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REVIEW

# Summary of the Detection Kits for SARS-CoV-2 Approved by the National Medical Products Administration of China and Their Application for Diagnosis of COVID-19

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## Abstract

The on-going global pandemic of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been underway for about 11 months. Through November 20, 2020, 51 detection kits for SARS-CoV-2 nucleic acids (24 kits), antibodies (25 kits), or antigens (2 kits) have been approved by the National Medical Products Administration of China (NMPA). Convenient and reliable SARS-CoV-2 detection assays are urgently needed worldwide for strategic control of the pandemic. In this review, the detection kits approved in China are summarised and the three types of tests, namely nucleic acid, serological and antigen detection, which are available for the detection of COVID-19 are discussed in detail. The development of novel detection kits will lay the foundation for the control and prevention of the COVID-19 pandemic globally.

**Keywords** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) · Detection kits · Real-time RT-PCR · Lateral flow immunoassay (LFIA) · Chemiluminescence immunoassay (CLIA)

## Introduction

The first reports of coronavirus disease 2019 (COVID-19) occurred in China on 31st December 2019 (Fanelli and Piazza 2020; Lu *et al*. 2020b; Remuzzi and Remuzzi 2020; Wang C *et al*. 2020; Zhu *et al*. 2020); globally, as of 23 November, 2020, 58,425,681 cases of COVID-19 have been confirmed, including 1,385,218 deaths, as reported to the World Health Organisation (WHO) (https://covid19.who.int/). The COVID-19 pandemic has had serious impacts around the world (Alwan *et al*. 2020; Paoli *et al*. 2020; Remuzzi and Remuzzi 2020; The Lancet 2020; The Lancet Infectious Diseases 2020). Convenient and reliable COVID-19 detection assays and equipment are urgently needed for efficient management of this pandemic. With effective prevention and control strategies and sufficient detection kits, China won a significant early victory against COVID-19, and is now focused on preventing the transmission of imported COVID-19 (Li Z *et al*. 2020; Wang J *et al*. 2020). Notably, in the early stage, nucleic acid detection kits for SARS-CoV and other coronaviruses were used for COVID-19 diagnosis, with varying specificity and sensitivity (Zhou *et al*. 2020; Zhu *et al*. 2020). Meanwhile, when detection kits were not available, imaging examinations, especially chest computed tomography (CT), played an important role in the diagnosis of COVID-19 (Zhou *et al*. 2020; Zhu *et al*. 2020), although these examinations are not specific to COVID-19. Soon after the genome of the pathogen underlying COVID-19, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), previously named as 2019 novel coronavirus (2019-nCoV), was identified (Lu *et al*. 2020b; Zhou *et al*. 2020) Novel quantitative real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays were rapidly developed in response to the emerging pandemic of COVID-19 (Niu *et al*. 2020), described in national technical guidelines for China (Center for Disease Control and Prevention 2020), and shared globally. Since then, these assays have been widely adopted for laboratory

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detection (Chen *et al*. 2020; Pan *et al*. 2020; Wang W *et al*. 2020). Subsequently, multiple detection kits for SARS-CoV-2 have been developed and utilised in the battle against COVID-19. As of November 20, 2020, a total of 51 detection kits for SARS-CoV-2 nucleic acids (24 kits), antibodies (25 kits) and antigens (2 kits) have been approved by the National Medical Products Administration of China (NMPA), some of which have been registered and employed worldwide.

Currently, commercially available COVID-19 detection kits approved for use in China can be divided into three categories. The first category includes molecular assays of SARS-CoV-2 RNA based on real-time reverse transcription polymerase chain reaction (rRT-PCR) techniques, isothermal amplification and genome sequencing. The second category includes serological assays that detect antibodies produced by individuals exposed to SARS-CoV-2 based on lateral flow immunoassay (LFIA), chemiluminescence immunoassay (CLIA) or enzyme-linked immunosorbent assay (ELISA). The third category includes LFIA-based antigen detection kits. These three categories of detection kits play complementary roles in the management of the COVID-19 pandemic. SARS-CoV-2 viral RNA and antigens can be identified in SARS-CoV-2-infected individuals during the acute phase of infection, while serological tests subsequently identify individuals who have developed antibodies to the virus, which can be used for close contact tracing and monitoring of the immune status of individuals and groups over time (Arun Krishnan *et al*. 2020; Hu *et al*. 2020; James and Alwneh 2020; Meo *et al*. 2020; Oliveira *et al*. 2020; Priyadarshi *et al*. 2020; Shen *et al*. 2020; Wang H *et al*. 2020; Xu T *et al*. 2020).

## Nucleic Acid-Based Assays for SARS-CoV-2

Currently, the most widely approved tests for the diagnosis of COVID-19 are based on PCR (Arun Krishnan *et al*. 2020; Hu *et al*. 2020; James and Alwneh 2020; Meo *et al*. 2020; Oliveira *et al*. 2020; Priyadarshi *et al*. 2020; Shen *et al*. 2020; Wang H *et al*. 2020; Xu T *et al*. 2020; Xu Y *et al*. 2020). Two different strategies are used for PCR-based assays: rRT-PCR and isothermal amplification PCR. By amplifying the viral genetic material, rRT-PCR achieves high sensitivity and specificity for COVID-19 diagnosis, and is quantitative in nature, whereas isothermal amplification PCR is qualitative (Arun Krishnan *et al*. 2020; Li and Ren 2020; Shen *et al*. 2020). Compared to rRT-PCR, the latter method is expected to be more cost effective and less time consuming. However, the accuracy of isothermal amplification remains to be determined, which has prevented its widespread adoption. Although rRT-PCR was the first RNA detection method used for SARS-CoV-2, improper sample collection, handling and transportation may lead to false negative results, markedly reducing the sensitivity of the assay.

