Elecsys® Anti-SARS-CoV-2 S

Immunoassay for the semi-quantitative determination of antibodies to the SARS-CoV-2 spike protein

Summary

SARS-CoV-2, the causative agent of Coronavirus Disease 2019 (COVID-19), is an enveloped, single-stranded RNA Beta-coronavirus. Seven coronaviruses have been identified as agents of human infection, causing disease ranging from mild common cold to severe respiratory failure.[1]

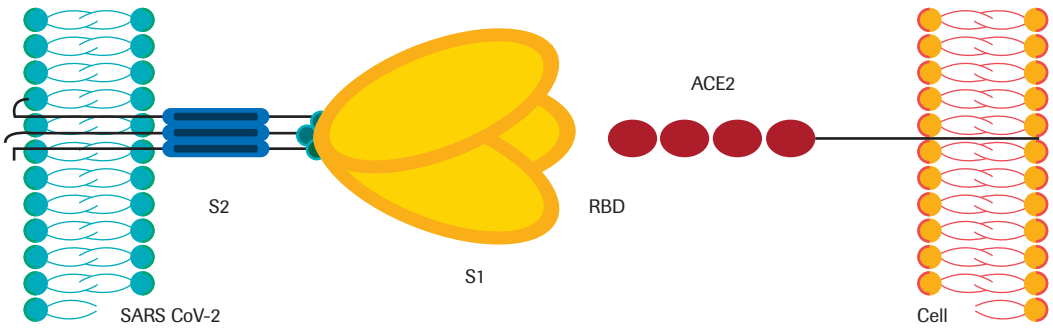
SARS-CoV-2 is transmitted primarily from person-to-person through respiratory droplets and aerosols.[2,3] The incubation period from infection to detectable viral load in the host commonly ranges from two to 14 days.[4,5] Detection of viral load can be associated with the onset of clinical signs and symptoms, although a considerable proportion of individuals remain asymptomatic or mildly symptomatic.[6–8] The interval during which an individual with COVID-19 is infectious has not yet been clearly established, however, transmission from symptomatic, asymptomatic, and pre-symptomatic individuals has been well described.[9–11]

Coronavirus genomes encode 4 main structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N).

The S protein is a very large transmembrane protein that assembles into trimers to form the distinctive surface spikes of coronaviruses. Each S monomer consists of an N-terminal S1 subunit and a membrane-proximal S2 subunit. The virus gains entry to the host cell through binding of the S protein to the angiotensin-converting enzyme 2 (ACE2) receptor, which is present on the surface of numerous cell types including the alveolar type II cells of the lung and epithelial cells of the oral mucosa.[12,13] Mechanistically, ACE2 is engaged by the receptor-binding domain (RBD) on the S1 subunit.[14,15]

Upon infection with SARS-CoV-2, the host usually mounts an immune response against the virus, typically including production of specific antibodies against viral antigens. IgM and IgG antibodies against SARS-CoV-2 appear to arise nearly simultaneously in blood.[16] There is significant inter-individual difference in the levels and chronological appearance of antibodies in COVID-19 patients, but median seroconversion has been observed at approximately two weeks.[17–20]

Structure of the SARS-CoV-2 spike protein and binding to host receptor

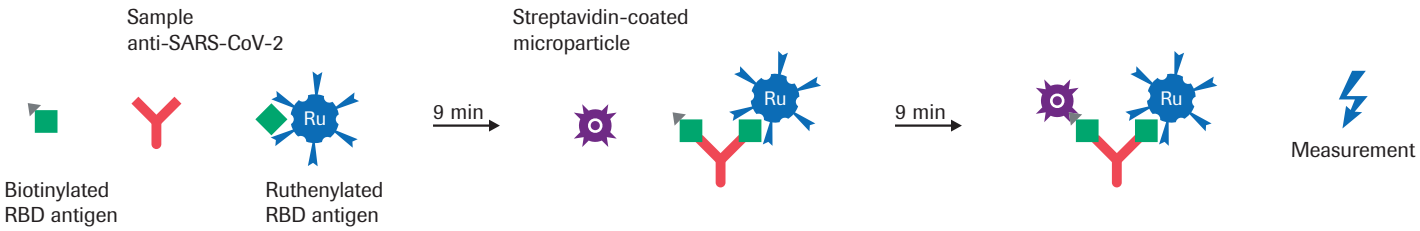


After infection or vaccination, the binding strength of antibodies to antigens increases over time – a process called affinity maturation[21]. High-affinity antibodies can elicit neutralization by recognizing and binding specific viral epitopes[22,23]. Antibodies against SARS-CoV-2 with strong neutralizing capacity, especially potent if directed against the RBD, have been identified.[24–27] Numerous vaccines for COVID-19 are in development, many of which focus on eliciting an immune response to the RBD.[28–30]

