Rapid point-of-care antibody cassette tests for severe acute respiratory syndrome coronavirus 2: practical considerations

To the editor In reference to a recent publication by Flisiak et al,[1] we would like to draw attention to the quickly evolving approach to rapid point-of-care antibody cassette tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Numerous manufacturers offer rapid point-of-care cassette tests, which detect immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to SARS-CoV-2 (TABLE 1).

Some manufacturers tested the cross-reactivity of their products with antibodies against different pathogens, but none of them tested antibodies against other coronaviruses. In almost all cases, corresponding manuals warn that a negative result does not exclude SARS-CoV-2 infection. They also recommend that results should not be considered as the sole criteria for the diagnosis of COVID-19 and must be interpreted together with other clinical data (and sometimes epidemiological and / or other laboratory results) available to the physician. Some manufactures reported additional limitations and requirements, as listed below:

- ACCU-TELL COVID-19 IgG / IgM Cassette: the continued presence or absence of antibodies may not be any criterion for either success or failure of therapy. Results from immunosuppressed patients should be interpreted carefully.
- 2019-nCoV IgG / IgM Rapid Test Cassette: the hematocrit level needs to be between 25% and 65% to obtain accurate results.
- Rapid test 2019-nCOV whole blood: the hematocrit level between 35% and 65% is recommended for the most accurate results.
- The StrongStep COVID-19 IgG / IgM Combo Test: clinical diagnosis should not be based on the result of a single test, but should be established after considering all the clinical findings, particularly including the reverse transcriptase–polymerase chain reaction test for SARS-CoV-2.
- STANDARD Q COVID-19 IgM / IgG Duo: for more accuracy of patients' immune status, additional follow-up testing using other laboratory methods is recommended.
- 2019-Novel Coronavirus (2019-nCoV) IgG / IgM GICA Rapid Test Kit: the test results of this product cannot be used as a basis for diagnosis.
- Novel Coronavirus (SARS-CoV-2) IgM / IgG Antibody Assay Kit: hemolysis, lipemia, and microbiological pollution can affect the test result, such specimen is not to be examined. Patients with impaired immunity after immunosuppression therapy, HIV-positive, and / or receiving immunosuppressive treatment after transplant or receiving therapy have impaired immunological response and their results can lead to an incorrect diagnosis. If the infection is suspected, the test should be repeated after 7 to 14 days. Both the first and the second specimen should be examined at the same time to determine whether seroconversion occurred in the primary infection. Each laboratory should work out its own appraisal for their test tubes.
- SARS-CoV-2 IgM / IgG Antibody Rapid Test: color intensity on the T-line may not be associated with the antibodies concentration in the specimen.
- Cellex qSARS-CoV-2 IgG / IgM Cassette Rapid Test: the intensity of the test band does not correlate with the virus titer in the specimen. Viruses with mutations in the epitope recognized by the antibody utilized in the test could provide a negative result. If symptoms persist, along with negative results, it is recommended to resample the patient after a few days or test them with an alternative testing device.
- The NADAL COVID-19 IgG / IgM Test: the continued either presence or absence of antibodies may not be used to determine the success or failure of therapy. The results of immunosuppressed patients should be interpreted with caution. A positive test result can also appear in case of negative polymerase chain reaction results, because antibodies are still present in the blood after the disease and, hence, can be detected.
- Wuhan Coronavirus Rapid Test (2019-nCoV, COVID-19) IgG / IgM: frozen and thawed samples (particularly repeatedly) contain particles that can block the membrane, slow down the flow of

TABLE 1 Comparison of selected rapid antibody cassette tests for severe acute respiratory syndrome coronavirus 2 (continued on the next page)

