AdviseDx SARS-CoV-2 IgG II

FOR USE WITH Alinity i

Read Highlighted Changes: Revised April 2022.

REF 06S6120

REF 06S6130

WARNING

For use under an Emergency Use Authorization (EUA) Only

Prescription Use only.

For *In Vitro* Diagnostic Use Only.

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

Instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from these instructions.

For laboratory professional use only.

NAME

AdviseDx SARS-CoV-2 IgG II (also referred to as CoV-2 IgG II or SARS-CoV-2 IgG II on the reagent cartridge label)

INTENDED USE

The AdviseDx SARS-CoV-2 IgG II assay is a chemiluminescent microparticle immunoassay (CMIA) intended for the qualitative and semi-quantitative detection of IgG antibodies to SARS-CoV-2 in human serum (including collected using a serum separator tube) and plasma (acid citrate dextrose, sodium citrate, dipotassium EDTA, tripotassium EDTA, lithium heparin, lithium heparin in a separator tube, and sodium heparin) on the Alinity i system. The AdviseDx SARS-CoV-2 IgG II assay is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection. At this time, it is unknown for how long antibodies persist following infection and if the presence of antibodies confers protective immunity. The AdviseDx SARS-CoV-2 IgG II assay should not be used to diagnose or exclude acute SARS-CoV-2 infection.

Testing is limited to laboratories certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, 42 U.S.C 263a, that meet requirements to perform moderate or high complexity tests.

Results are for the qualitative and semi-quantitative detection of SARS-CoV-2 IgG antibodies. IgG antibodies to SARS-CoV-2 are generally detectable in blood several days after initial infection, although the duration of time antibodies are present post-infection is not well characterized. Individuals may have detectable virus present for several weeks following seroconversion.

Laboratories within the United States and its territories are required to report all results to the appropriate public health authorities.

The sensitivity of the AdviseDx SARS-CoV-2 IgG II assay early after infection is unknown. Negative results do not preclude acute SARS-CoV-2 infection. If acute infection is suspected, direct testing for SARS-CoV-2 is necessary.

False positive results for the AdviseDx SARS-CoV-2 IgG II assay may occur due to cross-reactivity from pre-existing antibodies or other possible causes. Due to the risk of false positive results, confirmation of positive results should be considered using a second, different IgG assay.

Samples should only be tested from individuals that are 15 days or more post-symptom onset.

The AdviseDx SARS-CoV-2 IgG II assay is only for use under the Food and Drug Administration's Emergency Use Authorization.

SUMMARY AND EXPLANATION OF THE TEST

The AdviseDx SARS-CoV-2 IgG II assay is designed to detect immunoglobulin class G (IgG) antibodies to the receptor binding domain (RBD) of the S1 subunit of the spike protein of SARS-CoV-2 in serum and plasma from individuals who are suspected to have had coronavirus disease (COVID-19) or in serum and plasma of individuals that may have been infected by SARS-CoV-2.

COVID-19 is defined as illness caused by a novel coronavirus now designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV).[1] On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic.[2] The incubation period of COVID-19 ranges between 1 and 14 days, with the majority of cases manifesting between 3 and 10 days.[3, 4] The most common symptoms are fever, dry cough, and difficulty breathing.[4] A severe acute respiratory distress syndrome may develop.[5] Reported case fatality rates depend on geographic location, age, and comorbidities.[3, 6]

The causative agent of COVID-19 is a beta coronavirus and belongs to a family of viruses that are common in animals worldwide with potential to transfer to humans, as has likely happened with SARS-CoV-2.[7] SARS-CoV-2 RNA encodes for four structural proteins including spike (S), membrane (M), envelope (E), and nucleocapsid (N), with the S protein comprised of two subunits S1 and S2.[8] The receptor binding domain (RBD) is included within the S1 subunit and has a high affinity for the angiotensin converting enzyme 2 (ACE2) receptor on the cell surface membrane. Infection is mediated by interaction of the SARS-CoV-2 RBD with the ACE2 viral receptor on host cells.[8, 9]

Several studies have indicated that serum and plasma antibodies are typically produced to structural proteins (RBD, S, and N), with antibodies appearing as early as a few days to a few weeks after the onset of symptoms and often after the detection of viral ribonucleic acid (RNA) declines[10-16] or is no longer detectable.[7, 10-12, 17] The persistence of IgG antibodies allows for identification of subjects who have been infected in the past and recovered from the illness[18] and is useful in serological surveys to assess the prevalence of SARS-CoV-2 infection in selected groups or broader populations.[19]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

This assay is an automated, two-step immunoassay for the qualitative and semi-quantitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

Sample, SARS-CoV-2 antigen coated paramagnetic microparticles, and assay diluent are combined and incubated. The IgG antibodies to SARS-CoV-2 present in the sample bind to the SARS-CoV-2 antigen coated microparticles. The mixture is washed. Anti-human IgG acridinium-labeled conjugate is added to create a reaction mixture and incubated. Following a wash cycle, Pre-Trigger and Trigger Solutions are added.

The resulting chemiluminescent reaction is measured as a relative light unit (RLU). There is a direct relationship between the amount of IgG antibodies to SARS-CoV-2 in the sample and the RLU detected by the system optics.

For additional information on system and assay technology, refer to the Alinity ci-series Operations Manual, Section 3.

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REAGENTS

Kit Contents

AdviseDx SARS-CoV-2 IgG II Reagent Kit 06S61

NOTE: Some kit sizes may not be available. Please contact your local distributor.

