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Diagnostic performance of the Elecsys SARS-CoV-2 antigen assay in the clinical routine of a tertiary care hospital: Preliminary results from a single-center evaluation

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Abstract

Background: This report describes a manufacturer-independent evaluation of the diagnostic accuracy of the Elecsys SARS-CoV-2 antigen assay from Roche Diagnostics in a tertiary care setting.

Methods: In this single-center study, we used nasopharyngeal swabs from 403 cases from the emergency department and intensive care unit of our hospital. The reference standard for detecting SARS-CoV-2 was the reverse-transcription polymerase chain reaction (RT-PCR) assay. Cycle threshold (Ct) values were recorded for positive RT-PCR assays. The index test was the Elecsys SARS-CoV-2 antigen assay. This electrochemiluminescence immunoassay produces results as cutoff index (COI) values, with values ≥1.00 being reported as positive.

Results: Of the 403 cases, 47 showed positive results in RT-PCR assays. Of the 47 RT-PCR-positive cases, 12 showed positive results in the antigen assay. Of the 356 RT-PCR-negative cases, all showed negative results in the antigen assay. Thus, the antigen assay showed a sensitivity of 26% (95% CI, 14%-40%) and specificity of 100% (95% CI, 99%-100%). Analysis of the relationship between Ct values and COI values in the 47 RT-PCR-positive cases showed a correlation coefficient of −0.704 (95% CI, −0.824 to −0.522). The true-positive rate of the antigen assay for Ct values of 15–24.9, 25–29.9, 30–34.9, and 35–39.9 was 100%, 44%, 8%, and 6%, respectively.

Conclusions: The Elecsys SARS-CoV-2 antigen assay has a low sensitivity for detecting SARS-CoV-2 from nasopharyngeal swabs. Hence, we decided to not use this assay in the clinical routine of our hospital.

KEYWORDS
Antigen, COVID-19, diagnostic test, immunoassay, laboratory medicine, polymerase chain reaction, SARS-CoV-2, virology

Abbreviations: COI, cutoff index; COVID-19, coronavirus disease 19; Ct, cycle threshold; CV, coefficient of variation; ED, emergency department; ICU, intensive care unit; LoB, limit of blank; NAAT, nucleic acid amplification test; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1 | INTRODUCTION

The RNA virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19).[1] Infection with SARS-CoV-2 can be asymptomatic or may result in symptomatic disease ranging in severity from mild upper respiratory tract symptoms to severe pneumonia with respiratory failure and multiple organ failure.[1] The gold standard laboratory tests to detect SARS-CoV-2 from clinical specimens (eg, nasopharyngeal swabs, oropharyngeal swabs, and bronchoalveolar lavage fluid) are nucleic acid amplification tests (NAATs), mainly reverse-transcription polymerase chain reaction (RT-PCR) assays.[1,2] Currently, a variety of NAATs are commercially available for use in routine clinical practice.[1,3]

However, since the testing capacity afforded by NAATs is insufficient to cope with the COVID-19 pandemic, various manufacturers have also developed rapid antigen immunoassays, which do not require skilled personnel and dedicated instrumentation, for detection of the virus from nasopharyngeal and oropharyngeal swabs. SARS-CoV-2 rapid point-of-care antigen tests have also been commercially available for some time.[1,4] At present, antigen point-of-care tests in many countries help to ensure the necessary quantity of SARS-CoV-2 tests for their respective testing strategies,[1,4] but these tests have been criticized because of their lower clinical sensitivity in comparison with NAATs.[1,4]

Recently, Roche Diagnostics (Rotkreuz, Switzerland) launched a high-throughput antigen test for medical laboratories called "Elecsys SARS-CoV-2 antigen assay," which runs on the company's analyzers. We evaluated the diagnostic performance of the Elecsys SARS-CoV-2 antigen assay prior to its planned use in our clinical routine. Herein, we report the results of our evaluation.

