CLINITEST® Rapid COVID-19 Antigen Test

A test for detection of SARS-CoV-2 antigen
manufactured by Healgen Scientific Limited Liability Company

Report from the evaluation SKUP/2021/127

organised by SKUP at the request of Siemens Healthineers

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Attachments with raw data are included only in the copy to Siemens Healthineers.

1. Summary

Background
The CLINITEST Rapid COVID-19 Antigen Test is an in vitro antigen-detecting rapid diagnostic test (Ag-RDT) for detection of Severe Acute Respiratory Syndrome Coronavirus 2 antigen (SARS-CoV-2 Ag) in nasopharyngeal and nasal swab specimens. The product is intended for professional use. The test is manufactured by Healgen Scientific LLC and was launched into the Scandinavian market in October 2020. This SKUP evaluation was carried out from March to June 2021 at the request of Siemens Healthineers in Norway.

The aim of the evaluation
The aim of the evaluation was to assess the diagnostic performance and user-friendliness of CLINITEST COVID-19 Ag Test when using nasopharyngeal swab specimens under real life conditions by intended users at a dedicated COVID-19 testing centre.

Materials and methods
The evaluation was carried out in a COVID-19 respiratory outpatient clinic in Oslo. 672 subjects (≥16 years) exposed to individuals with confirmed SARS-CoV-2 infection within 10 days of exposure were included. Two nasopharyngeal swab samples were taken from separate nostrils from each participant. One of the nasopharyngeal swabs was measured directly on the CLINITEST COVID-19 Ag Test and the other was sent to an in-house RT-PCR comparison method at Oslo University Hospital, Norway. The diagnostic sensitivity and specificity of the CLINITEST COVID-19 Ag Test were calculated by comparing the test results with the RT-PCR results, for the total population and stratified on clinical subgroups and relevant cycle threshold (ct) values. The overall diagnostic performance was compared with the World Health Organization (WHO) minimum performance requirements of ≥80% sensitivity and ≥97% specificity. User-friendliness was assessed using a questionnaire with three ratings: satisfactory, intermediate and unsatisfactory, and with the quality goal of a total rating of "satisfactory".

Results
The prevalence of SARS-CoV-2 infection among the participants was 11 % (73 out of 666). The overall diagnostic sensitivity of the CLINITEST COVID-19 Ag Test was 53 % with a 90 % confidence interval (CI) of 44-63 %. Out of 34 false negative results, 23 had ct values ≥30. When only the participants with ct values below 30 were considered, the sensitivity increased to 75 % (CI: 62-85 %). Symptoms were reported by 33 % of the participants. Of those with symptoms, the sensitivity was 65 % (CI: 46-69 %). For participants without symptoms the sensitivity was 44 % (CI: 29-60 %). The diagnostic specificity was 99,3 % (CI: 98,5-99,7 %). The positive predictive value of the test was 91 % and the negative predictive value was 94,5 %. The user-friendliness was rated as satisfactory.

Conclusion
In this evaluation, WHO's suggested minimum performance requirement of ≥80 % sensitivity compared to a reference assay was not met by CLINITEST COVID-19 Ag Test when used under real-life conditions and with a prevalence of 11 %. WHO's suggested minimum performance requirement of ≥97 % specificity was met. The quality goal for user-friendliness was fulfilled.

Comments from Siemens Healthineers
A letter with comments from Siemens Healthineers is attached to the report.

This summary will also be published in Danish, Norwegian and Swedish at www.skup.org.

2. Abbreviations and Acronyms

Ag	Antigen
Ag-RDT	Antigen-detecting Rapid Diagnostic Test
BLS	Biomedical Laboratory Scientist
C-NPU	Committee on Nomenclature, Properties and Units
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
Ct value	Cycle threshold-value
DEKS	Danish Institute of External Quality Assurance for Laboratories in the Health Sector
ECDC	European Centre for Disease Prevention and Control
EQA	External Quality Assessment
Equalis	External quality assessment in laboratory medicine in Sweden
NAATs	Nucleic Acid Amplification Tests
Noklus	Norwegian Organization for Quality Improvement of Laboratory Examinations
NPV	Negative Predictive Value
POC	Point of care
PPV	Positive Predictive Value
QCMD	Quality Control for Molecular Diagnostics
RNA	Ribonucleic acid
RT-PCR	Real Time Polymerase Chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SKUP	Scandinavian evaluation of laboratory equipment for point of care testing
WHO	World Health Organization

3. Introduction

The purpose of the Scandinavian evaluation of laboratory equipment for point of care testing (SKUP) is to improve the quality of near patient testing in Scandinavia by providing objective information about analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP evaluations in point of care (POC) settings.

3.1. The concept of SKUP evaluations

SKUP evaluations follow common guidelines, and the results from various evaluations are comparable[1]. The evaluation set-up and details are described in an evaluation protocol and agreed upon in advance. The analytical results and user-friendliness are assessed according to pre-set quality goals. To fully demonstrate the quality of a product, the end-users should be involved in the evaluation. If possible, SKUP evaluations are carried out using three lot numbers of test cassettes from separate and time-spread productions.

3.2. Background for the evaluation

In December 2019, Wuhan city in Hubei Province, China, became the center of an outbreak of a severe pneumonia, later identified as caused by a novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. The virus causes coronavirus disease 2019 (COVID-19). Currently, COVID-19 is mainly diagnosed by detection of ribonucleic acid (RNA) from SARS-CoV-2 using nucleic acid amplification tests (NAATs), such as real time polymerase chain reaction (RT-PCR) assays in a sample collected with a swab from the upper airways [2]. RT-PCR is performed in clinical microbiology laboratories, requiring advanced analytical instruments and trained personnel. The ease-of-use and rapid turnaround time of antigen-detecting rapid diagnostic tests (Ag-RDTs) offer decentralized testing that potentially can expand access to testing and decrease delays in diagnosis [3].

The CLINITEST COVID-19 Ag Test is an in vitro diagnostic POC rapid test for detection of SARS-CoV-2 antigen (Ag) in nasopharyngeal and nasal swab specimens. The product is intended for professional use. The test is manufactured by Healgen Scientific LLC and supplied by Siemens Healthineers. The test was launched into the Scandinavian market in October 2020. This SKUP evaluation was carried out from March to June 2021 at the request of Siemens Healthineers in Norway.