Volumes (mL) listed in the following table indicate the volume per cartridge.

REF	06S6120	06S6130
Tests per cartridge	100	500
Number of cartridges per kit	2	2
Tests per kit	200	1000
MICROPARTICLES	6.6 mL	27.0 mL
CONJUGATE	6.1 mL	26.5 mL
ASSAY DILUENT	8.3 mL	36.9 mL

MICROPARTICLES Purified SARS-CoV-2 recombinant antigen coated microparticles in TRIS buffer with surfactant. Minimum concentration: 0.0675% solids. Preservatives: ProClin 950 and sodium azide.

CONJUGATE Anti-human IgG (mouse, monoclonal) acridinium-labeled conjugate in MES buffer with surfactants and protein (bovine) stabilizer. Minimum concentration: 6 ng/mL. Preservatives: ProClin 300 and antimicrobial agents.

ASSAY DILUENT MES buffer with protein (bovine) stabilizers. Preservatives: ProClin 300 and ProClin 950.

Warnings and Precautions

For Use Under An Emergency Use Authorization Only.

This assay is only for *in vitro* diagnostic use under the FDA Emergency Use Authorization.

- IVD
- For *In Vitro* Diagnostic Use
- Rx ONLY
- The results of this semi-quantitative test should not be interpreted as an indication or degree of immunity or protection from infection.
- This test has not been FDA cleared or approved but has been authorized for emergency use by FDA under an EUA for use by laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform moderate or high complexity tests.
- This test has been authorized only for detecting the presence of IgG antibodies against SARS-CoV-2, not for any other viruses or pathogens.
- The emergency use of this test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §360bbb-3(b)(1), unless the declaration is terminated or authorization is revoked sooner.

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials and all consumables contaminated with potentially infectious materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate regional, national, and institutional biosafety practices should be used for materials that contain, are suspected of containing, or are contaminated with infectious agents.[20-23]

The following warnings and precautions apply to: MICROPARTICLES	
WARNING	Contains methylisothiazolone and sodium azide.
H317	May cause an allergic skin reaction.
EUH032	Contact with acids liberates very toxic gas.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
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 in accordance with local regulations.

The following warnings and precautions apply to: ASSAY DILUENT	
WARNING	Contains methylisothiazolones.
H317	May cause an allergic skin reaction.
H402	Harmful to aquatic life.
H412	Harmful to aquatic life with long lasting effects.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
P273	Avoid release to the environment.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
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 in accordance with local regulations.

Follow local chemical disposal regulations based on your location along with recommendations and content in the Safety Data Sheet to determine the safe disposal of this product.

For the most current hazard information, see the product Safety Data Sheet.

Safety Data Sheets are available at www.corelaboratory.abbott or contact your local representative.

For a detailed discussion of safety precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 8.

Reagent Handling

- Reagents are shipped on wet ice.
- Upon receipt, gently invert the unopened reagent kit by rotating it over and back for a full 180 degrees, 5 times with green label stripe facing up and then 5 times with green label stripe facing down. This ensures that liquid covers all sides of the bottles within the cartridges. During reagent shipment, microparticles can settle on the reagent septum.
  - Place a check in the square on the reagent kit to indicate to others that the inversions have been completed.
- After mixing, place reagent cartridges in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- If a reagent cartridge is dropped, place in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- Reagents are susceptible to the formation of foam and bubbles. Bubbles may interfere with the detection of the reagent level in the cartridge and cause insufficient reagent aspiration that may adversely affect results.
- When handling conjugate vials, change gloves that have contacted human serum or plasma, since introduction of human IgG will result in a neutralized conjugate.

For a detailed discussion of reagent handling precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 7.

Reagent Storage

- Do not freeze.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened	2 to 8°C	Until expiration date	Store in upright position. If cartridge does not remain upright, gently invert the cartridge 10 times and place in an upright position for 1 hour before use.
Onboard	System Temperature	30 days	
Opened	2 to 8°C	Until expiration date	Store in upright position. If cartridge does not remain upright during storage off the system, discard the cartridge. Do not reuse original reagent caps or replacement caps due to the risk of contamination and the potential to compromise reagent performance.

Reagents may be stored on or off the system. If removed from the system, store reagents with new replacement caps in an upright position at 2 to 8°C. For reagents stored off the system, it is recommended that they be stored in their original trays or boxes to ensure they remain upright.

For information on unloading reagents, refer to the Alinity ci-series Operations Manual, Section 5.

Indications of Reagent Deterioration

Deterioration of the reagents may be indicated when a calibration error occurs or a control value is out of the specified range. Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary.

Refer to the AdviseDx SARS-CoV-2 IgG II control package insert REF 06S6110 for control values.

For troubleshooting information, refer to the Alinity ci-series Operations Manual, Section 10.

INSTRUMENT PROCEDURE

The AdviseDx SARS-CoV-2 IgG II assay file must be installed on the Alinity i system prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, refer to the Alinity ci-series Operations Manual, Section 2.

For information on printing assay parameters, refer to the Alinity ci-series Operations Manual, Section 5.

For a detailed description of system procedures, refer to the Alinity ci-series Operations Manual.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

The specimen types listed below were verified for use with this assay.

Other specimen types and collection tube types have not been verified with this assay.

