown in Table 2.

Table 2. Problems and solutions related to providing COVID-19 medical laboratory Services [17-20].

S/N	Difficult Tasks and Challenges	Action to be Taken
	Limited Resources	Be self dependent and utilize minimum resources.
	Imperfect knowledge towards Research and Development (R&D)	Provide platform and encourage for exposure on research and development
	Lack of Manpower	Select and empower well trained lab professionals.
	Not well manage Working environment	Focus and invest to construct well manage modern medical laboratory sectors.
	Poor team work amongst health workers	Provide training and workshops related to improvement of team works.
	Advance technologies	At least gain knowledge on new technology around the world.
	Lack of fund	Manage fund to battle against every pandemic
	Misdiagnosis	Training for well qualified laboratory professionals.
	Quality System Error	Manage quality control

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Limited Investment on Medical Laboratory Professionals by Nation.	Separate early country budget for improvement of laboratory professionals.

5. Discussion

Large mass of SARS-CoV-2 laboratory testing is only the major crucial point for the identification and diagnosis of coronavirus which will directly make comfort and easier for to restart the human normal life excluding lockdown. This will directly improve country economic status for to maintain normal human life globally. There have been around 6 billion COVID-19 tests administered worldwide as of March 11, 2022. At high rank of testing with around 960 million USA, 780 million India, 490 million United Kingdom and 470 million Spain are ahead [21]. The majority of nations administer two to three COVID-19 tests daily per 1,000 persons. By today, 400–1000 tests per 1000 persons have been conducted in the majority of nations. Countries with high-income sources like United Arab Emirate, Denmark, Austria, UK , USA etc. are testing around 20,000–15,000 COVID testing, rate per 1000 inhabitants, whereas countries having low economic status have performing less testing. [21,22].

Laboratory identification and detection of coronavirus is just as crucial as an realistic assessment for to study epidemiological situation on a national and international level because it is for a regulated return to pre-coronavirus life. Reverse transcription polymerase chain reaction of specimen collected from nasopharynx and oropharynx has been used as a nucleic acid amplification test (NAAT) for the validation and diagnosis of COVID-19 diseases, which has mostly been based on signs and symptoms assessment. Because PCR-based techniques are straightforward, extremely sensitive, and extremely specific, they can regularly and consistently identify corona virus infection in individuals.These tests begin with the reverse transcription of the corona virus ribonucleic acid (RNA) into complementary DNA. They are frequently employed to amplify small amounts of deoxyribonucleic acid (DNA) [9,13,15]. The DNA amplified as a consequence of the PCR is then submitted to specific detection using various analytical techniques. Most corona viruses, including SARS-CoV-2, may be found using the gold-standard technique of RT-PCR. Others molecular testing methods like LAMP, MCDA, ILFA, LFICS, CLIA, and EIA are related to NAAT. Rapid Antigen detection kits for SARS-CoV-2 are already feasible in the laboratory market and have recently been the subject of various investigations [3,9,10].

Despite the fact that the molecular screening test is the most frequently employed technique to assess COVID-19. In correlations with assessment of patient clinical finding the numerous different techniques are extensively applied in medical field like , lungs computed tomography (CT), biosensors based and artificial intelligence methods which are shown in table 1[11,12]. CT is a regularly used supplementary detection method for the diagnosis of many illnesses. In order to diagnose the corona virus, various testing techniques are employed in clinical, academic, and public health laboratories. These techniques have various output batching capacities, analytical result performances, unique infrastructure establishing requirements, and labor requirements [3,14].

6. Conclusion and Recommendation:

Inside this review, we gave a general description of the investigative techniques employed for COVID-19 identification along with significant laboratory-related problems. Whereas the reverse transcription polymerase chain reaction is the most worldwide applied technique for SARSCoV2 test. Its use may be constrained due to highly expensive cost for specialized lab infrastructure with testing, and the prevalence of incorrect negative results .The numerous, accurate, quick, affordable, and simple-to-implement diagnostic options discussed in this review will increase the detecting potential, which represents the most effective technique of restricting this pandemic's spread.

In additional to regular daily tasks, they played crucial roles in the battle against COVID-19. The world's governments have recognized the value of these efforts. Out place to guarantee accuracy and sensitivity—remain crucial. The opportunity to express gratitude to the unsung medical laboratory heroes and COVID0-19 pandemic allies is now greater than ever. Each year, Medical Laboratory

Professionals Week honors those who contribute key diagnostic data that helps save lives while also demonstrating gratitude for the essential work they did. The courageous medical professionals fighting the COVID-19 pandemic are being praised by regular people all across the world.

The COVID-19 diagnostic techniques have been the subject of many studies conducted throughout this epidemic. From the scenario of rapid production of molecular based and rapid diagnostic kits around globe many laboratories has been really quick and intensive, directly assisting nations to increase their testing capacity. Processes from sample collection to shipment to experimental analysis for COVID-19 remain crucial. Specialists in the world's leading medical and laboratory institutes are tackling threats to our global defense and wellness, including infectious diseases. No matter how far away from the patient they are, they create findings that have an immediate impact on patient treatment, even if they are working in a laboratory where the patient may be several hundred kilometers away.

Furthermore this review article recommended following aspects to provide strength, power and improvement in medical laboratory field for better public health matter.