3.3. The aim of the evaluation

The aim of the evaluation was to assess the diagnostic performance and user-friendliness of CLINITEST COVID-19 Ag Test when using nasopharyngeal swab specimens under real life conditions by intended users at a dedicated COVID-19 testing centre.

3.4. The model for the evaluation of CLINITEST COVID-19 Ag Test

The evaluation was carried out at a dedicated COVID-19 test centre, to evaluate the performance of CLINITEST COVID-19 Ag Test in the hands of the intended users, see flowchart in figure 1.

[1]SKUP evaluations are under continuous development. In some cases, it may be difficult to compare earlier protocols, results and reports with more recent ones.

The evaluation included:

- Examination of the diagnostic performance (diagnostic sensitivity and specificity) using nasopharyngeal swab specimens.
- Examination of the diagnostic performance related to different clinical subgroups and cycle threshold (ct) values from the RT-PCR results.
- Evaluation of the user-friendliness of the CLINITEST COVID-19 Ag Test and its manual.

In addition, the positive predictive value (PPV) and the negative predictive value (NPV) were calculated.

All the measurements on the CLINITEST COVID-19 Ag Test were performed by the intended users who were professional health care providers working at the test centre. Subjects exposed to a previously confirmed case of SARS-CoV-2 infection within 10 days of exposure were included e.g., targeted testing of household members or equivalent close contacts. Both symptomatic and asymptomatic participants were included. Household transmission of SARS-CoV-2 is reported to be high [4], and a prevalence of approximately 20 % was expected. Target number of participants was 100 positive results and 100 negative results, but maximum number included was initially set to 500. For comparison and assessment of the diagnostic sensitivity and specificity, a combined oropharyngeal-nasopharyngeal sample was measured on an RT-PCR comparison method.

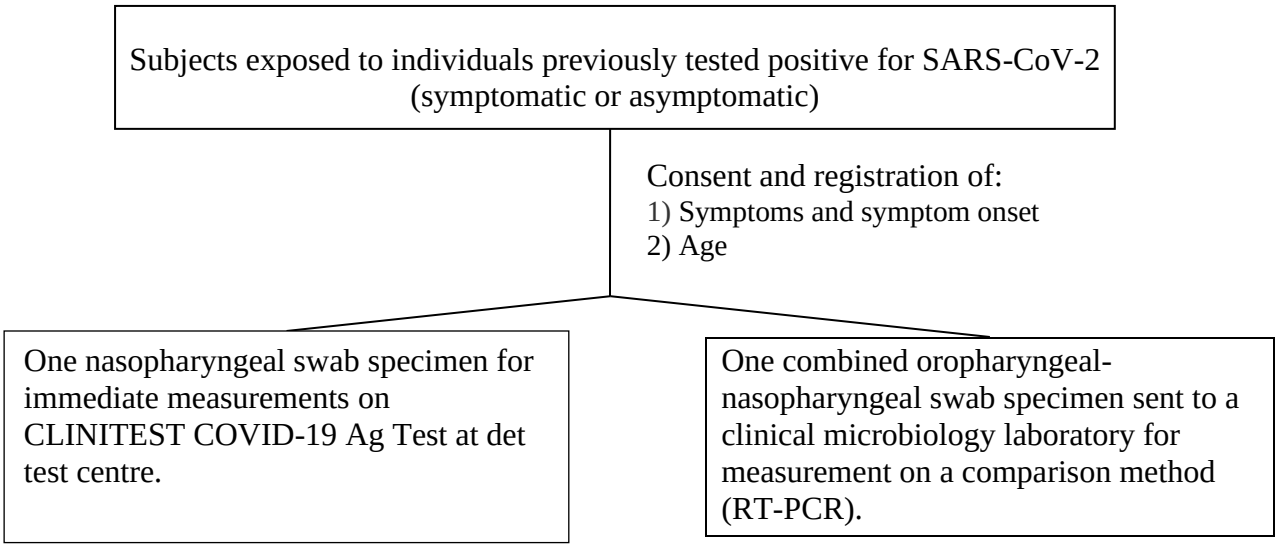

Figure 1. Flowchart illustrating the model of the evaluation. Enrolment of participants was planned to continue until at least 100 positive and at least 100 negative SARS-CoV-2 PCR results were achieved in the clinical microbiology laboratory, but maximum number included was initially set to 500.

4. Quality goals

4.1. Analytical quality

Present recommendations for diagnostic SARS-CoV-2 tests

The World Health Organization (WHO) suggests that SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of ≥80 % sensitivity and ≥97 % specificity compared to a NAAT reference assay can be used to diagnose SARS-CoV-2 infection where NAAT is unavailable, or where prolonged turnaround times preclude clinical utility. In settings with low prevalence of active SARS-CoV-2 infections, specificity should ideally be ≥99 % to avoid many false-positive [3]. The European Centre for Disease Prevention and Control (ECDC) agrees with the minimum performance requirements set by WHO but suggests aiming to use tests with a performance closer to RT-PCR, i.e., ≥90% sensitivity and ≥97% specificity [5].

4.2. User-friendliness

The evaluation of user-friendliness was carried out by asking the employees in the test centre to fill in a questionnaire, see section 5.5. The tested equipment must reach a total rating of "satisfactory" to fulfil the quality goal.

Technical errors

SKUP recommends that the fraction of tests wasted due to technical errors should not exceed 2 %.

4.3. Principles for the assessments

To qualify for an overall good assessment in a SKUP evaluation, the measuring system must show satisfactory analytical quality as well as satisfactory user-friendliness.

4.3.1. Assessment of the analytical quality

The analytical results are described and discussed related to literature. Statistical expressions and calculations used by SKUP are shown in attachment 5.

Diagnostic sensitivity

The diagnostic sensitivity was calculated as the fraction of the true positive CLINITEST COVID-19 Ag Test results in proportion to the positive RT-PCR results.

Diagnostic specificity

The diagnostic specificity was calculated as the fraction of the true negative CLINITEST COVID-19 Ag Test results in proportion to the negative RT-PCR results.

Positive and negative predictive values

PPV and NPV were calculated given the prevalence in the tested population and the achieved diagnostic accuracy of the test.

Assessment of three lots

Three lots of test cassettes were used for the purpose of having an evaluation less sensitive to the risk of a poor batch. Separate lot-to-lot calculations were not performed.