Specimen Types	Collection Tubes	Special Conditions
Serum	Serum Serum separator	
Plasma	Dipotassium EDTA Tripotassium EDTA Lithium heparin Lithium heparin separator Sodium heparin	
	Acid citrate dextrose[a] Sodium citrate[a]	To account for dilution effect, results from samples collected in acid citrate dextrose and sodium citrate tubes must be manually multiplied by a dilution factor to determine corrected concentration values.[a]

[a] It is the responsibility of the operator to manually apply the appropriate dilution factor, which can be determined using the equation below. Consult the tube manufacturer's labeling to determine the volume of anticoagulant in the tube and for additional guidance on the correction of the expected dilution effect.

$$\text{Dilution Factor} = \frac{\text{(Volume of Anticoagulant in Tube + Total Volume of Blood in Tube)}}{\text{Total Volume of Blood in Tube}}$$

- The instrument does not provide the capability to verify specimen types or collection tube types. It is the responsibility of the operator to verify that the correct specimen types and collection tube types are used in the assay.
- Liquid anticoagulants may have a dilution effect resulting in lower concentration values for individual specimens.
- Performance has not been established for the use of cadaveric specimens or the use of bodily fluids other than human serum/plasma.

Specimen Conditions

- Do not use:
  - heat-inactivated specimens
  - pooled specimens
  - grossly hemolyzed specimens
  - specimens with obvious microbial contamination
  - specimens with fungal growth
- For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter. Serum specimens from patients receiving anticoagulant or thrombolytic therapy may contain fibrin due to incomplete clot formation.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.
- Specimens should be free of bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

To ensure consistency in results, recentrifuge specimens prior to testing if:

- they contain fibrin, red blood cells, or other particulate matter.

NOTE: If fibrin, red blood cells, or other particulate matter are observed, mix by low speed vortex or by inverting 10 times prior to recentrifugation.

Prepare frozen specimens as follows:

- Frozen specimens must be completely thawed before mixing.
- Mix thawed specimens thoroughly by low speed vortex or by inverting 10 times.
- Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous.
- If specimens are not mixed thoroughly, inconsistent results may be obtained.
- Recentrifuge specimens that contain particulate matter.

Recentrifugation of Specimens

- Transfer specimens to a centrifuge tube and centrifuge.
- Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.

Specimen Storage

Specimen Type	Temperature	Maximum Storage Time	Special Instructions
Serum/Plasma	Room temperature (15 to 30°C)	2 days	Specimens may be stored on or off the clot, red blood cells, or separator gel.
	2 to 8°C	7 days	Specimens may be stored on or off the clot, red blood cells, or separator gel.
	-20°C or colder	7 days	Remove serum or plasma from the clot, red blood cells, or separator gel.

For additional information on sample handling and processing, refer to CLSI GP44-A4.[24]

The storage information provided here is based on data maintained by the manufacturer.

Avoid more than 2 freeze/thaw cycles.

Specimen Shipping

Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.

Do not exceed the storage limitations listed above.

PROCEDURE

Materials Provided

06S61 AdviseDx SARS-CoV-2 IgG II Reagent Kit

Materials Required but not Provided

- AdviseDx SARS-CoV-2 IgG II assay file
- Alinity ci-series system software version 1.1.0 or higher
- 06S6101 AdviseDx SARS-CoV-2 IgG II Calibrator Kit
- 06S6110 AdviseDx SARS-CoV-2 IgG II Control Kit
- Alinity Pre-Trigger Solution
- Alinity Trigger Solution
- Alinity i-series Concentrated Wash Buffer
- 09P1540 Alinity i Multi-Assay Manual Diluent

For information on materials required for operation of the instrument, refer to the Alinity ci-series Operations Manual, Section 1.

For information on materials required for maintenance procedures, refer to the Alinity ci-series Operations Manual, Section 9.

Assay Procedure

For a detailed description of how to run an assay, refer to the Alinity ci-series Operations Manual, Section 5.

- If using primary or aliquot tubes, refer to the Alinity ci-series Operations Manual, Section 4 to ensure sufficient specimen is present.
- Minimum sample cup volume is calculated by the system and printed on the Order List report. To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.
- Maximum number of replicates sampled from the same sample cup: 10
  - Priority:
    - Sample volume for first test: 75 µL
    - Sample volume for each additional test from same sample cup: 25 µL
  - ≤ 3 hours on the reagent and sample manager:
    - Sample volume for first test: 150 µL
    - Sample volume for each additional test from same sample cup: 25 µL
  - > 3 hours on the reagent and sample manager:
    - Replace with a fresh aliquot of sample.
- Refer to the AdviseDx SARS-CoV-2 IgG II calibrator package insert REF 06S6101 and/or AdviseDx SARS-CoV-2 IgG II control package insert REF 06S6110 for preparation and usage.
- For general operating procedures, refer to the Alinity ci-series Operations Manual, Section 5.
- For optimal performance, it is important to perform routine maintenance as described in the Alinity ci-series Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

Sample Dilution Procedures

Samples with a SARS-CoV-2 IgG value exceeding 25 000.0 AU/mL are flagged with the code "> 25,000.0 AU/mL" and may be diluted with either the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol

The system performs a 1:2 dilution of the sample and automatically calculates the concentration by multiplying the result by the dilution factor.

For details on configuring automated dilutions, refer to the Alinity ci-series Operations Manual, Section 2.

Manual Dilution Procedure

Suggested dilution: 1:2

Add 75 µL of the sample to 75 µL of Alinity i Multi-Assay Manual Diluent.

The operator must enter the manual dilution factor in the Specimen or Control tab of the Create Order screen. The system will use this dilution factor to automatically calculate the concentration of the sample and report the result.

The result should be ≥ 22.0 AU/mL before the manual dilution factor is applied.

