Elecsys Anti-SARS-CoV-2

cobas®

Materials provided

REF		Σ	SYSTEM
09203079190	09203079501	300	**cobas** e 402 **cobas** e 801

See "Reagents - working solutions" section for reagents

Materials required (but not provided)

REF	Description
09216928190	PreciControl Anti-SARS-CoV-2, for 4 x 1.0 mL
	General laboratory equipment
	cobas e analyzer

Additional materials for **cobas** e 402 and **cobas** e 801 analyzers:

REF	Description
06908799190	ProCell II M, 2 × 2 L system solution
04880293190	CleanCell M, 2 × 2 L measuring cell cleaning solution
07485409001	Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
06908853190	PreClean II M, 2 × 2 L wash solution
05694302001	AssayTip/AssayCup tray, 6 magazines × 6 magazine stacks × 105 assay tips and 105 assay cups, 3 wasteliners
07485425001	Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution / Elecsys SysClean for Liquid Flow Cleaning Detection Unit
07485433001	PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution / Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
11298500160	ISE Cleaning Solution / Elecsys SysClean, 5 × 100 mL system cleaning solution

For use in the USA only

System information

Short name	ACN (application code number)
ACOV2	10226

Intended use

Elecsys Anti-SARS-CoV-2 is an immunoassay intended for the in vitro qualitative detection of total antibodies to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in human serum and Li-heparin, K2-EDTA and K3-EDTA plasma collected on or after 15 days post-symptom onset. The test is intended as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas** e immunoassay analyzers.

Summary

SARS-CoV-2, the causative agent of Coronavirus Disease 2019 (COVID-19), is an enveloped, single-stranded RNA virus of the family *Coronaviridae*, genus *Betacoronavirus*. Viruses of this family share similarities in their genome and organization, including the 4 structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N). They cause diseases with symptoms ranging from those of a mild common cold to more severe ones such as the Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and COVID-19. Other coronaviruses known to infect humans include 229E, NL63, OC43 and HKU1. The latter group is ubiquitous and infection typically causes common cold or flu-like symptoms.[1,2]

SARS-CoV-2 is primarily transmitted person-to-person through exposure to respiratory fluids carrying infectious virus. Exposure occurs in 3 principal ways: (1) inhalation of respiratory droplets and aerosol particles, (2) deposition of respiratory droplets and particles on exposed mucous membranes, and (3) touching mucous membranes with contaminated hands.[3,4] In the respiratory tract, SARS-CoV-2 invades preferentially mucus-producing cells and ciliated cells, while endothelial lung cells are susceptible to infection. The spike protein interacts with the host cell receptor angiotensin-converting enzyme 2 (ACE2), followed by conformational changes which trigger membrane fusion. Once in the cytoplasm, the virus releases its RNA genome, which is then replicated and newly assembled viral particles are released from the infected cells.[5,6]

The mean incubation period of the ancestral SARS-CoV-2 strain was determined to be 6.6 days, but following variants of concern have increasingly shorter incubation periods, down to 3.4 days for Omicron.[7] The majority of SARS-CoV-2 transmission occurs early in the course of illness, potentially starting in the 1-2 days prior to onset of symptoms, and the contagious period ends between 5 and 10 days after, while severe cases may remain contagious for longer.[8,9]

Transmission from asymptomatic individuals has been described.[10] The spectrum of symptomatic infection ranges from mild (e.g., fever; upper respiratory symptoms) over moderate (e.g., lower respiratory disease) to critical (e.g., respiratory failure), with severe cases occurring predominantly in adults with advanced age or underlying medical comorbidities.[11,12]

Definitive diagnosis of acute SARS-CoV-2 infection entails direct detection of SARS-CoV-2 RNA by nucleic acid amplification technology (NAAT). Antigen tests can be used to diagnose acute infection in symptomatic individuals when NAAT is unavailable or not easily accessible.[13] Serological assays, which detect antibodies against SARS-CoV-2, can be used for clinical and public health purposes, such as serologic surveys.

Most immunocompetent persons develop an adaptive immune response following SARS-CoV-2 infection, triggering the generation of antibodies, including IgM, IgG, and IgA, directed against viral proteins. Antibodies can be detected in serum within 1-3 weeks after infection.[14,15,16] IgM and IgG antibodies often arise nearly simultaneously, but some cases have been reported where IgG appears before IgM, limiting the diagnostic utility of IgM testing.[17,18,19,20] IgG antibodies can be reliably detected 14 days after a SARS-CoV-2 infection. In most individuals, antibody levels peak 4-5 weeks after infection and will decrease in subsequent months after the infection has cleared, with IgM and IgA antibodies decaying more rapidly than IgG.[21,22] IgG antibodies persist for at least up to a year in most persons, but the precise duration of time that antibodies persist after infection is unknown.[23,24] After infection, the binding strength of antibodies to antigens increases over time due to a process called affinity maturation, and anti-N IgG avidity increases within the first month of symptom onset, remaining elevated following viral clearance.[25,26]

The Elecsys Anti-SARS-CoV-2 assay uses a recombinant protein representing the SARS-CoV-2 nucleocapsid (N) antigen in a double-antigen sandwich assay format.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, biotinylated SARS-CoV-2-specific recombinant antigen and SARS-CoV-2-specific recombinant antigen labeled with a ruthenium complex[a)] form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solution

The reagent **cobas** e pack (M, R1, R2) is labeled as ACOV2.

