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Current Diagnostic Methods for COVID-19: Review

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Abstract. On December 31, 2019, the World Health Organization (WHO) received an alert that a cluster of atypical pneumonia cases had appeared in Wuhan, China. Investigations have revealed that a new coronavirus is circulating and causing what we now know as "Coronavirus Disease 2019" (COVID-19). COVID 19 is a new disease caused by a virus recently identified as "Severe Acute Respiratory Syndrome-Coronavirus 2" (SARS-CoV-2). This virus is genetically related to other coronaviruses, including the one responsible for respiratory syndrome severe acute (SARS) and the one that causes Middle East Respiratory Syndrome (MERS). The diagnosis tools of COVID-19 available so far based mostly on molecular tests for which the detection of viral genes by RT-qPCR has been shown as the most reliable technique and immunological testing based on specific SARSCoV-2 viral antigen detection in the early phase of infection, then, the human antibody detection testing in the later phase of the disease. In the other hand, artificial intelligence-based techniques have an extraordinary capacity to offer an accurate and efficient system for the detection and diagnosis of COVID-19, the use of which in the processing of modalities would lead to a significant increase in sensitivity and specificity values. Furthermore, other techniques based on the use of ultraviolet rays are also used in the diagnosis of COVID-19 which are phototests and photopatch tests, these two techniques are valuable for an evaluation of various photodermatoses. In this study, the current methods of COVID-19 diagnostic were presented as well as the diagnostic approaches that are still in the early research state.

Keywords: COVID-19, diagnostics, molecular tests, immunological tests, artificial intelligence, phototests.

1 Introduction

Coronaviruses (CoVs) are a group of highly diverse RNA virus belong to the subfamily Orthocoronavirinae in the family Coronaviridae, Order Nidovirales that are divided in 4 genera :(α-CoV), Betacoronavirus (β-CoV), Gammacoronavirus

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(γ-CoV) and Deltacoronavirus (δ-CoV) that cause disease varying from mild to severe in human and animals [1,2,3]. However, two zoonotic coronaviruses have emerged causing severe disease in humans: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002-2003 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [4,5]. SARS-CoV-2, registered in the Wuhan City of China for the first time, represents the third major spill-over of a coronavirus from animals to humans during the last two decades [6], it contagious in humans, and it has rapidly spread worldwide through close human interactions or the spilled respirational material (cough, sneeze) of the infected people [7].This emerging disease has given rise to a pandemic, a first wave of which after its emergence in Asia, has successively affected Europe, America and Africa. On March 11, 2020, the novel coronavirus disease outbreak was officially declared as a public health emergency of international concern (PHEIC) by the World Health Organization (WHO) namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), previously known as 2019 novel coronavirus (2019-nCoV), then it has rapidly spread around the world, causing 14 million active cases with 582,000 deaths and 7,881,023 recovered as of July 2020 [8]. The SARS-CoV-2 is a single stranded positive RNA virus of 30,000 nucleotides in size which two-third of 5' contains open reading frame genes (ORF1a and ORF1b) that encrypt sixteen non-structural proteins (nsp) which are processed to form a Replication–Transcription Complex (RTC) that is involved in genome transcription and replication. For example, nsp3 and nsp5 encode for Papain-Like Protease (PLP) and 3CL-protease, respectively. Both proteins function in polypeptides cleaving and block the host innate immune response. nsp12 encodes for RNA-dependent RNA polymerase (RdRp), nsp15 encodes for RNA helicase. While the one-third of 3 consists of eight accessory genes, the structural genes and a poly (A) tail [9]. The accessory genes are distributed between the structural genes and their function is mostly unknown [10], structural gene unit encodes the structural proteins; the (S) surface glycoprotein, Envelope protein (E), Membrane glycoprotein (M), and Nucleocapsid protein (N) [11]. As shown in Fig. 1 the (S) surface glycoprotein is responsible for attachment to host cells (ACE2 receptor) and considered a critical target for the induction of antibodies capable of neutralizing the virus. The envelope protein (E) which adheres to the M protein to form the viral envelope and it is reported to play role in pathogenesis as it interacts with the tight junction related protein PALS1 [12]. The membrane protein (M) is important to generate the virus and it is responsible for the assembly of viral particles it has three domains, the cytoplasmic domain, the transmembrane domain, and the N hydrophilic domain [13]. The nucleocapsid (N) proteins that, along with the RNA genome, produce the nucleocapsid involved in the budding of new virions in the cell [14,15]. The Spike protein non-structural proteins, various host factors working together may contribute to the infection kinetics, high infectivity, rapid transmission, and a spectrum of clinical manifestations of COVID-19 [16,17].

To curb the spread of the COVID-19 pandemic, the world needs diagnostic systems capable of rapid detection and quantification of the novel coronavirus

(SARS-CoV-2). The present diagnostic assays for CoV-2 can be segregated into two broad classes: molecular and immunological. Molecular tests determine the presence of the virus by detecting its genome. For molecular assays, specimens can be collected from multiple relevant areas, such as the nasal swab, BAL, etc. Immunological tests detect either the presence of the antigen (a protein that is only expressed by the virus) or the antibodies (generated by the host's immune system in response to the infection) in blood samples. While PCR (molecular) and antigen tests detect the presence of the virus at the time of testing, antibody assays mainly determine previous infection. All these tests can identify both, symptomatic and asymptomatic carriers of the virus. The PCR assays include Reverse Transcription-PCR (RT-PCR), Recombinase Polymerase Amplification (RPA), Reverse Transcription-loop Mediated Isothermal Amplification (RT-LAMP), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas) based tests [18].

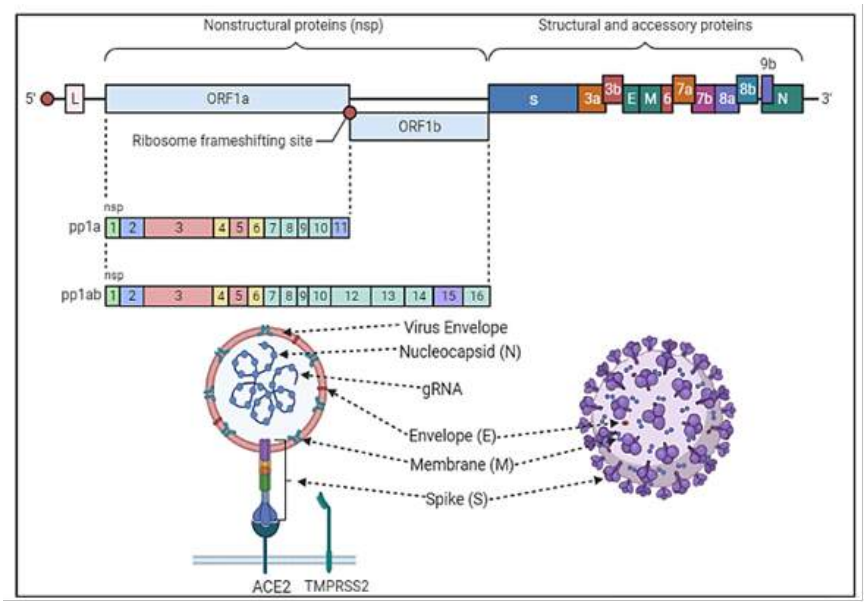

Fig. 1. The genomic structure of SARS-CoV-2. The genome encodes two large genes ORF1a and ORF1b, which encode 16 non-structural proteins (nsp1– nsp16). The structural genes encode the structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N). The accessory proteins are unique to SARS-CoV-2 in terms of number, genomic organization, sequence, and function. **Image created with BioRender.com**