2 | METHODS

2.1 | Study design and clinical samples

This report describes the findings of a single-center evaluation of the diagnostic accuracy of the Elecsys SARS-CoV-2 antigen assay as an index test in comparison with RT-PCR as the reference standard. Our manufacturer-independent evaluation was conducted from March 11, 2021, to April 26, 2021, at the Department of Clinical Pathology, Hospital of Bolzano, province of South Tyrol, Italy. During this period, the median 7-day incidence rate of new SARS-CoV-2-positive cases per 100,000 population was 149 (starting from 245 on March 11, 2021, and declining to 121 on April 26, 2021) in the province of South Tyrol (Amministrazione Provincia Bolzano, Sicurezza e protezione civile, web: http://www.provincia.bz.it/sicurezza-protezione-civile/protezione-civile/dati-attuali-sul-coronavirus.asp, last access: April 27, 2021). During this time, the Department of Clinical Pathology received 403 requests for simultaneous RT-PCR and antigen assays from the emergency department of the hospital and from the intensive care unit, which care for COVID-19 patients. These 403 requests pertained to 336 patients. In all 403 cases, two nasopharyngeal swabs were obtained simultaneously by skilled personnel, of which one was sent for the RT-PCR assay and the other was sent to run the antigen assay. We used the data from these 403 cases to evaluate the diagnostic performance of the Elecsys SARS-CoV-2 antigen assay. A referral to the ethics committee was not deemed necessary because the project was an assay validation/verification that was in line with good laboratory practice. Such evaluations are routinely performed in medical laboratories before introducing a new assay into the clinical routine.

2.2 | Reference standard—RT-PCR assay

The personnel from the emergency department of the hospital and from the intensive care unit used standard swabs and transport media from two different manufacturers, namely FLOQSwabs® (Ref. 503CS01, Copan Italia S.p.A., Brescia, Italy) in combination with the UTM Universal Transport Medium (Ref. 330C, filled with 3 ml UTM® medium, Copan Italia S.p.A., Brescia, Italy) and the combined specimen collection device ∑-Transwab® Liquid Amies (one Sigma swab plus 1 ml of liquid Amies transport medium, Ref. MW176S; Medical Wire, Corsham, United Kingdom). The nasopharyngeal swabs were handled as specified by the manufacturer. After the smear, samples were sent to our laboratory where the RT-PCR assay was performed immediately.

The RT-PCR assay was performed using the Xpert Xpress SARS-CoV-2 test (Ref. XPRSARS-COV2-10, Cepheid, Sunnyvale, CA, USA) on a GeneXpert® IV instrument (Cepheid, Sunnyvale, CA, USA). The Xpert Xpress SARS-CoV-2 test is a rapid, real-time RT-PCR test intended for qualitative detection of nucleic acids from SARS-CoV-2 in upper respiratory specimens. We performed the entire Xpert Xpress SARS-CoV-2 test procedure according to the manufacturer's instructions. The system uses single-use disposable cartridges that hold RT-PCR reagents and host the RT-PCR process. The sample-processing control and probe-check control are also included in the cartridge. The Xpert Xpress SARS-CoV-2 test provides test results based on the detection of two gene targets, namely the amplification of the SARS-CoV-2 E and N2 genes.[1,3] The limit of detection of this test was 250 copies/ml, and the time to result was 45 min.[1,3] The Xpert Xpress SARS-CoV-2 test includes an early assay termination function, which can provide an earlier time to result for high-titer specimens if the signal from the target nucleic acid reaches a predetermined threshold before the full 45 PCR cycles have been completed.

Using the GeneXpert software (Cepheid, Sunnyvale, CA, USA), we considered positive RT-PCR results when the SARS-CoV-2 signal for the N2 nucleic acid target had a PCR cycle threshold (Ct) value of <40.0, irrespective of the signal for the E nucleic acid target. In contrast, when the Ct value for the SARS-CoV-2 N2 gene was ≥40.0, or when the results of RT-PCR testing were definitely negative (with reference to a positive result for the sample-processing control), we classified the result of the RT-PCR test as negative. Further, we

categorized the results of RT-PCR tests that showed negative signals for the SARS-CoV-2 E and N2 genes as well as a negative signal for the sample-processing control as invalid; in these cases, we repeated the analysis.