M	Streptavidin-coated microparticles, 1 bottle, 16 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
R1	SARS-CoV-2-Ag~biotin, 1 bottle, 18.8 mL: Biotinylated SARS-CoV-2-specific recombinant antigen (E. coli) < 0.5 mg/L; HEPES[A)] buffer 50 mmol/L, pH 7.7; preservative.
R2	SARS-CoV-2 Ag~Ru(bpy), 1 bottle, 18.8 mL: SARS-CoV-2-specific recombinant antigen labeled with ruthenium complex < 0.5 mg/L; HEPES buffer 50 mmol/L, pH 7.7; preservative.

A) HEPES = [4-(2-hydroxyethyl)-piperazine]-ethane sulfonic acid

ACOV2 Cal1	Negative calibrator 1 (white cap), 2 bottles of 0.67 mL: Human serum, non-reactive for anti-SARS-CoV-2 antibodies; buffer; preservative.
ACOV2 Cal2	Positive calibrator 2 (black cap), 2 bottles of 0.67 mL: Human serum, reactive for anti-SARS-CoV-2 antibodies; buffer; preservative.

Warnings and precautions

For in vitro diagnostic use for healthcare professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste

Warning: Handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards

Apply all relevant local disposal regulations to determine safe disposal.

The Safety Data Sheet is available for professional users on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Elecsys Anti-SARS-CoV-2

Warning

H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing mist or vapours.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Hazardous components:

- 2-methyl-2H-isothiazol-3-one hydrochloride

Product safety labeling follows EU GHS guidance.

Contact phone: +1-800-428-2336

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A).

The serum containing anti-SARS-CoV-2 (ACOV2 Cal2) was heat-inactivated for 30 minutes at 56 °C.

However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[27,28]

Avoid foam formation in all reagents and sample types (specimens, calibrators, and controls).

Reagent handling

The reagents in the kit are ready-for-use and are supplied in bottles compatible with the system.

Calibrators:

The calibrators are supplied ready-for-use in bottles compatible with the system.

Store the calibrators at 2-8 °C for later use.

Perform **only one** calibration procedure per bottle.

All information required for correct operation is available via **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas** e pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the cobas e pack	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	30 days

Stability of the calibrators	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	30 days
on analyzers at 20-25 °C	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K_2-EDTA and K_3-EDTA plasma.

Li-heparin and K_2-EDTA plasma tubes containing separating gel can be used.

Stable for 7 days at 15-25 °C, 14 days at 2-8 °C, 28 days at -20 °C (± 5 °C). The samples may be frozen 3 times.

The sample types listed were tested with a selection of sample collection tubes or systems that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube/collection system manufacturer.

Specimens should not be subsequently altered with additives (e.g. biocides, anti-oxidants or substances that could possibly change the pH or ionic strength of the sample) in order to avoid erroneous findings.

Pooled samples and other artificial material may have different effects on different assays and thus may lead to discrepant findings.

Centrifuge samples containing precipitates and thawed samples before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

The performance of the Elecsys Anti-SARS-CoV-2 assay has not been established with cadaveric samples or body fluids other than serum and plasma.

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet.

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas** e pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas** e pack.

Calibrators:

Place the calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

Calibration frequency: Calibration must be performed once per reagent lot using ACOV2 Cal1, ACOV2 Cal2 and fresh reagent (i.e., not more than 24 hours since the **cobas** e pack was registered on the analyzer).

Renewed calibration is recommended as follows:

- every 11 weeks when using the same reagent lot
- every 14 days when using the same **cobas** e pack
- as required: e.g. quality control findings outside the defined limits

Quality control

PreciControl Anti-SARS-CoV-2 is recommended for routine quality control procedures.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

Results must be within the specified ranges. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

The open vial PreciControl stability is 28 days at 2-8 °C.

Stability of PreciControl on the analyzers is 10 hours.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of ACOV2 Cal1 and ACOV2 Cal2.

The result of a sample will be displayed with a "non-reactive" (negative) or "reactive" (positive) label.

