Diagnostic Automation/Cortez Diagnostics, Inc.
IMMUNO DIAGNOSTICS

AccuDiag™ Cardiolipin IgM ELISA Kit

REF 1492

PIC AD1492YS39

IVD | See External Label | 2°C – 8°C | Σ 96 Tests

Cardiolipin IgM ELISA	
Principle	Sandwich enzyme immunometric assay
Detection	2.08 – 80 AU/mL
Sample	10 µL serum/plasma
Incubation Time	135 minutes
Sensitivity	80%
Specificity	100%
Shelf Life	12 Months from the manufacturing date

PRODUCT FEATURES

- Very easy to use with little training
- Highly specific and consistent assay
- Provides accurate results quickly
- Reading of results both visually and as absorbance data

INTENDED USE

The Diagnostic Automation, Inc. Cardiolipin IgM is a manual in vitro diagnostic device intended for the quantitative determination of IgM class antibodies directed against cardiolipin in human serum or plasma. Results are to be used in conjunction with other clinical and laboratory data as an aid in the diagnosis of antiphospholipid syndrome (APS).

SIGNIFICANCE AND SUMMARY

Cardiolipin is a negatively charged phospholipid which is typically located in the inner mitochondrial membrane[1]. Autoantibodies directed against cardiolipin are part of a group known as antiphospholipid antibodies which includes anti-β2 glycoprotein 1 autoantibodies. Measurement of anti-cardiolipin autoantibodies is considered to be one of the most important markers to support diagnosis of antiphospholipid syndrome (APS)[2,3].

APS is a systemic autoimmune disorder characterised by a combination of arterial and/or venous thromboses, pregnancy complications, such as recurrent foetal loss, together with elevated levels of antiphospholipid antibodies[4]. APS was first described in patients with systemic lupus erythematosus (SLE), though it has subsequently been established that SLE may be independent of an underlying disease[5].

APS can occur alone – Primary APS, or in association with other conditions, such as SLE – Secondary APS[6] (6). However, it has been demonstrated that anti-cardiolipin antibodies (aCLs) can be detected in patients with SLE that do not develop Secondary APS[7-9]. However, thromboembolic events are the most common clinical manifestation of APS.

Anti-cardiolipin antibodies can recognise both cardiolipin and portions of the phospholipid-protein complex β2 glycoprotein 1-cardiolipin[10,11].

Studies have indicated an association of anti-cardiolipin IgG and IgM antibodies[2,7,11-16], with thrombotic events whereas others suggest these to be linked with IgG isotype, but not IgM[6,10,17].

aCL IgM antibodies have been shown to occur in infections such as chronic hepatitis C, leprosy, syphilis, but they are not directly involved in thrombotic events[17].

It is likely that the presence of antiphospholipid antibodies, including aCL IgG and IgM constitutes the single most recognisable risk factor in cases of recurrent pregnancy loss and late placenta-mediated obstetric complications[4-6,11,14-15,18,19]. Where patients can present with only adverse pregnancy outcomes with isolated vascular events or with both obstetric and thrombotic manifestations[6]. It has been suggested that anti-β2-glycoprotein I – cardiolipin antibodies are able to recognise the antigen on placental tissues, inhibiting the growth and differentiation of trophoblasts which may eventually cause defective placentation[20].

ASSAY PRINCIPLE

The Cardiolipin IgM assay is a two-step sandwich enzyme immunometric assay (ELISA) where patient samples, calibrators or controls are incubated on microtitre plates coated with the antigenic cardiolipin-β2 glycoprotein complex. During the incubation, antibodies present in the test sample bind to the immobilised antigen complex. After the incubation, the bound/free separation is performed by a simple solid phase washing.

A subsequent incubation occurs with anti-human IgM conjugated with horseradish peroxidase (HRP), which binds to the immobilised antibodies. A further wash step is performed to remove excess conjugate. Then, a chromogenic substrate solution containing TMB is dispensed into the wells which reacts with the conjugated HRP and a blue colour develops that changes into yellow when the Stop Solution (H_2SO_4) is added. The colour intensity is directly proportional to the Anti Cardiolipin IgM concentration in the sample.

Anti-cardiolipin antibody concentration in the sample is calculated through a calibration curve.