### rRT-PCR

After infecting a human, SARS-CoV-2 amplifies quickly. Therefore, nucleic acids of the virus can be detected from the early stage in samples such as nasopharynx swabs, oropharynx swabs, sputum, and stool (Li and Ren 2020; Paoli *et al*. 2020; Petrillo *et al*. 2020; Yan *et al*. 2020). Among all approved nucleic acid detection kits, the novel rRT-PCR techniques were developed in rapid response to the emergence of COVID-19 in China. The rRT-PCR reaction system includes a pair of specific primers and a TaqMan probe for the target nucleic acid. The probe is a specific oligonucleotide fragment complementary to a template sequence, and both ends of the probe are labelled with a reporter fluorescence group and fluorescence quenching group. The complete probe aligns perfectly with the template during PCR and the fluorescence signal emitted by the reporter group is absorbed by the quenching group; when PCR is performed and the target gene is amplified in the reaction system, DNA polymerase exerts its exonuclease activity, cleaving and degrading the probe, and then the reporting group and the quenched group separate, allowing fluorescence to be emitted. Each time a DNA strand is amplified, a fluorescent molecule is produced. The number of the threshold cycle (Ct value) is detected when the fluorescence generated reaches a fluorescence or signal threshold. The Ct value is related to the concentration of viral nucleic acid in the specimens tested, with higher concentrations of viral nucleic acid associated with smaller Ct values. The Ct value and the logarithm of the copy number of nucleic acids in the specimens have a linear relationship (Niu *et al*. 2020; Xu T *et al*. 2020). Initially, three gene targets, namely open reading frame 1ab (*ORF1ab*), nucleoprotein (*N*) and envelope (*E*), were evaluated via rRT-PCR to achieve high specificity and sensitivity (Fig. 1A). The results showed that the *ORF1ab* and *N* gene-based assays were specific, exactly matching the target genes in SARS-CoV-2. However, *E* gene-based rRT-PCR showed cross-reactivity with other betacoronaviruses, such as SARS-CoV. Therefore, *E* gene-based rRT-PCR was suggested as a universal screening tool for B lineages of betacoronavirus, including SARS-CoV, SARS-CoV-2, bat SARS-like coronavirus, and others (Niu *et al*. 2020). To avoid false negatives resulting from gene mutation, two gene targets of *ORF1ab* and *N* were adopted. Furthermore, *ORF1ab* and *N* gene-based rRT-PCR were confirmed to be the standards recommended and described in the Technical Guidelines for COVID-19 Laboratory Testing in China (Center for Disease Control and

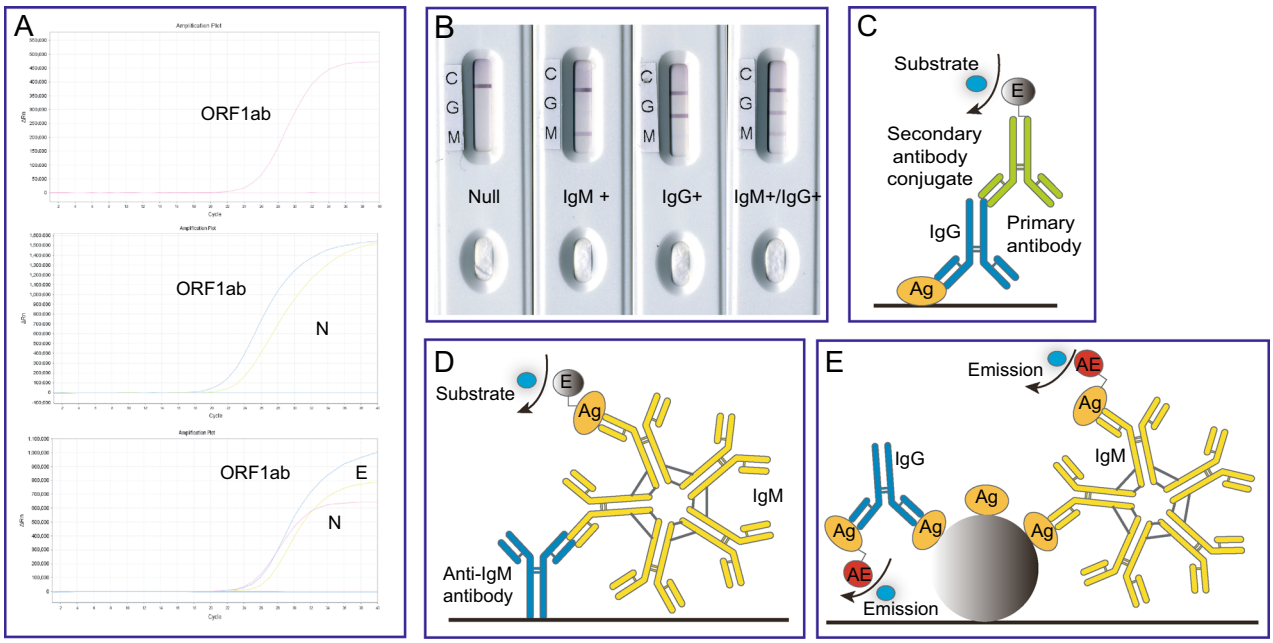


**Fig. 1** Representative detection methods developed for SARS-CoV-2. **A** Representative amplification plots of approved SARS-CoV-2 rRT-PCR kits targeting one (top), two (middle) or three (bottom) regions of the 2019-CoV genome. **B** Typical results of LFIA approved for 2019-nCoV antibody detection in China. Four lanes show negative, IgM positive, IgG positive, and both IgM and IgG positive results, respectively. **C–E** Schematic diagram of indirect ELISA for IgG detection; IgM-capture ELISA for IgM detection, and CLIA based on magnetic particle detection for all antibodies, including IgM and IgG.