Interpretation of results

Results obtained with the Elecsys Anti-SARS-CoV-2 assay can be interpreted as follows:

Numeric result	Result message	Interpretation
COI < 1.0	Non-reactive	Negative for anti-SARS-CoV-2 antibodies
COI ≥ 1.0	Reactive	Positive for anti-SARS-CoV-2 antibodies

Note: A numeric COI is provided as part of the result output. Do not report COI outside of the laboratory. Only the Result message with or without Interpretation should be reported outside the lab.

Limitations and interferences

- At this time, it is unknown for how long antibodies persist following infection and if the presence of antibodies confers protective immunity.
- Results are for the detection of total SARS-CoV-2 antibodies. Antibodies to SARS-CoV-2 are generally detectable in blood several days after initial infection, although the duration of time antibodies are present postinfection is not well characterized.
- This test should not be used to diagnose or exclude acute SARS-CoV-2 infection. An assay that directly detects the virus should be used to evaluate individuals for acute COVID-19, particularly those who have been in contact with the virus. Individuals may have detectable virus present for several weeks following seroconversion.
- No false negative results due to a high-dose hook effect were found with the Elecsys Anti-SARS-CoV-2 assay but occurrence of high-dose hook effect cannot be completely excluded.
- In rare cases, interference due to extremely high titers of antibodies to analyte specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.
- The results should always be assessed in conjunction with the patient's medical history, clinical examination and other laboratory data, as applicable.
- SARS-CoV-2 IgG antibodies may be below detectable levels in patients who have been exhibiting symptoms for less than 15 days. Samples should only be tested from individuals 15 days or more post-symptom onset.
- A positive result may not indicate previous SARS-CoV-2 infection. Consider other information including clinical history and local disease prevalence, in assessing the need for a second but different serology test to confirm an immune response.
- Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. A negative result can occur if the quantity of the anti-SARS-CoV-2 antibodies present in the specimen is below the detection limit of the assay, or the antibodies that are detected are not present during the stage of disease in which a sample is collected.
- False positive results for the Elecsys Anti-SARS-CoV-2 assay may occur due to cross reactivity from pre-existing antibodies or other possible causes.
- False positive results for the Elecsys Anti-SARS-CoV-2 assay may occur due to cross reactivity to MERS-CoV glycoprotein IgG.
- Accumulating evidence suggests that some people who are immunocompromised (have a weakened immune system) are less likely to develop antibodies following the infection with SARS-CoV-2. People can be considered to be immunocompromised (have a weakened immune system) due to several types of medical conditions and treatments. Examples include receiving active treatment for solid tumor and hematologic malignancies, receipt of solid-organ transplant and taking immunosuppressive therapy, having advanced or untreated HIV infection, or having long-term use of certain types of medicines that are immunosuppressive or immunomodulatory.
The Elecsys Anti-SARS-CoV-2 assay has not been validated with immunocompromised patients.[29,30]
- The performance characteristics for SARS-CoV-2 antibodies were established when the original B.1 lineage of the Wuhan-Hu-1 strain was prevalent and due to the propensity of the virus to mutate, new strains emerge over time which may affect the performance of this device and have serious public health implications.
- There is a risk of erroneous results (i.e., false negative results) due to the presence of novel emerging viral variants circulating in the intended use population.
- This test should not be used for screening of donated blood, plasma, cells, or tissues.
- Positive and negative predictive values are highly dependent on prevalence.

▪ Accurate results are dependent on adequate specimen collection, transport, storage, and processing (as applicable). Failure to observe proper procedures in any one of these steps can lead to incorrect results.

The performance of this test has not been established in individuals that have received a COVID-19 vaccine. The clinical significance of a positive or negative antibody result following COVID-19 vaccination has not been established, and the result from this test should not be interpreted as an indication or degree of protection from infection after vaccination.

Summary of clinical performance

The clinical performance claims of the Elecsys Anti-SARS-CoV-2 assay were established using both clinical performance evaluation studies data from a traditional clinical study and real-world data.

Traditional Clinical Study

The purpose of this study was to evaluate the clinical performance of the Elecsys Anti-SARS-CoV-2 assay on the **cobas** e 601 analyzer. The clinical performance of the Elecsys Anti-SARS-CoV-2 assay was evaluated testing clinical samples from the following populations, as indicated below:

▪ 9007 presumed SARS-CoV-2 negative samples collected prior to the COVID-19 pandemic (6305 from Germany and 2702 samples from US blood donors), and

▪ 303 archived clinical samples collected from individuals confirmed to have a prior SARS-CoV-2 positive result by RT-PCR.
These individuals were non-immunocompromised, non-vaccinated, US-enrolled, with COVID-19 symptom onset information, and prior RT-PCR positive test result. Demographic information from the 303 individuals with prior confirmed COVID-19 positive result by RT-PCR is provided in the table below.