2.3 | Index test—Elecsys SARS-CoV-2 antigen assay

Specimen collection and preparation for detection of the SARS-CoV-2 antigen was performed as recommended by Roche Diagnostics Italy and in accordance with the package insert of the Elecsys SARS-CoV-2 antigen assay. We prepared sample collection tubes without any additives (Vacuette® Z No Additive 4 ml, Ref. 454001, Greiner Bio-One, Kremsmunster, Austria) containing 1.0 ml of the SARS-CoV-2 extraction solution (Ref. 09370064190; Roche Diagnostics, Rotkreuz, Switzerland). The SARS-CoV-2 extraction solution is intended for the elution and transportation of samples for use in the Elecsys SARS-CoV-2 antigen assay. The personnel from the emergency department of the hospital and from the intensive care unit received these specifically prepared sample collection tubes and FLOQSwabs® (Ref. 519CS01, Copan Italia S.p.A., Brescia, Italy) for sample collection. The nasopharyngeal smear for detection of the SARS-CoV-2 antigen was performed in exactly the same way and at the same time as the smear for RT-PCR test. The collection tubes were opened; the swab was soaked in the solution; and the swab was stirred 20 times. The swab was then left in the solution for 2 min. Next, the personnel from the emergency department of the hospital or the intensive care unit removed the swab while pressing it against the tube wall to extract the liquid from the swab. The collection tube was then recapped and immediately sent to our laboratory, where the samples were stored for a maximum of 36 h at 2–8°C. According to the package insert of the Elecsys SARS-CoV-2 antigen assay, the samples have an in vitro stability of two days at 2–8°C. Finally, we performed the Elecsys SARS-CoV-2 antigen assay using the collection tubes.

The Elecsys SARS-CoV-2 antigen assay (Ref. 09345299190, Roche Diagnostics, Rotkreuz, Switzerland) is an electrochemiluminescence immunoassay for qualitative detection of the nucleocapsid antigen of SARS-CoV-2 in nasopharyngeal and oropharyngeal swab samples. This assay uses monoclonal antibodies directed against the SARS-CoV-2 nucleocapsid protein in a double-antibody sandwich assay format. In our evaluation, we ran this assay on a single Cobas e801 system (Roche Diagnostics, Rotkreuz, Switzerland) according to the manufacturer's instructions. This assay produces results as a cutoff index (COI; signal of sample divided by cutoff), wherein results ≥1.00 are reported as reactive/positive. For the internal quality control, we used the PreciControl SARS-CoV-2 antigen (Ref. 09345302190) once daily at two COI levels. We allowed sample measurements only if the controls were within the defined limits.

We determined the limit of blank (LoB) as previously suggested [5]: Measurements were obtained with the SARS-CoV-2 extraction solution in replicates of 20 and calculated $LoB = mean_{blank} + 1.645 (SD_{blank})$. Using this procedure, we found an LoB of 0.60 COI.

We evaluated the linearity of the Elecsys SARS-CoV-2 antigen assay according to the CLSI guideline EP6-A[6] using six different analyte concentrations. Fresh samples were used to prepare high- and low-concentration pools. We then conducted a direct dilution series with the low- and high-concentration patient sample pools in the following volume ratios (low-concentration pool +high-concentration pool): pool 1, low only; pool 2, 0.8 low +0.2 high; pool 3, 0.6 low +0.4 high; pool 4, 0.4 low +0.6 high; pool 5, 0.2 low +0.8 high; and pool 6, high only. Three measurements were performed for each concentration, and the default criteria were set at 5% for repeatability and 15 COI for nonlinearity. The mean COIs of the low- and high-concentration pools were 0.49 and 759, respectively. The standard errors of regression ($S_{y,x}$) and t-tests from regression analyses showed that the first-order model fitted better than the second- and third-order models: first-order model b_1, $S_{y,x} = 12.457$; t-test = 86.878 ($p < 0.001$); second-order model b_2, $S_{y,x} = 11.622$; t-test = 1.839 ($p = 0.086$); and third-order model b_3, $S_{y,x} = 10.755$; t-test = 1.875 ($p = 0.082$). In addition, all default criteria were met, so the method was linear up to 750 COI.

To evaluate the precision of the Elecsys SARS-CoV-2 antigen assay in our laboratory, we performed a replication study according to the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) guideline EP5-A.[7] Two pooled patient samples with COI values near the reactive/positive cutoff values of the assay were aliquoted into ten plastic tubes for each concentration level and frozen at −80°C. We analyzed these samples in duplicate in two runs per day for 10 days within 2 weeks of sample collection. Within-run and total analytical precision (CV) were calculated using the CLSI double-run precision evaluation test.[7] The Elecsys SARS-CoV-2 antigen assay had a within-run CV of 3.3% and a total CV of 3.5% at a mean concentration of 1.12 COI (pool 1) and a within-run CV of 3.1% and a total CV of 5.7% at a mean concentration of 1.82 COI (pool 2).