Recently, medical images such as chest X-ray and Computed Tomography (CT) scan images have been used to determine COVID 19 positive patients [19, 20]. Several early works have reported that the sensitivity of CT scan and X-

ray imaging are noticeably greater than that of the RT-PCR test at the initial representations of the disease, making them great candidates for developing new and sophisticated methodologies for analysis and classification of COVID-19 cases [21].

COVID-19 detection by using CT scan and X-ray images is possible by manual interpretation of images expert radiologists. However, interpreting and analyzing these images might encounter some problems leading to reduced sensitivity. Moreover, it can be a time consuming and daunting task, especially when manually quantifying the infected regions on the CT scan and X-ray images [22]. To cope with these limitations, there is a pressing need to develop intelligent algorithms to accurately and automatically detect COVID-19 cases using radiological images. The one of the most uses global technology right now is Artificial Intelligence (AI) that can identify abnormal patterns of CT and X-ray images [23]. Artificial intelligence methods have been shown to accurately detect COVID-19 and distinguish this condition from other pulmonary disorders. AI is a broad umbrella consisting of many sub-areas. These subareas include learning, preparation, thinking, representation of information and searching. Machine Learning (ML) and Deep Learning (DL) are a subset of AI areas that consist of several algorithms that mimic human brains and behaviors based on data monitoring to identify or cluster particular tasks [23]. Using these methods, it is possible to assess certain segment regions and take precise structures in chest CT images facilitating diagnostic purposes. Ultraviolet (UV) therapy is an effective and well-tolerated therapeutic method for various dermatologic conditions due to its antiproliferative and immunosuppressive effects. UV radiation covers three solar spectrum ranges : UVA, 320 to 400 nm ; ultraviolet B rays (UVB), 290 to 320 nm ; and UVC, 200 to 290 nm. Current phototherapy (PhT) includes broadband UVB, narrowband UVB (NB-UVB), ultraviolet A1 rays (UVA1), psoralen plus ultraviolet A or psoralen ultraviolet A rays (PUVA), and excimer laser, with traditional Goeckerman and Ingram methods having only historic value. Phototests and photopatch tests are valuable for an evaluation of various photodermatoses [24]. Phototesting is used to evaluate the skin's response to light and attempt to establish the spectrum of radiation that will cause adverse reactions or inhibit them [25]. Photopatch testing combines the techniques of two subspecialties in Dermatology, patch testing for allergic contact dermatitis and phototesting for photodermatology [26].

This article aims to review the range of current methods available to testing COVID-19 based on molecular tests, immunological tests, artificial intelligence and phototesting techniques exploring their advantages and limitations.

2 Clinical diagnostic pathophysiology and diagnosis of COVID-19 patients

The SARS-CoV-2 affects people differently depending upon the genetic predisposition, immune status and diseases associated with the respiratory system [27,28]. Te people $>$ 60 years of age are at higher risk of exacerbating the dis-

ease [29,30,31]. The mean incubation period of SARS-CoV-2 is estimated to be 3–7 days (range, 2–14 days) [32,33], indicating a long transmission period of SARS-CoV-2. The main manifestations of COVID-19 noted by the U.S. CDC: fatigue, fever, chills, cough, dyspnea, muscle pain, loss of taste or smell, with less common symptoms being nasal congestion, headache, runny nose, sore throat, nausea, vomiting and diarrhoea [34]. Hospital admission data suggests that fever and cough are the most frequent manifestations [35]. Of note, critical patients can also only present with a low fever, or even no obvious fever, and mild patients show only low fever, mild fatigue and no pneumonia [36,37]. These asymptomatic or mild cases can also spread SARS-CoV-2 between humans. More recent data also suggest that conjunctivitis, dermatologic findings (maculopapular and vesicular lesions), and Multisystem Inflammatory Syndrome in Children (MIS-C), which clinically resembles Kawasaki disease, are associated with infection [38,39]. Computed Tomography (CT) scan was used as an early diagnosis tool for COVID-19 in many countries mostly due to lack of testing kits. Abnormal observations in the chest CT scan image were used as a diagnostic feature for COVID-19 [40,41,42]. CT presentations of COVID-19 patients include bilateral pulmonary parenchymal ground-glass opacity, pulmonary consolidation and nodules, bilateral diffuse distribution, sometimes with a rounded morphology, and a peripheral lung distribution [43,44]. Reliance upon widely available markers (C reactive proteins, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), creatinine kinase, alanine aminotransferase (ALT), aspartate transaminase (AST), D-dimer) was especially common early in the pandemic, when specific testing capacity was extremely limited [45,46]. In addition to the clinical diagnostic including biomarkers and imaging that also contribute to the diagnosis of COVID, confirmation of this viral disease is made by the identification of SARS-CoV-2 RNA in biological samples.

3 Molecular diagnostic tests for COVID-19

3.1 Real-time RT-PCR assays

Reverse Transcription quantitative-PCR (RT-qPCR) is a molecular biological diagnosis technology based on nucleic acid sequence, is used to quantify the viral load in a sample and to measure the change over time, it is reliable, very sensitive and specialized, allowing a reliable diagnosis to be made in just three hours, although laboratories generally take six to eight hours on average. It is much faster than other virus isolation methods available and presents a lower risk of contamination or error since all steps can be performed in a closed tube. Among the available methods, it remains the most precise for the detection of the coronavirus [47]. Isolation of RNA from the nasal or nasopharyngeal swabs is the initial step of the RT-qPCR assay and critical for the assay's reproducibility and biological relevance. Purified RNA template is converted into a cDNA (complementary DNA) by reverse transcriptase (an RNA-dependent DNA polymerase enzyme). Subsequently, cDNA is amplified in a polymerase chain reaction (PCR) in three steps: (i) denaturation of cDNA at 95°C, (ii) annealing