If the operator does not enter the manual dilution factor, the result must be manually multiplied by the appropriate manual dilution factor before reporting the result. If a diluted sample result is less than 22.0 AU/mL, do not report the result. Rerun using an appropriate dilution.

For detailed information on ordering dilutions, refer to the Alinity ci-series Operations Manual, Section 5.

Calibration

For instructions on performing a calibration, refer to the Alinity ci-series Operations Manual, Section 5.

Calibrators A-F are tested in duplicate.

A single sample of each control level must be tested to evaluate the assay calibration.

Ensure that assay control values are within the ranges specified in the control package insert.

Once a calibration is accepted and stored, it may be used for 30 days. During this time, all subsequent samples may be tested without further calibration unless:

- A reagent kit with a new lot number is used.
- Daily quality control results are outside of quality control limits used to monitor and control system performance.

This assay may require recalibration after maintenance to critical parts or subsystems or after service procedures have been performed.

Quality Control Procedures

The recommended control requirement for the AdviseDx SARS-CoV-2 IgG II assay is that a single sample of each control level be tested once every 24 hours each day of use.

Additional controls may be tested in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.

To establish initial statistically-based control limits, each laboratory should establish its own concentration target and ranges for new control lots and for each control level. This can be accomplished by assaying a minimum of 20 replicates over multiple days. A minimum of 10 days enables some day-to-day sources of variability using the reported results to establish the expected average (target) and variability about this average (range) for the laboratory. Sources of variation that should be included in this study in order to be representative of future system performance include:

- Multiple stored calibrations
- Multiple reagent lots
- Multiple calibrator lots
- Multiple processing modules (if applicable)
- Data points collected at different times of the day

Refer to published guidelines for information or general control recommendation, for example Clinical and Laboratory Standards Institute (CLSI) Guideline C24, 4th ed., or other published guidelines, for general quality control recommendations.[25]

- If more frequent control monitoring is required, follow the established quality control procedures for your laboratory.
- If quality control results do not meet the acceptance criteria defined by your laboratory, sample results may be suspect. Follow the established quality control procedures for your laboratory. Recalibration may be necessary. For troubleshooting information, refer to the Alinity ci-series Operations Manual, Section 10.
- Review quality control results and acceptance criteria following a change of reagent or calibrator lot.

Controls should be used according to the guidelines and recommendations of the control manufacturer. Concentration ranges provided in the control package insert should be used only for guidance.

For any control material in use, the laboratory should ensure that the matrix of the control material is suitable for use in the assay per the assay package insert.

Quality Control Guidance

Refer to "Basic QC Practices" by James O. Westgard, Ph.D. for guidance on laboratory quality control practices.[26]

Verification of Assay Claims

To verify package insert claims, follow CLIA recommendations or internal laboratory procedures.

For protocols to verify package insert claims, refer to Verification of Assay Claims in the Alinity ci-series Operations Manual.

RESULTS

Calculation

The AdviseDx SARS-CoV-2 IgG II assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration and results.

The result unit for the AdviseDx SARS-CoV-2 IgG II assay is AU/mL.

Interpretation of Results

The cutoff is 50.0 AU/mL.

As with all analyte determinations, the result should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

AU/mL	Interpretation
< 50.0	Negative
≥ 50.0	Positive, numeric value within the measuring interval
> 25 000.0	Positive,"> 25,000.0 AU/mL"

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the Alinity ci-series Operations Manual, Section 5.

Measuring Interval

Based on representative data for the limit of quantitation (LoQ) and the limit of detection (LoD), the analytical measuring interval (AMI) and extended measuring interval (EMI) are provided below according to the definitions from CLSI EP34, 1st ed.[27]

	AU/mL
Analytical Measuring Interval (AMI)[a]	22.0 - 25 000.0
Extended Measuring Interval (EMI)[b]	25 000.0 - 50 000.0

[a] AMI: The AMI extends from the LoQ to the upper limit of quantitation (ULoQ). This is determined by the range of values in AU/mL that demonstrated acceptable performance for linearity, imprecision, and bias.

[b] EMI: The EMI extends from the ULoQ to the ULoQ × dilution factor. The value reflects a 1:2 dilution factor.

NOTE: Numerical results below 22.0 AU/mL should not be reported. Numerical results below 50.0 AU/mL should not be reported outside of the laboratory.

LIMITATIONS OF THE PROCEDURE

- **For use under an Emergency Use Authorization only.**
- This assay is for *in vitro* diagnostic use under FDA Emergency Use Authorization only.
- This test should only be used for testing samples collected 15 days after symptom onset.
- This assay is for clinical laboratory use only. It is not for point of care or home use.
- Immunocompromised patients who have COVID-19 may have a delayed antibody response and produce levels of antibody which may not be detected as positive by the assay.
- Performance has only been established with specimen types listed in the Intended Use.
- Results obtained with this assay may not be used interchangeably with results obtained with different manufacturers' test methods.
- It is unknown for how long antibodies persist following SARS-CoV-2 infection. It is not known at this time if the presence of antibodies to SARS-CoV-2 confers immunity to infection.
- The clinical applicability of semi-quantitative results is currently unknown and cannot be interpreted as an indication or degree of immunity, nor protection from infection, nor compared to other SARS-CoV-2 antibody assays.
- 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.
- A negative result for an individual subject indicates the absence of detectable anti-SARS-CoV-2 antibodies. 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 in the specimen is below the detection limits of the assay, or if the antibodies are not present during the stage of disease in which a sample is collected.
- This device should not be used to diagnose or exclude acute SARS-CoV-2 infection. Direct testing for SARS-CoV-2 with a molecular assay should be performed to evaluate for acute infection in symptomatic individuals.
- Not to be used to determine SARS-CoV-2 infection in donated blood units. This test should not be used for blood donor screening.
- Potentially interfering disease states and other cross reactants have been evaluated and are represented in the SPECIFIC PERFORMANCE CHARACTERISTICS section of this package insert.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits such as AdviseDx SARS-CoV-2 IgG II that employ mouse monoclonal antibodies.[28, 29]
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference, and anomalous values may be observed.[30]
- Rheumatoid factor (RF) in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.[30]
- 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.
- The performance of this test was established based on the evaluation of a limited number of clinical specimens. Clinical performance has not been established with all circulating variants but is anticipated to be reflective of the prevalent variants in circulation at the time and location of the clinical evaluation. Performance at the time of testing may vary depending on the variants circulating, including newly emerging strains of SARS-CoV-2 and their prevalence, which change over time.