Elecsys® Anti-SARS-CoV-2 S for use on the cobas e analzyers is an electrochemiluminescence immunoassay intended for qualitative and semi-quantitative detection of antibodies to SARS-CoV-2 spike (S) protein receptor binding domain (RBD) in human serum and plasma. The assay uses a recombinant protein representing the RBD of the S antigen in a double-antigen sandwich assay format, which favors detection of high affinity antibodies against SARS-CoV-2. The Elecsys Anti-SARS-CoV-2 S assay is intended as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection.[31]

Electro-chemiluminescence immunoassay (ECLIA)

Test principle: double-antigen sandwich assay (testing time: 18 minutes)[31]



Step 1 (9 minutes)
20 µL* / 12 µL** of the patient sample are incubated with a mix of biotinylated and ruthenylated RBD antigen. Double-antigen sandwich immune complexes are formed in the presence of corresponding antibodies.

Step 2 (9 minutes)
After addition of streptavidin-coated microparticles, the DAGS complexes bind to the solid phase via interaction of biotin and streptavidin.

Step 3 (measurement)
The reagent mixture is transferred to the measuring cell, where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are subsequently removed. Electrochemiluminescence is then induced by applying a voltage and measured with a photomultiplier. The signal yield increases with the antibody titer.

* **cobas e** 411 analyzer and **cobas e** 601/602 modules
** **cobas e** 801 module

Elecsys® Anti-SARS-CoV-2 S assay characteristics[31]

Systems	**cobas e** 411 analyzer **cobas e** 601 / **cobas e** 602 modules	**cobas e** 801 module
Testing time	18 minutes	
Test principle	One-step double antigen sandwich assay	
Traceability	Internal Roche standard for anti-SARS-CoV-2-S consisting of monoclonal antibodies. 1 nM of these antibodies correspond to 20 U/mL of the Elecsys® Anti-SARS-CoV-2 S assay	
Linear range	0.4 to 250 U/mL	
Calibration	2-point (separate CalSet)	
Interpretation	<0.8 U/mL = negative, ≥0.8 U/mL = positive	
Specimen types	Serum collected using standard sampling tubes or tubes containing separating gel; Li-heparin, K_2-EDTA-, K_3-EDTA-, and sodium citrate plasma; Plasma tubes containing separating gel can be used	
Sample volume	20 µL	12 µL
Onboard stability	14 days	
Intermediate precision in positive samples	**cobas e** 411 analyzer: CV* 1.9 – 2.9 % **cobas e** 601 / **cobas e** 602 modules: CV 2.3 – 3.6 %	CV 1.4 – 2.4 %

Clinical Positive Percent Agreement[31]

A total of 1,485 samples from 331 symptomatic patients (including 172 samples from 172 hospitalized patients) with a PCR confirmed SARS-CoV-2 infection were tested with the Elecsys® Anti-SARS-CoV-2 S assay. One or more sequential samples from these patients were collected at various time points after PCR confirmation. Positive percent agreement (PPA) was correlated with days post PCR specimen collection, and the results are shown for the first bleed per time bin.

233 of the tested samples had a sampling date of 15 days or later after diagnosis with PCR. 225 of these 233 samples were determined with ≥ 0.8 U/mL in the Elecsys Anti-SAR-CoV-2 S assay and hence considered positive, resulting in a PPA of 96.6% (95% CI: 93.35 98.51%) in this sample cohort.

Days post PCR confirmation	N	Non-reactive	PPA (95 % CI*)
0 – 7 days	32	3	**90.6 %** (75.0 – 98.0 %)
8 – 14 days	77	10	**87.0 %** (77.4 – 93.6 %)
≥ 15 days	233	8	**96.6 %** (93.4 – 98.5 %)

*confidence interval

Further PPA analysis is possible for patients with additional samples collected ≥ 15 days after a PCR confirmed SARS-CoV-2 infection. PPA is shown for the first collected timepoint in each of the following additional time bins: 15-21 days, 22-28 days, 29-35 days, and ≥ 36 days[32].

Days post PCR confirmation	N	Non-reactive	PPA (95 % CI*)
15 – 21 days	82	7	**91.5 %** (83.2 – 96.5 %)
22 – 28 days	142	1	**99.3 %** (96.1 – 100.0 %)
29 - 35 days	129	0	**100.0 %** (97.2 – 100.0 %)
≥ 36 days	145	0	**100.0%** (97.5 – 100.0 %)

*confidence interval

Analytical specificity[31]

A total of 1,100 potentially cross-reactive samples collected before October 2019, including anti-MERS-CoV positive samples, samples from individuals with common cold symptoms, and samples from individuals confirmed to be infected with one of the four common cold coronaviruses were tested with the Elecsys® Anti-SARS-CoV-2 S assay. Overall specificity in this cohort of potentially cross-reactive samples was **100 % (95 % CI: 99.7 – 100 %).**