of the primers and probe to the respective denatured cDNA strands at 60 °C, and (iii) extension or synthesis of RNA copies by DNA polymerase at 72 °C. The amplified products follow the same cycle to generate a large number of RNA copies as shown in 2. Sequence-specific forward and reverse primers and a dual-labeled fluorogenic probe are designed and utilized in real-time RT-PCR diagnostics. The oligonucleotide probes used in RT-PCR assays are dual-labeled with a fluorophore (fluorescent reporter) and a quencher covalently attached to the 50 and 30 ends, respectively; and are often called TaqMan probes that used to quantify RNA copies by producing fluorescence signal during amplification cycles The DNA polymerase extends the primers to synthesize new DNA strands. In this process, the polymerase displaces and separates the fluorescent reporter (F) and the quencher. At the ground state, the quencher is in close proximity to the reporter, and thus suppresses its emission. Upon cleavage by the polymerase (during extension step), the reporter is released. This relieves its inhibition thereby producing a fluorescent signal. During amplification, the fluorescence signals are detected in real-time and the fluorescence emission data is plotted against the replication cycles [18]. A fluorescent signal threshold is decided by the standard deviation of the average baseline fluorescence of cycles 3–15 [48]. In general, for diagnosis of COVID-19 infection, Cycle threshold (Ct < 40) is considered clinically positive. China CDC recommends a Ct value of 37, a suspect is judged clinically positive if Ct is < 37. A Ct value of > 40 is considered clinically negative, while it is recommended to repeat the test if Ct is 37–40 [49,50].

RT-qPCR can be performed in one or two steps. In a one-step assay, reverse transcription and PCR amplification are consolidated into one reaction utilizing a single tube and buffer for RT and PCR steps. In a two-step assay, the reactions are done sequentially in separate tubes with independently optimized buffers [51,52]. One-step RT-PCR is reproducible and may reduce risk of cross contamination [53]. However, two-step RT- PCR is longer and offers higher sensitivity and lower detection limits [54]. Usually, PCR is directed at amplifying only a small region within a gene, Therefore, choosing the target gene and region within that gene is important, as it needs to be specific to the virus, excluding any overlap with the host genome or any other parasite/virus. For CoV-2 PCR, regions within the N, E, RdRP, S and ORF1ab genes have been successfully used as tar-gets for RT-PCR [55]. Use of multiple PCR targets helps to avoid false negatives associated with mutations in the primer site, especially mismatches at the 3' end [56]. In addition to the viral genes, the human RNase P gene which is present ubiquitously in all cells is also amplified separately [57].

To improve the diagnostic efficiency, duplex or multiplex real time RT-PCR test kits are developed, which enable the simultaneous detection of two or more specific sequences. The U.S. Food and Drug Administration (FDA)'s and Centers for Disease Control and Prevention ou (US.CDC) recommend assays detecting viral nucleocapsids N1 and N2 and human RNase P genes as the primary targets and internal control (IC), respectively [58]. A cycle threshold (Ct) value of < 40 for all target genes is defined as a positive test, while a Ct value <40 for only

one of the two nucleocapsid proteins is considered indeterminant and requires confirmation by retesting [59]. RT-PCR kits for SARS-CoV-2 detection mainly include the reverse transcription and amplification enzymes, two to three sets of primers and probes for amplification of the specific viral genome regions, and authorized reagents for negative, positive, and internal controls [7,49].

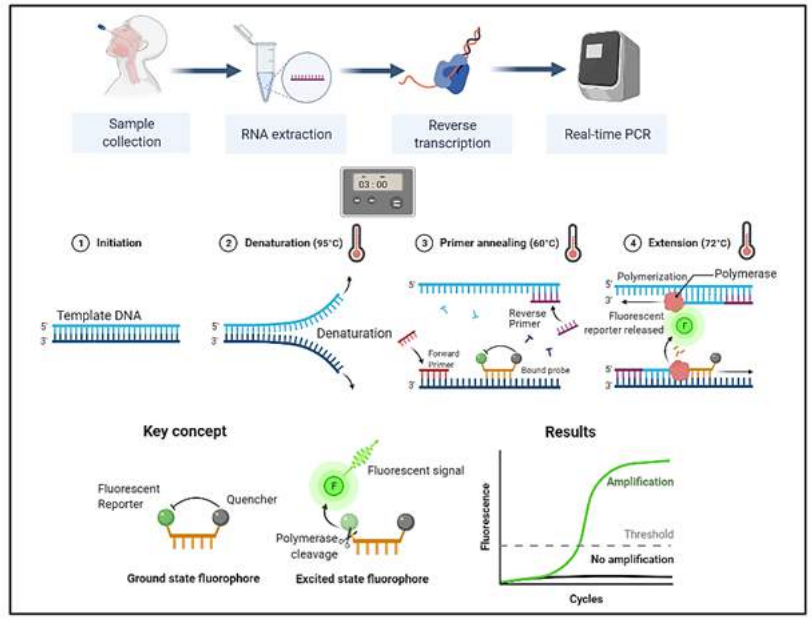

Fig. 2. Principale of RT-qPCR. The RT-qPCR method involves sample collection and extraction of viral RNA sample. The extracted RNA sample is converted to its complementary DNA (cDNA) by the reverse transcription. Finally, the amplification of this DNA sample is performed in qPCR, and the viral cDNA is detected by a fluorescent signal. **tImage created with BioRender.com**

The Pan American Health Organization (PAHO) implemented the first protocol made available by WHO, developed by the Charité Hospital, Berlin Germany on January 2020. This protocol has been published and can be accessed on the following link: `https://www.eurosurveillance.org` The protocol is based on the detection of 3 different markers: genes N, E and RdRp. The assays for the genes E and N are intended as screening protocols to detect any bat-associated beta-coronavirus (do not detect common human coronavirus); the RdRp is specific for SARS and SARS-like coronavirus (including the 2019-nCoV). Therefore, for a routine workflow, it is suggested to run first the N or the E gene assay (it is not necessary to run both) as the screening tool, followed by confirmatory testing with the RdRp gene assay [60]. Either E or RdRP genes can be used for the diagnosis; nevertheless, the E gene PCR has demonstrated slightly higher