MATERIALS AND COMPONENTS

Materials provided with the test kit

1. **Calibrators** (5 vials, 1.2 mL each)
   Phosphate buffer 0.1M, NaN_3 < 0.1%, human serum
   CAL0
   CAL1
   CAL2
   CAL3
   CAL4
2. **Controls** (2 vials, 1.2 mL each, ready to use)
   Phosphate buffer 0.1M, NaN_3 < 0.1%, human serum
   Negative Control
   Positive Control
3. **Sample Diluent** (1 vial, 100 mL)
   Phosphate buffer 0.1M, NaN_3 <0.1%
4. **Conjugate** (1 vial, 15 mL)
   Anti h-IgM conjugate with horseradish peroxidase (HRP), BSA 0.1%, ProClin < 0.0015%
5. **Coated Microplate** (1 breakable microplate)
   Microplate coated with antigenic Cardiolipin-β2-Glycoprotein complex
6. **TMB Substrate** (1 vial, 15 mL)
   H2O2-TMB (0.26 g/L) (avoid any skin contact)
7. **Stop Solution** (1 vial, 15 mL)
   Sulphuric acid 0.15M (avoid any skin contact)
8. **10X Conc. Wash Solution** (1 vial, 50 mL)
   Phosphate buffer 0.2M pH 7.4

Materials required but not provided
1. Distilled water.

Auxiliary materials and instrumentation
1. Automatic dispenser.
2. Precision Pipetting Devices.
3. Microplate reader (450 nm, 620-630 nm).

REAGENT STORAGE AND STABILITY

Store the kit at 2 – 8°C in the dark.
1. The kit is stable at 2 – 8°C until the expiry date stated on the external kit label.
2. Once opened, the kit is stable at 2 – 8°C for 6 months.
3. The diluted wash solution is stable for 30 days at 2-8°C.

Important note: open the bag containing the Coated Microplate only when it is at room temperature and close it immediately after use.

SAMPLE COLLECTION AND STORAGE

The assay should be performed using serum (standard sampling tubes or tubes containing serum separating gel) or plasma (lithium heparin, sodium heparin, potassium EDTA) samples.

Sample Storage	Duration
2–8°C	96 hours
Freeze/thaw cycles	3 cycles

ASSAY PROCEDURE

1. Preparation of the Calibrators
The calibrators and controls are ready to use.

The calibrators are approximately the following concentrations:

	C_0	C_1	C_2	C_3	C_4
AU/mL	0	5	10	20	80

2. Preparation of the Wash Solution
Dilute the content of the vial "10X Conc. Wash Solution" with distilled water to a final volume of 500 mL prior to use. For smaller volumes respect the 1:10 dilution ratio.

It is possible to observe the presence of crystals within the concentrated wash solution; in this case mix at room temperature until the complete dissolution of crystals. For greater accuracy, dilute the whole bottle of concentrated wash solution to 500 mL, taking care also to transfer crystals completely by rinsing of the bottle, then mix until crystals are completely dissolved.

3. Preparation of Samples
All serum and plasma samples must be diluted 1:100 with sample diluent.
e.g., 10 µL of sample should be diluted with 990 µL of sample diluent.

4. Procedure
- **Allow all reagents to reach room temperature (22-28°C) for at least 30 minutes.** At the end of the assay, immediately store the reagents at 2-8°C: avoiding long exposure to room temperature.
- Unused coated microwell strips should be released securely in the foil pouch containing desiccant and stored at 2-8°C.
- To avoid potential microbial and/or chemical contamination, unused reagents should never be transferred into the original vials.
- As it is necessary to perform the determination in duplicate in order to improve accuracy of the test results, prepare two wells for each point of the standard curve (C_0-C_4), two for each control, two for each sample, one for blank.

Reagents	Calibrator	Sample/ Controls	Blank
Calibrator C_0-C_4	100 µL		
Controls		100 µL	
Diluted Sample		100 µL	
Incubate for 60 minutes at room temperature (22-28°C). Remove the content from each well; wash the wells 3 times with 300 µL diluted wash solution. **Important note:** during each washing step, gently shake the plate for 5 seconds and remove excess solution by tapping the inverted plate on an absorbent paper towel. **Automatic washer:** If you use automated equipment, wash the wells at least 5 times.			
Conjugate (IgG or IgM)	100 µL	100 µL	
Incubate for 60 minutes at room temperature (22-28°C). Remove the content from each well; wash the wells 3 times with 300 µL diluted wash solution. **Washing:** follow the same indications of the previous point.			
TMB Substrate	100 µL	100 µL	100 µL
Incubate for 15 minutes in the dark at room temperature (22-28°C).			
Stop Solution	100 µL	100 µL	100 µL
Shake the microplate gently. Read the absorbance (E) at 450 nm against a reference wavelength of 620-630 nm or against Blank within 5 minutes.			