Examination of different clinical subgroups
Sensitivity and specificity were calculated for results stratified on symptoms/no symptoms and days since symptom onset.

Examination of different ct values from the RT-PCR method
The ct value is defined as the number of cycles of amplification required with RT-PCR for the fluorescent signal of the RT-PCR method to reach a threshold above the background signal. The ct value is inversely proportional to the amount of target nucleic acid in the sample (i.e., the lower the ct value the greater the amount of target nucleic acid in the sample). Sensitivity was calculated for positive results stratified on ct values; ct <33, ct<30 and ct<25.

4.3.2. Assessment of user-friendliness

User-friendliness was assessed according to answers and comments given in the questionnaire (see section 6.5). For each question, the evaluator can choose between three given ratings: satisfactory, intermediate and unsatisfactory. To achieve the overall rating "satisfactory", the tested equipment must reach a total rating of "satisfactory" in all four subareas of characteristics described in section 6.5.

Technical errors
The evaluators registered failed measurements and technical errors during the evaluation. The proportion of tests wasted due to technical errors was calculated and taken into account in the assessment of the user-friendliness. User errors related to the handling of the samples were excluded from the calculations.

4.4. SKUP's quality goals in this evaluation

For this evaluation, there were no pre-set quality goals for the diagnostic performance of the test. The results are nevertheless discussed related to present literature, specifically WHO recommendations.

For assessment of the user-friendliness:

User-friendliness, overall rating..... Satisfactory

5. Materials and methods

5.1. Definition of the measurand

The measurement systems intend to detect SARS-CoV-2 in secrete collected from the upper airways. The CLINITEST COVID-19 Ag Test detects the antigens specific for SARS-CoV-2 in nasopharyngeal and nasal specimens. For the comparison method, the RNA from SARS-CoV-2 was identified by RT-PCR in a combined oropharyngeal-nasopharyngeal specimen. The results were expressed on an ordinal scale (positive or negative) for both methods. The Committee on Nomenclature, Properties and Units (C-NPU) systematically describes clinical laboratory measurands in a database [6]. The NPU code related to the CLINITEST COVID-19 Ag Testis in this evaluation is NPU59310. The NPU code related to the comparison method is NPU59106. In this protocol, the term SARS-CoV-2 will be used for the measurand.

5.2. The evaluated measurement system CLINITEST COVID-19 Ag Test

The information in this section derives from the company's information material.

CLINITEST COVID-19 Ag Test (figure 2) is a point-of-care test intended for professional use for detection of SARS-CoV-2. The CLINITEST COVID-19 Ag Test does not differentiate between SARS-CoV and SARS CoV-2.

CLINITEST COVID-19 Ag Test kit includes:

- CLINITEST COVID-19 Ag Test cassettes
- Sterile swabs
- Extraction tubes and tips
- Extraction buffer vials
- Workstation
- Package insert

Figure 2. CLINITEST Rapid COVID-19 Antigen Test

The CLINITEST COVID-19 Ag Test is an immunochromatographic membrane assay that uses highly sensitive monoclonal antibodies to detect nucleocapsid protein from SARS-CoV-2 in nasopharyngeal and nasal swab specimens. The test procedure involves collecting nasopharyngeal specimen using a swab provided with the kit and inserting the swab into a tube containing extraction buffer. Four drops of the specimen in extraction buffer are added to the test strip using the tip provided for the extraction tube. The test result can be read visually after exactly 15 minutes, but not after 20 minutes. Any shade of colour in the test line region should be considered positive. The formation of a coloured line in the control line region of each test cassette serves as a procedural control, indicating that the proper volume of specimen has been added and membrane wicking has occurred.

For technical details about the CLINITEST COVID-19 Ag Test, see table 1. For more information about the CLINITEST COVID-19 Ag Test, and name of the manufacturer and the suppliers in the Scandinavian countries, see attachments 2 and 3. For product specifications in this evaluation, see attachment 4.

Table 1. Technical details for CLINITEST COVID-19 Ag Test

Sample material	Nasopharyngeal or nasal specimen
Stability of extraction buffer including specimen	Specimen should be tested immediately after collection
Measuring time	15 minutes

5.3. The selected comparison method

A selected comparison method is a fully specified method which, in the absence of a Reference method, serves as a common basis for the comparison of the evaluated method.

5.3.1. The selected comparison method in this evaluation

The selected comparison method in this evaluation was the routine RT-PCR method for SARS-CoV-2 at Oslo University Hospital, Norway, hereafter called "the comparison method". The laboratory is accredited according to NS-EN ISO/IEC 15189 (2012) (Norsk Standard_Europeisk Norm International Organization for Standardization). The division performing the PCR measurements has approximately 28 employees.

Instruments: TecanFluent 1080 (Tecan Trading AG) and EZ1 (Qiagen N.V.) and AriaDX (Agilent Technologies Inc.)

Reagents: Magnetic nanoparticles (Norwegian University of Science and Technology), primers (TIB Molbiol Syntheselabor GmbH), Invitrogen Superscript III, RT/Platinum Taq mix (Thermo Fisher Scientific Inc.) and E-gen-Probe (Integrated DNA Technologies Inc.)

Principle: In-house RT-PCR detection of the E gene of the Sarbeco Betacorona virus, including SARS-CoV-2 [7].

Internal analytical quality control

Internal analytical control, bacteriophage MS2 with RNA (TIB Molbiol Syntheselabor GmbH) added to each sample.

External analytical quality control

The hospital laboratory participates in the Quality Control for Molecular Diagnostics (QCMD, United Kingdom) EQA scheme for SARS-CoV-2 with five samples and one challenge per year.

5.3.2. Verification of the analytical quality of the comparison method

Trueness

The trueness of the RT-PCR method for detection of SARS-CoV-2 was verified with EQA results for a period circumventing the evaluation period.

5.4. The evaluation

5.4.1. Planning of the evaluation

Inquiry about an evaluation
Siemens Healthineers in Norway via POC team leader Vibeke Lind-Nilsen, applied to SKUP in October 2020 for an evaluation of CLINITEST COVID-19 Ag Test.