sensitivity [61]. WHO provided a recipe document (Maschinen et al., 2020) for in house RT-PCR-based SARS-CoV-2 detection that summarizes the methods from well-known institutions worldwide, including China CDC (China), Institute Pasteur (France), USA CDC (USA), Charité (Germany), National Institute of Infectious Diseases (Japan), University of Hong Kong (Hong Kong) and National Institute of Health (Thailand). Nalla et al. (2020J) ; Jung et al. (2020) ; Vogels et al. (2020) and Corman et al. (2020) stated that all the tested primer and probes sets were found to be highly specific for the SARS-CoV-2 genes, and no cross-reactivity with other respiratory viruses was observed [7,62,63,64,65]. To improve diagnostic efficiency and reliability, duplex or multiplex real-time RT-PCR tests are developed. These allow simultaneous detection of two or more target sequences via specific fluorescent-labeled probes (43). For instance, the FDA emergency use authorized Abbott RealTime SARS-CoV-2 assay is a dual target RT-PCR assay that detects RdRp and N genes; the TaqPathTM COVID19 Combo Kit by Life Technologies (Thermo Fisher Scientific, Inc.) employs quantitative recognition of ORF1ab, N, and S genes simultaneously [66,67]. Molecular detection of COVID-19 virus using well-designed protocols is usually very specific; thus, a positive result confirms the detection of the virus. On the contrary, a negative result might not always mean the absence of COVID-19 virus infection [68]. Several reasons might explain a negative result in a person infected with COVID-19 virus, mainly: (i) Poor sample quality, handling, transportation and/or storage (to control for this, the qualitative detection of a human housekeeping gene (eg., RNase P can be performed) [18]. (ii) Poor/failed sample extraction, presence of PCR inhibitors in the extracted RNA (to control for this, an extraction control can be used, or the detection of a housekeeping gene undertaken as mentioned above). (iii) The sample was collected at a time where the patient was not shedding sufficient amounts of virus, for instance very early or very late during infection (this point is particularly relevant as the dynamics of the viral presence in different sample types has not been fully established) [69]. The nucleic acid of SARS-CoV-2 can be detected by RT-qPCR or by viral gene sequencing of nasopharyngeal and oropharyngeal swabs, stool, sputum or blood samples [69,70]. Performance data for different respiratory tract samples is not available though some studies suggest that NP swabs are more sensitive and accurate than OP swabs [71,72]. To et al. (2020) found that SARS-CoV-2 could be effectively detected in the saliva specimens of infected patients [73]. Saliva is a leading candidate, as SARS-CoV2 RNA is reliably detected within the first week of symptom onset [74]. Lower respiratory tract specimens (tracheal aspirates, bronchoalveolar lavage (BAL), fbrobronchoscopy brush biopsy, or sputum) are also valuable for diagnostic testing, as they demonstrate higher positivity rates than upper respiratory specimens, especially later in disease course [75]. Similarly, Non-respiratory samples such as blood, feces, urine, semen, or cerebrospinal fluid (CSF) have been used, though their interpretation remains controversial [76,77]. RT-qPCR analysis complet other investigations (clinical, biological, and radiological). Although the specificity of RT-qPCR for the diagnosis of COVID is high, its sensitivity largely depends on the type of sample,

the time of collection, the sampling technique and the quality of the test and the test team. The patients can be categorized as SARS-CoV-2 positive or SARS-CoV-2 negative based on the RT-PCR results. However, this technique does not give information for the patients who have already recovered from the SARS-CoV-2, since the viral load is cleared out of the body after recovery. Equally, the patients who are in the very first days of the viral infection may not respond "positive" with this test due to the inadequate amount of the virus on the swabs [51]. False-negative results can occur with RT-PCR that have been reported to occur in 30% (range 10–40%) of patients with COVID-19 [58]. This result must therefore be interpreted in the light of all the results: too early or too late, it may not be informative because the patient is in the presymptomatic phase in the first case, or already on the road to recovery in the second case, with in these two cases an "undetectable viral load". This is noticeably higher the day before and the first days of the onset of symptoms [78]. It should be remembered that a perfect, specific and 100% sensitive test does not exist, and that the sample it self can be a source of negative results due to a non-compliant sample, because it was carried out at the entrance nasal cavity and not in a deep site (in contact with the mucous membrane of the nasopharynx). Although nucleic acid testing (PCR) is the gold standard test for SARS-CoV-2, this test is relatively expensive, time-consuming and labor-intensive and may not be suitable in some settings, especially in the African Region, where laboratory systems are often poor. The availability of reagents used by automated nucleic acid analysis platforms continues to increase, resulting in increased throughput and reduced test turnaround times on some platforms, although it is noted that the opposite effect on other platforms. Therefore, a number of immunodiagnostic tests have been developed to screen for COVID-19, with the aim of providing a cost-effective and rapid COVID-19 detection methodology [79]. Because viruses are only present in the body for a certain period of time, real-time RT-PCR cannot determine whether an individual has been infected in the past, which is useful for understanding the development and the spread of virus. To detect, track and study past infections, especially asymptomatic infections that may have contributed to the spread of the virus, other methods are needed.

3.2 LAMP (loop-mediated isothermal amplification)

LAMP is another isothermal amplification technique which produces long, self-complementary looping DNA strands to generate a detectable signal. It combined with reverse transcription (RT-LAMP) has been developed as RT-qPCR alternative since it does not require expensive thermocycler instruments that operate alternating temperatures for the amplification [52]. RT-LAMP is highly specific that employs DNA polymerase and 4–6 primers that bind distinct target regions of the genome; it allows direct detection of SARS-CoV-2 genes such as ORF1ab, S, E, and/or N gene [80,81]. and strand-displacement polymerase enzymes Bst 2.0 ; this enzyme can separate the two template DNA strands (plus and minus) as it builds the new strand, thus removing the denaturation step from PCR. The self-complementary regions of the primers promote the formation of looped

DNA products Fig. 3. This allows LAMP to yield concatemers of various lengths, which are long DNA strands with multiple copies of the target region aligned back to each other [82]. All the amplification reaction is processed in one single tube at around 60–65°C and can synthesize up to 109 copies of the target gene in less than an hour [7]. Detection is based on photometric measurement of turbidity resulting from magnesium pyrophosphate precipitation that occurs as a by-product of amplification. Dye molecules could also be employed in the reaction such as phenol red Color change can be measured by the naked eye or simple analytical devices [82]. Several studies have shown promising RT-LAMP results in SARS-CoV-2, However, this assay is challenged by low specificity due to presence of multiple pair primers that may increase non-specific by product formation [83].