- Across all global medical matters, health professional must always depend on the findings of clinical laboratory studies and not just COVID-19.
- Every COVID-19 lab tests and instruments must be updated or inspected regularly.
- Properly building as well as updating diagnostic laboratories used to investigate COVID-19 as well as other issues affecting public health
- Like a reference for developing strategies and initiatives, organizations interested in COVID-19 must accumulate scientific and clinical evidence on all health and safety concerns, including vaccination.
- The authorities have to offer all health science specialists competitive combat pay including health insurance.
- Ensure that all laboratory personnel receive updated training to keep up with just about any forthcoming COVID-19 waves.
- Appropriate measures should be implemented to address multiple aspects hampering the global behavior of individual clinical laboratories.

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References

1. Farnoosh G, Alishiri G, Farahani AJ, Javidi N, Farhangi Z, Bahadori M, Ravangard R. Coronavirus disease (COVID-19): challenges and opportunities. Disaster Medicine and Public Health Preparedness. 2022 Apr;16(2):431-3.
2. Bahadur Khadka R, Bhandari R, Gyawali R, Neupane B, Pant D. Epidemiology and pathogenesis of coronavirus disease (Covid-19). Novel Research in Microbiology Journal. 2020 Apr 1;4(2):675-87.
3. Gyawali R, Karki KD, Bhandari R, Neupane B, Kafle RR, Pant D, Khadka RB. Coronaviruses: Diagnostic approaches for covid-19. Dr. Kuldeep Dhama. 2020 Oct:9.
4. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. Nature reviews Molecular cell biology. 2022 Jan;23(1):3-20.
5. Kaul D. An overview of coronaviruses including the SARS-2 coronavirus–molecular biology, epidemiology and clinical implications. Current medicine research and practice. 2020 Mar 1;10(2):54-64.

6. Sachs JD, Karim SS, Aknin L, Allen J, Brosbøl K, Colombo F, Barron GC, Espinosa MF, Gaspar V, Gaviria A, Haines A. The Lancet Commission on lessons for the future from the COVID-19 pandemic. The Lancet. 2022 Oct 8;400(10359):1224-80.
7. Zuckerman DM. Emergency use authorizations (EUAs) versus FDA approval: implications for covid-19 and public health. American Journal of Public Health. 2021 Jun;111(6):1065-9.
8. Marble HD, Bard AZ, Mizrachi MM, Lennerz JK. Temporary Regulatory Deviations and the Coronavirus Disease 2019 (COVID-19) PCR Labeling Update Study Indicate What Laboratory-Developed Test Regulation by the US Food and Drug Administration (FDA) Could Look Like. The Journal of Molecular Diagnostics. 2021 Oct 1;23(10):1207-17.
9. Rai P, Kumar BK, Deekshit VK, Karunasagar I, Karunasagar I. Detection technologies and recent developments in the diagnosis of COVID-19 infection. Applied microbiology and biotechnology. 2021 Jan;105(2):441-55.
10. El Jaddaoui I, Allali M, Raoui S, Sehli S, Habib N, Chaouni B, Al Idrissi N, Benslima N, Maher W, Benrahma H, Hamamouch N. A review on current diagnostic techniques for COVID-19. Expert Review of Molecular Diagnostics. 2021 Feb 1;21(2):141-60.
11. Carter LJ, Garner LV, Smoot JW, Li Y, Zhou Q, Saveson CJ, Sasso JM, Gregg AC, Soares DJ, Beskid TR, Jervey SR. Assay techniques and test development for COVID-19 diagnosis.
12. Choi JR. Development of point-of-care biosensors for COVID-19. Frontiers in chemistry. 2020 May 27;8:517.
13. Nandy Chatterjee T, Bandyopadhyay R. A molecularly imprinted polymer-based technology for rapid testing of COVID-19. Transactions of the Indian National Academy of Engineering. 2020 Jun;5(2):225-8.
14. Böger B, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. American journal of infection control. 2021 Jan 1;49(1):21-9.
15. Khadka RB, Gyawali R. Establishing PCR testing in Nepal for COVID-19: Challenges and opportunities. Kathmandu University Medical Journal. 2020 Sep 30;18(3):309-12.
16. Lo IL, Lio CF, Cheong HH, Lei CI, Cheong TH, Zhong X, Tian Y, Sin NN. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. International journal of biological sciences. 2020;16(10):1698.
17. Hu E. COVID-19 testing: challenges, limitations and suggestions for improvement.
18. Afriyie DK, Asare GA, Amponsah SK, Godman B. COVID-19 pandemic in resource-poor countries: challenges, experiences and opportunities in Ghana. The Journal of Infection in Developing Countries. 2020 Aug 31;14(08):838-43.
19. Uchejeso OM, Rinpan JI, Chongs ME, Ekpere-Ezeugwu MO. Fighting COVID-19: The Medical Laboratory Involvement. Fighting the COVID-19 Pandemic. 2021 Aug 17:301.
20. Binnicker MJ. Challenges and controversies to testing for COVID-19. Journal of clinical microbiology. 2020 Oct 21;58(11):e01695-20.
21. Mathur R, Rentsch CT, Morton CE, Hulme WJ, Schultze A, MacKenna B, Eggo RM, Bhaskaran K, Wong AY, Williamson EJ, Forbes H. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. The Lancet. 2021 May 8;397(10286):1711-24.
22. Filchakova O, Dossym D, Ilyas A, Kuanysheva T, Abdizhamil A, Bukasov R. Review of COVID-19 testing and diagnostic methods. Talanta. 2022 Mar 31:123409.