QUALITY CONTROL

Good Laboratory Practice (GLP) requires the use of quality control specimens in each series of assays in order to check the performance of the assay. Controls should be treated as unknown samples, and the results analysed with appropriate statistical methods.

The kit controls provided in the kit should be tested as unknowns and are intended to assist in assessing the validity of results obtained with each assay plate.

The mean concentration of each control level is documented in the QC report included with each kit. These mean concentration levels are determined over several assays which are run in duplicate in multiple locations across each plate. This test is only valid if the optical density at 450 nm for the controls as well as for the calibrators (C_0-C_4) fall within with the respective range indicated on the Quality Control Certificate enclosed in each test kit.

Diagnostic Automation Inc. recommends the users to maintain graphic records of the control values generated with each assay run, including the running means, SDs and %CVs. This information will facilitate the controls trending analysis relating to the performance of current and historical control lots relative to the supplied Quality Control data. The trending will assist in the identification of assays which give control values significantly different from their average range.

When interpreting control data, users should note that this product was designed and developed as a manual product. The range stated on the QC certificate should be appropriate for assays that are performed manually and with strict adherence to the Assay Procedure described above. It is recognised by Quality Control professionals, that as a result of differences in conditions and practices, there will always be variability in the mean values and precision of control measurements between different laboratories[21].

CALCULATION OF RESULTS

A variety of data reduction software packages are available, which may be employed to generate the mean calibration curve and to calculate the mean concentrations of unknown samples and controls. A 4-parameter logistic (4PL) curve fit with lin-log coordinates, **including Calibrator 0 is required.** A smoothed spline fit including Calibrator 0 can be used. Other curve fitting algorithms are not recommended.

Alternatively, a calibration curve may be prepared on semi-log graph paper by plotting mean absorbance on the Y-axis against concentration of analyte on the X-axis. Calibrator 0 should be included in the calibration curve. Read the mean absorbance value of each unknown sample off the curve.

MEASURING RANGE

The assay measuring range (AMR) is 2.08 – 80 AU/mL.
Any value that reads below 2.09 AU/mL should be reported as "< 2.08 AU/mL".
Any value that reads above 80 AU/mL should be reported as "> 80 AU/mL".

METROLOGY AND TRACEABILITY

The calibrators of this kit are traceable to the Center for Disease Control (CDC) Human IgM Anti-Cardiolipin Monoclonal AntibodyEY2C9 - Catalogue [IS2718].

RESULTS

Index/Concentration	Interpretation
< 8 AU/mL	The sample should be considered negative
8 – 10 AU/mL	The sample should be graded equivocal and repeat testing / sampling should be performed according to internal practices
> 10 AU/mL	The sample should be considered positive

Determination of a range of expected values for a "normal" population of a given method is dependent on many factors, such as specificity and sensitivity of the method used and type of population under investigation. Therefore, each laboratory should consider the range given by the Manufacturer as a general indication and produce their own range of expected values based on the indigenous population.

Positive results should be verified concerning the entire clinical status of the patient, with the decision for therapy being taken on an individual basis. It is recommended that each laboratory establishes its own normal and pathological ranges of Cardiolipin IgM values.

PERFORMANCE CHARACTERISTICS

Representative performance data are shown. Results obtained at individual laboratories may vary.

Detection Capability
The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) were determined with guidance from CLSI EP17-A, "Protocols for Determination of Limits of Detection and Limits of Quantitation" using 6 blanks and 6 low level samples.

Sensitivity	Concentration
Limit of Blank (LoB)	0.76 AU/mL
Limit of Detection (LoD)	1.45 AU/mL
Limit of Quantitation (LoQ)	2.08 AU/mL

Trueness
Trueness of the Cardiolipin IgM assay has been demonstrated through performance of a recovery test using the CDC Human IgM Anti-Cardiolipin Monoclonal Antibody EY2C9 - Catalogue [IS2718].