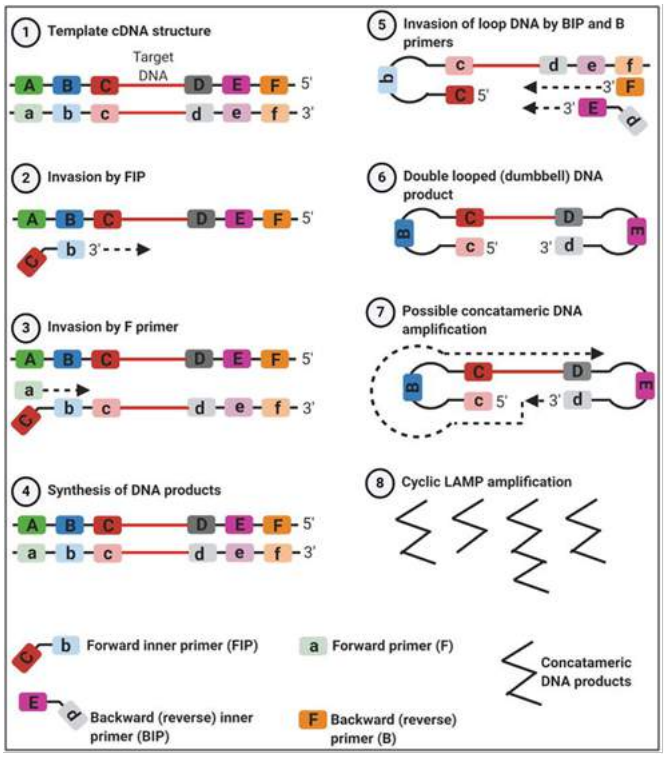

Fig. 3. Process of Loop-mediated isothermal amplification (LAMP). LAMP uses 4-6 primers recognizing 6-8 distinct regions of target DNA. A strand-displacing DNA polymerase initiates synthesis and 2 of the primers form loop structures to facilitate subsequent rounds of amplification [18].

3.3 Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

CRISPR (Clustered regularly interspaced short palindromic repeats-Cas (CRISPR-associated nuclease) technology has been recently tested for its potency in the field of diagnostics. This technique, which was given recognition through the Nobel Prize in Chemistry 2020, is a modified biological process of the bacterial (prokaryotic) adaptive immune system [84]. CRISPR belongs to a family of palindromic nucleic acid repeats found in bacteria, which are recognized and cut by a unique set of effector enzymes known as the CRISPR-associated (Cas) proteins [85]. The Cas enzymes are exceptionally sensitive and specific as they can be programmed to identify and cut SARS-CoV-2 RNA sequences [53].

In case of CoV-2, the virus ssRNA will need to be reverse transcribed to cDNA which will be either amplified as DNA products or through in vitro transcription as RNA products. The cDNA can be processed either through Cas9 or Cas12a, while the ss RNA can be cleaved through Cas13a. The single-guide RNA (sgRNA) or crRNA is complementary to the region of interest, and thus guides the Cas nuclease to the site. After target cleavage, collateral cleavage activity cleaves and releases the reporter from quencher inhibition. This produces a detectable fluorescent signal, which is proportional to the amount of target DNA in the reaction as shown in Fig. 4 [18].

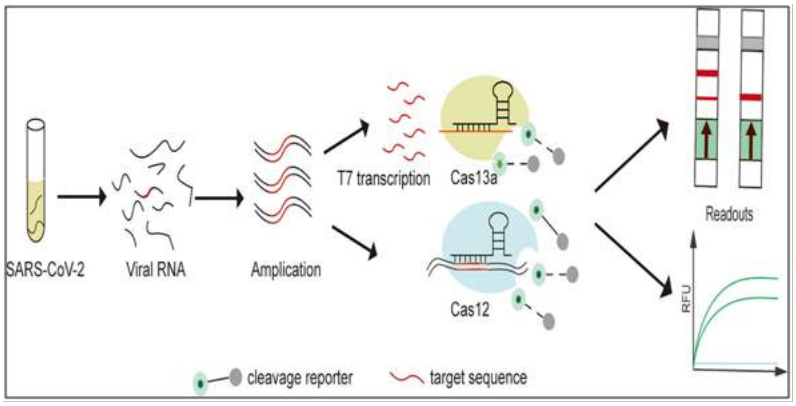

Fig. 4. CRISPR-Cas cleavage system. The extracted SARS-CoV-2 viral RNA is first pre-amplified into double-stranded DNA (dsDNA). For Cas13a-SHERLOCK assay, ds-DNA is first T7 transcribed into single-stranded RNA (ssRNA), followed by activation of the Cas13a cleavage reporter. For Cas12a or Cas12b assays, direct detection of pre-amplified dsDNA enables activation of the Cas12a or Cas12b cleavage reporter. Visualization of CRISPR/Cas assay results by fluorescence and lateral flow readouts [87].

A recently invented SHERLOCK (Specific high-sensitivity enzymatic reporter unlocking) technique includes the crRNA-Cas13a complex to target RNA

molecules [84]. This technique is able to consistently detect target sequences of SARS-CoV-2 in a range between 20 and 200 aM (10–100 copies per microliter of input). This test can be read out using a dipstick in n ¡1 h, without requiring elaborate instrumentation. Compared with RT-qPCR, the SHERLOCK technique is more accurate and the detection time is reduced by one-half. Thus, use of the SHERLOCK technique for the detection of SARS-CoV-2 in clinical patient samples is expected [86]. Another variation of CRISPR-Cas technique named "SARS-CoV-2 DETECTOR" processes where it is combined with RT-LAMP amplification extracted RNA samples (10 min) first with RT-PCR to increase the copy numbers of the selected E, N, and RNAse P genes in the sample solution (62°C for 20s) [7].

The sensitivity of CRISPR-based assays is higher than the other mentioned tests. However, Specificity of CRISPR-based assays is lower than that reported for RT-PCR. Currently, there are no portable CRISPR-based devices which have been developed for CoV-2. Thus, more research is needed in this field [18].

LAMP and CRISPR mechanisms are evolving at a rapid pace [88]. However, many of these diagnostics have not been approved by the health-care authorities worldwide or have not been independently assessed yet.

3.4 Genomic sequencing

Viral sequencing can be used to confirm the presence of virus and may also inform molecular epidemiology studies. Regular sequencing of a percentage of samples from clinical cases can help monitor mutations of the viral genome that could alter the effectiveness of medical interventions, including diagnostic tests [79]. The outcomes of the genomic sequencing of SARS-CoV-2 are regularly shared on the GISAID database and GenBank [89]. Sequencing protocols may be used for nCoV specific identification laboratories with Sanger or Next Generation Sequencing (NGS) capacity only in PCR positive samples are being applied to rapidly generate genome sequences [90,91].

4 4. Immunological Tests

Although nucleic acid testing (PCR) is the gold standard test for SARS-CoV-2 diagnosis, this test is relatively expensive, time-consuming and labor-intensive and may not be suitable in some settings, especially in the African countries, where laboratory systems are often poor. Therefore, in the aim to provide a cost-effective and rapid detection, a number of immunodiagnostic tests have generated as an alternative or complement to RT-PCR. Serological test based in detection of the presence of biomarkers such antibody or viral antigens using a rapid diagnostic test (RDT) or enzyme-linked immunosorbent assay (ELISA) [79]. Currently, there are three major types of serological diagnostic tests: enzyme-linked immunosorbent assays (ELISA), chemiluminescence immunoassays (CLIA), and rapid diagnostic tests (RDT) [92,93].

