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DCM091-10
Ed. 01/2024

Anti PR-3 (c-ANCA)

for routine analysis

Quantitative determination of IgG class antibodies against proteinase 3 (PR-3) in human serum or plasma

RUO

LOT
See external label

2°C 8°C

Σ = 96 tests

REF DKO091

1. INTENDED PURPOSE

For Research Use Only in the US
For Laboratory Professional Use

Anti PR-3 (c-ANCA) assay is a manual device intended for the quantitative determination of IgG class autoantibodies against proteinase 3 (PR-3) in human serum or plasma from an adult population. Results are to be used in conjunction with other clinical and laboratory data as an aid in the diagnosis of certain autoimmune vasculitides such as Wegener´s granulomatosis.

2. CLINICAL SIGNIFICANCE

Proteinase 3 (PR-3 or PR3) is a small serine protease located in the primary granules and secretory vesicles in the cytoplasm of neutrophils. PR3 is stored in the cytoplasmatic granules in resting neutrophils, whilst the expression of the protein on cell surface increases during the activation of neutrophils and during apoptosis[1]. PR3 is also found in neutrophil extracellular traps (NETs), that consist of chromatin released by neutrophils as defence against pathogens.

Autoantibodies against the PR3 are frequently detected in a specific class of autoimmune vasculitides known as Anti-neutrophil cytoplasmatic autoantibodies (ANCA) associated vasculitis (AAV). These vasculitides are characterised by the presence of autoantibodies against cytoplasmatic components of neutrophils that may have, cytoplasmatic staining (c-ANCA) or a perinuclear staining (p-ANCA)[1-3].

The mechanism of autoimmunity for ANCA antigens is not still being evaluated. Activated neutrophils can undergo apoptosis creating NETs, which are involved in the induction of inflammation. Persistence of NETs during the infection can lead to an autoimmune response[3,4]. Increased expression of MPO and PR3 in neutrophils and monocytes can influence the pathogenic autoimmune response leading to ANCA-neutrophils activation[3].

ANCA-associated vasculitides is classified as small vessel vasculitis (SVV), which predominantly affect the small vessels, intraparenchymal arteries, arterioles, capillaries and venules[5]. ANCA-associated vasculitides are necrotising vasculitis characterised by a lack of immune deposits in vessel walls causing conditions such as Microscopic polyangiitis (MPA) and Granulomatosis with polyangiitis (GPA, formerly known as Wegner's syndrome).

The frequency of serotype (MPO or PR3), clinical manifestation and geographic distribution of ANCA-associated vasculitides varies, suggesting a role of the environment and the genetic background of patients affected by this category of pathologies[1,3,6].

3. PRINCIPLE OF THE METHOD

The Anti PR-3 (c-ANCA) assay is an indirect enzyme immunometric assay (ELISA) where anti- PR3 (antibody) in the sample binds to human neutrophil proteinase 3 coated into the microplate (solid phase). In the first step the antibodies in calibrators, controls or prediluted patient samples bind to the inner surface of the wells. After a 60-minute incubation, the microplate is washed to remove non-reactive serum components. In the second step an anti-human-IgG horseradish peroxidase (HRP) conjugated solution binds to the IgG class antibodies bound to the immobilised antigens. After a further incubation step, any excess enzyme conjugate which is not specifically bound is washed away.

A chromogenic substrate solution containing TMB is then dispensed into the wells. After a further incubation step, the enzyme HRP in the bound fraction reacts with the Substrate (H_2O_2) and the TMB Substrate and develops a blue colour that changes into yellow when the Stop Solution (H_2SO_4) is added. The colour intensity is directly proportional to the concentration of IgG antibodies in the sample.

The concentration of anti- PR3 IgG antibodies in the sample is calculated through a calibration curve.