Diagnostic Sensitivity and Specificity
The sensitivity and specificity were determined with guidance from CLSI EP-24 "Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves" using 73 negative and 62 positive samples run on two reagent lots.

		Cardiolipin IgM		Total
		Positive	Negative	
True State	Positive	50	12	62
	Negative	0	73	73
Total		50	85	135

Diagnostic Sensitivity: 80%
Diagnostic Specificity: 100%
Precision
Precision of the Cardiolipin IgM assay was determined by performing a complex precision study.

Repeatability: A total of 6 serum samples were assayed in 5 replicates, once a day for 5 days by 3 operators.
Data from one representative lot is shown below:

Sample	N	Mean (Conc. AU/mL)	Within Run (Repeatability)	
			SD	CV
1	75	7.74	0.40	5.2%
2	75	12.46	0.51	4.1%
3	75	21.06	0.99	4.7%
4	75	32.07	1.46	4.6%
5	75	55.15	1.19	2.2%
6	75	75.45	2.33	3.1%

Reproducibility: A total of 6 serum samples were assayed in 5 replicates, once a day for 5 days by 3 operators.
Results for the combined data from two lots is shown below:

Sample	N	Mean (Conc. AU/mL)	Within Laboratory (Reproducibility)	
			SD	CV%
1	150	7.65	0.46	6.0%
2	150	12.33	0.74	6.0%
3	150	21.03	1.60	7.6%
4	150	31.89	1.98	6.2%
5	150	54.28	2.70	5.0%
6	150	75.46	2.63	3.5%

Linearity
Linearity was evaluated based on CLSI EP-06, "Evaluation of the Linearity of Quantitative Measurement Procedures". For Cardiolipin IgM concentration by Cardiolipin IgM, the measurement procedure shows linearity for the interval from 0.82 to 86.88 AU/mL within the allowable deviation of linearity (ADL) of ±15 %.

Analytical Specificity
The following substances do not interfere with a bias of > ±15% in the Cardiolipin IgM assay when the concentrations are below the stated threshold presented in the following table.

Potentially Interfering Reagent	Threshold Concentration
Bilirubin, conjugated	15 mg/dL
Bilirubin, unconjugated	15 mg/dL
Haemoglobin	200 mg/dL
Total Protein	10 g/dL
Triglyceride	500 mg/dL

Serum-plasma study
The Cardiolipin IgM matrix comparison study was performed to evaluate the difference across tube types (serum separator tubes (SST), lithium heparin plasma, sodium heparin plasma and K2 EDTA plasma) versus the control samples (red top serum, without additive) following CLSI EP9-A3 guidelines. A total of 20 samples (16 native, 4 spiked) to cover the range were evaluated. Linear regression analysis was performed on the comparative data:

Sample Type	Slope [95% CI]	Intercept (ng/mL) [95% CI]	Correlation coefficient (r)
SST	1.02 [0.94 to 1.09]	0.19 [-1.34 to 1.72]	0.99
Lithium Heparin	0.93 [0.82 to 1.04]	0.73 [-1.49 to 2.95]	0.97
Sodium Heparin	0.93 [0.84 to 1.01]	0.64 [-1.00 to 2.28]	0.98
EDTA	0.96 [0.86 to 1.05]	0.65 [-1.19 to 2.49]	0.98