Prevention 2020), which have been widely applied. Although each manufacturer determines the criteria used by their product, most amplification plots of rRT-PCR kits approved by NMPA target *ORF1ab* and *N* (Table 1). Laboratory confirmation of positive cases requires either positive RT-PCR results for both *ORF1ab* and *N* in the same specimen, a positive RT-PCR result for only one target (*ORF1ab* or *N*) in two types of specimens, or two positive results from the same type of sample. Fortunately, the detection time could be shortened greatly by combining the detection kits with a special fluorescent PCR device, for example in the detection tests from Coyote Bioscience Co., Ltd., Sansure Biotech Inc., and Daan Gene Co., Ltd. of Sun Yat-Sen University (Table 1). Notably, negative nucleic acid detection results cannot rule out SARS-CoV-2 infection. Therefore, interference factors should be considered carefully (Chinese Center for Disease Control and Prevention 2020).

## Isothermal Amplification Test (IAT)

An alternative technology to rRT-PCR is urgently needed to support real-time detection of SARS-CoV-2 (Augustine *et al.* 2020; Subsoontorn *et al.* 2020). This technology should serve as a point-of-care testing (POCT) method, providing results in less than 30 min and with low operating costs. IAT amplifies nucleic acids at a constant temperature in a streamlined and exponential manner for detection, and does not require thermocycling like rRT-PCR. Multiple strategies exist for amplifying target genes, including reverse transcriptase and loop-mediated isothermal amplification (RT-LAMP), recombinase polymerase amplification (RPA), helicase-dependant amplification (HDA), strand displacement amplification (SDA), and nucleic acid sequence-based amplification (NASBA) (Obande and Singh 2020; Shen *et al.* 2020). In these strategies, primers first bind to a template, and then amplification is performed at a constant temperature using a polymerase with strand-displacement activity that separates the strand annealed to the target sequence for detection. Amplified gene products can be detected through photometry, chemiluminescence, immunofluorescence due to hybridisation capture and lateral flow immunoassay (Annamalai *et al.* 2020; Arun Krishnan *et al.* 2020; Li and Ren 2020). The precise strategy used in the IAT for detection of SARS-CoV-2 approved by the China NMPA is not available, as it is a business secret, and the efficiency must be further validated. Notably, not all IAT tests have been demonstrated in the POCT context, which requires results in about 30 min (Table 1). Therefore, IAT as a diagnostic tool for COVID-19 is expected to be much faster, particularly at the point of care. However, isothermal amplification tests have recently emerged as potential technologies for use in airports, community clinics and hospitals to identify both symptomatic and asymptomatic

**Table 1** Molecular diagnostic tests used to detect viral genetic material in SARS-CoV-2 approved by the NMPA.

| No. | Manufacture, organization name | Test name | Test type | Gene or region detected | Sample source | Limits of detection | Test result time/ additional information | Throughput information | Country of approval |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Shanghai ZJ Bio-Tech Co., Ltd. | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-fluorescence probing) | Real-time RT-PCR | *ORF1ab*, *E* and *N* gene | Throat swab, sputum, and BALF | 1000 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400057) 1/26/2020, WHO, CE |
| 2 | Shanghai GeneoDX Biotech Co., LTD | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-fluorescence probing) | Real-time RT-PCR | *ORF1ab* and *N* gene | Nasopharyngeal swab and BALF | 500 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400058) 1/26/2020 |
| 3 | BGI Biotechnology (Wuhan) CO., LTD | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-fluorescence probing) | Real-time RT-PCR | *ORF1ab* | Throat swab and Bronchoalveolar Lavage Fluid (BALF) samples | 100 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400060) 1/26/2020/CE Marked/FDA Authorized/ PMDA Approved |
| 4 | Daan Gene Co., Ltd. of Sun Yat-Sen University | 2019 Novel Coronavirus (2019-nCOV) RNA Detection Kit | Real-time RT-PCR | *ORF1ab* and *N* gene | Throat swab, sputum, nasopharyngeal swab | 500 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400063) 1/28/2020, CE |
| 5 | Sansure Biotech Inc. | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-Fluorescence probing) | Real-time RT-PCR | *ORF1ab* and *N* gene | Throat swab and Bronchoalveolar Lavage Fluid (BALF) samples | 200 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400064) 1/28/2020, CE, FDA EUA |
| 6 | Shanghai BioGerm Medical Biotechnology Co., Ltd. | Novel Coronavirus (2019-nCoV) Nucleic Acid Detection Kit | Real-time RT-PCR | *ORF1ab* and *N* gene | Oropharyngeal, nasopharyngeal, and sputum | 500 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400065) 1/31/2020 |
| 7 | Beijing Applied Biological Technologies Co., Ltd. | Multiple Real-time PCR kit for Detection of 2019-nCoV | Real-time RT-PCR | *ORF1ab*, *E* and *N* gene | Sputum and throat swab | 200 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400179) 2/27/2020, CE |
| 8 | Maccura Biotechnology Co., Ltd. | SARS-CoV-2 Fluorescent PCR Kit (for the COVID-19 Coronavirus) | Real-time RT-PCR | *ORF1ab*, *E* and *N* gene | Throat swab and Sputum | 1000 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400184) 3/1/2020 |