Protocol, arrangements and contract
In April 2021, the protocol for the evaluation was approved, and Siemens Healthineers and SKUP signed a contract for the evaluation. Feberpoliklinikk Vest, a COVID-19 respiratory outpatient clinic in Oslo, agreed to represent the intended users, and the Department of Microbiology, Oslo University Hospital Norway agreed to perform the comparison measurements.

Training
Siemens Healthineers in Norway was responsible for the necessary training of the intended users at the test centre. The training reflected the training usually given to the end-users. Siemens Healthineers was not allowed to contact or supervise the evaluators during the evaluation period.

5.4.2. Evaluation sites and persons involved

In the test centre, ten professional health care providers participated in the evaluation. They were all trained in collecting samples from upper airways and used both nasopharyngeal and oropharyngeal swab specimens in the routine work.

5.4.3. The evaluation procedure

Internal analytical quality control
Once available, towards the end of the evaluation, two levels of internal analytical quality control samples (CLINITEST Rapid COVID-19 Antigen Control Kit, Healgen LLC), were performed each evaluation day alternating between the positive and the negative control level.

Recruitment of participants and ethical considerations
Subjects, 16 years or older, exposed to an individual who had previously tested positive for SARS-CoV-2, were invited to participate in the evaluation of CLINITEST COVID-19 Ag Test. Participation was voluntary and verbal informed consent was considered sufficient. Approval from a regional ethical committee was not necessary because the evaluation was considered a quality assurance project. The project was approved by the Data protection officer at Haraldsplass Deaconess Hospital.

Handling of the samples and measurements
Tests, extraction buffer and specimens were kept at room temperature (15-30°C) prior to testing.

Nasopharyngeal swab specimens were used for the measurements on the CLINITEST COVID-19 Ag Test. In the same sampling session, a separate nasopharyngeal swab was used to obtain a combined oropharyngeal-nasopharyngeal specimen for measurement on the comparison method.

The sampling from each patient was carried out in the following order:
1. Combined oropharyngeal-nasopharyngeal specimen from one nostril for the comparison method
2. Nasopharyngeal swab specimen from the other nostril for the CLINITEST COVID-19 Ag Test

The swab specimens were collected according to local guidelines and immediately placed into the test tube containing extraction buffer. The extracted samples were analysed in accordance with the instructions from the manufacturer. Any shade of colour in the test line region was considered a positive result. In case of technical errors and failed measurements, the test was repeated if possible until a result was obtained. Four lot numbers of test cassettes were used, alternating between the lot numbers.

The swabs for the comparison method were placed immediately into sterile tubes containing 2-3 mL of viral transport media. The tubes were kept at room temperature until transported to the clinical laboratory, where the samples were analysed on the comparison method. All samples were treated according to the internal procedures of the laboratory regarding potential interfering substances. For results with ct values >35, repeated measurements were performed.

6. Results and discussion

Statistical expressions and calculations used by SKUP are shown in attachment 5.

6.1. Number of samples and study population characteristics

The practical work was performed during spring and summer 2021. Towards the end of the evaluation the test station was involved in a major outbreak of COVID-19 among students. In total, 672 participants provided samples for the evaluation, of which 666 results from the CLINITEST COVID-19 Ag Test were successfully matched to their corresponding RT-PCR result. The vast majority were exposed to individuals who had previously tested positive for SARS-CoV-2 and 66 % (n=441) of the participants were in the age-group ≤19 years (table 2). 33 % (n=217) were symptomatic of whom 68 % (n=148) had a symptom duration of ≤5 days. Of those with symptoms, 56 % (n=122) reported two or more symptoms, of which sore throat and dry cough were most commonly reported. 11 % (n=73) of participants were PCR positive. This was a substantially higher prevalence of SARS-CoV-2 infection than in the total tested population during the same time-period. However, testing of exposed subjects is highly relevant for contact tracing in institutions, semi-closed communities and among household members or equivalent close contacts.

Table 2. Participant characteristics

	Total successfully included n (% of all)	**PCR positive results n (% of subgroup)**	**PCR negative results n (% of subgroup)**
Total	666 (100)	73 (11)	593 (89)
Age			
≤ 19	441 (66,2)	45 (10,2)	396 (89,8)
20-29	84 (12,6)	13 (15,5)	71 (85,5)
≥30	141 (21,2)	15 (10,6)	126 (89,4)
Unknown	18 (2,7)	1 (5,6)	17 (94,4)
Symptomatic			
No	449 (67,4)	25 (5,6)	424 (94,4)
Yes	217 (32,6)	48 (22,1)	169 (77,9)
Symptom duration	**n (% of symptomatic)**		
≤ 5 days	148 (68,2)	26 (17,6)	122 (82,4)
> 5 days	21 (9,7)	4 (19,0)	17 (81,0)
Unknown	48 (22,1)	18 (37,5)	30 (62,5)

An account of samples not included in the calculations, is given below.

Missing results

- ID 94; no result from the comparison method as the sample never arrived the clinical laboratory.
- ID 252 and 667; invalid Ag test
- ID 293; the nozzle for the extraction tube fell off during sample application.
- ID 316 and 367; defect test cassettes.
- ID 510; ct value was not registered.

Omitted results
There were no omitted results.

Recorded technical errors and failed measurements
Three incidences were interpreted as technical errors (defect test cassettes and poorly fitted nozzle) and two failed measurements were caused by invalid tests. The fraction of tests wasted due to technical errors was estimated to (2/672) x 100 = 0,3 %. Thus, the SKUP recommendation of a fraction of ≤2 % tests wasted caused by technical errors was achieved.

6.2. Analytical quality of the selected comparison method

6.2.1. Internal analytical quality control
All results from the internal analytical quality controls were in accordance with the assigned level of the quality control material (data not shown).

6.2.2. The trueness of the comparison method
The trueness of the RT-PCR method for detection of SARS-CoV-2 was verified with EQA results for the period circumventing the evaluation period (table 3).

Table 3. EQA controls measured on the comparison method.

