Ordering information

Product	Material configuration	Material number
Elecsys® Anti-SARS-CoV-2 a)	200 tests	09 203 095 190
Elecsys® Anti-SARS-CoV-2 b)	300 tests	09 203 079 190
PreciControl Anti-SARS-CoV-2	4 × 1.0 mL	09 216 928 190
Diluent MultiAssay* a)	2 × 16 mL	03 609 987 190
Diluent MultiAssay* b)	45.2 mL	07 299 010 190

* optionally required for the preparation of positive control material from positive sample
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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Elecsys® Anti-SARS-CoV-2

Immunoassay for the qualitative detection of antibodies against SARS-CoV-2

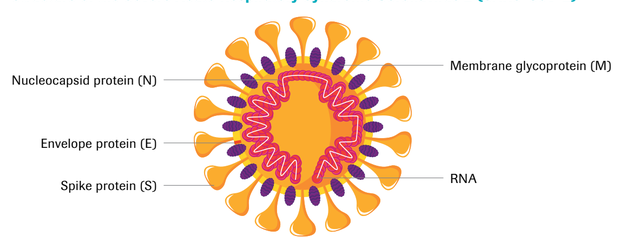
Summary
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus of the family Coronaviridae. Coronaviruses share structural similarities and are composed of 16 nonstructural proteins and 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). Coronaviruses cause diseases with symptoms ranging from those of a mild common cold to more severe ones such as Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2[1,2].

SARS-CoV-2 is transmitted from person-to-person primarily via respiratory droplets, while indirect transmission through contaminated surfaces is also possible[3-6]. The virus accesses host cells via the angiotensin-converting enzyme 2 (ACE2), which is most abundant in the lungs[7,8].

The incubation period for COVID-19 ranges from 2 – 14 days following exposure, with most cases showing symptoms approximately 4 – 5 days after exposure[3,9,10]. The spectrum of symptomatic infection ranges from mild (fever, cough, fatigue, loss of smell and taste, shortness of breath) to critical[11,12]. While most symptomatic cases are not severe, severe illness occurs predominantly in adults with advanced age or underlying medical comorbidities and requires intensive care. Acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease. Critical cases are characterized by e.g., respiratory failure, shock and/or multiple organ dysfunction, or failure[11,13,14].

Definite COVID-19 diagnosis entails direct detection of SARS-CoV-2 RNA by nucleic acid amplification technology (NAAT)[21-23]. Serological assays, which detect antibodies against SARS-CoV-2, can contribute to identify individuals, which were previously infected by the virus, and to assess the extent of exposure of a population. They might thereby help to decide on application, enforcement or relaxation of containment measures[24].

Structure of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)



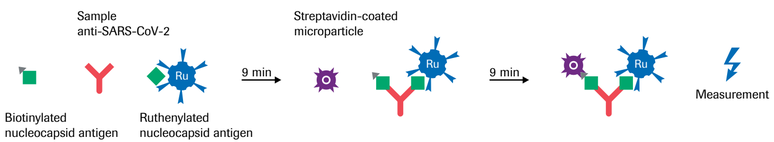
Upon infection with SARS-CoV-2, the host mounts an immune response against the virus, including production of specific antibodies against viral antigens. Both IgM and IgG have been detected as early as day 5 after symptom onset[25,26]. Median seroconversion has been observed at day 10 – 13 for IgM and day 12 – 14 for IgG[27-29], while maximum levels have been reported at week 2 – 3 for IgM, week 3 – 6 for IgG and week 2 for total antibody[25-31]. Whereas IgM seems to vanish around week 6 – 7[32,33], high IgG seropositivity is seen at that time[25,32,33]. While IgM is typically the major antibody class secreted to blood in the early stages of a primary antibody response, levels and chronological order of IgM and IgG antibody appearance seem to be highly variable for SARS-CoV-2. Anti-SARS-CoV-2 IgM and IgG often appear simultaneously, and some cases have been reported where IgG appears before IgM, limiting its diagnostic utility[26,27,29,34,35].

After infection or vaccination, the binding strength of antibodies to antigens increases over time – a process called affinity maturation[36]. High-affinity antibodies can elicit neutralization by recognizing and binding specific viral epitopes[37,38]. In SARS-CoV-2 infection, antibodies targeting both the spike and nucleocapsid proteins, which correlate with a strong neutralizing response, are formed as early as day 9 onwards, suggesting seroconversion may lead to protection for at least a limited time[34,39-42].

Elecsys® Anti-SARS-CoV-2 is an immunoassay for the in vitro qualitative detection of antibodies (including IgG) to SARS-CoV-2 in human serum and plasma. The assay uses a recombinant protein representing the nucleocapsid (N) antigen in a double-antigen sandwich assay format, which favors detection of high affinity antibodies against SARS-CoV-2. Elecsys® Anti-SARS-CoV-2 detects antibody titers, which have been shown to positively correlate with neutralizing antibodies in neutralization assays[43, 44]. The test is intended as an aid in the determination of the immune reaction to SARS-CoV-2.[45]

Electro-chemiluminescence immunoassay (ECLIA)

Test principle: double-antigen sandwich assay (testing time: 18 minutes)[45]



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

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

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.