**Table 1** (continued)

| No. | Manufacture, organization name | Test name | Test type | Gene or region detected | Sample source | Limits of detection | Test result time/ additional information | Throughput information | Country of approval |
|---|---|---|---|---|---|---|---|---|---|
| 9 | Wuhan EasyDiagnosis Biomedicine Co. Ltd | COVID-19 (SARS-CoV-2) Nucleic Acid test Kit | Real-time RT-PCR | *ORF1ab* and *N* gene | Oropharyngeal, nasopharyngeal, and sputum | 137 copies/ mL | Results in ~ 3 h after extraction | Depended on the real-time instrument | China NMPA (20203400212) 3/12/2020, CE, TGA, Brazil, South Africa, South East Asia |
| 10 | Shanghai Fosun Long March Medical Science Co., Ltd. | Novel Coronavirus (2019-nCoV) RT-PCR Detection Kit | Real-time RT-PCR | *ORF1ab*, *E* and *N* gene | Throat swab and Sputum | - | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400299) 3/24/2020 |
| 11 | Beijng Kinghawk Pharmaceutical Co., Ltd. | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-fluorescence probing) | Real time RT-PCR | *ORF1ab* and *N* gene | Throat swab and Sputum | 500 copies/ mL | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400322) 4/3/2020 |
| 12 | Jiangsu Bioperfectus Technologies Co., Ltd | COVID-19 Coronavirus Real Time PCR Kit | Real time RT-PCR | *ORF1ab* and *N* gene | Oropharyngeal, nasopharyngeal, and sputum | - | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400384) 4/16/2020 |
| 13 | Zhejiang Oriental genetic biological products Co., Ltd | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-fluorescence probing) | Real time RT-PCR | *ORF1ab* and *N* gene | Throat swab and Sputum | 500 copies/ mL | Results in 50-75 min | Depended on the real-time instrument | China NMPA (20203400520) 5/21/2020, PEUA |
| 14 | Shenzhen United Medical Science and Technology Co., Ltd. | Real Time PCR Kit for Novel Coronavirus 2019-nCoV (ORF1ab, N) | Real time RT-PCR | *ORF1ab* gene | Throat swab and Sputum | 200 copies/ mL | Results in ~ 1.5 h | Depended on the real-time instrument | China NMPA (20203400535) 6/5/2020 |
| 15 | Beijing NaGene Diagnosis Reagent Co., Ltd | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-fluorescence probing) | Real time RT-PCR | *ORF1ab* and *N* gene | Oropharyngeal swab and sputum specimens | - | Results in ~ 2 h after extraction | Depended on the real-time instrument | China NMPA (20203400537) 6/9/2020 |
| 16 | Coyote Bioscience Co., Ltd. | DirectDetect$^{TM}$COVID-19 Detection Kit | Real time RT-PCR | *ORF1ab* and *N* gene | Oropharyngeal swab and sputum specimens | 400 copies/ mL | Results in 30 min ~ 90 min with the instrument of Mini8 plus | 4 samples/run | China NMPA (20203400644) 7/13/2020, CE, Mexico, Columbia, Indonesia, the Philippines, Aaudi Arabia, Australia |

**Table 1** (continued)

| No. | Manufacture, organization name | Test name | Test type | Gene or region detected | Sample source | Limits of detection | Test result time/ additional information | Throughput information | Country of approval |
|---|---|---|---|---|---|---|---|---|---|
| 17 | Daan Gene Co., Ltd. of Sun Yat-Sen University | Detection Kit for SARS-CoV-2 RNA (Fast PCR-Fluorescence Probing) | Real time RT-PCR | *ORF1ab* and *N* gene | Throat swab or sputum | 500 copies/ mL | Results in 50-62 min, with the instrument of AGS4800 | 8 samples/run | China NMPA (20203400749) 9/21/2020, CE |
| 18 | BGI Biotechnology (Wuhan) CO., LTD | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (Combined probe anchored polymerization sequencing) | Sequencing | SARS-CoV-2 | Throat swab and Bronchoalveolar Lavage Fluid (BALF) samples | 100 copies/ mL | Gene sequencer DNBSEQ-T7,and Automatic sample loading instrument MGIDL-T7 | - | China NMPA (20203400059) 1/16/2020/CE Marked/FDA Authorized/ PMDA Approved |
| 19 | Chengdu CapitalBio Jingxin Biotechnology Co., Ltd. | Nucleic Acid Detection Kits for Six Kinds of Respiratory Virus (isothermal amplification based on chip) | Isothermal Amplification based on Disk Chip | SARS-CoV-2 S and N gene, Influenza A, new Influenza A H1N1 Virus (2009) Influenza A H3N2, Influenza B, RSV | Throat swab | - | - | - | China NMPA (20203400178) 2/22/2020 |
| 20 | Ustar Biotechnologies (Hangzhou), Ltd. | EasyNAT Diagnostic Kit for 2019-nCoV RNA (Isothermal Amplification Real Time Florescence Assasy) | Isothermal Amplification-rt-PCR | *ORF1ab* and *N* gene | Throat swab and sputum specimens | 1000 copies/ mL | Results in 79 min | 2 samples/run | China NMPA (20203400241) 3/16/2020, CE |
| 21 | Anbio (Xiamen) Biotechnology Co., Ltd | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (RNA Hybrid Capture-Immunofluorescence Assay) | Hybrid capture-immunofluorescence assay | *ORF1ab*, *N* and *E* gene | Throat swab and sputum specimens | 500 copies/ mL | Results in 45 min | 120 samples in 1 h, instantaneous measurement | China NMPA (20203400298) 3/24/2020 |

**Table 1** (continued)

| No. | Manufacture, organization name | Test name | Test type | Gene or region detected | Sample source | Limits of detection | Test result time/ additional information | Throughput information | Country of approval |
|---|---|---|---|---|---|---|---|---|---|
| 22 | Rendu (Shanghai) Biotechnology Co., Ltd | Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (RNA Hybrid Capture-Immunofluorescence Assay) | Magnetic based target RNA capturing technology, Isothermal Amplification and real-time Immunofluorescence assay | *ORF1ab* gene | Oropharyngeal swab and sputum | 250 copies/ mL | Results in 90 min | 80 samples/run | China NMPA (20203400300) 3/26/2020 |
| 23 | Wuhan Zhongzhi Biotechnologies Inc. | Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit (RNA Amplification Lateral Flow Assay) | Isothermal Amplification and gold probe-based Chromatography | *ORF1ab* and *E* gene | Throat swab, sputum specimens, nasopharyngeal swab and Bronchoalveolar Lavage Fluid (BALF) samples | 1000 copies/ mL | Results in 1 h | 1 sample/run, continuously detected | China NMPA (20203400301) 3/31/2020, CE |
| 24 | Wuhan Zhongzhi Biotechnologies Inc. | Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit (Dual amplification) | Isothermal Amplification based on reverse amplification and T7 RNA polymerase, and chemiluminescence | *ORF1ab* and *E* gene | Throat swab, sputum specimens, nasopharyngeal swab and Bronchoalveolar Lavage Fluid (BALF) samples | 100 copies/ mL | Results in $\sim$ 3 h | Highthroughput, 192 samples in 1 run in 3 h | China NMPA (20203400302) 3/31/2020 |

Note: "-" means information was not available

individuals rapidly, potentially reducing the spread of COVID-19 (Arun Krishnan *et al*. 2020; Carter *et al*. 2020).