Time of measurements	EQA scheme	Sample	Assigned value, SARS-CoV-2 dPCR Log10 Copies/ml	Results from the RT-PCR method (ct value)
Week number 31 in 2020	QCMD	SCV2_C1-01	hCorona229E/negative	negative
		SCV2_C1-02	4,12	positive (31,9)
		SCV2_C1-03	3,15	positive (36,3)
		SCV2_C1-04	2,82	positive (37,5)
		SCV2_C1-05	2,82	positive (38,4)
Week number 22 in 2021	QCMD	SCV2_21C1B-01	4,13	positive (30,7)
		SCV2_21C1B-02	2,51	positive (33,5)
		SCV2_21C1B-03	2,00	positive (35,0)
		SCV2_21C1B-04	2,94	positive (33,2)
		SCV2_21C1B-05	3,15	positive (34,1)

Discussion
The trueness of the comparison method during the evaluation period was confirmed by the results from the QCMD EQA scheme for SARS-CoV-2.

6.3. Analytical quality of CLINITEST COVID-19 Ag Test

The results below reflect the analytical quality of CLINITEST COVID-19 Ag Test under real-life conditions in the hands of intended users at a dedicated COVID-19 test centre.

6.3.1. Internal analytical quality control

The results from the internal analytical quality control (one positive and one negative CLINITEST Rapid COVID-19 Antigen Control) were in accordance with the assigned level of the quality control material (data not shown). In total, 23 measurements were performed, 12 with the positive control level and 11 with the negative control level. Raw data is attached for the requesting company only (attachment 6).

6.3.2. The diagnostic sensitivity of CLINITEST COVID-19 Ag Test

The diagnostic sensitivity of CLINITEST COVID-19 Ag Test was calculated as described in Attachment 5 using the RT-PCR results as true values, both for the total population and stratified on clinical subgroups and relevant ct values. The calculated results (table 4) are given with a 90 % confidence interval (CI) (for information only). Raw data is attached to the requesting company only (attachment 7).

Table 4. Diagnostic sensitivity of CLINITEST COVID-19 Ag Test measured in nasopharyngeal specimen. Results achieved by intended users. Overall results and stratified on clinical subgroups and relevant ct values.

	Number of positive results PCR	Number of true positive results CLINITEST	Number of false negative results CLINITEST	Diagnostic sensitivity, % (90 % CI)
Total	73	39[1]	34[2]	53 (44-63)
Symptomatic				
No	25	11	14	44 (29-60)
Yes	48	28	20	58 (46-69)
≤ 5 days	26	17	9	65 (49-79)
> 5 days	4	3	1	*
Unknown	18	8	10	44 (27-63)
Ct values				
<33	58	37	21	64 (53-73)
<30	40	30	10	75 (62-85)
<25	24	20	4	83 (67-93)

*n <8; not reported due to high degree of uncertainty in the estimated sensitivity.

[1]Median ct value for the true positive results = 24,9 (18,8-34,4)

[2]Median ct value for the false negative results = 31,4 (22,6-36,5). Unpaired t test (Excel) p-value <0,001 when comparing the means for the true positive and false negative results. Ct value for SKUP ID 94 was missing. An account for the number of samples is given in section 6.1.

6.3.3. The diagnostic specificity of CLINITEST COVID-19 Ag Test

The diagnostic specificity of CLINITEST COVID-19 Ag Test was calculated as described in Attachment 5 using the RT-PCR results as true values, both for the total population and stratified on clinical subgroups. The calculated results (table 5) are given with a 90 % confidence interval (CI) (for information only). Raw data is attached to the requesting company only (attachment 7).

Table 5. Diagnostic specificity of the CLINITEST COVID-19 Ag Test measured in nasopharyngeal specimen. Results achieved by intended users. Overall results and stratified on clinical subgroups.

	Number of negative results PCR	Number of true negative results CLINITEST	Number of false positive results CLINITEST	Diagnostic specificity % (90 % CI)
Total	593	589	4	99,3 (98,5-99,7)
Symptomatic				
No	424	424	0	100 (99,5-100)
Yes	169	165	4	97,6 (94,7-99,1)
≤ 5 days[1]	122	120	2	98,4 (94,9-99,7)
> 5 days[1]	17	17	0	100 (89,5-100)
Unknown	30	28	2	93,3 (81-98,5)

Discussion

The overall diagnostic sensitivity of the CLINITEST COVID-19 Ag Test was 53 % with a 90 % CI of 44-63 % when compared to the results from the comparison method. PPV was 91 % at prevalence 11 %.

COVID-19 symptoms were reported by 33 % of the participants (table 2). The majority (68 %) stated that the symptoms had lasted for five days or less. For these participants, the sensitivity was 65 % (table 4). Participants tested more than 5-7 days since onset of symptoms are more likely to have lower viral loads, and the likelihood of false negative results with Ag-RDTs is higher [3]. For participants without symptoms (67 %), the sensitivity was 44 %, indicating that the test might have a lower sensitivity in asymptomatic than in symptomatic participants although the 90 % CIs are overlapping. This is consistent with findings generally on antigen test performance in asymptomatic individuals [8] and emphasizes the importance of careful evaluation of the target population before implementing Ag-RDTs for SARS-CoV-2.

The ct values from the comparison method are inversely proportional to the amount of target nucleic acid in the samples measured. The ct value can therefore give some indication of the viral load in the participant. When only the participants with ct values below 30 were considered, the sensitivity increased to 75 % (table 4). The median ct values for the false negative CLINITEST COVID-19 Ag Test results were considerable higher than for the true positive results. Of the 34 false negative results, 23 had ct values ≥30. Thus, low viral load may have contributed to a considerable proportion of the false negative results, which suggests that the participants at the time of sampling either were in a pre-symptomatic phase or in a late phase of the infection, and probably non-infectious [9]. From an infection tracing perspective, however, they are still important.

The results stratified by ct values should be interpreted with caution. Due to differences in PCR technology across laboratories, ct values may differ despite equal RNA concentrations in a sample. There is no universal ct value indicating contagiousness. In addition, the viral load in a sample may be affected by preanalytical conditions e.g., poor sampling can result in different viral loads in samples measured by the CLINITEST COVID-19 Ag Test and the comparison method even if collected from the same patient at the same time and by the same health care provider.

The overall diagnostic specificity was 99,3 % with a 90 % CI of 98,5-99,7 %. NPV was 94,5 % at prevalence 11 %. The main concern when using an Ag-RDTs instead of a PCR method is the risk of false negative results, but if the disease prevalence is low (<1 %), the proportion of false positive results may still become noticeable [10]. WHO recommends a higher specificity (≥99 %) for the Ag-RDT tests if used in a low prevalence setting [3].