CONDITIONS OF AUTHORIZATION FOR THE LABORATORIES

The AdviseDx SARS-CoV-2 IgG II Letter of Authorization, along with the authorized Fact Sheet for Healthcare Providers, the authorized Fact Sheet for Patients, and authorized labeling are available on the FDA website: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas

Authorized laboratories using the AdviseDx SARS-CoV-2 IgG II ("your product" in the conditions below), must adhere to the Conditions of Authorization indicated in the Letter of Authorization as listed below:

A. Authorized laboratories* using your product must include with result reports, all authorized Fact Sheets. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.

B. Authorized laboratories using your product must use your product as outlined in the authorized labeling. Deviations from the authorized procedures, including the authorized instruments, authorized clinical specimen types, authorized control materials, authorized other ancillary reagents and authorized materials required to use your product are not permitted.

C. Authorized laboratories that receive your product must notify the relevant public health authorities of their intent to run your product prior to initiating testing.

D. Authorized laboratories using your product must have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.

E. Authorized laboratories must collect information on the performance of your product and report to DMD/OHT7-OIR/OPEQ/CDRH (via email: CDRH-EUA-Reporting@fda.hhs.gov) and Abbott Laboratories at https://www.corelaboratory.abbott/us/en/offerings/segments/infectious-disease/sars-cov-2 any suspected occurrence of false positive or false negative results and significant deviations from the established performance characteristics of your product of which they become aware.

F. All laboratory personnel using your product must be appropriately trained in automated immunoassay techniques and use appropriate laboratory and personal protective equipment when handling this kit, and use your product in accordance with the authorized labeling. All laboratory personnel using the assay must also be trained in and be familiar with the interpretation of results of the product.

G. Abbott Laboratories, authorized distributors, and authorized laboratories using your product must ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

* The letter of authorization refers to, "Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform moderate or high complexity tests" as "authorized laboratories."

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

The Alinity i system and the ARCHITECT i2000SR System utilize the same reagents and sample/reagent ratios.

Some performance characteristics for the Alinity i assay were established using the ARCHITECT i System.

Precision

Within-Laboratory Precision

A study was performed based on guidance from CLSI EP05-A3.[31] Testing was conducted using 2 lots of the AdviseDx SARS-CoV-2 IgG II Reagent Kit, 2 lots of the AdviseDx SARS-CoV-2 IgG II Calibrator Kit, and 1 lot of the AdviseDx SARS-CoV-2 IgG II Control Kit and 1 Alinity i instrument. Three controls and 3 human plasma panels were assayed in replicates of 3, at 2 separate times per day, on 5 different days, for a total of 30 replicates for each test sample. The performance from a representative combination is shown in the following table.

			Within-Run (Repeatability)		Within-Laboratory[a]	
Sample	n	Mean (AU/mL)	SD	%CV	SD (Range[b])	%CV (Range[b])
Negative Control	30	2.0	1.20	N/A	1.86 (0.43-1.86)	N/A
Positive Control 1	30	168.4	3.70	2.2	3.70 (3.70-3.99)	2.2 (2.2-2.4)
Positive Control 2	30	597.7	8.03	1.3	10.85 (10.85-12.83)	1.8 (1.8-2.0)
Low Panel	30	48.1	1.39	2.9	1.41 (1.35-1.41)	2.9 (2.9-2.9)
Medium Panel	30	86.9	1.79	2.1	1.79 (1.79-2.34)	2.1 (2.1-2.7)
High Panel	30	19 402.3	524.10	2.7	545.60 (545.60-979.48)	2.8 (2.8-5.1)

N/A = Not applicable

[a] Includes within-run, between-run, and between-day variability.

[b] Minimum and maximum SD or %CV across all reagent lot and instrument combinations.

System Reproducibility

A study was performed based on guidance from CLSI EP05-A3.[31] Testing was conducted using 2 lots of the AdviseDx SARS-CoV-2 IgG II Reagent Kit, 2 lots of the AdviseDx SARS-CoV-2 IgG II Calibrator Kit, and 1 lot of the AdviseDx SARS-CoV-2 IgG II Control Kit and 2 Alinity i instruments. Three controls and 3 human plasma panels were assayed in replicates of 3, at 2 separate times per day, for 5 days. The performance across reagent lots and instruments is shown in the following table.