### Genetic Sequencing

Most specific pathogens can be detected through PCR, but trace pathogens may not be detected. Metagenomics next-generation sequencing (mNGS) is used to identify pathogens through sequencing of nucleic acid fragments, followed by analysing and comparing biological information and databases with high accuracy. Theoretically, mNGS can amplify most nucleic acid components in clinical samples and thereby obtain sequence information for pathogens in the samples. First, DNA or RNA in the sample is extracted and a library is constructed for analysis by the sequencer. Then, sequencing is performed, and bioinformatics analysis is conducted to obtain the necessary information. By pretreatment and enrichment of the samples, the most likely pathogen can be identified through gene sequencing, which provides essential information for clinical diagnosis. To identify the pathogen driving the outbreak of pneumonia in Wuhan, Hubei Province, in late December, 2019, next-generation sequencing of samples from bronchoalveolar lavage fluid (BALF) and cultured isolates from nine inpatients was conducted, and a new human-infecting betacoronavirus, SARS-CoV-2 was identified (Lu *et al*. 2020b). In China, a novel coronavirus SARS-CoV-2 nucleic acid detection kit employing the probe anchoring polymerisation sequencing method produced by BGI Biotechnology (Wuhan) CO., LTD was approved on January 26, 2020, which could be used as a supplement to rRT-PCR. mNGS is generally used for genetic mapping rather than diagnostic testing due to its high cost and long detection time. With the reduction of sequencing cost and optimisation of this technology, high-throughput sequencing is expected to be more widely used for laboratory detection.

## Serological Assays

"Although rRT-PCR is considered the 'gold standard' for the diagnosis of COVID-19, it has limitations, including a short positive time of SARS-CoV-2 RNA in most infected individuals" (Carinci *et al*. 2020; Oliveira *et al*. 2020). The limitations of rRT-PCR increase the importance of serological assays, which can be utilised for a long time after infection. Infection with SARS-CoV-2 can be detected indirectly by measuring patients' antibodies, which appear 1–2 weeks after nucleic acids (Sethuraman *et al*. 2020). The plaque reduction neutralisation test (PRNT) and pseudovirus particle neutralisation test (ppNT) are not widely available due to their requirements for specific facilities, such as a Biological Safety Level (BSL) 2 or 3 laboratory. Therefore, immunoassays have been developed by companies in China for detection of COVID-19 infection in serum, plasma and whole blood (Table 2). Among these strategies, lateral flow immunoassays (LFIA) based on gold particles, up-converting phosphor, or quantum dot fluorescence, along with CLIA and ELISA, are the most promising approaches.

### Lateral Flow Immunoassay (LFIA)

The design of the LFIA relies on a strip or dipstick containing immobilised test reagents, which is enclosed in a cassette. For example, for the detection of SARS-CoV-2 IgG antibody using gold particle-based LFIA, the cassette is usually composed of a sample pad (region 1), gold conjugate release pad (region 2), nitrocellulose (NC) membrane containing antibodies or antigens (region 3 for the test line and region 4 for the control line), and an absorbent pad. When the SARS-CoV-2 IgG antibody is detected through the indirect immunoassay, gold-labelled SARS-CoV-2-specific antigens along with gold-labelled rabbit IgG, anti-human IgG, and anti-rabbit IgG polyclonal antibodies were immobilised in regions 2, 3 and 4, respectively. When deposited into the sampling well (region 1), the sample pad receives the sample and acts as a filter to aid flow, the sample rehydrates the gold-conjugated SARS-CoV-2 antigens or rabbit IgG on the conjugate pad (region 2) and the specific IgG for SARS-CoV-2 binds to SARS-CoV-2 antigens. The sample continues to flow along the NC membrane through capillary action, while test lines (T line) immobilised with anti-human IgG and control lines (C line) immobilised with anti-rabbit IgG indicate the result. The labels provide visible colour for the C and T lines. In this case, a lack of binding at the T line indicates a negative result. The appearance of the C line indicates that the test has run correctly (Koczula and Gallotta 2016; Arun Krishnan *et al*. 2020; Carter *et al*. 2020; Demey *et al*. 2020; Santiago 2020). When IgM is detected, anti-human IgM antibody is immobilised on the NC membrane (region 3). Typical detection results are shown in Fig. 1B. A positive antibody result indicates binding between the coating antigen and antibodies as well as binding by the secondary antibody.