Conclusion

In this evaluation, the overall diagnostic sensitivity of CLINITEST COVID-19 Ag Test did not fulfill WHO's minimum performance requirement for diagnostic sensitivity (≥80 %), but it did fulfill the performance requirement for diagnostic specificity (≥97 %) when used under real life-conditions with a prevalence of 11 % by intended users.

6.4. Evaluation of user-friendliness

6.4.1. Questionnaire to the evaluators

The most important responses regarding user-friendliness come from the intended users themselves. The end-users of point-of-care equipment often emphasise other aspects than those pointed out by more extensively trained laboratory personnel.

At the end of the evaluation period, the intended users filled in a questionnaire about the user-friendliness of the measurement system. SKUP has prepared detailed instructions for this.

The questionnaire is divided into four subareas:

Table A) Rating of operation facilities. Is the system easy to handle?
Table B) Rating of the information in the manual / insert / quick guide
Table C) Rating of time factors for the preparation and the measurement
Table D) Rating of performing internal and external analytical quality control

The intended users filled in table A and B. SKUP filled in table C and D and in addition, topics marked with grey colour in table A and B.

In the tables, the first column shows what property is evaluated. The second column in table A and B shows the rating by the users at the evaluation sites (one letter per evaluator). The rest of the columns show the rating options. The overall ratings from all the evaluating sites are marked in coloured and bold text. The total rating is an overall assessment by SKUP of the described property, and not necessarily the arithmetic mean of the rating in the rows. Consequently, a single poor rating can justify an overall poor rating, if this property seriously influences on the user-friendliness of the system.

Unsatisfactory and intermediate ratings are marked with a number and explained below the tables. The intermediate category covers neutral ratings assessed as neither good nor bad.

An assessment of the user-friendliness is subjective, and the topics in the questionnaire may be emphasised differently by different users. The assessment can therefore vary between different persons and between the countries. This will be discussed and taken into account in the overall assessment of the user-friendliness.

Comment
In this evaluation, the user-friendliness was assessed individually by two assistants, one health secretary and one general practitioner.

Table A. Rating of operation facilities

Topic	Rating	Rating	Rating	Rating	Option
To prepare the test / instrument	S, S, I[1], S	Satisfactory	Intermediate	Unsatisfactory	No opinion
To prepare the sample	S, S, I[1], S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Application of specimen	I[2], S, S, I[2]	Satisfactory	Intermediate	Unsatisfactory	No opinion
Specimen volume*	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Number of procedure step	I[1], I[1], I[1], S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Instrument / test design	I[2], I[2], S, U[2]	Satisfactory	Intermediate	Unsatisfactory	No opinion
Reading of the test result	S, S, S, S	Easy	Intermediate	Difficult	No opinion
Sources of errors	I[2], N, S, I[2]	Satisfactory	Intermediate	Unsatisfactory	No opinion
Cleaning / Maintenance	N, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Hygiene, when using the test	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Size and weight of test kit	S, I[2], S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Storage conditions for tests, unopened package	S	+15 to +30°C	+2 to +8°C	–20°C	
Storage conditions for tests, opened package	S	+15 to +30°C or disposable	+2 to +8°C	–20°C	
Environmental aspects: waste handling	S	No precautions	Sorted waste	Special precautions	
Intended users	S	Health care personnel or patients	Laboratory experience	Biomedical laboratory scientists	
Total rating by SKUP		Satisfactory			

*E.g., assessed on whether the volume of extraction buffer was sufficient for repeated measurements.
[1] One minute in extraction buffer is too long. Too many steps.
[2] The nozzle was small/ hard to get attached to the extraction tube and on one occasion it fell off after being attached. Easy to spill.

Additional positive comments: Quite simple to use. Easy to learn.

Additional negative comments: None.

Table B. Rating of the information in the insert/ quick guide

Topic	Rating	Rating	Rating	Rating	Option
Table of contents/Index	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Preparations/Pre-analytic procedure	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Specimen collection	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Measurement procedure	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Reading of result	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Description of the sources of error	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Help for troubleshooting	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Readability / Clarity of presentation	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
General impression	S, S, S, S	Satisfactory	Intermediate	Unsatisfactory	No opinion
Measurement principle	S	Satisfactory	Intermediate	Unsatisfactory	
Available insert in Danish, Norwegian, Swedish	S	Satisfactory	Intermediate	Unsatisfactory	
Total rating by SKUP		Satisfactory			

Additional positive comments: Good explanations.

Additional negative comments: None.

Table C. Rating of time factors (filled in by SKUP)

Topic	Rating	Rating	Rating
Required training time	**<2 hours**	2 to 8 hours	>8 hours
Durations of preparations/ Pre-analytical time	**<6 min.**	6 to 10 min.	>10 min.
Duration of measurement	**<20 min.**	20 to 30 min.	>30 min.
Stability of test, unopened package	**>5 months**	3 to 5 months	<3 months
Stability of test, opened package	**>30 day or disposable**	14 to 30 days	<14 days
Stability of quality control material, unopened	**>5 months**	3 to 5 months	<3 months
Stability of quality control material, opened	**>6 days or disposable**	2 to 6 days	≤1 day
Total rating by SKUP	**Satisfactory**		

Table D. Rating of analytical quality control (filled in by SKUP)

Topic	Rating	Rating	Rating
Reading of the internal quality control	**Satisfactory**	Intermediate	Unsatisfactory
Usefulness of the internal quality control	**Satisfactory**	Intermediate	Unsatisfactory
External quality control	**Satisfactory**	Intermediate	Unsatisfactory
Total rating by SKUP	**Satisfactory**		

6.4.2. Assessment of the user-friendliness

Assessment of the operation facilities (table A)
The operation facilities were overall assessed as satisfactory, but there were some intermediate and unsatisfactory ratings. The motivations for the lower ratings mainly concerned problems with the buffer tube nozzle.

Assessment of the information in the manual (table B)
The information in the insert was assessed as satisfactory with the comment of being good explanations.

Assessment of time factors (table C)
The time factors were assessed as satisfactory.

Assessment of analytical quality control possibilities (table D)
The analytical quality control possibilities were assessed as satisfactory.

Conclusion
The user-friendliness of CLINITEST COVID-19 Ag Test and its manual was rated as satisfactory. The quality goal for user-friendliness was fulfilled.