			Within-Run (Repeatability)		Within-Laboratory[a]		Reproducibility[b]	
Sample	n	Mean (AU/mL)	SD	%CV	SD	%CV	SD	%CV
Negative Control	60	2.1	0.44	N/A	0.50	N/A	0.50	N/A
Positive Control 1	60	163.7	3.82	2.3	5.17	3.2	5.17	3.2
Positive Control 2	60	617.2	14.26	2.3	15.13	2.5	21.01	3.4
Low Panel	60	46.7	1.65	3.5	1.76	3.8	1.96	4.2
Medium Panel	60	87.0	2.23	2.6	2.58	3.0	2.58	3.0
High Panel	60	19 694.2	828.70	4.2	876.43	4.5	1267.70	6.4

N/A = Not applicable

[a] Includes within-run, between-run, and between-day variability.

[b] Reproducibility contains repeatability (within-run), between-run, between-day, and between-instrument variability.

Accuracy by Recovery

Seven normal human plasma samples with known spiked target concentrations of SARS-CoV-2 IgG were tested in replicates of 6 on the AdviseDx SARS-CoV-2 IgG II assay. The percent recovery relative to the target concentration was calculated for each sample.

Sample No.	N	Mean SARS-CoV-2 IgG Concentration (AU/mL)	Target SARS-CoV-2 IgG Concentration (AU/mL)	% Recovery[a]
1	6	45.8	50.0	-8.4
2	6	133.4	150.0	-11.1
3	6	4799.9	5000.0	-4.0
4	6	10 256.5	10 000.0	2.6
5	6	14 925.8	15 000.0	-0.5
6	6	20 312.2	20 000.0	1.6
7	6	24 626.3	25 000.0	-1.5

[a] $\% \text{ Recovery} = \frac{\text{Mean SARS-CoV-2 IgG Concentration} - \text{Target SARS-CoV-2 IgG Concentration}}{\text{Target SARS-CoV-2 IgG Concentration}} \times 100$

Lower Limits of Measurement

A study was performed based on guidance from CLSI EP17-A2.[32] Testing was conducted using 2 lots of the AdviseDx SARS-CoV-2 IgG II reagents on each of 2 instruments over a minimum of 3 days. The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) values are summarized below. These representative data support the lower limit of the analytical measuring interval.

	AU/mL
LoB[a]	2.8
LoD[b]	7.2
LoQ[c]	22.0

[a] The LoB represents the 95th percentile from n ≥ 60 replicates of zero-analyte samples.

[b] The LoD presented in the table is in alignment with the AdviseDx SARS-CoV-2 IgG II assay on the ARCHITECT i System. The observed LoD on the Alinity i system was 4.8 AU/mL and represents the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

[c] The LoQ presented in the table is in alignment with the low end of the AMI for the AdviseDx SARS-CoV-2 IgG II assay on the Alinity i system. The observed LoQ on the Alinity i system was 7.2 AU/mL. The LoQ is defined as the lowest concentration at which a maximum allowable precision of 20 %CV was met and was determined from n ≥ 60 replicates of low-analyte level samples.

Linearity

A study was performed based on guidance from CLSI EP06-A.[33] Three clinical plasma samples were used to prepare a dilution series comprised of 11 levels. Each level was tested with a minimum of 4 replicates using 1 lot of the AdviseDx SARS-CoV-2 IgG II Reagent Kit, 1 lot of the AdviseDx SARS-CoV-2 IgG II Calibrator Kit, and 1 lot of the AdviseDx SARS-CoV-2 IgG II Control Kit, and 2 Alinity i instruments.

Linearity was demonstrated across the analytical measuring interval of 22.0 to 25 000.0 AU/mL. Taking into consideration the estimates of LoB, LoD, LoQ, precision, and linearity, the analytical measuring interval is 22.0 to 25 000.0 AU/mL.

Analytical Specificity

These studies were performed on the ARCHITECT i2000SR System.

Potentially Cross-Reacting Antibodies

The AdviseDx SARS-CoV-2 IgG II assay was evaluated for potentially cross-reacting antibodies. A total of 152 specimens from 32 different categories were tested. All 152 specimens were negative by the AdviseDx SARS-CoV-2 IgG II assay. The data are summarized in the following table.

Category	n	Positive	Negative
Anti-Hepatitis A Virus (HAV)	5	0	5
Anti-Hepatitis C Virus (HCV)	5	0	5
Anti-Hepatitis D Virus (HDV)	5	0	5
Anti-Herpes Simplex Virus (HSV)	5	0	5
Anti-Human T-Lymphotropic Virus (HTLV) Type 1	5	0	5
Anti-HTLV Type 2	5	0	5
Anti-Respiratory Syncytial Virus (RSV)	5	0	5
Anti-Varicella Zoster Virus (VZV)	5	0	5
Antinuclear Antibody (ANA)	5	0	5
Cytomegalovirus (CMV) Immunoglobulin Class G	5	0	5
CMV IgM	5	0	5
Double-Stranded Deoxyribonucleic Acid (dsDNA) Antibody	5	0	5
Enterovirus IgG	5	0	5
Enterovirus IgM	5	0	5
Epstein-Barr Virus (EBV) IgG	5	0	5
EBV IgM	5	0	5
Escherichia coli (E. coli) Antibody	5	0	5
HAMA	5	0	5
Hepatitis B Core (HBc) IgM	4	0	4
Heterophilic Antibody Positive	5	0	5
Hyper IgM	5	0	5
Monoclonal Hyper IgG	5	0	5
Mycoplasma IgM	5	0	5
Parainfluenza IgG	5	0	5
Parainfluenza IgM	2	0	2
Polyclonal Hyper IgG	3	0	3
Rheumatoid Factor	5	0	5
Rheumatoid Factor IgM	4	0	4
Rubella IgG	5	0	5
Rubella IgM	5	0	5
Toxoplasmosis IgG	5	0	5
Toxoplasmosis IgM	4	0	4
Total	152	0	152

Potentially Interfering Medical Conditions

The AdviseDx SARS-CoV-2 IgG II assay was evaluated for potential cross-reactivity from individuals with potentially interfering medical conditions. A total of 99 specimens from 17 different categories were tested. All 99 specimens were negative by the AdviseDx SARS-CoV-2 IgG II assay. The data are summarized in the following table.