2.4 | Statistical analysis

We performed a purely descriptive statistical analysis by calculating the sensitivity, specificity, area under the ROC curve, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value for the Elecsys SARS-CoV-2 antigen assay against the reference standard. Sensitivity, specificity, positive and negative predictive values, and disease prevalence were expressed as percentages. The confidence intervals for sensitivity and specificity were the "exact" Clopper-Pearson confidence intervals. The confidence intervals for the likelihood ratios were calculated using the log method, as suggested by Altman et al.[8] Confidence intervals for the predictive values were the standard logit confidence intervals given by Mercaldo et al.[9] The area under the ROC curve was estimated using established procedures.[10-12] For correlation analysis, we calculated the Spearman correlation coefficient (rho) with a p-value and a 95% confidence interval (CI) for the correlation coefficient. Data analysis was performed using MedCalc software package MedCalc 17.2 (MedCalc Software Ltd, Ostend, Belgium).

3 | RESULTS

In this study on the diagnostic accuracy of the Elecsys SARS-CoV-2 antigen assay, we used the samples obtained in 403 clinical requests for simultaneous RT-PCR and antigen assays. The 403 requests were from 336 patients (median age, 74 years; range, 15–100 years; 188 males [56%]). Specifically, 330 requests for SARS-CoV-2 testing were from 321 patients in the emergency department of the hospital, and 73 requests were from 15 patients in the intensive care unit, which cared for patients with severe COVID-19. For the emergency department patients, RT-PCR assays were ordered by the treating physicians to decide whether the patients were to be admitted to the COVID-19 wards or to the "clean" COVID-19-free wards. In the intensive care unit, RT-PCR assays were ordered by the treating physicians for follow-up evaluations of patients with severe COVID-19. In the 403 cases, 47 RT-PCR-positive results were obtained. This corresponds to an RT-PCR-positive prevalence of 12% (95% CI, 9–15) in our cohort. Of the 330 requests for SARS-CoV-2 testing from the emergency department, 11 showed positive results with the RT-PCR assay (median Ct value, 32.5; range, 19.2–39.6). Of the 73 requests for SARS-CoV-2 testing from the intensive care unit, 36 showed positive results with the RT-PCR assay (median Ct value, 33.7; range, 18.6–39.5).

Table 1 details the overall results from the Elecsys SARS-CoV-2 antigen assay against the RT-PCR assay. Our data yielded the following findings: sensitivity, 26% (95% CI, 14–40); specificity, 100% (95% CI, 99–100); area under the ROC curve, 0.63 (95% CI, 0.58–0.68); positive likelihood ratio, not applicable; negative likelihood ratio, 0.74 (95% CI, 0.63–0.88); positive predictive value, 100%; and negative predictive value, 91% (95% CI, 90–92).

Next, we examined the 47 RT-PCR-positive cases with respect to the Ct values of the SARS-CoV-2 signal for the N2 nucleic acid target found in RT-PCR and the COI values in the Elecsys SARS-CoV-2 antigen assay. Analysis of the relationship between the Ct values and COI values in the 47 RT-PCR-positive cases showed a Spearman's coefficient of rank correlation (rho) of −0.704 (95% CI, −0.824 to −0.522; $p < 0.0001$). Figure 1 shows the respective scattergrams. In Table 2, we compared the results of the 47 RT-PCR-positive cases categorized by viral load (expressed as Ct values) with the corresponding results of the Elecsys SARS-CoV-2 antigen assay. The results showed that the true-positive rate of the Elecsys SARS-CoV-2 antigen assay was 100% for Ct values of 15–24.9, 44% for Ct values of 25–29.9, 8% for Ct values of 30–34.9, and 6% for Ct values of 35–39.9. Table S1 shows the individual results of the 47 RT-PCR-positive cases.

4 | DISCUSSION

Although this is only a small single-center study, the main characteristics of the Elecsys SARS-CoV-2 antigen assay can be determined from our results. The Elecsys SARS-CoV-2 antigen assay had high specificity (it showed no false-positive results compared to the RT-PCR assay), but the assay showed lower sensitivity compared with the RT-PCR assay (it yielded many false-negative results). The assay showed a sensitivity of 26% in our cohort, which was fairly low. As expected, the rate of false-negative results with the Elecsys SARS-CoV-2 antigen assay decreased with increasing viral load. In our evaluation, all Elecsys SARS-CoV-2 antigen assay results were positive in cases with Ct values of 15–24.9. However, for Ct values of 30–39.9, the Elecsys SARS-CoV-2 antigen assay had a sensitivity of only 6%–8% in our cohort. This seems to be too low for a tertiary care setting. Therefore, we decided to not use this assay in the clinical routine of our hospital.

