BECKMAN COULTER

ACCESS
Immunoassay Systems

Instructions For Use

ACCESS SARS-CoV-2 IgG II
SARS-CoV-2 IgG

REF C69057

FOR PROFESSIONAL USE ONLY

For *In Vitro* Diagnostic Use

FOR USE ON ACCESS FAMILY OF IMMUNOASSAY SYSTEMS

PRINCIPLE

CAUTION

The concentration of SARS-CoV-2 IgG in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. Values obtained with different assay methods should not be used interchangeably.

The results of this semi-quantitative test should not be interpreted as an indication or degree of immunity or protection from reinfection.

INTENDED USE

The Access SARS-CoV-2 IgG II assay is a paramagnetic particle, chemiluminescent immunoassay intended for the semi-quantitative and qualitative determination of IgG antibodies to SARS-CoV-2 in human serum, serum separator tubes and plasma (EDTA, citrate and heparin) using the Access Immunoassay Systems.

The Access SARS-CoV-2 IgG II assay is intended for use as an aid in diagnosis of SARS-CoV-2 infection and as an aid in identifying patients with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection in conjunction with clinical presentation and other laboratory tests. Results of the Access SARS-CoV-2 IgG II assay should not be used as the sole basis for diagnosis of SARS-CoV-2 infection.

SUMMARY AND EXPLANATION

Coronavirus disease-2019 (COVID-19) is caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has spread worldwide in 2020 causing a global pandemic. COVID-19 is characterized by fatigue, fever, cough, shortness of breath and other respiratory symptoms.[1] The virus uses the transmembrane receptor angiotensin-converting enzyme 2 (ACE-2) to infect epithelial cells in the airways and lungs.[2] Some individuals infected with SARS-CoV-2 have no, or mild symptoms while others develop severe respiratory distress requiring mechanical ventilation.[3] Infected individuals develop an immune response to the virus in the form of anti-SARS-CoV-2 IgM and IgG antibodies over the course of days to weeks.[4] Testing for the presence of IgM/IgG antibodies to SARS-CoV-2 can help to inform clinical management of patients with current, or recent COVID-19.

Evidence shows that recovered COVID-19 patients can generate immunoglobulin G (IgG)-type antibodies specifically binding to various structure proteins of SARS-CoV-2 after the onset of disease, at variable levels.[5,6,7] A significant correlation between severity of illness and neutralizing antibody titers specific to the receptor binding domain (RBD) of the S1 protein has been identified.[8,9,10]

Multiple laboratories and companies are working to rapidly develop vaccine candidates in a short period of time employing vaccine strategies targeting the RBD of the S1 protein[10,11,12] with initial data indicating that an antibody response from

this region may be neutralizing to SARS-CoV-2. The ability to identify neutralizing antibodies to the RBD of the S1 protein may prove to be an important tool to study the immune response of SARS-CoV-2.

METHODOLOGY

The Access SARS-CoV-2 IgG II assay is a two-step enzyme immunoassay. A sample is added to a reaction vessel with buffer, and paramagnetic particles coated with recombinant SARS-CoV-2 protein specific for the receptor binding domain (RBD) of the S1 protein.[8] After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. A monoclonal anti-human IgG alkaline phosphatase conjugate is added and the conjugate binds to the IgG antibodies captured on the particles. A second separation and wash step remove unbound conjugate. A chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of SARS-CoV-2 IgG antibody in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

SPECIMEN

SPECIMEN STORAGE AND STABILITY

Stability				
Specimen	**Type**	**20°C to 25°C (hours)**	**2°C to 8°C (days)**	**-20°C or colder (days)**
Serum	Serum separator tube	48	7	30
Plasma	Heparin EDTA Citrate	48	7	30

Do not thaw samples more than two times.