LFIA can be utilised as a preliminary testing tool for COVID-19 in case of community or mass population screening (Koczula and Gallotta 2016; Arun Krishnan *et al*. 2020; Demey *et al*. 2020; Santiago 2020). Currently, SARS-CoV-2 IgG/IgM antibody detection kits based on LFIA are widely available in China (Wang D *et al*. 2020; Zhang *et al*. 2020). Upon SARS-CoV-2 infection, IgM and IgG antibodies are induced, which develop from 7 to 10 days and 14–20 days after infection, respectively. IgM

**Table 2** Serological tests used to detect antibodies to SARS-CoV-2 approved by NMPA.

| No. | Manufacture, organization name | Test name | Test type | Ab type | Sample source | Test result time/additional information | Country of approval |
|---|---|---|---|---|---|---|---|
| 1 | Guangzhou Wondfo Biotech CO., Ltd. | Wondfo SARS-CoV-2 Antibody Test (Lateral Flow Method) | LFIA based on gold particle | IgM/IgG | Serum, plasm, and blood | Results in 15 min | China NMPA (20203400176) 2/22/2020 |
| 2 | Innovita (Tangshan) Biological Technology Co., Ltd | COVID-19 IgM/IgG Antibody Test Kit (colloidal gold method) | LFIA based on gold particle | IgM/IgG | Serum and plasm | Results in 15 min | China NMPA (20203400177) 2/22/2020 |
| 3 | Guangdong Hexin Health Technology Co., Ltd | COVID-19 IgM Antibody Test Kit (colloidal gold method) | LFIA based on gold particle | IgM | Serum and plasm | Results in 15 min | China NMPA (20203400199) 3/11/2020 |
| 4 | Vazyme (Nanjing) Biotech Co., Ltd | 2019-nCoV IgG/IgM Detection Kit (Colloidal Gold-Based) | LFIA based on gold particle | IgM/IgG | Serum and plasm | Results in 10 min | China NMPA (20203400239) 3/13/2020 |
| 5 | Zhuhai Livzon Diagnostics Inc | The Diagnostic Kit for IgM/IgG Antibody to Coronavirus (SARS-CoV-2) (Lateral Flow) | LFIA based on gold particle | IgM/IgG | Serum, plasm, and blood | Results in 15 min | China NMPA (20203400240) 3/14/2020, CE mark |
| 6 | Shanghai Outdo Biotech Co., Ltd. | Novel coronavirus (SARS-CoV-2) antibody (IgM/IgG) test | LFIA based on gold particle | IgM/IgG | Serum, plasm, and blood | - | China NMPA (20203400367) 4/10/2020 |
| 7 | Beijing Zinxing Sihuan Biotech Co., Ltd | 2019-nCoV antibody IgM test (Colloidal Gold-Based) | LFIA based on gold particle | IgM | Serum and plasm | Results in 10-15 min | China NMPA (20203400457) 5/8/2020 |
| 8 | Bioscience (Chongqing) Diagnostic Technology Co., Ltd | Diagnostic kit for novel coronavirus (2019-nCoV) IgM antibody (Magnetic particle CLIA) | CLIA based on magnetic particle | IgM | Serum | Chemiluminescence immunoassay Axceed 260 | China NMPA (20203400182) 2/29/2020 |
| 9 | Bioscience (Chongqing) Diagnostic Technology Co., Ltd | Diagnostic kit for novel coronavirus (2019-nCoV) IgG antibody (Magnetic particle CLIA) | CLIA based on magnetic particle | IgG | Serum | Chemiluminescence immunoassay Axceed 260 | China NMPA (20203400183) 2/29/2020 |
| 10 | Xiamen InnodxBiotech Co. Ltd. | Diagnostic kit for novel coronavirus (2019-nCoV) IgM/IgG antibody (Magnetic particle CLIA) | CLIA based on magnetic particle | IgM/IgG | Serum and plasm | - | China NMPA (20203400198) 3/6/2020 |
| 11 | Dynamiker Biotechnology (Tianjin) Co., Ltd. | Diagnostic kit for novel coronavirus (2019-nCoV) IgG antibody (Magnetic particle CLIA) | CLIA based on magnetic particle | IgG | Serum and plasm | - | China NMPA (20203400365) 4/10/2020 |
| 12 | Dynamiker Biotechnology (Tianjin) Co., Ltd. | Diagnostic kit for novel coronavirus (2019-nCoV) IgM antibody (Magnetic particle CLIA) | CLIA based on magnetic particle | IgM | Serum and plasm | - | China NMPA (20203400366) 4/10/2020 |