Demographic information for subjects enrolled with prior confirmed COVID-19 positive result by RT-PCR

Days post-symptom onset (DPSO)	White N (%)	Black or African American N (%)	Asian N (%)	American Indian or Alaska Native N (%)	Other N (%)	Unknown N (%)	Total N (%)
8-14	14 (93.33)	1 (6.67)	0 (0)	0 (0)	0 (0)	0 (0)	15 (4.95)
≥ 15	199 (69.10)	29 (10.07)	9 (3.13)	2 (0.69)	17 (5.90)	32 (11.11)	288 (95.05)
Total	213 (70.30)	30 (9.90)	9 (2.97)	2 (0.66)	17 (5.61)	32 (10.56)	303 (100)

Negative percent agreement (NPA)

To establish the NPA of the assay, a total of 9007 pre-pandemic specimens were tested with the Elecsys Anti-SARS-CoV-2 assay. All specimens were presumed negative because they were obtained before December 2019; 2702 specimens were collected in the United States and 6305 specimens were collected in Germany. Out of 9007 specimens, 17 false positive results were observed, resulting in a NPA of 99.81 %. The lower limit of the 95 % confidence interval was 99.70 %.

Number of Specimens Tested (obtained prior to the COVID-19 pandemic)	Non-reactive	NPA (%)	95 % Confidence Interval (%) (Wilson Score)
9007	8990	99.81	(99.70 - 99.88 %)

Positive percent agreement (PPA)

The clinical performance of the Elecsys Anti-SARS-CoV-2 assay was evaluated in a clinical performance evaluation study in which results were obtained under routine laboratory conditions and compared to the results of a composite comparator method comprised of 3 SARS-CoV-2 serology assays. SARS-CoV-2 seropositivity was determined by majority rule (≥ 2 out of 3) of FDA-de novo and Emergency Use Authorized (EUA) Anti-SARS-CoV-2 serology assays. Performance of the Elecsys Anti-SARS-CoV-2 assay relative to the composite comparator was established using specimens collected from individuals with a history of SARS-CoV-2 infection confirmed by a prior SARS-CoV-2 positive test result using a FDA authorized RT-PCR test and calculated and reported as PPA. Serum and plasma samples were tested at 2 clinical laboratories on the **cobas** e 601 analyzer.
Due to clinical relevance, the performance of the Elecsys Anti-SARS-CoV-2 assay was determined by the results from samples collected ≥ 15 days post-symptom onset (DPSO) after exclusion of immunocompromised subjects.

A total of 303 specimens (157 serum and 146 plasma) were tested on the Elecsys Anti-SARS-CoV-2 assay and the composite comparator method. Blood samples were collected within the United States between April and December of 2020. Of these, 15 specimens were collected in between 0-14 DPSO and 288 collected ≥ 15 DPSO. PPA and NPA with corresponding Wilson score 95% confidence intervals are summarized below.

DPSO			Composite Comparator Results				
			Positive	Negative		PPA (n/N)[A] (95 % CI)	NPA (n/N) (95 % CI)
8-14	Elecsys Anti-SARS-CoV-2	Positive	7	0		53.85 % (7/13) (29.14-76.79 %)	100.0% (2/2) (34.24-100.0 %)
		Negative	6	2			
		Total	13	2			
≥15	Elecsys Anti-SARS-CoV-2	Positive	251	1		98.82 % (251/254) (96.59-99.60%)	97.06 % (33/34) (85.08-99.48 %)
		Negative	3	33			
		Total	254	34			
	Total = 303		267	36			

A) The number of observed agreements (n) out of the total number of composite comparator results (N).

PPA

Estimation Using Real-World Data

In addition, the clinical performance of the Elecsys Anti-SARS-CoV-2 assay was assessed using real-world data with RT-PCR result information as the comparator where samples were collected during routine clinical practice at a collaborating institution in the United States from March 2020 - March 2021.

Test data (Elecsys Anti-SARS-CoV-2 and RT-PCR) were collected directly from the laboratory information system, whereas patient demographics and clinical variables were manually extracted through medical chart review. The PPA was calculated as the percentage of positive serology test results among evaluable samples. An initial cohort of 1178 subjects who tested positive on a high-sensitive FDA authorized SARS-CoV-2 RT-PCR test and were also tested with the Elecsys Anti-SARS-CoV-2 assay during the specified period were identified. After excluding 611 subjects based on pre specified criteria (e.g., having no reported date of symptom onset, having no serology test result on or after symptom onset, or potentially having received a COVID-19 vaccination), 567 eligible subjects remained in the final cohort. Considering clinical relevance, the primary population of interest for the PPA calculation was non-immunocompromised, non-vaccinated subjects with a positive SARS-CoV-2 RT-PCR test within 7 days before or 14 days after symptom onset and having serology samples collected ≥ 15 days after symptom onset (N = 285 samples). The PPA in this population was 96.49 % (95 % CI:93.66, 98.08 %).