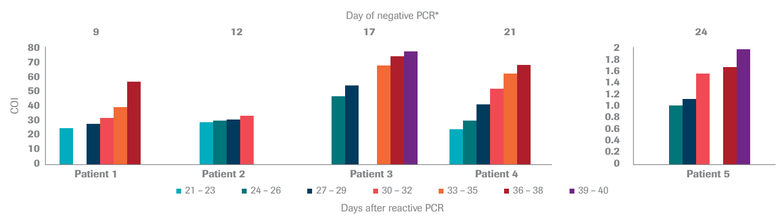
Elecsys® Anti-SARS-CoV-2 assay characteristics

Systems	**cobas e** 411 analyzer **cobas e** 601 / **cobas e** 602 modules	**cobas e** 801 module
Testing time	18 minutes	
Calibration	2-point	
Result interpretation	COI* <1.0 = non-reactive COI ≥1.0 = reactive	
Sample material	Serum collected using standard sampling tubes or tubes containing separating gel. Li-heparin, K_2-EDTA and K_3-EDTA plasma as well as Li-heparin and K_2-EDTA plasma tubes containing separating gel. Capillary blood collected in serum, Li-heparin or K_2-EDTA sampling tubes	
Sample volume	20 µL	12 µL
Onboard stability	14 days	
Intermediate precision in positive samples	**cobas e** 411 analyzer: CV** 4.2 – 5.7 % **cobas e** 601 / **cobas e** 602 modules: CV 2.3 – 6.5 %	CV 2.1 – 4.5 %

* cutoff index; ** coefficient of variation

Seroconversion sensitivity[45]

After recovery from infection, confirmed by a negative PCR result, 26 sequential samples from 5 individuals were tested with the Elecsys® Anti-SARS-CoV-2 assay.



* Day 0 represents initial positive PCR

Clinical sensitivity[45]

A total of 496 samples from 102 symptomatic patients with a PCR confirmed SARS-CoV-2 infection were tested with the Elecsys® Anti-SARS-CoV-2 assay. One or more sequential specimens from these patients were collected after PCR confirmation at various time points.

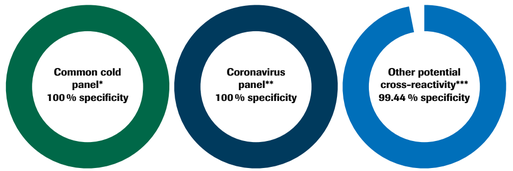
Days post PCR confirmation	N	Non-reactive	Sensitivity (95 % CI**)
0 – 6 days	161	64	60.2 % (52.3 – 67.8 %)
7 – 13 days	150	22	85.3 % (78.6 – 90.6 %)
≥14 days	185	1*	99.5 % (97.0 – 100 %)

* 1 patient was non-reactive at day 14 (0.696 COI) but reactive at day 16 (4.48 COI); ** confidence interval

Analytical specificity[45]

Overall specificity in a cohort of 792 potentially cross-reactive samples was **99.5 % (95 % CI: 98.63 – 99.85 %).**

* 40 samples from individuals with common cold symptoms, collected before Dec 2019
** 40 samples from individuals following an infection with Coronavirus HKU1, NL63, 229E or OC43, confirmed by PCR
*** N=712



Clinical specificity[45]

A total of 10,453 samples from diagnostic routine and blood donors obtained before December 2019 were tested with the Elecsys® Anti-SARS-CoV-2 assay.

Cohort	N	Reactive	Specificity % (95 % CI)
Diagnostic routine	6,305	12	99.81 % (99.67 – 99.90 %)
Blood donors	4,148	9	99.78 % (99.59 – 99.90 %)
Overall	**10,453**	**21**	**99.80 % (99.69 – 99.88 %)**

Correlation to serum neutralization[45]

The Elecsys® Anti-SARS-CoV-2 assay was compared to a VSV-based pseudo-neutralization assay[46] in 46 clinical samples from individual patients.

		Pseudo-NT*	
		Positive	**Negative**
Elecsys® Anti-SARS-CoV-2	**Reactive**	38	0
	Non-reactive	6	2
Percent Positive Agreement	86.4 % (95 % CI 73.3 % – 93.6 %)		
Percent Negative Agreement	100 % (95 % CI: 34.2 – 100 %)		
Percent Overall Agreement	87.0 % (95 % CI 74.3 % – 93.9 %)		

* A titer of 1:20 was used as the positive cut-off for the pseudo-NT assay.

Estimated course of markers in SARS-CoV-2 infection[47]