**Table 2** (continued)

| No. | Manufacture, organization name | Test name | Test type | Ab type | Sample source | Test result time/additional information | Country of approval |
|---|---|---|---|---|---|---|---|
| 13 | Zhengzhou Autobio Diagnostics Co., Ltd | 2019-nCoV IgM CLIA chemiluminescence | CLIA based on magnetic particle | IgM | Serum and plasm | AutoLumo A2000Plus | China NMPA (20203400494) 5/15/2020 |
| 14 | Zhengzhou Autobio Diagnostics Co., Ltd | 2019-nCoV IgG CLIA chemiluminescence | CLIA based on magnetic particle | IgG | Serum and plasm | AutoLumo A2000Plus | China NMPA (20203400495) 5/15/2020 |
| 15 | Maccura Biotechnology Co., Ltd. | SARS-CoV-2 IgG (CLIA) | CLIA | IgG | Serum and plasm | 20 min, sensitivity: 96.24%; specificity: 98.13%; total coincidence rate: 97.15% | China NMPA (20203400496) 5/18/2020 |
| 16 | Maccura Biotechnology Co., Ltd. | SARS-CoV-2 IgM (CLIA) | CLIA | IgM | Serum and plasm | 20 min, sensitivity: 86.99%; specificity: 100.00%; total coincidence rate:93.25% | China NMPA (20203400497) 5/18/2020 |
| 17 | Bioscience (Tianjin) Diagnostic Technology Co., Ltd | Diagnostic kit for novel coronavirus (2019-nCoV) IgG antibody (CLIA) | CLIA | IgG | Serum | Chemiluminescence immunoassay Axceed 260 | China NMPA (20203400498) 5/19/2020 |
| 18 | Bioscience (Tianjin) Diagnostic Technology Co., Ltd | Diagnostic kit for novel coronavirus (2019-nCoV) IgM antibody (CLIA) | CLIA | IgM | Serum | Chemiluminescence immunoassay Axceed 260 | China NMPA (20203400499) 5/19/2020 |
| 19 | Beijing Hotgen Biotech Co., Ltd. | Novel Coronavirus 2019-nCoV Antibody Test (Up-converting Phosphor Immunochromatographic Technology) | Up-converting Phosphor Immunochromatographic Technology | IgM/ IgG | Serum and plasm | Results in 15-20 min, hand-held UPT, UPT-3A-1200, UPT-3A-1800 | China NMPA (20203400523) 5/25/2020 |
| 20 | Beijng Kinghawk Pharmaceutical Co., Ltd. | Novel Coronavirus 2019-nCoV Antibody Test (Quantum dot fluorescence immunochromatography) | Quantum dot fluorescence immunochromatography | IgM/ IgG | Serum, plasm, and blood | Results in 15-20 min | China NMPA (20203400536) 6/9/2020 |
| 21 | BGI Biotechnology (Beijing) CO., LTD | Novel Coronavirus 2019-nCoV Antibody Test (ELISA) | ELISA | IgM/ IgG | Serum and plasm | Results in 2 h | China NMPA (20203400567) 6/17/2020 |
| 22 | Shenzhen YHLO Biotech Co., Ltd. | iFLASH-SARS-CoV-2-IgM | CLIA | IgM | Serum and plasm | 300 tests/h with iFLASH-3000 | China NMPA (20203400769) 9/27/2020 |
| 23 | Shenzhen YHLO Biotech Co., Ltd. | iFLASH-SARS-CoV-2-IgG | CLIA | IgG | Serum and plasm | 300 tests/h with iFLASH-3000 | China NMPA (20203400770) 9/27/2020 |
| 24 | Xiamen Aode Biotechnology Co., Ltd. | Novel Coronavirus 2019-nCoV Antibody Test (Rare Earth Materials-based Nanofluorescence immunochromatography) | Rare Earth Materials-based Nanofluorescence immunochromatography | IgM/ IgG | Serum | Results in 15 min | China NMPA (20203400776) 9/29/2020 |
| 25 | Beijing Zinxing Sihuan Biotech Co., Ltd | Novel Coronavirus 2019-nCoV Antibody Test (colloidal gold method) | LFIA based on gold particle | IgG | Serum and plasm | Results in 15 min | China NMPA (20203400796) 10/12/2020 |

Note: "-" means information was not available

can be detected earlier but decreases and disappears very soon, whereas IgG appears slightly later but can persist for a long time after infection (Al Kahlout *et al.* 2019; Lijia *et al.* 2020; Liu *et al.* 2020; Norman *et al.* 2020; Wolff *et al.* 2020; Xia *et al.* 2020; Xiang *et al.* 2020). Although antibody test kits are reliable for preliminary screening, they may not be appropriate as a confirmatory test due to nonspecific interactions of antibodies and other proteins in the blood with the capture and detector molecules in the membrane, which may result in false positive or false negative results. The LFIA kit is characterised by easy standardisation and rapid detection. The main advantage of LFIA is that it can be used for rapid POCT.

### ELISA and CLIA

SARS-CoV-2 N, S, or fragments of N or S are adsorbed onto the surface of a 96-well plate as the capture molecule, and anti-human IgG/IgM antibody conjugated with horseradish peroxidase is used as the detector molecule for ELISA (Fig. 1C, D). Manual ELISA kits for detection of COVID-19 were developed by BGI Biotechnology (Beijing) CO., LTD in China (Table 2). ELISA-based COVID-19 antibody and antigen detection kits are currently under development by many manufacturers.

Generally, several reagents are prepared for CLIA based on magnetic particles, including reagent 0 (magnetic particles-anti-FITC antibody), reagent 1 (FITC-labelled novel coronavirus recombinant antigen), reagent 2 (alkaline phosphatase-labelled mouse anti-human IgG monoclonal antibody), negative control, positive control, and other necessary auxiliary reagents. CLIA is designed on the principle of indirect detection of the anti-SARS-CoV-2 IgG antibody in human serum (Fig. 1E). Reagent 0, reagent 1 and the sample are first mixed in the reaction tube. Anti-SARS-CoV-2 IgG in the samples forms a complex with the recombinant antigen and simultaneously binds to the magnetic particles, and then the unbound components in the tube are washed away. Subsequently, reagent 2 is added to the reaction tube. The alkaline phosphatase-labelled antibody acts as a secondary antibody and binds to the IgG antibody in the sample, forming an alkaline phosphatase-labelled mouse anti-human Ab-human IgG-recombinant antigen-magnetic particle complex, and then the unbound components are washed away. The luminescence value (RLU) of each sample tube is determined through addition of a substrate solution to the automatic immunoassay system, followed by catalysis of luminescence from the substrate solution by alkaline phosphatase. The luminescence value of the sample was positively correlated with the IgG antibody concentration of the novel coronavirus, allowing detection of the IgG antibody of SARS-CoV-2 in human serum. The main advantage of automated CLIA analysers over rapid LFIA tests is the very high throughput of samples. CLIA platforms are widely used as serological techniques for the quantitative detection of specific antigens or antibodies in samples (Johnson *et al.* 2020; Lijia *et al.* 2020; Liu *et al.* 2020; Wan *et al.* 2020; Xia *et al.* 2020). Various detection kits have been developed in China since the outbreak of SARS-CoV-2 (Lijia *et al.* 2020; Liu *et al.* 2020; Wan *et al.* 2020; Wang P *et al.* 2020; Xia *et al.* 2020).

Antibody detection results can help to determine the infection stage of a patient. This method is usually used for supplementary testing of cases with negative SARS-CoV-2 nucleic acid tests, used in conjunction with nucleic acid tests for the diagnosis of suspected cases, or used in serological surveys and past exposure surveys of high-risk population groups (Arun Krishnan *et al.* 2020; Li H *et al.* 2020; Liu *et al.* 2020). According to the Technical Guidelines for COVID-19 Laboratory Testing of China, laboratory-confirmed positive cases must meet one of the following two conditions: 1. Serum IgM antibodies and IgG antibodies to SARS-CoV-2 are positive; 2. Serum IgG antibodies to SARS-CoV-2 turn from negative to positive or IgG antibody titres during the recovery period are four times the level in the acute phase or higher. Suggested rules for these judgements are provided in Table 3.