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7. References

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8. Cochrane Database of Systematic Reviews (Dinnes et al). Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection 2021. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013705.pub2 (accessed 2021-06-30).
9. He X., Lau E.H.Y., Wu P. et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020; **26**: 672 – 675.
10. Norwegian Directorate of Health. COVID-19 pandemic: Evaluation of Abbot's Panbio COVID-19 rapid antigen test in Norway, December 2020, https://www.helsedirektoratet.no/rapporter/evaluation-of-abbots-panbio-covid-19-rapid-antigen-test-in-norway/ (accessed 2021-06-30).

Attachments

1. The organisation of SKUP
2. Facts about CLINITEST COVID-19 Ag Test
3. Information about manufacturer, retailers and marketing
4. Product specifications for this evaluation, CLINITEST COVID-19 Ag Test
5. Statistical expressions and calculations
6. Raw data, internal analytical quality control results, CLINITEST COVID-19 Ag Test
7. Raw data, CLINITEST COVID-19 Ag Test and the comparison method
8. Comments from Siemens Healthineers

Attachments with raw data are included only in the copy to Siemens Healthineers.

The organisation of SKUP

Scandinavian evaluation of laboratory equipment for point of care testing, SKUP, is a co-operative commitment of DEKS[1] in Denmark, Noklus[2] in Norway and Equalis[3] in Sweden. SKUP was established in 1997 at the initiative of laboratory medicine professionals in the three countries. SKUP is led by a Scandinavian *steering committee* and the secretariat is located at Noklus in Bergen, Norway.

The purpose of SKUP is to improve the quality of near patient testing in Scandinavia by providing objective and supplier-independent information about analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP *evaluations*.

SKUP offers manufacturers and suppliers evaluations of laboratory equipment for point of care testing. Provided the equipment is not launched onto the Scandinavian market, it is possible to have a confidential pre-marketing evaluation. The company requesting the evaluation pays the actual testing costs and receives in return an impartial evaluation.

There are *general guidelines* for all SKUP evaluations and for each evaluation a specific *SKUP protocol* is worked out in co-operation with the manufacturer or their representatives. SKUP signs *contracts* with the requesting company and the evaluating laboratories. The analytical results are assessed according to *pre-set quality goals*. To fully demonstrate the quality of a product, the *end-users* should be involved in the evaluations.

Each evaluation is presented in a *SKUP report* to which a unique *report code* is assigned. The code is composed of the acronym SKUP, the year the report was completed and a serial number. A report code, followed by an asterisk (*), indicates an evaluation with a more specific objective. The asterisk is explained on the front page of these protocols and reports.

SKUP reports are published at www.skup.org.

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[1] DEKS (Danish Institute for External Quality Assurance for Laboratories in the Health Sector) is a non-profit organisation owned by the Capital Region of Denmark on behalf of all other Regions in Denmark.

[2] Noklus (Norwegian Organization for Quality Improvement of Laboratory Examinations) is a national not for profit organisation governed by a management committee consisting of representatives from the Norwegian Government, the Norwegian Medical Association and the Norwegian Society of Medical Biochemistry, with the Norwegian Association of Local and Regional Authorities (KS) as observer.

[3] Equalis AB (External quality assessment in laboratory medicine in Sweden) is a limited company in Uppsala, Sweden, owned by “Sveriges Kommuner och Regioner” (Swedish Association of Local Authorities and Regions), “Svenska Läkaresällskapet” (Swedish Society of Medicine) and IBL (Swedish Institute of Biomedical Laboratory Science).

Facts about CLINITEST COVID-19 Ag Test

This form is filled in by Siemens Healthineers in Norway.

Table 1. Basic facts

Name of the measurement system:	CLINITEST Rapid COVID-19 Antigen Test
Dimensions and weight:	Width: 22 mm Depth: 5 mm Height: 68 mm Weight: 4.8 g
Components of the measurement system:	The test strip is composed of sample pad, reagent pad, reaction membrane and absorbing pad. The reagent pad contains the colloidal-gold conjugated with the monoclonal antibodies against the nucleocapsid protein of SARS-CoV-2; the reaction membrane contains the secondary antibodies for nucleocapsid protein of SARS-CoV-2. The whole strip is fixed inside a plastic device.
Measurand:	SARS CoV-2 antigen
Sample material:	Nasopharyngeal (NP) swab or nasal swab
Sample volume:	Approximately 100 µl
Measuring principle:	CLINITEST Rapid COVID-19 Antigen Test is an immunochromatographic membrane assay that uses highly sensitive monoclonal antibodies to detect nucleocapsid protein from SARS-CoV-2 in direct nasopharyngeal (NP) swab or nasal swab.
Traceability:	N/A
Calibration:	N/A
Measuring range:	Qualitative test. The Limit of Detection of the CLINITEST Rapid COVID-19 Antigen Test is 1.15 x 102 TCID 50 / mL
Haematocrit range:	N/A
Measurement time:	15 minutes
Operating conditions:	Room temperature 15-30ºC
Electrical power supply:	Not required
Recommended regular maintenance:	Not required – Single use
Package contents:	20 Test Cassettes 2 Extraction Buffer Vials 20 Sterile Swabs 20 Extraction Tubes and Tips 1 Workstation 1 Package Insert
Necessary equipment not included in the package:	Clock, timer or stopwatch

Table 2. Post analytical traceability

Is input of patient identification possible?	Mobile device can be used for data entry if used with the Siemens Healthineers Health Pass Web App or iSTOC IDA and IDA Cloud.
Is input of operator identification possible?	Mobile device can be used for data entry if used with the Siemens Healthineers Health Pass Web App or iSTOC IDA and IDA Cloud.
Can the instrument be connected to a bar-code reader?	Mobile device can be used for data entry if used with the Siemens Healthineers Health Pass Web App or iSTOC IDA and IDA Cloud.
Can the instrument be connected to a printer?	N/A
What can be printed?	N/A
Can the instrument be connected to a PC?	N/A
Can the instrument communicate with LIS (Laboratory Information System)? If yes, is the communication bidirectional?	N/A
What is the storage capacity of the instrument and what is stored in the instrument?	N/A
Is it possible to trace/search for measurement results?	Mobile device can be used for data entry if used with the Siemens Healthineers Health Pass Web App or iSTOC IDA and IDA Cloud.