Test	Manufacturer	Sensitivity	Specificity	Total accuracy	Recommended sample type	Sample size	Time
ACCU-TELL COVID-19 IgG/IgM Cassette	AccuBioTech Co., Ltd., China	IgG: 97.4%; IgM: 86.8%	IgG: 99.3%; IgM: 98.6%	IgG: 98.9%; IgM: 96.1%	serum, plasma, whole blood	10 µl	10 min
2019-nCoV IgG/IgM Rapid Test Cassette (Whole Blood/Serum/Plasma)	Hangzhou AllTest Biotech Co., Ltd., China	IgG: 100%; IgM: 85%	IgG: 98%; IgM: 96%	IgG: 98.6%; IgM: 92.9%	serum, plasma, whole blood	10 µl of serum or plasma; 20 µl of fingertip blood or whole blood	10 min
Rapid test 2019-nCOV blood	myLAB, Poland	–	–	–	whole blood	20 µl	10 min
The StrongStep COVID-19 IgG/IgM Combo Test	Liming Bio-Products Co., Ltd., China	IgG: 93.1%; IgM: 64.7%	IgG: 100%; IgM: 100%	–	serum, plasma, whole blood	10 µl	15 min
Novel Coronavirus (2019-nCoV) Antibody IgG/IgM Assay (Colloidal Gold)	Avioq Biotechnology Co., Ltd., China	–	–	–	serum, plasma, whole blood	10 µl	15 min
2019-nCoV IgG & IgM Antibody Determination Kit	Beijing Diagreat Biotechnologies Co., Ltd., China	–	–	–	serum, plasma, whole blood	–	15 min
COVID-19 IgM/IgG Rapid Test	BioMedomics, Inc., United States	88.66%	90.63%	–	serum, plasma, fingertip blood, whole blood	–	15 min
OnSite COVID-19 IgG/IgM Rapid Test	CTK Biotech, Inc., United States	96.9%	99.4%	–	–	–	10 min
STANDARD Q COVID-19 IgM/IgG Duo	SD BIOSENSOR, Inc., Korea	81.8%	96.6%	–	serum, plasma, whole blood	10 µl	10–15 min
2019-Novel Coronavirus (2019-nCoV) IgG/IgM GICA Rapid Test Kit	Shenzhen Bioeasy Biotechnology Co., Ltd., China	89.56% (plasma: 90.3%; serum: 89.47%; whole blood: 88.89%)	99.8% (plasma: 100%; serum: 99.39%; whole blood: 100%)	94.68%	serum, plasma, whole blood	10 µl	10–15 min
VivaDiagTM COVID-19 IgM/IgG Rapid Test	VivaChek Laboratories, Inc., United States	100%	Infection time, 4–10 days; IgM and IgG: 81.25% Infection time, 11–24 days; IgM and IgG: 97.1%	Infection time, 4–10 days; IgM and IgG: 94.6% Infection time, 11–24 days; IgM and IgG: 99.3% and 95.1%, respectively	whole blood	10 µl	15 min
SARS-CoV-2 IgG/IgM Rapid Qualitative Test Kit	Xiamen Biotime Biotechnology Co., Ltd., China	–	–	–	–	10 µl	10–15 min
One Step Test for Novel Coronavirus (2019-nCoV) IgM/IgG Antibody	Getein Biotech, Inc., China	94.1%	95.1%	–	serum, plasma, fingertip blood, whole blood	10 µl of serum or plasma; 20 µl of fingertip blood or whole blood	10–20 min

TABLE 1 Comparison of selected rapid antibody cassette tests for severe acute respiratory syndrome coronavirus 2 (continued from the previous page)

Test	Manufacturer	Sensitivity	Specificity	Total accuracy	Recommended sample type	Sample size	Time
Coronavirus Rapid Test COVID-19 IgM/IgG	Zhuhai Encode Medical Engineering Co., Ltd., China	–	–	–	serum, plasma, whole blood	–	–
Novel Coronavirus (SARS-CoV-2) IgM/IgG Antibody Assay Kit	Shenzhen Watmind Medical Co., Ltd., China	–	–	–	serum, plasma, whole blood, fingertip blood	10 µl of serum or plasma; 20 µl of fingertip blood or whole blood	15 min
SARS-CoV-2 IgM/IgG Antibody Rapid Test	Qingdao Hightop Biotech Co., Ltd., China	IgG: 93%; IgM: 82%	IgG: 97.5%; IgM: 96%	IgG: 96.5%; IgM: 92.8%	serum, plasma, whole blood	10 µl of serum or plasma; 20 µl of whole blood	15–20 min
Cellex qSARS-CoV-2 IgG/IgM Cassette Rapid Test	Cellex, Inc., United States	98.43%	96.4%	97.09%	serum, plasma, whole blood	10 µl	15 min
NADAL COVID-19 IgG/IgM Test	nal von minden GmbH, Germany	94.1% (86.8%–98.1%)	99.2% (97.7%–99.8%)	98.2% (96.6%–99.2%)	serum, plasma, whole blood	10 µl	10 min
Wuhan Coronavirus Rapid Test (2019-nCoV, COVID-19) IgG/IgM	Novazym s.c., Poland	IgG: 91.8%; IgM: 95.7%	IgG: 96.4%; IgM: 97.3%	IgG: 95%; IgM: 96.8%	serum, plasma, whole blood	5 µl of serum or plasma; 10 µl of whole blood	15 min

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M

reagents, and may lead to a high background color, making the interpretation of results difficult. Specimens containing the unusually high titer of heterophile antibodies or rheumatoid factor also may affect results.