4.1 Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is a plaque assessment method for detecting and quantifying biomolecules, including proteins, such as hormones and antibodies or peptides [94]. ELISA assays can be found in a variety of formats and the most common are direct ELISA, competitive or sandwich ELISA (figure 5a). During the COVID-19 pandemic, the ELISA test has been widely used in relation to the time to obtain results which is short, and the ability to adapt to very high throughput and simplicity available ELISA kits are able to detect IgA, IgG, IgM, or IgG and IgM [95].

4.2 Chemiluminescence Immunoassay (CLIA)

CLIA, also called modified ELISA, is an assay that combines the technique of chemiluminescence with immunochemical reactions. In fact, in this assay, an antigen is deposited on the surface of the test plate and the antibodies present in the sample bind to the attached antigens, forming an antigen-antibody complex. Secondary antibody binding is confirmed by a separate chemiluminescent substrate (luminescent molecule) which is used as an indicator [96]. This test contributes to the understanding of the antibody response (kinetics of IgM, IgG antibodies) during COVID-19 infection [97], as well as the ability to perform more clinical tests for other biomarkers, such as protein C-reactive (CRP), which should also be monitored in COVID-19 suspects [98,99].

4.3 Rapid Diagnostic Tests (RDT)

Numerous RDT based on immunochromatography (IC) or lateral flow immunoassays (LFIA) have developed. These tests are based on the capillary action of a membrane (usually a nitrocellulose membrane) that is able to capture and detect antibodies [100]. The device is composed of a cassette, enclosing a strip of the polymer membrane, usually containing two lines: a control line and the test line uses anti-human IgM antibodies (test line IgM), anti-human IgG (test line IgG) and goat anti-rabbit IgG (control line C) immobilized on a nitrocellulose strip. The burgundy-colored conjugate buffer contains colloidal gold conjugated with recombinant COVID-19 antigens conjugated to colloidal gold (COVID-19 conjugates) and rabbit IgG-gold conjugates. When a sample followed by assay buffer is added to the sample well, IgM and / or IgG antibodies, if present, bind to COVID-19 conjugates, forming antigen-antibody complexes. This complex migrates by capillary action across the nitrocellulose membrane. When the complex is bound to the test line, a burgundy colored band is visible, which confirms a reactive test result. The absence of a colored band in the test area indicates a non-reactive test result. To serve as a process control, a colored line in the control line area always turns from blue to red, indicating that the correct sample volume has been added and the membrane has been wetted. (The steps of the test are shown in figure 5b).

There is great variability in the performance of commercially available LFIA tests, this may be related to the type of kit used and the day of disease onset

and to differences in validation protocols [101,102]. Shen et al. 2020, reported that the LFIA test has been shown to be a useful test to complement PCR-based assays for confirmation of COVID-19 [103].

Several studies have shown a low sensitivity of the LFIA test for the diagnosis of COVID-19 [104,105,106]. Indeed, the LFIA test had a low sensitivity at the early phase of the infection and therefore the LFIA test alone is not recommended for the initial diagnosis of COVID-19 test. Additionally, some reports from many European countries, such as Spain, Italy, the Netherlands, and the United Kingdom, reported that most of the rapid tests purchased from China did not show any good analytical performance [107,108].

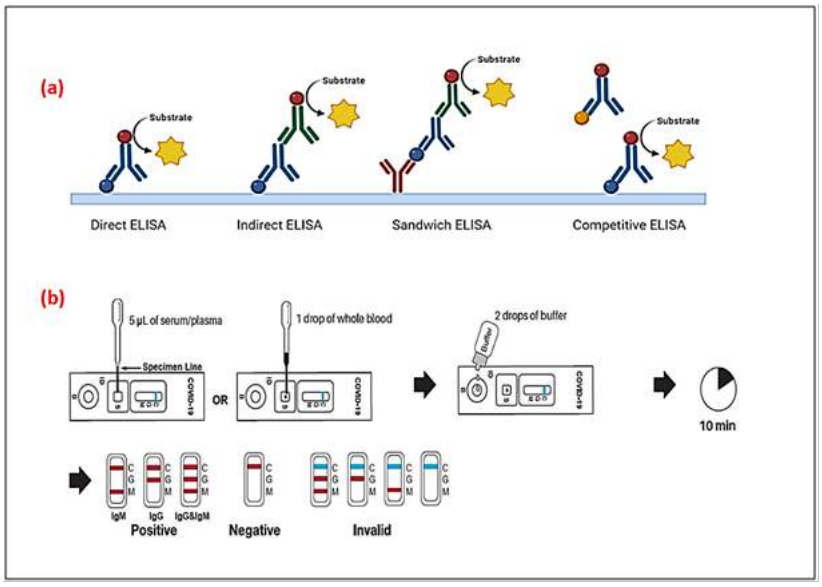

Fig. 5. Illustration of serological tests. (a): ELISA (enzyme-linked immunosorbent assay) overview; (b); LFIA (lateral flow immunoassay) steps. ***Image created with BioRender.com***

Serology-based antibody tests can help to estimate the incidence of SARS-CoV-2 and complete the nucleic acid-based tests. It also helps to understand the ability of patients to produce antibodies [109]. Compared to RT-qPCR, serological tests are less expensive and the diagnostic time is shorter. In addition, the stages of carrying out the tests are less complex. Although, the sensitivity of antibody detection increases after day 7, a negative serology result after day 7 should be interpreted carefully before excluding a case. In contrast, a positive result between days 7-14 indicates a previous contact and does not exclude the presence of the virus. For this reason, serology alone should not be used as a criterion to exclude a case or to consider the patient as non-infectious. Likewise,

a patient who has already been in contact with the virus but who later becomes infected with another circulating pathogen that generates symptoms (influenza or other pathogen), may present for a clinical consultation and a positive result for COVID-19 antibodies would lead to a misdiagnosis; for this reason, the use of serology (by itself) to confirm that a case needs to be carefully evaluated [110].

Therefore, antibody detection tests may have low sensitivity and their use should depend on the purpose of the test. These types of tests can inform investigations of an ongoing epidemic and retrospective assessment of the rate or extent of an epidemic. These tests cannot diagnose an acute infection; and may be limited due to cross-reactivity with other coronaviruses which are normally present in the community and which make interpretation of the results difficult [111].