Category	n	Positive	Negative
Adenovirus	5	0	5
Autoimmune Hepatitis	5	0	5
Hemodialysis	5	0	5
Hepatitis B Virus (HBV)	5	0	5
Human Coronavirus 229E	10	0	10
Human Coronavirus HKU1	9	0	9
Human Coronavirus NL63	5	0	5
Human Coronavirus OC43	10	0	10
Human Immunodeficiency Virus (HIV)	5	0	5
Influenza A	5	0	5
Influenza A/B	5	0	5
Influenza B	5	0	5
Influenza Vaccine	5	0	5
Lupus	5	0	5
Picornavirus	5	0	5
Pregnant Females	5	0	5
Pregnant Females, Multiparous	5	0	5
Total	99	0	99

Interference

These studies were performed on the ARCHITECT i2000SR System.

Potentially Interfering Endogenous Substances

A study was performed based on guidance from CLSI EP07, 3rd ed.[34] Each substance was tested at 3 levels of the analyte (< 50 AU/mL, low positive samples targeted between 50 and 70 AU/mL, and > 600 AU/mL). The observed interference was within or equal to ± 15% for samples with concentrations ≥ 35 AU/mL; therefore, the study showed no interference was observed at the following endogenous substance interferent levels.

Potentially Interfering Endogenous Substance	Interferent Level
Unconjugated Bilirubin	40 mg/dL
Conjugated Bilirubin	40 mg/dL
Hemoglobin	1000 mg/dL
Triglycerides (Intralipid)	2000 mg/dL
Total Protein	15 g/dL

Potentially Interfering Substances

A study was performed based on guidance from CLSI EP07, 3rd ed.[34] Each substance was tested at 3 levels of the analyte (< 50 AU/mL, low positive samples targeted between 50 and 70 AU/mL, and > 600 AU/mL). The observed interference was within or equal to ± 15% for samples with concentrations ≥ 35 AU/mL; therefore, the study showed no interference was observed at the following interferent levels.

Potentially Interfering Substance	Interferent Level
Acetaminophen	15.6 mg/dL
Alprazolam	0.0258 mg/dL
Ascorbic Acid	5.25 mg/dL
Azithromycin	1.11 mg/dL
Biotin	4250 ng/mL
Captopril	0.264 mg/dL
Fluoxetine	0.142 mg/dL
Guaifenesin	0.450 mg/dL
Hydroxychloroquine	388.8 ng/mL
Ibuprofen	21.9 mg/dL
Remdesivir	27 µmol/L

Clinical Performance

A study was performed to determine the clinical performance of the AdviseDx SARS-CoV-2 IgG II assay.

All specimens tested were assayed in single replicates using 2 lots of the AdviseDx SARS-CoV-2 IgG II Reagent Kit, 2 lots of the AdviseDx SARS-CoV-2 IgG II Calibrator Kit, and 1 lot of the AdviseDx SARS-CoV-2 IgG II Control Kit on 2 Alinity i instruments.

To estimate the positive percent agreement (PPA) between the AdviseDx SARS-CoV-2 IgG II assay and the polymerase chain reaction (PCR) comparator, 404 retrospective frozen serum and plasma specimens, collected between March 2020 and June 2020, were purchased from medical institutions in the US and Spain, from a total of 124 subjects whose respiratory samples tested positive for SARS-CoV-2 by a US FDA EUA-authorized PCR method and who also presented with COVID-19 symptoms. Specimens from a total of 5 immunocompromised subjects were not included in the data analysis. There were 219 specimens from the remaining 119 immunocompetent study subjects included in the data analysis. The PPA and the 95% confidence interval (CI) were calculated using the initial sample collected in each of the 3 designated time frames after symptom onset (i.e. ≤ 7 days, 8-14 days, and ≥ 15 days), per subject. The performance summary data are illustrated in the tables below.

Positive Percent Agreement by Days Post-Symptom Onset

Days Post-Symptom Onset	n	Positive	Negative	PPA (95% CI)
≤ 7	75[a]	37	38	49.33% (38.33, 60.40)
8 - 14	92[a]	74	18	80.43% (71.18, 87.25)
≥ 15	52[a]	51	1	98.08% (89.88, 99.90)

[a] Seven (7) specimens from 5 immunocompromised patients were excluded from the study. Refer to the LIMITATIONS OF THE PROCEDURE section of this package insert for further information. When the results from these specimens were included, the PPA at ≤ 7 days post-symptom onset was 48.68% (95% CI: 37.78, 59.71), the PPA at 8 - 14 days post-symptom onset was 79.57% (95% CI: 70.28, 86.51), and the PPA at ≥ 15 days post-symptom onset was 92.98% (95% CI: 83.30, 97.24).