Table 3. Facts about the reagent/test strips/test cassettes

Name of the reagent/test strips/test cassettes:	CLINITEST Rapid COVID-19 Antigen Test
Stability in unopened sealed vial:	24 Months
Stability in opened vial:	1 hour
Package contents:	20 Test Cassettes 2 Extraction Buffer Vials 20 Sterile Swabs 20 Extraction Tubes and Tips 1 Workstation 1 Package Insert

Table 4. Quality control

Electronic self check:	N/A
Recommended control materials and volume:	CLINITEST COVID-19 Antigen Control Kit
Stability in unopened sealed vial:	24 months
Stability in opened vial:	Individually sealed control swab stable for 24 months. Should be opened and used immediately prior to each control test.
Package contents:	5 negative control swabs, 5 positive control swabs, Instructions for use

Information about manufacturer, retailers and marketing

This form is filled in by Siemens Healthineers in Norway.

Table 1. Marketing information

Manufacturer:	
Retailers in Scandinavia:	Denmark: Siemens Healthineers Norway: Siemens Healthineers Sweden: Siemens Healthineers
In which countries is the system marketed:	Globally ☐ Scandinavia ☒ Europe ☒
Date for start of marketing the system in Scandinavia:	October 2020
Date for CE-marking:	October 2020
In which Scandinavian languages is the manual available:	Norwegian, Swedish, Danish

Product specifications for this evaluation

CLINITEST Rapid COVID-19 Antigen Test, REF. GCCOV-502a

Lot index used in evaluation	Lot no	Expiry date
a	2010189	2022-09-30
b	2010191	2022-09-30
c	2010195	2022-09-30
d	2011311	2022-10-31
Swabs	20200902JZ	2023-09-01

CLINITEST Rapid COVID-19 Antigen Control Kit, REF. 11556017

Control kit	Lot no	Expiry date
Controls, negative and positive	2102201/2102202	2023-01-31

Statistical expressions and calculations

This attachment is valid for evaluations of qualitative test methods with results on the ordinal scale.

Statistical terms and expressions

The definitions and formulas in this section originate from the Geigy document [a].

Statistical calculations

Diagnostic sensitivity is true positive/(true positive + false negative)

Diagnostic specificity is true negative/(false positive + true negative)

Positive predictive value (PPV) is true positive/(true positive + false positive)

Negative predictive value (NPV) is true negative/(true negative + false negative)

Prevalence is true positive/(true positive + true negative + false positive + false negative)

See table 1 for an illustration.

Table 1. Illustration of statistical calculations

	Truth		
	Positive	**Negative**	
Evaluated test positive	a	b	PPV = a/(a+b)
Evaluated test negative	c	d	NPV = d/(d+c)
	Diagnostic sensitivity = a/(a+c)	Diagnostic specificity = d/(b+d)	

Calculation of confidence intervals

Estimation of CI for fractions/proportions is performed according to Adjusted Walds [b]. The CIs are given for information only.

Relationship between PPV / NPV and prevalence

Contrary to diagnostic sensitivity and specificity, the PPV and NPV are related to the prevalence of the disease in a specific population (figure 1). PPV and NPV are also related to the diagnostic sensitivity and specificity of a diagnostic test.

a. Documenta Geigy. Mathematics and statistics. CIBA-GEIGY Limited, Basel, Switzerland 1971; p 186 formula # 772.
b. http://www.measuringu.com/wald.htm (accessed 2021-01-27).

Raw data, internal analytical quality control results, CLINITEST COVID-19 Ag Test

Shown to the requesting company only.

Raw data, CLINITEST COVID-19 Ag Test and the comparison method

Shown to the requesting company only.

Comments from Siemens Healthineers

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October 19, 2021

To Whom It May Concern:

Re: Comments on the SKUP Evaluation report on CLINITEST Rapid COVID-19 Antigen Test

Thank you for sharing the SKUP evaluation results. We at Siemens Healthineers appreciate your putting an exemplary effort into the study design, execution, data analysis, and report. However, after carefully reviewing this study report with our R&D PhD scientists, we would like to share our comments regarding the limitations of this study that may account for the discrepancies that were observed between your findings and the findings of our own internal studies and those reported in third-party publications.

There were some limitations in the study population that may have affected the results of the assay sensitivity. Only 73 RT-PCR–positive samples were included in this study, which is lower than the minimum number of 100 positive samples for the rapid antigen testing study recommended by the European Centre for Disease Prevention and Control (ECDC), suggesting that insufficient samples tested may have contributed to the low sensitivity as shown. Furthermore, 67.4% of the patients enrolled in the CLINITEST® Rapid COVID-19 Antigen Test evaluation were asymptomatic and presumably less likely to have detectable antigen. Imbalanced populations should be considered and highlighted when presenting the data so that results from different tests can be objectively compared. The characteristics of the study population used in the evaluation are critical for interpreting the results of assay sensitivity.

The majority of the PCR-positive samples collected in this study were likely to be from patients with low viral load. The number of positive samples collected with an RT-PCR cycle threshold (Ct) value <30 was 55% of the total positive results, with only 33% having Ct <25. Sensitivity values from these groups show results at 75% and 83% respectively. However, the overall sensitivity becomes much lower when the high-Ct-value samples are included. We understand the difficulty in collecting samples with Ct values evenly distributed across the range. However, the observed low sensitivity of the CLINITEST Rapid COVID-19 Antigen Test might be due to low viral load, evidenced by high Ct values. Given that the "rapid antigen tests may be sensitive enough to detect cases with a high viral load, i.e. pre-symptomatic and early symptomatic cases (up to five days from symptom onset; or low RT-PCR cycle threshold (Ct) value <25), which likely account for a significant proportion of transmissions", the CLINITEST Rapid COVID-19 Antigen Test has demonstrated reliable performance, with a sensitivity of 83% at Ct <25 in this report.

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Taken together, the observed low sensitivity of the CLINITEST Rapid COVID-19 Antigen Test might be due to low viral load and insufficient sample tested from the imbalanced target population. When interpreting the testing results of a sensitivity of 83% at Ct <25 in this report, the above observations should be taken into serious consideration.

Sincerely,

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The CLINITEST Rapid COVID-19 Antigen Test is not available for sale in the U.S. Product availability may vary from country to country and is subject to varying regulatory requirements. Distributed by Siemens Healthineers.