4.4 Antigenic test

During the first days after symptom onset (approximately 1 to 5), viral proteins (antigens) are generated and can be detected by the previous tests [112,113]. Antigen tests are immunoassays that are capable of detecting viral components (i.e., S glycoprotein, M protein, or released N protein) or the virus directly without thermal amplification steps in specimens collected from NP swabs or nasal cavity which implies a current viral infection. Unlike assays that detect antibodies because antigens precede antibodies and are target-specific, these tests could be more reliable than antibodies ones [114,115]. Viral proteins should be detected by antigen-capture methods (antibodies, aptamers) which are routinely used for other viral assays, such as human immunodeficiency virus (HIV) and hepatitis B virus. Based on previous experience with antigen testing in SARS and MERS, the N protein is considered as an excellent target for a diagnostic sandwich assay using monoclonal antibodies [116]. Diao et al. (2020), developed a fluorescent immunochromatographic LFA assay for detecting the nucleocapsid (N) protein of SARS-CoV-2. Nasopharyngeal swabs and urine were used as the samples [117]. In general, antigen detection assays have acceptable specificity (depending on the assay) and can therefore be used as a confirmation criterion (in conjunction with the case definition, and the clinical and epidemiological history) and to make public health decisions (e.g., isolation). However, these assays (particularly in the RDT format) often have lower sensitivity than molecular assays (68%). Therefore, a negative result (at any stage of infection) should not be used as a criterion to rule out a case; therefore, additional testing with molecular assays is recommended.

Antigen detection assays should undergo independent evaluation to establish diagnostic performance and inform implementation modalities [112].

5 Artificial Intelligence Techniques for COVID-19 Detection based on X-ray and CT scan images

Researchers worldwide are actively participating to find effective diagnostic procedures and accelerate the development of a vaccine and treatments. The daily

increments in COVID-19 cases worldwide and the limitations of the current diagnostic tools impose challenges in identifying and managing the pandemic [118].

The above-mentioned conventional methods require medical experts for the judgment of diagnostic tests. To automate this type of diagnosis, a computer-aided diagnosis (CAD) system provides vital solutions to researchers detecting corona virus by using classification approaches. CAD has now become the center of research. In the case of COVID-19, CAD employs machine learning and deep learning techniques to evaluate all kinds of patient data, either images or clinical data, and predict the patient's condition. This evaluation improves diagnosis and support for medical experts in decision making and improves diagnosis [119]. Artificial intelligence can prove helpful in the diagnosis of various infectious diseases (eg, SARS, HIV, and Ebola) when used in conjunction with medical imaging technologies such as CT, magnetic resonance imaging (MRI), and X-ray. Radiological images (CT and X-ray) have been used by clinicians to confirm COVID-19–positive cases; these imaging findings also serve as an important complement to the RT-PCR test [120].

ML is a mathematical and statistical technique that gives computers the ability to learn from data and elaborate a convoluted framework. DL consists of a group of algorithms applied to develop an expert system that can identify problems and yield predictions [119]. These ML and DL techniques produce intelligence into a computer that can elicit the patterns relative to specific data and then proceeds for automatic reasoning [121]. In 2006, Hinton and Salakhutdinov published an article in the Science journal that was a gateway to the age of DL. They showed that a neural network with hidden layers played a key role in increasing the learning power of features. These algorithms can enhance the accuracy of classifying different types of data [122]. One of the major applications of DL in radiology practices was the detection of tissue-skeletal abnormalities and the classification of diseases. The convolutional neural network has proven to be one of the most important DL algorithms and the most effective technique in detecting abnormalities and pathologies in chest radiographs [123]. In literature, several ML/DL techniques have been proposed as intelligent systems to provide highly accurate results in a short time for the prediction, detection and diagnosis of COVID-19 [120, 124].

With a lack of proper medical facilities and trained medical personnel, combating community spread in remote and rural areas is quite challenging. Hence, there is a need for an easily accessible computer aided diagnostic system that can be used for the rapid diagnosis of the virus. AI techniques have been employed in the health care domain on different scales ranging from the prediction of disease spread trajectory to the development of diagnostic and prognostic models [125].

The typical CT imaging generally shows ground glass opacities, crazy paving pattern, and subsegmental consolidation specially in the lower lobes [126, 127], and according to the time of the onset and the response of the body to the virus, the CT demonstrates 5 stages including ultra-early stage, early stage, rapid progression stage, consolidation stage, and dissipation stage [128]. Alzubi et al. [129]

used an ensemble of weight optimized neural network for automatic diagnosis of lung cancer. Liang et al. [130] have used a residual convolutional neural network to diagnose pediatric pneumonia using chest X-ray images. Li et al. [131] designed a COVID-19 detection model called COVNet by extracting features from chest CT. Other non-pneumonia and community-acquired pneumonia (CAP) CT exams are conducted to evaluate the robustness of the model. Their model could discriminate CAP from other lung diseases, accurately. Wang et al. [132] utilized the deep learning strategies to derive the graphical features from the CT images of COVID-19 patients. In these images, there are radiographic changes in the case of infected patients. Gozes et al. [133] proposed an automated approach using CT images for quantification, detection, and monitoring of COVID-19 patients. Ghoshal and Tucker (2020) used a dataset of 5941 images and achieved 92.9% accuracy [134].

It was revealed that in most of the cases, the data from CT and X-Ray images were studied, whereas a few investigations were conducted using RT-PCR and clinical blood test data to diagnose COVID-19 by using machine and deep learning techniques. The percentage contribution of different diagnostic methods used for COVID-19 detection is presented in Fig. 6. It can be noticed that X-ray image-based detection was the most utilized diagnostic method, contributing 47% of the total. CT scan image-based models were the second-largest diagnostic methods accounting for 30%, whereas the approaches with the least utilization for diagnosis of the virus were X-Ray and CT scan image-based combined models (10%), clinical blood test (8%), and RT-PCR data-based models (5%).

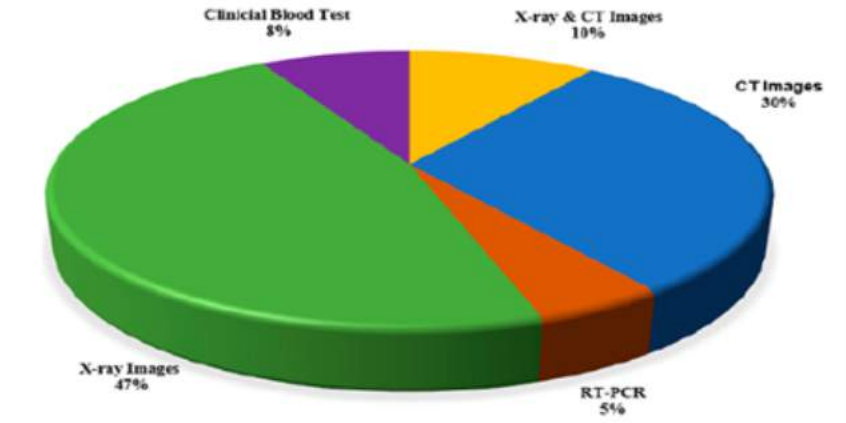

Fig. 6. Percentage utilization of various diagnostic techniques for the detection of COVID-19 [119]

The study revealed that ML/DL-based approaches can significantly promote intelligent diagnosis systems, which are promising for healthcare professionals to

make fast and reliable detection of the virus. It will also eliminate the manual flaws during the diagnosis by physicians and radiologists. Moreover, it will be a step towards time-efficient and accurate diagnoses to facilitate both hospitals and the patients [119].