4. REAGENTS, MATERIALS AND INSTRUMENTATION

4.1. Reagents and materials supplied in the kit

1. Calibrators (5 vials, 1.2 mL each)
Phosphate buffer 0.1M, NaN_3 <0.1%, human serum

CAL0	**REF DCE002/09106-0**
CAL1	**REF DCE002/09107-0**
CAL2	**REF DCE002/09108-0**
CAL3	**REF DCE002/09109-0**
CAL4	**REF DCE002/09110-0**

2. Controls (2 vials, 1.2 mL each)
Phosphate buffer 0.1M, NaN_3 <0.1%, human serum

Negative control	**REF DCE045/09101-0**
Positive control	**REF DCE045/09102-0**

3. Sample Diluent (1 vial, 100 mL)
Phosphate buffer 0.1 M, NaN_3 < 0.1%
REF DCE053-0

4. Conjugate (1 vial, 15 mL)
Anti h-IgG conjugated with horseradish peroxidase (HRP), BSA 0.1%, contains ProClin™ >0.0015%
REF DCE002/09102-0

5. Coated Microplate (1 breakable microplate)
Microplate coated with human neutrophil proteinase 3
REF DCE002/09103-0

6. TMB Substrate (1 vial, 15 mL)
H_2O_2-TMB 0.26 g/L *(avoid any skin contact).* Contains ProClin™ <0.0015%
REF DCE004-0

7. Stop Solution (1 vial, 15 mL)
Sulphuric acid 0.15M *(avoid any skin contact)*
REF DCE005-0

8. 10X Conc. Wash Solution (1 vial, 50 mL)
Phosphate buffer 0.2M, pH 7.4, contains ProClin™ >0.0015%
REF DCE054-0

4.2. Materials required but not provided

Distilled water

4.3. Auxiliary materials and instrumentation

Automatic dispenser
Precision Pipetting Devices
Microplate reader (450 nm, 620-630 nm)

5. WARNINGS

- This kit is intended for *in vitro* use by professional persons only. Not for internal or external use in Humans or Animals.
- Use appropriate personal protective equipment while working with the reagents provided.
- Follow Good Laboratory Practice (GLP) for handling blood products.
- ⚠ All human source material used in the preparation of the reagents have been tested and found negative for antibodies 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, the Calibrators and the Controls should be handled in the same manner as potentially infectious material.
- ⚠ 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.
- Some reagents (conjugate and wash solution) contain small amounts of ProClin™ 300 (>0.0015%, <0.06%) as preservative. Avoid contact with skin or mucosa.
- Classification according to Regulation (EC) No. 1272/2008 [CLP]

Skin sensitivity, Category 1

Warning

Contains: ProClin 300

Hazard statements:
H317 - May cause an allergic skin reaction.

Precautionary statements:
P261 - Avoid breathing dust / fume / gas / mist / vapours / spray.
P280 - Wear protective gloves/ protective clothing / eye protection / face protection / hearing protection.
P321 - Specific treatment (see supplemental first aid instruction on this label).
P333+P313 - If skin irritation or rash occurs: Get medical advice/attention.
P362+P364 - Take off contaminated clothing and wash it before reuse.

- Some reagents (calibrators, controls and sample diluent) contain small amounts of Sodium Azide (NaN_3) <0.1% which 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, wash through with large amounts of water to prevent azide build-up.
- The TMB Substrate contains an irritant, which harmful if inhaled, ingested or absorbed through the skin. To prevent injury, avoid inhalation, ingestion or contact with skin and eyes.
- The Stop Solution consists of a diluted sulphuric acid solution. Sulphuric acid is poisonous, corrosive and can be toxic if ingested. To prevent chemical burns, avoid contact with skin and eyes.
- Avoid the exposure of reagent TMB/H_2O_2 to direct sunlight, metals or oxidants. Do not freeze the solution.

6. PRECAUTIONS

- 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.
- All reagents should be stored refrigerated at 2-8°C in their original container. Any exceptions are clearly indicated.
- Allow all kit components and specimens to reach room temperature (22-28°C) and mix well prior to use.
- 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.
- If you use automated equipment, the user has the responsibility to make sure that the kit has been appropriately tested.
- 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 number of washes.

- 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.
- 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.
- Observe the guidelines for performing quality control in medical laboratories by assaying controls and/or pooled sera.
- Maximum precision is required for reconstitution and dispensation of the reagents.
- Samples microbiologically contaminated, highly lipemic, icteric or haemolysed should not be used in the assay.
- Plate readers measure vertically. Do not touch the bottom of the wells.
- **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, deproteinisation and decontamination are effective in avoiding contamination of the conjugate; this procedure is highly recommended when the kit is processed using analysers which are not equipped with disposable tips.
  For this purpose, Diametra supplies a separate decontamination reagent for cleaning needles.
- Fresh disposable tips must be used when pipetting assay reagents including samples, calibrators and controls to mitigate the risk of carryover contamination. Failure to do so may lead to invalid results.