## Antigen-Based Assays for SARS-CoV-2

Two antigen-based kits for rapid SARS-CoV-2 detection have recently been approved by the NMPA of China. These antigen-based detection kits were developed based on LFIA using the double antibody sandwich method. Conjugated mouse IgG (antibody 1) specific to SARS-CoV-2 antigen, the paired mouse antibody (antibody 2) against SARS-CoV-2 antigen and goat anti-mouse IgG are immobilised on regions 2, 3 and 4, respectively. In contrast to the serum, plasma and blood samples used for serological detection, the samples used for antigen detection are pharyngeal and nasopharyngeal swabs, which must be treated with protein extraction liquor provided in the kits prior to detection. Antigen detection kits were used solely during the acute stage of SARS-CoV-2 infection, and nucleic acid detection, imaging examination, epidemiological history, and other diagnostic techniques should also be considered when making an ultimate diagnosis.

## Discussion

rRT-PCR has played an important role in early detection, and is considered the ‘gold standard’ for COVID-19 testing. However, false negative results due to inappropriate

**Table 3** Interpretation of the clinical status of individuals based on nucleic acid and antibody detection results.

| No. | Nucleic acid | IgM | IgG | Interpretation | Treatment measures |
|---|---|---|---|---|---|
| 1 | + | – | – | Patients may be during the "window period" of SARS-CoV-2 infection, typically within 2 weeks after infection | Isolation, observation or clinical treatment |
| 2 | + | + | – | May be at early infection phage of SARS-CoV-2 | |
| 3 | + | – | + | May be during the mid and late infection stage or recurrent infection. When the IgG antibody in the recovery period increases by 4 times or more compared with the acute phase, a recurrent infection can be diagnosed | |
| 4 | + | + | + | The patient is in the active infection phase, a certain immunity to SARS-CoV-2 has already been developed | |
| 5 | – | + | – | One is likely to be in the acute phase of SARS-CoV-2 infection. Nucleic acid testing results should be confirmed first. Other factors such as rheumatoid factors have been found to cause weak IgM positive or positive tests. The result may suggest that one might have been vaccinated recently | Vaccination should be ruled out firstly. Observe, exclude the possibility of false negative of nucleic acid, detect the nucleic acids in different kind of samples once more every 3-5 days, and recheck the antibody level about 7-14 days later to confirm whether elevation appeared. One with both IgM and IgG positive could be diagnosed as a patient. Someone would be isolated according to clinical manifestation and epidemiological history |
| 6 | – | – | + | One might have recovered, and the virus has been cleared. The IgG could be detected for a long time in the blood. The result may suggest that one might have been vaccinated previously | |
| 7 | – | ± | – | One experience the first infection, during an early stage. Thus, the viral load is lower than the lower limit of nucleic acid detection. A small amount of IgM has been produced while IgG has not; a false positive result might be caused by rheumatoid factor. The result may suggest that one might have been vaccinated recently | |
| 8 | – | + | + | One might be recently infected with SARS-CoV-2 and is during the recovery period. The virus has been cleared, but the IgM has not been reduced to the lower limit of detection; or the nucleic acid test result might be false negative and the patient is indeed in the active infection stage. The result may suggest that one might have been vaccinated recently | |

Note: "+", positive; "-", negative; "±", weak positive

sample collection timing, sample type, sampling technique or other problems have limited its usage and thus increased the importance of serological testing (Coupeau *et al*. 2020; Lee *et al*. 2020; Li and Ren 2020; Li H *et al*. 2020; Petrillo *et al*. 2020; Wolff *et al*. 2020). Serological assays can detect previous SARS-CoV-2 infection and provide information on the progression of the disease, but the tests must be performed within the correct time frame after the onset of the disease (Arun Krishnan *et al*. 2020; Carinci *et al*. 2020; Lee *et al*. 2020; Xu Y *et al*. 2020). For the antibody detection assay, both IgG and IgM antibodies against SARS-CoV-2 are target analytes, with IgM appearing in the blood within a week after infection, while IgG expression requires more than 10 days (Demey et al. 2020; Lou *et al*. 2020; Xiang *et al*. 2020). The combined utilisation of both molecular and serological tests can help to clarify the progression of disease and the proper response (Table 3). In the seventh edition of the Technical Guidelines for COVID-19 Laboratory Testing delivered by the National Health Commission, in addition to nucleic acid detection results, antibody IgM and IgG positivity have been added as some of the criteria for identifying positive COVID-19 cases. Different results determine the most appropriate treatment measures (Table 3). More importantly, the diagnosis of a case might not be based solely on the nucleic acid and antibody tests but should also involve comprehensive consideration of the clinical manifestation, biochemical tests, and imaging examination. In particular, when nucleic acid detection tests are unavailable, clinical observation plays an essential role.

Nucleic acid-based diagnostic methods, serological assays, and antigen detection techniques provide strong tools for COVID-19 diagnosis. Currently, quality control of the diagnostic tests being developed is very important. Notably, although serological diagnosis of COVID-19 has developed rapidly, many concerns regarding the sensitivity and specificity of the assays remain (Norman *et al*. 2020; Xia *et al*. 2020; Xu Y *et al*. 2020). The development of innovative, well standardised, highly sensitive and specific, and low-cost serological assays for COVID-19 diagnosis has been extremely rapid due to the complexity, cost and limitations of nucleic acid-based diagnostic tools. Meanwhile, the battle against COVID-19 is likely to support the development of accurate and efficient POCT for nucleic

acid detection (Augustine *et al*. 2020; Lu *et al*. 2020a; Subsoontorn *et al*. 2020).

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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