Cohort	N	Reactive	Specificity (95 % CI)
MERS-CoV*	7	0	**100 %** (59.0 – 100 %)
Common cold panel**	21	0	**100 %** (83.4 – 100 %)
Coronavirus panel***	94	0	**100 %** (96.2 – 100 %)
Other potentially cross-reactive samples****	978	0	**100 %** (99.6 – 100 %)
Overall	**1,100**	**0**	**100 % (99.7 – 100 %)**

* positive for IgG antibodies against the Middle East respiratory syndrome-related coronavirus (MERS-CoV) spike protein subunit S1

** samples from individuals with common cold symptoms, collected before October 2019

*** from individuals with past infection with coronavirus HKU1, NL63, 229E, or OC43, confirmed by antigen testing

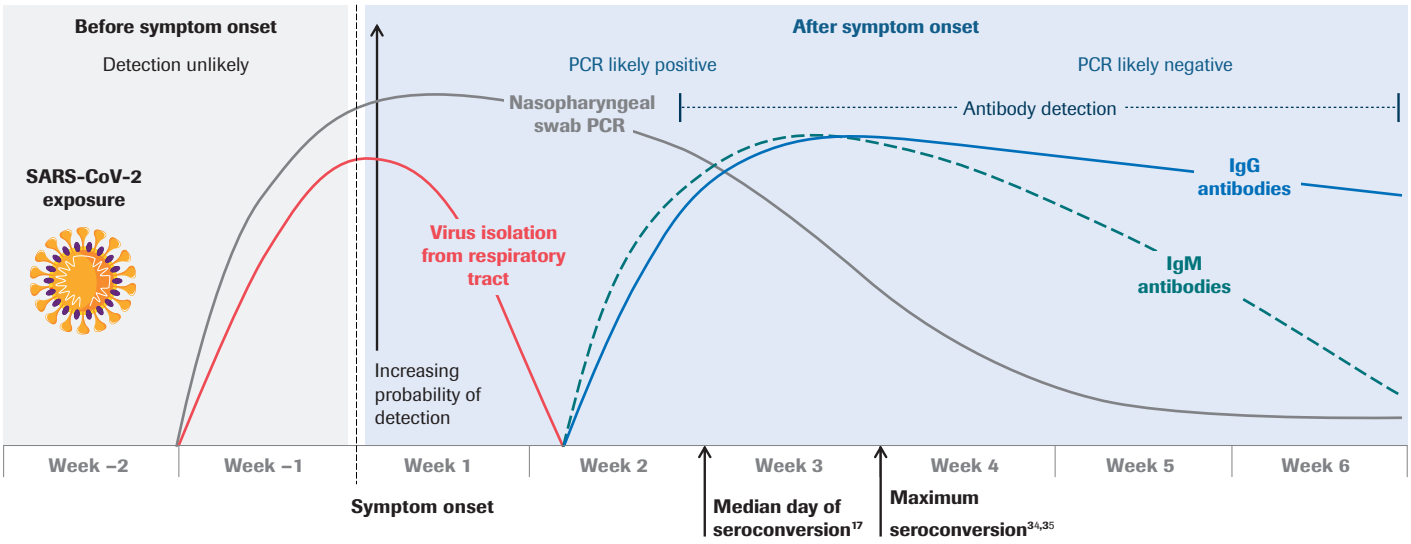
**** pre-pandemic samples with reactivity for various other indications, which could have an elevated potential for unspecific interference

Negative Percent Agreement (NPA)[31]

A total of 5,991 samples from diagnostic routine and blood donors drawn before October 2019 were tested with the Elecsys® Anti-SARS-CoV-2 S assay. Overall NPA in this cohort of potentially cross-reactive samples was **99.98 % (95 % CI: 99.91 – 100 %).**

Cohort	N	Reactive	NPA (95 % CI) 100 %
Diagnostic routine	2,528	0	(99.85 – 100 %)
US blood donors	2,713	1	99.96 % (99.79 – 100 %)
African blood donors	750	0	100 % (99.51 – 100 %)
Overall	**5,991**	**1**	**99.98 % (99.91 – 100 %)**

Estimated course of markers in SARS-CoV-2 infection[33]



Ordering information

Product	Material configuration	Material number
Elecsys® Anti-SARS-CoV-2 S a)	200 tests	09289267190
Elecsys® Anti-SARS-CoV-2 S b)	300 tests	09289275190
Calset Anti-SARS-CoV-2 S ab)	4 × 1.0 mL	09289291190
PreciControl Anti-SARS-CoV-2 S ab)	4 × 1.0 mL	09289313190
CalCheck Anti-SARS-CoV-2 S ab)	5 × 1.0 mL	09290702190

a) for use on the **cobas e** 411 analyzer and the **cobas e** 601/602 modules
b) for use on the **cobas e** 801 module

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- Not for screening of donated blood
- This test has not been FDA cleared or approved
- This test has been authorized by FDA under an EUA for use by authorized laboratories
- This test has been authorized only for detecting the presence of antibodies against SARS-CoV-2, not for any other viruses or pathogens
- This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb- 3(b)(1), unless the authorization is terminated or revoked sooner

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