SPECIMEN COLLECTION AND PREPARATION

Blood Specimen

1. The role of preanalytical factors in laboratory testing has been described in a variety of published literature.[13,14] To minimize the effect of preanalytical factors observe the following recommendations for handling and processing blood samples:[13]
   A. Collect all blood samples observing routine precautions for venipuncture.
      a. Follow blood collection tube manufacturer's recommendations for centrifugation.
      b. Ensure residual fibrin and cellular matter has been removed prior to analysis.
   B. Allow serum samples to clot completely before centrifugation in a vertical position, with the collection tube closure directed upwards.
      a. Follow the tube manufacturer's recommendations for the length of serum/cells contact time before centrifuging samples. The clotting may be slower at cooler temperatures, or if the patient is on anticoagulant therapy.
2. Each laboratory should determine the acceptability of its own blood collection tubes and separation products that are in use. There may be variations in these products between manufacturers and between manufacturing lots.
3. Alternate collection types may be appropriate if the laboratory has established its own performance characteristics as defined by applicable law.
4. Avoid assaying lipemic or hemolyzed samples.

REAGENTS

CONTENTS

Access SARS-CoV-2 IgG II Reagent Pack

Ref. No. C69057, 200 determinations, 2 packs, 100 tests/pack

Well	Ingredients
R1a:	Paramagnetic particles coated with recombinant SARS-CoV-2 protein in TRIS buffer with surfactant, protein (bovine), < 0.1% sodium azide and 0.1% ProClin* 300.
R1b:	MES buffer, surfactant, protein (bovine), < 0.1% sodium azide and 0.1% ProClin 300.
R1c:	MES buffer, mouse monoclonal anti-human IgG antibody alkaline phosphatase conjugate, surfactant, protein (bovine), < 0.1% sodium azide and 0.1% ProClin 300.
R1d:	TRIS buffer, surfactant, protein (bovine), < 0.1% sodium azide and 0.1% ProClin 300.
R1e:	TRIS buffer, surfactant, protein (bovine), < 0.1% sodium azide and 0.1% ProClin 300.

*ProClin™ is a trademark of The Dow Chemical Company (“Dow”) or an affiliated company of Dow.

WARNING AND PRECAUTIONS

- For *in vitro* diagnostic use.
- Samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices,[15] regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- For hazards presented by the product refer to the following sections: REACTIVE INGREDIENTS and GHS HAZARD CLASSIFICATION.

REACTIVE INGREDIENTS

⚠ CAUTION

Sodium azide preservative may form explosive compounds in metal drain lines. See NIOSH Bulletin: Explosive Azide Hazard (8/16/76).
To avoid the possible build-up of azide compounds, flush wastepipes with water after the disposal of undiluted reagent. Sodium azide disposal must be in accordance with appropriate local regulations.

GHS HAZARD CLASSIFICATION

SARS-CoV-2 IgG II Particles (Compartment R1a) — WARNING

H317 — May cause an allergic skin reaction.

	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
SARS-CoV-2 IgG II Conjugate Diluent (Compartment R1b)	WARNING	
		
	H317	May cause an allergic skin reaction.
	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
SARS-CoV-2 IgG II Conjugate (Compartment R1c)	WARNING	
		
	H317	May cause an allergic skin reaction.
	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
SARS-CoV-2 IgG II Ancillary Diluent (Compartment R1d)	WARNING	

H316	Causes mild skin irritation.
H317	May cause an allergic skin reaction.
H319	Causes serious eye irritation.
H412	Harmful to aquatic life with long lasting effects.
P273	Avoid release to the environment.
P280	Wear protective gloves, protective clothing and eye/face protection.
P332+P313	If skin irritation occurs: Get medical advice/attention.
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P337+P313	If eye irritation persists: Get medical advice/attention.
P362+P364	Take off contaminated clothing and wash it before use.
	Ethoxylated lauryl alcohol 1 - < 3%
	reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%

SARS-CoV-2 IgG II Ancillary Diluent (Compartment R1e)

WARNING

H316	Causes mild skin irritation.
H317	May cause an allergic skin reaction.
H319	Causes serious eye irritation.
H412	Harmful to aquatic life with long lasting effects.
P273	Avoid release to the environment.
P280	Wear protective gloves, protective clothing and eye/face protection.
P332+P313	If skin irritation occurs: Get medical advice/attention.
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P337+P313	If eye irritation persists: Get medical advice/attention.
P362+P364	Take off contaminated clothing and wash it before use.
	Ethoxylated lauryl alcohol 1 - < 3%
	reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%