Rapid antibody tests are simple in use, fast, and cheap, but they have several limitations. First of all, they are useless for the detection of infection in early and even mid phases. The number of antibodies produced in response to SARS-CoV-2 infection increases relatively late, several days after the onset of symptoms.[2-4] This disqualifies such tests from „on admission" diagnostic workup due to a huge number of false-negative results. This observation was reported in Poland, Czech Republic, Spain, and Italy.[5] None of the analyzed kits was tested for potential cross-reactivity with antibodies against other *Betacoronaviruses* (HKU1, NL63, OC43, or 229E), which could be potentially responsible for false-positive results. The initial World Health Organization protocols and the Wuhan handbook, followed by regional experts, did not recommend the use of rapid antibody tests in the diagnostic procedures related to COVID-19.[6] The reference methods for diagnosing patients infected with SARS-CoV-2 involve the molecular approach. Currently, enormous progress in this field is being observed. The Food and Drug Administration approved the use of a few point-of-care molecular analyzers and tests worldwide or limited to the United States territory.[7] Also in China and Europe, similar technology has been developed. Bosch Healthcare Solutions presented the rapid molecular diagnostic test on the Vivalytic analysis device.[8] However, the shortage of molecular tests, their relatively high prices, particularly as compared with antibody measurements, and the increasing number of convalescents, including persons after an oligosymptomatic and even asymptomatic course of the disease, may change this situation. In particular, the percentage of asymptomatic cases is not clear and ranges from 10% to 80% of the entire infected population.[9,10] The molecular testing of a person belonging to this crescent group of convalescents is useless due to the absence of the virus. Therefore, the need for antibody testing was developed by the World Health Organization in the interim guidelines as of March 19, 2020.[11] This necessity was also noted by the Food and Drug Administration and other national associations, which approved 5 rapid antibody test kits for detecting SARS-CoV-2 on March 30, 2020.[1,12] These tests can be used solely by medical professionals, because only this group can ensure that the samples are processed properly and the results are interpreted correctly. Additionally, the European Commission and the European Union member states are funding fast-track clinical validation studies on rapid diagnostic tests for SARS-CoV-2, conducted by hospital laboratories in several European Union member states. It is expected that the utility and reliability of the subsequent tests will be soon defined.[13] It should be clearly stated that, according

to current global recommendations, molecular testing is the only way to diagnose the presence of SARS-CoV-2 infection. However, in our opinion, antibody cassette tests for SARS-CoV-2 should be considered in the following situations: 1) to cohort immunocompetent and nonimmunocompetent persons. The cost-effectiveness of such testing is still limited due to the yet relatively low number of convalescents, but within several weeks or months, with an increasing number of ill and convalescent persons, rapid antibody testing would be an easy diagnostic tool of low cost. First of all, it should be recommended for medical staff, soldiers, and persons working close to each other, as well as be used to optimize qualification for quarantine. But finally, population testing should be considered. Healthy, immunocompetent persons may return to normal activities and work, because they have already been infected and, possibly, they are resistant to reinfection and epidemiologically safe (they do not transmit infection); 2) to verify epidemiological monitoring: tracking of patients' contacts, identification of virus "reservoirs," the spread of infection in the observed population, and identification of asymptomatic infections in particular; 3) to support epidemiological monitoring of patients in quarantine or isolation in the absence of molecular tests or even as a cheaper alternative for a molecular test. We suggest testing in 7-day intervals (on day 7, 14, and 21). Such a procedure should be efficient for identifying infected patients, even those asymptomatic, and follow-up time is long enough to confirm healthy status in those with negative test results. Also, new technologies could be involved. For example, the patient can take a photo of the cassette after performing the test and share it with the physician, who will professionally interpret the result remotely.

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