DPSO[A]	Number of Samples Tested[B] (with Positive RT-PCR result) (N)	Elecsys Anti-SARS-CoV-2 Result in RWE[C] Clinical Performance Study		
		Reactive (n)	PPA (%) (n/N)	95 % Confidence Interval (%) Wilson Score
0-7 days	64	34	53.13 % (34/64)	41.07 - 64.82 %
8-14 days	27	18	66.67 % (18/27)	47.82 - 81.36 %
≥ 15 days	285	275	96.49 % (275/285)	93.66 - 98.08 %

A) Days Post Symptom Onset

B) Subjects can contribute multiple Elecsys Anti-SARS-CoV-2 testing records for the performance calculation; if so, only the first testing record per subject within each time bin was used and excessive testing records were excluded from here.

C) Real-World Evidence

Summary of analytical performance

Representative performance data on the analyzers are given below. The analytical performance of the Elecsys Anti-SARS-CoV-2 assay was evaluated on the **cobas** e 601 analyzer unless otherwise specified in the tables below.

Results obtained in individual laboratories may differ.

Analytical Cutoff Sensitivity

The analytical cutoff sensitivity of the Elecsys Anti-SARS-CoV-2 assay is 4.776 BAU/mL using the First International Standard for anti-SARS-CoV-2 immunoglobulin (human) code: 20/136.

Interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interference was tested up to the listed concentration and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 1000 mg/dL or ≤ 10 g/L
Intralipid	≤ 2000 mg/dL
Cholesterol	≤ 400 mg/dL

Compound	Concentration tested
Triglycerides	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 7.0 g/dL or ≤ 70 g/L
IgA	≤ 1.6 g/dL or ≤ 16 g/L
IgM	≤ 1.0 g/dL or ≤ 10 g/L
Antinuclear Antibodies (ANA)	≤ titer of 1:1280

Biotin interference

This assay has no biotin interference in serum concentrations up to 1200 ng/mL. Some studies have shown that serum concentrations of biotin can reach up to 355 ng/mL within the first hour after biotin ingestion for subjects consuming supplements of 20 mg biotin per day[31] and up to 1160 ng/mL for subjects after a single dose of 300 mg biotin.[32]

Exogenous substances

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special drugs were tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested
Interferon alpha-2a	21600 IU/mL
Interferon alpha-2b	3000 IU/mL
Zanamivir	0.006 mg/mL
Ribavirin	0.750 mg/mL
Oseltamivir	0.090 mg/mL
Peramivir	0.360 mg/mL
Lopinavir	0.480 mg/mL
Ritonavir	0.240 mg/mL
Arbidol	0.120 mg/mL
Remdesivir	0.120 mg/mL
Actemra (Tocilizumab)	0.384 mg/mL
Levofloxacin	0.300 mg/mL
Azithromycin	0.300 mg/mL
Ceftriaxone	2.40 mg/mL
Meropenem	3.60 mg/mL
Tobramycin	0.360 mg/mL
Fexofenadine	0.108 mg/mL
Hydroxychloroquine	0.480 mg/mL

Drug interferences are measured based on recommendations given in CLSI guidelines EP07 and EP37 and other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute) with 2 runs per day for 21 days with 2 determinations per sample.

The following results were obtained:

cobas e 801 analyzer[A]					
Sample	Mean COI	Repeatability[B]		Intermediate precision[C]	
		SD COI	CV %	SD COI	CV %
Human Sample 1	5.22	0.138	2.6	0.332	6.3
Human Sample 2	0.073	0.002	2.7	0.002	3.3
Human Sample 3	0.949	0.024	2.5	0.060	6.3
Human Sample 4	22.3	0.594	2.7	1.55	6.9
Human Sample 5	1.24	0.035	2.8	0.066	5.3
Human Sample 6	0.988	0.031	3.1	0.062	6.2
Human Sample 7	0.072	0.002	3.0	0.002	3.2
Human Sample 8	1.04	0.031	3.0	0.068	6.5
PreciControl ACOV2 1	0.085	0.002	2.3	0.002	2.7
PreciControl ACOV2 2	2.68	0.055	2.0	0.217	8.1

A) The precision data generated on the **cobas** e 402 analyzer was equivalent to that of the **cobas** e 801 analyzer.