SDS	Safety Data Sheet is available at beckmancoulter.com/techdocs

MATERIALS NEEDED BUT NOT SUPPLIED WITH REAGENT KIT

1. Access SARS-CoV-2 IgG II Calibrator
   Provided as zero and approximately 5.0, 25.0, 100, 200 and 450 AU/mL
   Ref. No. C69058
2. QC (Quality Control) materials: Access SARS-CoV-2 IgG II QC
   Ref. No. C69059
3. Access Sample Diluent A
   Ref. No. 81908
   Diluent Pack Ref. No. A79783 (for use with the UniCel DxI system onboard dilution feature.)
4. Access Substrate
   Ref. No. 81906
5. Access Wash Buffer II, Ref. No. A16792
   UniCel DxI Wash Buffer II, Ref. No. A16793

REAGENT PREPARATION

Provided ready to use.

REAGENT STORAGE AND STABILITY

Stability	
Unopened at 2°C to 10°C	Up to stated Expiration Date
After opening at 2°C to 10°C	28 days

- Store upright.
- Refrigerate at 2°C to 10°C for a minimum of two hours before use on the instrument.
- Signs of possible deterioration are a broken elastomeric layer on the pack or quality control values out of range.
- If the reagent pack is damaged (e.g., a broken elastomer), discard the pack.
- Discard reagents if any discoloration is observed.

CALIBRATION

CALIBRATION INFORMATION

An active calibration is required for all tests. For the SARS-CoV-2 IgG II assay, a calibration is required every 28 days. See calibrator Instructions for Use (IFU) for additional calibration information. Refer to the appropriate system manuals and/or Help system for information on calibration method, configuring calibrators, calibrator test request entry, and reviewing calibration data.

QUALITY CONTROL

Quality control materials simulate the characteristics of samples and are essential for monitoring the system performance of immunochemical assays. Include quality control materials in each 24-hour time period, or as required by individual

laboratory procedures, because samples may be processed at any time in a “random access” format rather than a “batch” format.

Include Access SARS-CoV-2 IgG II QC or other commercially available quality control materials that cover at least two levels of analyte.

More frequent use of quality controls or the use of additional controls is left to the discretion of the operator, based upon good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer’s instructions for reconstituting and storing controls. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results that were generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

TESTING PROCEDURE(S)

PROCEDURE

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
   A. The system default unit of measure for sample results is AU/mL.
2. Mix the contents of a new (unpunctured) reagent pack by gently inverting the pack several times before loading it on the instrument. Do not invert an open (punctured) pack.
3. Use twenty (20) µL of sample for each determination in addition to the sample container and system dead volumes when requesting the Access SARS-CoV-2 IgG II assay. Use twenty-five (25) µL of sample in addition to the sample container and system dead volumes for each determination run with the DxI system onboard dilution feature (test name: dCOVG). Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.
   A. Select COVG as the test name for assaying samples containing SARS-CoV-2 IgG concentrations up to the concentration of the Access SARS-CoV-2 IgG II S5 calibrator.
   B. UniCel DxI users use the UniCel DxI onboard dilution feature (test name: dCOVG) for assaying samples containing SARS-CoV-2 IgG concentration greater than the Access SARS-CoV-2 IgG II S5 calibrator.

LIMITATIONS

1. Results obtained with the assay may not be used interchangeably with values obtained with different manufacturers’ test methods.
2. For assays that employ antibodies, the possibility exists for interference by heterophile antibodies in the test sample. Patients who are regularly exposed to animals, or are subjected to medical treatments that utilize immunoglobulins or immunoglobulin fragments, may produce human anti-animal antibodies, e.g. HAMA, that interfere with immunoassays. These interfering antibodies may cause erroneous results.
3. Other potential interferences could be present in the sample and may cause erroneous results in immunoassays. Some examples that are documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[16] Carefully evaluate results if the sample is suspected of having these types of interferences.
4. The Access SARS-CoV-2 IgG II assay results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests, and other appropriate information.
5. Results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform infection status.