7. REAGENT STORAGE AND STABILITY

Store the kit at 2 – 8°C in the dark.

- The kit is stable at 2 – 8°C until the expiry date stated on the external kit label.
- Once opened, the kit is stable at 2 – 8°C for 6 months.
- 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.

8. 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, or potassium EDTA) samples.

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

9. PROCEDURE

9.1. Preparation of Calibrators and Controls

Since no international reference preparation for Anti-proteinase 3 antibodies is available, the assay system is calibrated in relative arbitrary units. The Calibrators are ready to use and have the following concentration:

	C_0	C_1	C_2	C_3	C_4
AU/mL	0	10	20	40	160

The controls are ready to use; the concentration of the control is printed on the label.

9.2. Preparation of the Conjugate

The conjugate is ready to use. Mix gently, for 5 minutes, on a roller mixer.

9.3. 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.

9.4. Preparation of Samples

The determination of Anti PR-3 IgG can be performed in human serum or plasma samples.

All serum or plasma samples must be prediluted 1:100 with sample diluent; for example, 10 µL of sample should be diluted with 990 µL of sample diluent.

Fasting samples are not necessary and no special sample preparations are required.

Collect blood by venepuncture into vacutainers and separate serum (after clot formation) or plasma from the cells by centrifugation. Testing of heat-inactivated sera is not recommended.

Store the sample at -20°C if the determination is not performed on the same day of the sample collection. Before using, mix gently, for 5 minutes, with a roller mixer.

9.5. 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 calibration curve (C_0-C_4), two for each Control, two for each sample, one for Blank.

Reagent	Calibrator	Sample/ Controls	Blank
Calibrator C_0-C_4	**100 µL**		
Controls		**100 µL**	
Diluted Sample		**100 µL**	
Incubate 60 minutes at room temperature (22-28°C). Remove the content from each well, wash the wells 3 times with 300 µL of 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	**100 µL**	**100 µL**	
Incubate 30 minutes at room temperature (22-28°C). Remove the contents from each well, wash the wells 3 times with 300 µL of diluted wash solution. **Washing**: follow the same indications of the previous point.			
TMB Substrate	**100 µL**	**100 µL**	**100 µL**
Incubate 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.			

10. 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.

DiaMetra 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[7].

11. 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, **including Calibrator 0 is required.** A smoothed spline and log-log 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.

In order for the test results to be considered valid, all of the criteria listed below must be met. If any of these are not met, the test should be considered invalid and the assay repeated:

- The absorbance of the prediluted PR-3 IgG Positive Control must be greater than the absorbance of the prediluted Negative Control.
- The negative and positive controls are intended to monitor for substantial reagent failure and they will not ensure precision at the assay cut-off.
- This test is only valid if the optical density at 450 nm for Negative Control and Positive Control as well as for the Calibrator C_0-C_4 complies with the respective range indicated on the Quality Control Certificate enclosed to each test kit: if any of these criteria is not met, the results are invalid and the test should be repeated.

12. MEASURING RANGE

The assay measuring range (AMR) is 3 – 160 AU/mL.
Any value that reads below 3 AU/mL should be reported as "< 3 AU/mL". Any value that reads above 160 AU/mL should be reported as "> 160 AU/mL".

13. METROLOGY AND TRACEABILITY

The calibrators of this kit are traceable to the Centres for Disease Control and Prevention (CDC) Human Reference Serum #16 for Anti-Proteinase 3 Ab Catalogue #IS2721.

14. EXPECTED VALUES

The following ranges were determined using the Anti PR-3 (c-ANCA) assay and are provided for information only. The 90 % reference interval for apparently healthy adults were calculated by a non-parametric method following guidance from CLSI C28-A3 "Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory".

No. of subjects	73
Mean (AU/mL)	8.71
SD (AU/mL)	3.21
Median (AU/mL)	8.12
Reference Interval (AU/mL)	4.19 – 14.40

The above ranges should be considered as guidelines only; it is recommended that each laboratory establish its own expected range based upon its own patient population.