6 Phototests and photopatch tests

6.1 Relationship between dermatological diseases and COVID-19

It is clear that the dermatologists are unable to find a solution to divers problems of SARS-CoV-2 infection. According to studies carried out by dermatologists in Wuhan, most patients in the dermatology department have skin lesions that facilitate the transmission of SARS-CoV-2 by indirect contact [135]. but currently the modes of transmission available are inhalation of droplets and aerosols, or contact with contaminated surfaces followed by contact with the mouth, nose or eyes [136]. On the other hand to define if specific mucosal or skin lesions are associated with SARS-CoV-2 infection, Recalcati S. analyzed the cutaneous involvement in COVID-19 patients hospitalized in the Lecco Hospital, Lombardy, Italy. From the collected data (88 patients), 18 patients (20.4%) developed cutaneous manifestations. 8 patients developed cutaneous involvement at the onset, 10 patients after the hospitalization. Cutaneous manifestations were erythematous rash (14 patients), widespread urticaria (3 patients) and chickenpox-like vesicles (1 patient). Trunk was the main involved region. Itching was low or absent and usually lesions healed in a few days. Apparently there was not any correlation with disease's severity [137]. In a study in Thailand where there are 48 accumulated COVID-19 cases. Joob B et al. found that there was an interesting case among these 48 cases, in which the patient presented with a skin rash with petechiae and a low platelet count, this case was initially diagnosed as dengue, suggesting that also vascular lesions may be early signs of the infection. They observed a diffuse papular eruption in a woman with COVID-19 febrile infection [138], as reported in Fig. 7.

6.2 Rôle of phototest and photopatch test in the diagnostic of COVID-19

There are a number of skin conditions that can be triggered or made worse by sunlight. They are usually caused by the invisible ultraviolet (UV) part of sunlight and, more rarely, by visible light. We use phototesting to find out which part of sunlight is causing your skin problem, and how sensitive you are to sunlight. This helps your dermatologist diagnose and treat your skin condition [140]. Phototesting session can determine a) the minimal erythema dose (MED), which is to say the lowest dose of UV radiation able to cause visible erythema; b) abnormal responses to UV-A light; and c) abnormal responses to visible light. Although phototesting guidelines have recently become available, the UV irradiation doses able to induce erythema in healthy individuals and standardized

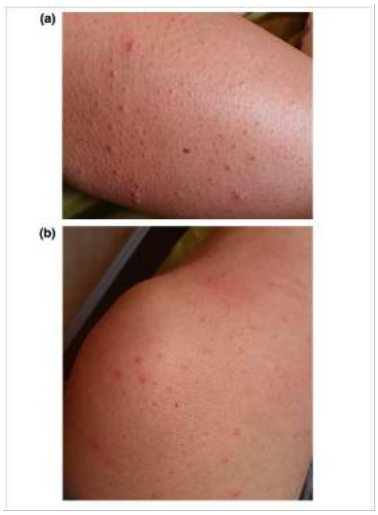

Fig. 7. Diffuse papular eruption involving the lower limbs in a woman with confirmed febrile COVID-19 infection. (a) Details of lesions on the inner thigh and (b) knee area. Images kindly provided by Dr. Anna Di Landro [139]

MED doses for testing have not been well established in the literature [141]. Photopatch testing is an important tool in the diagnosis of photoallergic contact dermatitis, it is used to detect photoallergic reactions to various antigens such as sunscreens and drugs. Photosensitive dermatitis can be caused due to antigens like parthenium, fragrances, rubbers and metals [142].

The diagnosis of photosensitive drug eruptions is based on the history of drug intake and the appearance of the eruption on sun-exposed areas. The diagnostic methods include phototesting, photopatch testing, and rechallenge testing [143]. Phototest and photopatch tests are used to detect abnormal UV and visible light reaction to various substances, such as sunscreens, medications, and in particular nonsteroidal anti-inflammatory drugs, prescribed in the treatment of COVID-19 [142]. It combines two techniques–patch testing and long- wave UVA exposure with 50 to 75% of the MED dose, and is capable of distinguishing photoallergic from phototoxic reactions. In exceptional cases, UVB irradiation is needed to prove photosensitivity, for example, systemic photosensitivity due to ambroxol [24].

The primary investigation for the detection of photodermatitis is the photopatch test, which helps in the investigation and detection of specific allergens that cause photodermatitis in a susceptible individual [144]. The primary indication for the test would be dermatitis predominantly limited to sun exposed sites of uncertain aetiology [145]. The antigens used in the photopatch series include sunscreens, nonsteroidal anti-inflammatory drugs (NSAIDs), and fragrances; specific antigens are added based on information provided by the patient [146]. Common photosensitizing agents include chemicals present in sun-

screens, antiseptic agents, fragrances, and nonsteroidal anti-inflammatory drugs. In India, Parthenium hysterophorus is probably the most common cause of photoallergic contact dermatitis and airborne contact dermatitis [147].

The diagnosis of a photodermatitis is based on the history and clinical examination and is confirmed by photopatch testing. It is important to rule out other causes of photoexposed site reactions such as connective tissue disease, drugs, allergic contact dermatitis, and pophyrias while investigating a patient of suspected photoallergy [141].

7 Conclusion and futures directions

Current diagnostic tests provide variable degrees of sensitivity and specificity to the detection of SARS-CoV2. Indeed, the studies available in the scientific literature showed that the main problem associated with molecular and serological tests for the detection of SARS-CoV-2 is the analytical performance, causing the appearance of false negatives and false positive results. To overcome this problem, the diagnosis combining different techniques is necessary.

Selection of the appropriate diagnostic method depends on the situation, including the presentation of the patient, the timing of the disease. It is clear that at present, there is no single test that answers all requirements, it should also be remembered that a perfect, specific and 100% sensitive test simply does not exist and that the sample itself can be a source of negative results

Furthermore, there is a portentous need to regularly monitor, analyze and update data on the genetic mutations and evolution of SARS-CoV-2 in different communities globally.

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