B) Repeatability = within-run precision

C) Intermediate precision = within laboratory

cobas e 601 analyzer[A]					
Sample	Mean COI	Repeatability[B]		Intermediate precision[C]	
		SD COI	CV %	SD COI	CV %
Human Sample 1	4.90	0.084	1.7	0.236	4.8
Human Sample 2	0.063	0.002	2.5	0.003	4.7
Human Sample 3	0.869	0.014	1.6	0.042	4.8
Human Sample 4	20.8	0.388	1.9	1.17	5.6
Human Sample 5	1.14	0.020	1.7	0.057	5.0
Human Sample 6	0.910	0.020	2.2	0.057	6.2
Human Sample 7	0.063	0.002	2.7	0.003	5.1
Human Sample 8	0.977	0.015	1.5	0.058	5.9
PreciControl ACOV2 1	0.076	0.002	2.4	0.004	4.8
PreciControl ACOV2 2	2.53	0.028	1.1	0.149	5.9

A) Precision results on the **cobas** e 601 are comparable to the **cobas** e 602 analyzer

B) Repeatability = within-run precision

C) Intermediate precision = within laboratory

cobas e 601 analyzer					
Sample	Mean COI	Between-Run		Between-Day	
		SD COI	CV %	SD COI	CV %
Human Specimen 1	4.90	0.045	0.9	0.216	4.4
Human Specimen 2	0.063	0.001	1.3	0.002	3.8
Human Specimen 3	0.869	0.017	2.0	0.035	4.0
Human Specimen 4	20.8	0.153	0.7	1.09	5.3
Human Specimen 5	1.14	0.021	1.9	0.049	4.3
Human Specimen 6	0.910	0.010	1.0	0.052	5.7
Human Specimen 7	0.063	0.001	1.2	0.003	4.2
Human Specimen 8	0.977	0.015	1.6	0.053	5.5
PreciControl ACOV2 1	0.076	0.000	0.0	0.003	4.1
PreciControl ACOV2 2	2.53	0.041	1.6	0.140	5.5

Reproducibility

A study was performed based on guidance from CLSI EP05 A3 (n = 270).

Reproducibility was assessed with 3 lots of the Elecsys Anti-SARS-CoV-2 assay and PreciControl Anti-SARS-CoV-2 tested at 3 test sites, with all 3 lots tested at each site in 2 runs per day for 5 days on **cobas** e 601 analyzers. The following results were obtained:

		Repeatibility		Reproducibility	
Sample	**Mean COI**	**SD**	**% CV**	**SD**	**% CV**
PreciControl ACOV2 1	0.101	0.004	3.52	0.007	6.69
PreciControl ACOV2 2	2.79	0.038	1.38	0.064	2.30
Human Sample 3	0.086	0.003	3.67	0.007	7.57
Human Sample 4	0.516	0.007	1.27	0.019	3.67
Human Sample 5	2.53	0.036	1.44	0.080	3.14
Human Sample 6	7.39	0.106	1.44	0.341	4.61

Sample	**Mean COI**	**Between-Run**		**Between-Day**		**Between-Lot**		**Between-Site**	
		SD	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
PreciControl ACOV2 1	0.101	0.001	0.684	0.002	1.90	0.002	1.76	0.005	5.02
PreciControl ACOV2 2	2.79	0.018	0.636	0.030	1.06	0.037	1.32	0.009	0.326
Human Sample 3	0.086	0.002	1.83	0.002	1.92	0.002	2.19	0.005	5.66
Human Sample 4	0.516	0.003	0.492	0.007	1.34	0.016	3.09	0.003	0.546
Human Sample 5	2.53	0.014	0.543	0.033	1.29	0.050	1.99	0.035	1.38
Human Sample 6	7.39	0.027	0.366	0.087	1.17	0.287	3.88	0.120	1.63

Analytical specificity - Potential Cross-Reactivity

A study was conducted to evaluate the Elecsys Anti-SARS-CoV 2 assay for potential cross-reactivity.

Out of 1836 potentially cross-reacting samples, 8 samples showed false reactivity with the Elecsys Anti-SARS-CoV-2 assay. Among those, 2 out of 7 samples containing antibodies to MERS-CoV Glycoprotein, showed false positive results (2 out of 7). The following are results of samples grouped by indication.

Potential cross-reactants	**N of Samples Tested**	**Elecsys Anti-SARS-CoV-2 Results**	
		NR[A)]	**RX[B)]**
Common cold panel[C)]	40	40	0
Coronavirus panel[D)]	40	40	0
CMV (Cytomegalovirus) Antibodies	116	115	1
EBV (Epstein-Barr virus) Antibodies	105	103	2
Borrelia burgdorferi Antibodies	6	6	0
Chlamydia pneumoniae Antibodies	8	8	0
E. coli (anti-E. coli-reactive)	10	10	0
Neisseria gonorrhoeae infection	5	5	0
HAV (Hepatitis A virus) Antibodies	40	40	0
HBV (Hepatitis B virus) Antibodies	71	71	0
HCV (Hepatitis C virus) Antibodies	66	66	0
HEV (Hepatitis E virus) Antibodies	12	12	0
HIV (Human immunodeficiency virus) Antibodies	10	10	0
HSV-1 and HSV-2 (Herpes Simplex virus) Antibodies	24	24	0
HTLV (Human T-lymphotropic virus) Antibodies	6	6	0
Influenza vaccinees	25	25	0
Listeria Antibodies	6	6	0
Measles Antibodies	10	10	0