Our data suggest a clear relationship between the Ct value (as a surrogate measure of viral load) and the sensitivity of the Elecsys SARS-CoV-2 antigen assay. A recently published study, for example, demonstrated that SARS-CoV-2 infectivity varies with the viral load, among other factors.[13,14] Individuals with high viral loads (as determined by Ct values) were the most infectious.[13] Although rapid point-of-care antigen tests for detection of SARS-CoV-2 have been criticized because of their lower clinical sensitivity than NAATs, these assays may help detect the most infectious cases.[13] These rapid point-of-care antigen tests usually have a relatively high sensitivity in respiratory specimens with high viral loads (typically >80% in specimens with Ct values <25), while their positive rate in samples with a low viral load (eg, Ct values >25/30) is usually <80%.[4,15,16] These data support the use of rapid point-of-care antigen tests for the detection of SARS-CoV-2 in high-viral-load individuals. These considerations might also hold true for the Elecsys SARS-CoV-2 antigen assay. However, our data do not conclusively determine whether the diagnostic performance of the Elecsys SARS-CoV-2 antigen assay is adequate for population screening programs of asymptomatic or pre-symptomatic individuals to reduce transmission of SARS-CoV-2. Further studies in larger cohorts are necessary to address these issues.

TABLE 1 Overall performance of the Elecsys SARS-CoV-2 antigen assay (ie, index test) versus the RT-PCR assay (ie, reference standard) in 403 cases

	RT-PCR-positive	RT-PCR-negative	Total
Antigen assay–positive	$n = 12$ (true-positive rate: 26%)	$n = 0$ (false-positive rate: 0%)	$n = 12$
Antigen assay–negative	$n = 35$ (false-negative rate: 74%)	$n = 356$ (true-negative rate: 100%)	$n = 391$
Total	$n = 47$	$n = 356$	$n = 403$

Abbreviations: RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

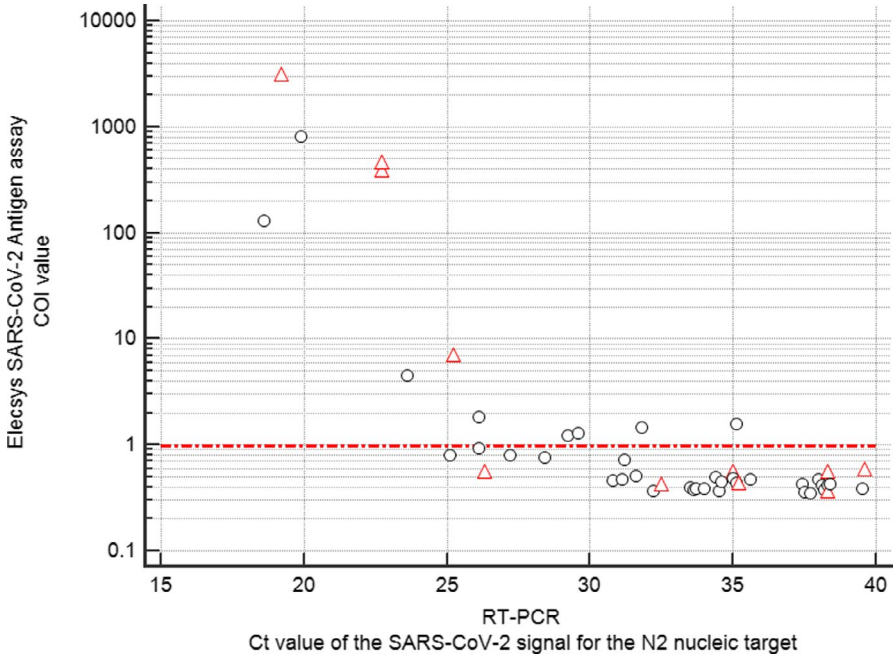

FIGURE 1 Scatterplot of the cycle threshold (Ct) values of SARS-CoV-2 RT-PCR versus the cutoff index (COI) values of the Elecsys SARS-CoV-2 antigen assay in our 47 RT-PCR-positive cases. The horizontal dotted line indicates the cutoff value of the Elecsys SARS-CoV-2 antigen assay (negative, COI <1.0; positive, COI ≥1.0). Open triangles indicate requests from the emergency department; open circles indicate requests from the intensive care unit. Abbreviations: COI, cutoff index; Ct, cycle threshold; RT-PCR, reverse-transcription polymerase chain reaction; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2 Comparison of the 47 SARS-CoV-2 RT-PCR-positive cases categorized by virus load (expressed as Ct values) versus the results of the Elecsys SARS-CoV-2 antigen assay