6. Negative results do not preclude acute SARS-CoV-2 infection. IgG antibodies may not be detected in the first few days of infection; the sensitivity of the Access SARS-CoV-2 IgG II assay early after infection is unknown. If acute infection is suspected, direct testing for SARS-CoV-2 is necessary.
7. 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 an alternative serology test to confirm an immune response. Positive results may be due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as coronavirus HKU1, NL63, OC43, or 229E.

RESULTS INTERPRETATION

Test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data. The test results can be viewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

REPORTING RESULTS

Samples can be accurately measured within the analytical range of the lower limit of quantitation and the highest calibrators value (approximately 2.00 – 450 AU/mL).

- If a sample contains less than the lower limit of quantitation (LoQ) for the assay, report the result as less than that value (i.e. < 2.00 AU/mL). When the DxI system onboard dilution feature is used, the system will report results as less than 380 AU/mL.
- If a sample contains more than the stated value of the highest Access SARS-CoV-2 IgG II Calibrator (S5), report the result as greater than that value (> 450 AU/mL). Alternatively, dilute one volume of sample with nineteen volumes of Access Sample Diluent A.

Refer to the appropriate system manuals and/or Help system for instruction on entering a sample dilution in a test request. The system reports the results adjusted for the dilutions.

Onboard Dilution Feature for use on the UniCel DxI systems:

The DxI system onboard dilution feature automates the dilution process, using one volume of sample with nineteen volumes of Access Sample Diluent A, allowing samples to be quantitated up to approximately 8,000 AU/mL. The system reports the results adjusted for the dilution.

Result	Interpretation	Reporting Instructions
< 10 AU/mL SARS-CoV-2 IgG II	Non-Reactive	Report result as non-reactive with AU/mL for SARS-CoV-2 IgG antibodies
≥ 10 AU/mL SARS-CoV-2 IgG II	Reactive	Report result as reactive with AU/mL for SARS-CoV-2 IgG antibodies

PERFORMANCE CHARACTERISTICS

PERFORMANCE CHARACTERISTICS

CLINICAL SENSITIVITY

The clinical sensitivity of the Access SARS-CoV-2 IgG II assay was evaluated in 148 individual serum and plasma samples from symptomatic individuals collected between 3 and 131 days between symptom onset and blood sample draw diagnosed with SARS-CoV-2 by PCR methods from France and the United States. The results are presented in the following table, classified by days between symptom onset and the blood sample draw. The 95% confidence interval was determined by the Wilson Score method.

Days post symptom onset	Total Samples	Number Non-Reactive	Number Reactive	Clinical Sensitivity (95% CI)
0-7	11	2	9	81.8% (52.3-94.9%)
8-14	25	1	24	96.0% (80.5-99.3%)
15-60	92	1	91	98.9% (94.1-99.8%)
> 60	20	8	12	60.0% (38.7-78.1%)

In some patients, a decline in the antibody response over time has been observed following SARS-CoV-2 infection.[17,18]

CLINICAL SPECIFICITY

The clinical specificity of the Access SARS-CoV-2 IgG II assay was evaluated in a study of 1,448 samples collected prior to December 2019* in France and the United States. This total includes 1,028 samples from blood donors in France and 214 samples from routine clinical laboratory diagnostic samples in France and 206 samples from the United States. Based on this evaluation, the overall clinical specificity of the Access SARS-CoV-2 IgG II assay is 99.9% (1,446/1,448), with a 95% confidence interval of 99.5%-100.0% determined by the Wilson Score method.

Population	Total Samples	Number Non-Reactive	Number Reactive	Clinical Specificity (95% CI)
Blood Donors (France)	1,028	1,026	2	99.8% (99.3%-99.9%)
Diagnostic Samples (France)	214	214	0	100.0% (98.2%-100.0%)
Diagnostic Samples (United States)	206	206	0	100.0% (98.2%-100.0%)
Total	1,448	1,446	2	99.9% (99.5%-100.0%)

*It has been shown that over 90% of the adult population have antibodies to all four common circulating coronaviruses.[19,20]

LINEARITY

The Access SARS-CoV-2 IgG II assay demonstrated acceptable linearity throughout the analytical measuring range of 2.00 AU/mL to approximately 450 AU/mL. Based on CLSI EP06-A,[21] two high SARS-CoV-2 IgG samples (1 serum and 1 plasma), one moderate SARS-CoV-2 IgG sample (plasma) and two SARS-CoV-2 IgG low samples (1 serum and 1 plasma) were each diluted with a negative sample to make 9 discrete dilutions. Four replicates of each dilution and 8 replicates of the negative sample were tested on the Access 2 Immunoassay System.