Positive Percent Agreement by Days Post-Positive PCR

Days Post-Positive PCR	n	Positive	Negative	PPA (95% CI)
≤ 7	107[a]	60	47	56.07% (46.62, 65.11)
8 - 14	71[a]	68	3	95.77% (88.30, 98.55)
≥ 15	40[a]	39	1	97.50% (87.12, 99.87)

[a] Seven (7) specimens from 5 immunocompromised patients were excluded from the study. Refer to the LIMITATIONS OF THE PROCEDURE section of this package insert for further information. When the results from these specimens were included, the PPA at ≤ 7 days post-positive PCR result was 55.05% (95% CI: 45.69, 64.05), the PPA at 8 - 14 days post-positive PCR result was 94.44% (95% CI: 86.57, 97.82), and the PPA at ≥ 15 days post-positive PCR result was 93.18% (95% CI: 81.77, 97.65).

To estimate the negative percent agreement (NPA), frozen serum and plasma specimens from 2008 unique study subjects were tested using the AdviseDx SARS-CoV-2 IgG II assay. All specimens were collected prior to September 2019 (pre-COVID-19 outbreak) and were therefore assumed to be negative. The NPA and the 95% CI were calculated. The performance summary data are illustrated in the table below.

Negative Percent Agreement

AdviseDx SARS-CoV-2 IgG II Results			
n	Positive	Negative	NPA (95% CI)
2008	8	2000	99.60% (99.22, 99.80)

Longitudinal Study

From the positive percent agreement study above, a subset of 104 subjects with 2 or more blood draws post-symptom onset were assessed longitudinally. Out of the 104 subjects, 67 presented positive results in all bleeds, 3 presented negative results in all bleeds, while 34 subjects showed SARS-CoV-2 IgG seroconversion. Representative AdviseDx SARS-CoV-2 IgG II seroconversion results are provided below. Seroconversion was detected by the AdviseDx SARS-CoV-2 IgG II assay at 10 days, 8 days, 7 days, and 16 days post-symptom onset for subjects 13, 19, 23, and 120 respectively.

Subject	Draw	Days Post-Symptom Onset	Result (AU/mL)	Interpretation
13	1	1	4.2	Negative
	2	3	22.2	Negative
	3	10	3671.9	Positive
	4	15	18 157.2	Positive
	5	22	21 928.1	Positive
19	1	0	1.8	Negative
	2	4	6.8	Negative
	3	8	991.6	Positive
	4	11	9492.7	Positive
	5	14	11 280.5	Positive
23	1	0	6.6	Negative
	2	4	5.9	Negative
	3	7	182.3	Positive
	4	14	21 636.6	Positive
	5	20	> 25 000.0	Positive
120	1	5	0.0	Negative
	2	16	11 920.5	Positive
	3	20	13 847.1	Positive
	4	28	16 262.6	Positive
	5	33	> 25 000.0	Positive

ARCHITECT i2000SR vs. Alinity i Analyzers Equivalence

A study was performed based on guidance from CLSI EP09c, Third Edition[35] to demonstrate equivalence between the ARCHITECT i2000SR and Alinity i analyzers using the Passing-Bablok regression method. Three hundred twenty-five samples, including 75 serum and 250 plasma specimens, were tested in 1 replicate using 2 lots each of reagents and calibrators, 1 lot of controls, over a minimum of 3 days on 2 Alinity i and 2 ARCHITECT i2000SR instruments.

AdviseDx SARS-CoV-2 IgG II on Alinity i vs AdviseDx SARS-CoV-2 IgG II on ARCHITECT

	n	Units	Correlation Coefficient	Intercept	Slope	Concentration Range
Serum and Plasma	325	AU/mL	1.00	0.1	0.95	24.1 - 24 755.8

Class Specificity

This study was performed on the ARCHITECT i2000SR System.

The anti-human IgG antibody used in the AdviseDx SARS-CoV-2 IgG II assay demonstrates class-specific reactivity only to human SARS-CoV-2 IgG. No binding interactions were observed to human SARS-CoV-2 IgM.

A class specificity study was conducted to determine the impact of dithiothreitol (DTT) treatment on the detection of IgG and/or IgM positive samples by the AdviseDx SARS-CoV-2 IgG II assay. DTT dissolves IgM antibody disulfide bonds and eliminates activity of the antibody. Upon treatment with DTT, five SARS-CoV-2 patient samples (initially positive for both IgG and IgM) remained positive for IgG when tested with the AdviseDx SARS-CoV-2 IgG II assay and were negative for IgM when tested with the Abbott AdviseDx SARS-CoV-2 IgM assay. This establishes the specificity of the AdviseDx SARS-CoV-2 IgG II kit to the IgG class of antibodies.

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Key to Symbols

ISO 15223 Symbols	
	Consult instructions for use
	Manufacturer
	Sufficient for
	Temperature limitation
	Use by/Expiration date
IVD	*In Vitro* Diagnostic Medical Device
LOT	Lot Number
REF	List Number
SN	Serial number

Other Symbols	
ASSAY DILUENT	Assay Diluent
CONJUGATE	Conjugate
CONTAINS: AZIDE	Contains Sodium Azide. Contact with acids liberates very toxic gas.
FOR USE WITH	Identifies products to be used together
INFORMATION FOR USA ONLY	Information needed for United States of America only
INVERSIONS PERFORMED	Inversions Performed
MICROPARTICLES	Microparticles
PRODUCT OF IRELAND	Product of Ireland
Rx ONLY	For use by or on the order of a physician only (applicable to USA classification only).
WARNING: SENSITIZER	Warning: May cause an allergic reaction.

Note for number formatting:

- A space is used as thousands separator (example: 10 000 specimens).
- A period is used to separate the integer part from the fractional part of a number written in decimal form (example: 3.12%).

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