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Potential cross-reactants	N of Samples Tested	Elecsys Anti-SARS-CoV-2 Results	
		NR[A)]	RX[B)]
Mumps Antibodies	14	14	0
Parvovirus B19 Antibodies	30	30	0
Plasmodium falciparum (Malaria) Antibodies	8	8	0
Rubella Antibodies	12	12	0
Toxoplasma gondii Antibodies	8	8	0
Treponema pallidum (Syphilis) Antibodies	62	62	0
VZV (Varicella Zoster) Antibodies	30	30	0
AMA (anti-mitochondrial antibodies)	30	30	0
ANA (anti-nuclear antibodies)	26	26	0
SLE (systemic lupus erythematosus)	10	9	1
RA (rheumatoid arthritis)	10	10	0
Parainfluenza 1-3 IgG	31	31	0
Haemophilus influenzae B IgG	40	40	0
Candida albicans IgG	13	13	0
MERS-CoV Glycoprotein (S1) IgG	7	5	2
Enterovirus Antibodies	38	38	0
RSV (Respiratory syncytial virus) IgG	66	66	0
Bordetella pertussis IgG	34	34	0
Coronavirus HKU1 Antibodies	44	44	0
Coronavirus OC43 Antibodies	54	54	0
Coronavirus 229E Antibodies	57	57	0
Coronavirus NL63 Antibodies	44	44	0
EBV Nuclear Antigen (EBNA)	38	38	0
Mycoplasma pneumoniae IgG	54	54	0
C. pneumoniae IgG	47	47	0
C. trachomatis IgG	6	6	0
Influenza B Virus Antibodies	70	70	0
Influenza A Virus Antibodies	59	59	0
Dengue IgG	14	14	0
Parainfluenza 1-4 IgG	51	51	0
Adenovirus IgG	25	25	0
M. pneumoniae IgM	12	12	0
Legionella Antibodies	7	7	0
B. pertussis IgM	15	15	0
C. pneumoniae IgM	7	7	0
H. influenzae IgG	49	49	0
Metapneumovirus (MPV) IgG	15	15	0
M. tuberculosis IgG	15	15	0
Pneumocystis jirovecii IgG	15	15	0
Pseudomonas aeruginosa IgG	14	14	0
Staphylococcus epidermidis IgG	15	15	0
Streptococcus pneumoniae IgG	15	14	1
Streptococcus pyogenes IgG	15	14	1
SARS-CoV-1 IgG	10	10	0
Total	1836		

A) NR = non-reactive

B) RX = reactive

C) 40 potentially cross-reactive samples from individuals with common cold symptoms, collected before Dec 2019

D) 40 potentially cross-reactive samples from individuals following an infection with Coronavirus HKU1, NL63, 229E or OC43, confirmed by PCR

Matrix Comparison

Studies were conducted to verify the types of blood collection tubes that can be used with the Elecsys Anti-SARS-CoV-2 assay. Samples were collected into matched serum (reference) and plasma collection tubes from 60 donors and assayed in singlicate with the Elecsys Anti-SARS-CoV-2 assay on the **cobas** e 601 immunoassay analyzer. 60 matched pairs were collected in the evaluation of each of the following blood collection tubes:

- K_2-EDTA
- K_3-EDTA
- Li-heparin

Statistical evaluations were performed to analyze the COI data for overall bias using orthogonal linear regression. Summary of the results is included below:

Sample type	Slope (95 % CI)	Intercept (95 % CI)	Correlation Coefficient (R)
K_2-EDTA plasma	1.002 (0.989 ; 1.015)	-0.056 (-0.126 ; 0.014)	1.000
K_3-EDTA plasma	0.988 (0.961 ; 1.016)	-0.088 (-0.235 ; 0.060)	1.000
Li-heparin plasma	0.995 (0.982 ; 1.008)	0.017 (-0.055 ; 0.090)	0.999

References

1 Su S, Wong G, Shi W, et al. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol 2016;24(6):490-502.

2 Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382(8):727-733.

3 Centers for Disease Control and Prevention. Scientific Brief: SARS-CoV-2 Transmission. [Internet; updated 2021 May 7; cited 2023 Jan 20]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html.

4 Bak A, Mugglestone MA, Ratnaraja NV, et al. SARS-CoV-2 routes of transmission and recommendations for preventing acquisition: joint British Infection Association (BIA), Healthcare Infection Society (HIS), Infection Prevention Society (IPS) and Royal College of Pathologists (RCPath) guidance. J Hosp Infect. 2021;114:79-103.