INTERFERING SUBSTANCES

High concentrations of endogenous serum components were assessed for interference in the Access SARS-CoV-2 IgG II assay. The test protocol was based on CLSI EP07, Interference Testing in Clinical Chemistry, 3rd Edition.[22] Endogenous substances were spiked in two (2) plasma samples containing SARS CoV-2 IgG antibodies (one low and one moderate) and in one (1) negative serum. None of the substances tested demonstrated significant interference in the Access SARS-CoV-2 IgG II assay as defined by a shift is concentration greater than 20% using the test concentrations indicated in the table below.

Substance	Interferent Concentration Tested
Bilirubin (conjugated)	43 mg/dL
Bilirubin (unconjugated)	43 mg/dL
Hemoglobin	300 mg/dL
Triglycerides (Intralipid)	1,771 mg/dL

CROSS REACTIVITY

Cross-reactivity of the Access SARS-CoV-2 IgG II assay was evaluated by testing serum and plasma samples for each of the potentially cross-reacting conditions listed in the following table. No cross-reactivity was observed for the Access SARS-CoV-2 IgG II assay.

Category	Number of Samples	Number of Reactive Samples	Number of Non-Reactive Samples
Anti-Influenza A	5	0	5
Anti-Influenza B	5	0	5
Anti-Hepatitis C Virus (HCV)	5	0	5
Anti-Hepatitis B Virus (HBV)	5	0	5
Anti-HIV	10	0	10
Anti-Nuclear Antibodies (ANA)	5	0	5
Anti-Adenovirus Positive IgG	2	0	2
Cytomegalovirus (CMV) IgG	7	0	7
Rheumatoid Factor (RF)	5	0	5

ANALYTICAL SENSITIVITY

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) studies were conducted on the Access 2 Immunoassay System following CLSI guideline EP17-A2[23]. The LoB study included of a minimum of 4 blank samples tested on two reagent lots on one instrument over a minimum of 3 days. The LoD and LoQ studies included a minimum of 6 low level samples tested on two reagent lots and one instrument over a minimum of 5 days.

Parameter	Criteria (AU/mL)
Limit of Blank (LoB)	≤ 1.00
Limit of Detection (LoD)	≤ 2.00
Limit of Quantitation (LoQ)	20% CV at ≤ 2.00

DILUTION RECOVERY

Dilution of five human samples containing elevated levels of SARS-CoV-2 IgG with Sample Diluent A at a 1:20 dilution using the UniCel DxI onboard dilution and manual dilutions are shown in the following table.

Sample	DxI Onboard Dilution AU/mL	Manual Dilution 1:20 AU/mL	% Recovery vs Manual
1	992	952	104%
2	789	815	97%
3	646	605	107%
4	1,087	998	109%
5	816	782	104%
		Overall Mean % Recovery	104%

STANDARDIZATION

The Access SARS-CoV-2 IgG II standardization is traceable to an internal standard based on agreement of known positive and negative SARS-CoV-2 specimens.

Currently no reference standard is available for this assay.

ADDITIONAL INFORMATION

REVISION HISTORY

Revision A

New release.

Revision B

Change test name.

Revision C

Add new languages

SYMBOLS KEY

Glossary of Symbols is available at beckmancoulter.com/techdocs (document number C02724).

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EC REP Beckman Coulter Eurocenter S.A., 22, rue Juste-Olivier. Case Postale 1044, CH - 1260 Nyon 1, Switzerland
Tel: +41 (0)22 365 36 11

Beckman Coulter, Inc., 250 S. Kraemer Blvd., Brea, CA 92821 U.S.A.
www.beckmancoulter.com