PRECAUTIONS

1. Please adhere strictly to the sequence of pipetting steps provided in this protocol. The performance data represented here were obtained using specific reagents listed in this Instruction For Use.
2. All reagents should be stored refrigerated at 2-8°C in their original container. Any exceptions are clearly indicated. The reagents are stable until the expiry date when stored and handled as indicated.
3. Allow all kit components and specimens to reach room temperature (22-28 °C) and mix well prior to use.
4. Do not interchange kit components from different lots. The expiry date printed on box and vials labels must be observed. Do not use any kit component beyond their expiry date.
5. **WARNING: the conjugate reagent is designed to ensure maximum dose sensitivity and may be contaminated by external agents if not used properly:** therefore, it is recommended to use disposable consumables (tips, bottles, trays, etc.) For divided doses, take the exact amount of conjugate needed and do not re-introduce any waste product into the original bottle. In addition, **for doses dispensed with the aid of automatic and semi-automatic devices,** before using the conjugate, it is advisable to clean the fluid handling system, ensuring that the procedures of washing, deproteinization and decontamination are effective in avoiding contamination of the conjugate; this procedure is highly recommended when the kit is processed using analyzers which are not equipped with disposable tips.
   For this purpose, Diagnostic Automation, Inc. supplies a separate decontamination reagent for cleaning needles
6. If you use automated equipment, the user has the responsibility to make sure that the kit has been appropriately tested.
7. The incomplete or inaccurate liquid removal from the wells could influence the assay precision and/or increase the background. To improve the performance of the kit on automatic systems is recommended to increase the numbers of washes.
8. It is important that the time of reaction in each well is held constant for reproducible results. Pipetting of samples should not extend beyond ten minutes to avoid assay drift. If more than 10 minutes are needed, follow the same order of dispensation. If more than one plate is used, it is recommended to repeat the dose response curve in each plate.
9. Addition of the TMB Substrate solution initiates a kinetic reaction, which is terminated by the addition of the Stop Solution. Therefore, the TMB Substrate and the Stop Solution should be added in the same sequence to eliminate any time deviation during the reaction.
10. Observe the guidelines for performing quality control in medical laboratories by assaying controls and/or pooled sera.
11. Maximum precision is required for reconstitution and dispensing of the reagents.
12. Samples which are microbiologically contaminated, highly lipemeic or haemolysed should not be used in the assay.
13. Plate readers measure vertically. Do not touch the bottom of the wells.

WARNINGS

1. This kit is intended for in vitro use by clinical professional only. Not for internal or external use in Humans or Animals.
2. Use appropriate personal protective equipment while working with the reagents provided.
3. Follow Good Laboratory Practice (GLP) for handling blood products.
4. All human source material used in the preparation of the reagents has been tested and found negative for antibody to HIV 1 & 2, HbsAg, and HCV. No test method however can offer complete assurance that HIV, HBV, HCV or other infectious agents are absent. Therefore, Standards and Controls should be handled in the same manner as potentially infectious material.
5. Material of animal origin used in the preparation of the kit has been obtained from animals certified as healthy and the bovine protein has been obtained from countries not infected by BSE, but these materials should be handled as potentially infectious.
6. Some reagents contain small amounts of Sodium Azide (NaN3) or Proclin 300™ as preservatives. Avoid the contact with skin or mucosa.
7. Sodium Azide may be toxic if ingested or absorbed through the skin or eyes; moreover, it may react with lead or copper plumbing to form potentially explosive metal azides. If you use a sink to remove the reagents, allow scroll through large amounts of water to prevent azide build-up.
8. The TMB Substrate contains an irritant, which may be harmful if inhaled, ingested or absorbed through the skin. To prevent injury, avoid inhalation, ingestion or contact with skin and eyes.
9. The Stop Solution consists of a diluted sulphuric acid solution. Sulphuric acid is poisonous and corrosive and can be toxic if ingested. To prevent chemical burns, avoid contact with skin and eyes.
10. Avoid the exposure of reagent TMB/H2O2 to directed sunlight, metals or oxidants. Do not freeze the solution.

LIMITATIONS OF USE

1. As in the case of any diagnostic procedure, results must be interpreted in conjunction with the patient's clinical presentation and other information available to the physician.
2. The performance characteristics of this assay have not been established in a paediatric population.
3. Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays[22]. Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed.
4. The presence of immune complexes or other immunoglobulin aggregates in the patient sample may cause an increased level of non-specific binding and produce false positives in this assay.

WASTE MANAGEMENT

Reagents must be disposed of in accordance with local regulations.

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PRODUCT COMPLAINTS AND TECHNICAL SUPPORT

For a patient/user/third party in the European Union and in countries with similar regulatory regime (Regulation 2017/746/EU on IVD Medical Devices); if, during the use of this device or as a result of its use, a serious incident has occurred, please report it to the manufacturer and/or its authorized representative and to your national regulatory authority.
The manufacturer can be contacted through their customer service or technical support team. The contact details can be found below and on the company website: www.rapidtest.com.

MANUFACTURER AND BRAND DETAILS

ISO 13485:2016

bsi ISO 13485 Quality Management for Medical Devices CERTIFIED

Diagnostic Automation/Cortez Diagnostics, Inc.
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Date Adopted	**2025-04**
Brand Name	**AccuDiag™**
REF 1492	**AccuDiag™ - Cardiolipin IgM ELISA**
PIC	**AD1492YS39**
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