15. INTERPRETATION OF RESULTS

Concentration	Interpretation
< 16 AU/mL	The sample should be considered negative
16 – 20 AU/mL	The sample should be graded equivocal and repeat testing / sampling should be performed according to internal practices
≥ 20 AU/mL	The sample should be considered positive

The above index and interpretation should be considered as guidelines only. Positive results should be verified concerning the entire clinical status of the patient. Also, every decision for therapy should be taken on an individual patient basis.

It is recommended that each laboratory establishes its own normal and pathological ranges of anti- PR3.

16. PERFORMANCE CHARACTERISTICS

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

16.1. 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)	0.6 AU/mL
Limit of Detection (LoD)	1.6 AU/mL
Limit of Quantitation (LoQ)	3.2 AU/mL

16.2. Trueness

Trueness has been demonstrated through a recovery test of the Anti PR-3 (c-ANCA) assay with the human Anti-Proteinase 3 reference serum #16 from the Centres for Disease Control and Prevention (CDC).

16.3. Precision

Precision of the Anti PR-3 (c-ANCA) assay was determined by performing a complex precision study.

Repeatability: A total of 6 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	16.51	0.96	5.8%
2	75	23.94	0.93	3.9%
3	75	40.03	1.23	3.1%
4	75	59.68	3.40	5.7%
5	75	86.96	2.80	3.2%
6	75	136.70	6.24	4.6%

Reproducibility: A total of 6 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	16.57	1.49	9.0%
2	150	23.95	1.53	6.4%
3	150	40.59	2.67	6.6%
4	150	60.11	4.15	6.9%
5	150	86.69	6.12	7.1%
6	150	137.19	9.63	7.0%

16.4. Linearity

Linearity was evaluated based on CLSI EP-06, "Evaluation of the Linearity of Quantitative Measurement Procedures". For anti- PR3 concentration by Anti PR-3 (c-ANCA) assay, the measurement procedure shows linearity for the interval from 1.73 to 162.62 AU/mL within the allowable deviation of linearity (ADL) of ±15 %.

16.5. 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 50 positive samples run on a single reagent lot.

		DKO091		Total
		Positive	Negative	
True state	Positive	50	0	**50**
	Negative	2	71	**73**
Total		**52**	**71**	**123**

Diagnostic sensitivity: 100%

Diagnostic specificity: 97.3%

16.6. Interferents

The following substances do not interfere with a bias of > ±15% in the Anti PR-3 (c-ANCA) 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
Triglycerides	500 mg/dL

16.7. Serum-plasma study

The Anti PR-3 (c-ANCA) assay 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 or diluted) to cover the range of 2.80 to 74.40 AU/mL were evaluated. Linear regression analysis was performed on the comparative data:

Sample type	Slope [95% CI]	Intercept (AU/mL) [95% CI]	Correlation coefficient (r)
SST	1.0 [0.97 to 1.08]	0.14 [-1.17 to 1.45]	0.99
Lithium Heparin	1.1 [1.06 to 1.21]	-0.46 [-2.09 to 1.17]	0.99
Sodium Heparin	1.1 [1.05 to 1.14]	-0.91 [-1.88 to 0.06]	1.00
EDTA	1.1 [1.0 to 1.12]	0.00 [-1.79 to 1.78]	0.99

17. LIMITATIONS OF USE

- 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.
- The performance characteristics of this assay have not been established in a paediatric population.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays[8]. Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed.

18. WASTE MANAGEMENT

Reagents must be disposed of in accordance with local regulations.

All materials that have come into contact with samples and reagents must be disposed of in accordance with country, state and local regulations.

19. BIBLIOGRAPHY

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20. REVISION IDENTIFIER

Additions or changes to the IFU are indicated by grey highlighting.

21. 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 authorised 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.diametra.com.

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Fax +39-0742-316197

DiaMetra	Packaging Information Sheet	Mod. PIS000-2

RUO	EN	Research Use Only Medical Device		DE ES FR EN IT PT	Hergestellt von Elaborado por Fabriqué par Manufacturer Produttore Produzido por
	DE ES FR EN IT PT	Achtung, Begleitdokumente Precaución, consulte los documentos adjuntos Attention, veuillez consulter les documents d'accompagnement Caution, consult accompanying documents Attenzione, consultare la documentazione allegata Atenção,consultar os documentos de acompanhamento	 yyyy-mm	DE ES FR EN IT PT	Herstellungs datum Fecha de fabricacion Date de fabrication Date of manufacture Data di produzione Data de produção
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