RT-PCR		Elecsys SARS-CoV–2 antigen assay			
Ct value (range)	Number	Positive results	Negative results	True-positive rate (ie, sensitivity)	Median COI (range)
15.0–24.9	*n* = 6	*n* = 6	*n* = 0	100%	434 (4.49–3155)
25.0–29.9	*n* = 9	*n* = 4	*n* = 5	44%	0.93 (0.57–7.07)
30.0–34.9	*n* = 14	*n* = 1	*n* = 13	8%	0.44 (0.37–1.47)
35.0–39.9	*n* = 18	*n* = 1	*n* = 17	6%	0.44 (0.35–1.57)

Abbreviations: COI, cutoff index; Ct, cycle threshold; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

When comparing the results of our evaluation with the data from the package insert of the Elecsys SARS-CoV-2 antigen assay, considerable differences in the diagnostic performance were noted. The package insert describes the performance of the antigen assay in comparison with the Roche Diagnostics SARS-CoV-2 RT-PCR assay. According to Roche Diagnostics, the Elecsys SARS-CoV-2 antigen assay has a relative sensitivity of approximately 97% at Ct values <30; however, our evaluation showed a relative sensitivity of approximately 67% at Ct values <30. Furthermore, while the package insert described a relative sensitivity of approximately 84% at Ct values of 30–35, our evaluation showed a relative sensitivity of approximately 8% at Ct values of 30–35. According to the manufacturer, the Elecsys SARS-CoV-2 antigen assay has a relative sensitivity of approximately 61% for Ct values of 35–40, but our evaluation showed a relative sensitivity of approximately 6% for Ct values of 35–40. Thus, our assay evaluation suggested that the diagnostic sensitivity of the Elecsys SARS-CoV-2 antigen assay was worse than that indicated in the package insert. However, we cannot provide a definitive explanation for these differences with the data available to us. We speculate that the large differences in the reported assay performance data may be related to the use of the SARS-CoV-2 extraction solution. Indeed, the package insert of the Elecsys SARS-CoV-2 antigen assay did not specify anything about the use of the SARS-CoV-2 extraction solution, whereas we were advised by Roche Diagnostics, Italy, to use 1.0 ml of the SARS-CoV-2 extraction solution for each nasopharyngeal swab (as described in the Methods). The use of 1.0 ml of this SARS-CoV-2 extraction solution may have led to a dilution effect of the SARS-CoV-2 antigen, which could have negatively affected the sensitivity of the Elecsys SARS-CoV-2 antigen assay. However, as mentioned above, this consideration is speculative.

A diverse range of rapid point-of-care antigen tests for the detection of SARS-CoV-2 from nasopharyngeal swabs and oropharyngeal swabs are currently available in the market. Some excellent publications have described the evaluation results for these rapid point-of-care assays,[17-23] and meta-analyses on this topic have also been published.[15,16] A summary of the published data suggests that the sensitivity of these rapid point-of-care antigen assays is generally low, ranging from 20% to 95% depending on the assay and the virus load. Therefore, the diagnostic performance of the Elecsys SARS-CoV-2 antigen assay is not better than that of rapid point-of-care assays described in the literature, with the advantage of a high

throughput and the disadvantage of a relatively long time to obtain the results.

In conclusion, it remains to be established whether the Elecsys SARS-CoV-2 antigen assay can be considered for detecting potentially infective individuals and thus for reducing the virus spread. If this is true, the Elecsys SARS-CoV-2 antigen assay could be useful for population screening of asymptomatic or pre-symptomatic individuals in accordance with the respective testing strategies of the authorities. In a tertiary care setting, however, the Elecsys SARS-CoV-2 antigen assay does not appear to be useful in its current form for clinical decision-making, in our opinion.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Thomas Mueller: Conceptualization, data collection, data analysis and interpretation, drafting of the article. Julia Kompatscher: Data collection, data analysis and interpretation, critical revision of the article. Mario La Guardia: Data collection, data analysis and interpretation, critical revision of the article. All authors: Final approval of the article.

DATA AVAILABILITY STATEMENT

The original anonymized data are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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