5 Jackson CB, Farzan M, Chen B, et al. Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol. 2022;23:3–20.

6 Pizzato M, Baraldi C, Boscato Sopetto G, et al. SARS-CoV-2 and the Host Cell: A Tale of Interactions. Front. Virol. 2021;1:815388.

7 Wu Y, Kang L, Guo Z, et al. Incubation Period of COVID-19 Caused by Unique SARS-CoV-2 Strains: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5:e2228008.

8 World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions [Internet; updated 2020 July 9; cited 2023 Jan 20]. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions.

9 Centers of Disease Control and Prevention. CDC Updates and Shortens Recommended Isolation and Quarantine Period for General Population. [Internet; updated 2021 Dec 27; cited 2023 Jan 20]. Available from: https://www.cdc.gov/media/releases/2021/s1227-isolation-quarantine-guidance.html.

10 Methi F, Madslien EH. Lower transmissibility of SARS-CoV-2 among asymptomatic cases: evidence from contact tracing data in Oslo, Norway. BMC Med. 2022;20:427.

11 National Institute of Health. Clinical Spectrum of SARS-CoV-2 Infection [Internet; updated 2022 Sep 26; cited 2023 Jan 20]. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum.

12 Ramadori GP. SARS-CoV-2-Infection (COVID-19): Clinical Course, Viral Acute Respiratory Distress Syndrome (ARDS) and Cause(s) of Death. Med Sci. 2022;10:58.

13 Christensen BB, Azar MM, Turbett SE. Laboratory Diagnosis for SARS-CoV-2 Infection. Infect Dis Clin North Am. 2022;36:327-347.

14 Qu J, Wu C, Li X, et al. Profile of immunoglobulin G and IgM antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71:2255-8.

15 Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465-469.

16 Iyer AS, Jones FK, Nodoushani A, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol. 2020;5.

17 To K, Tsang O, Leung W, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020;20:565-574.

18 Long Q-X, Liu B-Z, Deng H-J, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020 Apr 29.

19 Zhao J, Yuan Q, Wang H, et al. Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. Clin Infect Dis. 2020;71:2027-2034.

20 Okba N, Müller MA, Li W, et al. Severe Acute Respiratory Syndrome Coronavirus 2–Specific Antibody Responses in Coronavirus Disease Patients. Emerg Infect Dis. 2020;26:1478-1488.

21 Sun B, Feng Y, Mo X, et al. Kinetics of SARS-CoV-2 specific IgM and IgG responses in COVID-19 patients. Emerg Microbes Infect. 2020;9:940-948.

22 Zhang G, Nie S, Zhang Z, et al. Longitudinal Change of Severe Acute Respiratory Syndrome Coronavirus 2 Antibodies in Patients with Coronavirus Disease 2019. J Infect Dis. 2020;222:183-188.

23 Krutikov M, Palmer T, Tut G, et al. Prevalence and duration of detectable SARS-CoV-2 nucleocapsid antibodies in staff and residents of long-term care facilities over the first year of the pandemic (VIVALDI study): prospective cohort study in England. Lancet Healthy Longev. 2022;3:e13-e21.

24 Zeng F, Wu M, Wang J, et al. Over 1-year duration and age difference of SARS-CoV-2 antibodies in convalescent COVID-19 patients. J Med Virol. 2021;93:6506-11.

25 Abbas A, Lichtman A, and Pillai S. B Cell Activation and Antibody Production. In: Cellular and Molecular Immunology. 10th ed. Elsevier; 2021.

26 Benner SE, Patel EU, Laeyendecker O, et al. SARS-CoV-2 Antibody Avidity Responses in COVID-19 Patients and Convalescent Plasma Donors. J Inf Dis. 2020;222:1974–198.

27 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

28 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

29 Centers for Disease Control and Prevention (CDC). People Who Are Immunocompromised. Updated 19 October 2022. Available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html. Accessed 16 November 2022.

30 Centers for Disease Control and Prevention (CDC). COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised. Updated 11 June 2025. Available at https://www.cdc.gov/covid/vaccines/immunocompromised-people.html Accessed 18 July 2025.

31 Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. Int J Pharmacokinet 2017;2:247-256, Future Science Ltd London, UK. cited 2018 Jan 1. Available from: http://www.future-science.com/doi/10.4155/ipk-2017-0013

32 Piketty ML, Prie D, Sedel F, et al. High-dose biotin therapy leading to false biochemical endocrine profiles: validation of a simple method to overcome biotin interference. Clin Chem Lab Med 2017;55(6):817-825.

Additional information

For further information, refer to the appropriate User Guide for the corresponding analyzer, to the corresponding application sheets, and to the Method Sheets of all necessary components.

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Elecsys Anti-SARS-CoV-2

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Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany
www.roche.com
+800 5505 6606

Roche Diagnostics
9115 Hague Road
Indianapolis, IN 46256, USA
+1 800 428 2336