Elecsys Anti-CCP

cobas®

REF		Σ	SYSTEM
07251670190	07251670500	100	**cobas e** 402 **cobas e** 801

English

System Information

Short name	ACN (application code number)
ACCP	10084

Please note

The measured anti-CCP value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the anti-CCP assay method used. Anti-CCP values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations. Therefore, the results reported by the laboratory to the physician should include: "The following results were obtained with the Elecsys Anti-CCP assay. Results from assays of other manufacturers cannot be used interchangeably."

Intended use

Immunoassay for the in vitro semi-quantitative determination of human IgG autoantibodies to cyclic citrullinated peptides in human serum. The results of the assay are intended to be used as an aid in the diagnosis of rheumatoid arthritis in combination with other clinical and laboratory findings.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases, affecting 0.5-1 % of the world population. This systemic disease is characterized by chronic inflammation of the synovial joints and progressive joint degeneration eventually leading to disability of affected individuals.[1]

The diagnosis of RA often relies on clinical manifestations and laboratory tests such as rheumatoid factor (RF) and C-reactive protein (CRP). However, RF is non-specific for RA and may be present in healthy elderly persons or in patients with other autoimmune and infectious diseases and CRP is a general inflammation marker.

Recently, the identification of citrulline as a target of a whole set of autoantibodies like anti-perinuclear factor (APF), anti-keratin antibodies (AKA), anti-filaggrin antibodies (AFA) etc. detected in the sera of RA patients has led to the development of anti-CCP assays that possess a high specificity for RA. The clinical performance of anti-CCP assays has been further improved by the use of multiple citrullinated peptides, resulting in a second generation of anti-CCP assays.[2,3,4,5,6,7,8,9,10,11]

The Elecsys Anti-CCP assay uses a set of cyclic citrullinated peptides and is therefore a so-called second-generation assay.

In 2010, the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) have developed new classification criteria for RA to improve earlier diagnosis. Anti-CCP assay as one diagnostic element has been added to the recommendation.[12] Strong association of anti-CCP antibodies and RA was confirmed in an observational study with 1162 patients.[13]

Test principle

IgG-capture test principle. Total duration of assay: 18 minutes.

- 1st incubation: 9 µL of sample are incubated with biotinylated cyclic citrullinated peptides and ruthenylated[a)] monoclonal antibody against human IgG, forming a complex when CCP-specific antibodies are present in the sample.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as ACCP.

M Streptavidin-coated microparticles, 1 bottle, 5.8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 CCP~biotin, 1 bottle, 9.9 mL:
Biotinylated cyclic citrullinated peptides (synthetic) approximately 1.1 µg/mL, phosphate buffer 100 mmol/L, pH 5.0; preservative.

R2 Anti-human aggregated IgG~$Ru(bpy)_3^{2+}$, 1 bottle, 10.3 mL:
Ruthenylated monoclonal anti-human IgG antibody (mouse) 0.75 µg/mL; phosphate buffer 100 mmol/L, pH 6.0; preservative.

ACCP Cal1 Anti-CCP calibrator 1 (lyophilized), 2 bottles for 1.0 mL each:
Anti-CCP antibodies (human) approximately 20 U/mL in a human serum matrix.

ACCP Cal2 Anti-CCP calibrator 2 (lyophilized), 2 bottles for 1.0 mL each:
Anti-CCP antibodies (human) approximately 200 U/mL in a human serum matrix.

Calibrators: The exact lot-specific calibrator values are available via the **cobas** link.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317 May cause an allergic skin reaction.

Prevention:

P261 Avoid breathing dust/fume/gas/mist/vapours/spray.

P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

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P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved by the FDA or that are in compliance with the legal rules applicable to placing in vitro diagnostic medical devices for human use on the market in the European Union.

The calibrators (ACCP Cal1, ACCP Cal2) have been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[14,15]

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

Calibrators

Carefully dissolve the contents of one bottle by adding exactly 1.0 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation. Transfer the reconstituted calibrators into the supplied empty labeled snap-cap bottles (CalSet Vials). Attach the supplied labels to the additional bottles. Store the aliquots immediately at -20 °C.

Perform **only one** calibration procedure per aliquot.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Stability of the calibrators:	
lyophilized calibrators	up to the stated expiration date
reconstituted calibrators at -20 °C	8 weeks (freeze only once)
on the analyzers at 20-25 °C	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Stable for 3 days at 20-25 °C, 8 days at 2-8 °C, 12 months at -20 °C (± 5 °C).

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates and thawed samples before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels
- 4 empty labeled snap-cap bottles

Materials required (but not provided)

- REF 05031664190, PreciControl Anti-CCP, for 4 x 2.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- **cobas e** analyzer
- Distilled or deionized water

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibrators:

Place the reconstituted calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

Traceability: This method has been standardized against a commercially available second-generation anti-CCP assay.

The predefined master curve is adapted to the analyzer using ACCP Cal1 and ACCP Cal2.

Calibration frequency: Calibration must be performed once per reagent lot using ACCP Cal1 and ACCP Cal2 and fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

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Quality control

For quality control, use PreciControl Anti-CCP.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in U/mL.

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 427 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.311 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 287 nmol/L or ≤ 70 ng/mL
Rheumatoid factors	≤ 150 IU/mL
IgA	≤ 0.4 g/dL
IgM	≤ 0.230 g/dL

Criterion: For concentrations of 8-25 U/mL the deviation is ≤ 5 U/mL. For concentrations > 25 U/mL the deviation is ≤ 15 %.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

Autoantibodies are heterogeneous and this gives rise to non-linear dilution phenomena for certain individual samples.

There is no high-dose hook effect at anti-CCP concentrations up to 7000 U/mL.

IgG (hypergammaglobulinemia)

Interference with pathologic levels of unspecific IgG can not be excluded.

The anti-CCP test results can be false negative in patients with hypergammaglobulinemia. Results from patients suffering from this disorder should not be used for diagnostic purposes.

However, the coincidence of RA and gammopathy in one patient has been reported to be very low.[16]

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals and in addition on methotrexate and prednisolone. No interference with the assay was found.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

8-500 U/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 8 U/mL. Values above the measuring range are reported as > 500 U/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 7 U/mL

Limit of Detection = 8 U/mL

Limit of Quantitation = 8 U/mL

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

It has been determined using low concentration anti-CCP samples.

Dilution

Samples with anti-CCP concentrations above the measuring range can be diluted manually using an anti-CCP negative serum pool. The recommended dilution is 1:2 to 1:5.

After manual dilution, multiply the result by the dilution factor.

Note: Autoantibodies are heterogeneous and this gives rise to non-linear dilution phenomena for certain individual samples.[17,18]

Expected values

In an external study using the Elecsys Anti-CCP assay on samples from 420 asymptomatic healthy individuals, 792 confirmed RA patients and 907 patients with other rheumatic and non-rheumatic disorders an optimal cutoff of 17 U/mL was determined; samples with a concentration ≥ 17 U/mL being considered positive for anti-CCP (for details see section "Clinical Sensitivity and Specificity").

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human serum 1	13.4	0.202	1.5	0.291	2.2
Human serum 2	15.2	0.189	1.2	0.261	1.7
Human serum 3	21.8	0.307	1.4	0.393	1.8
Human serum 4	112	1.42	1.3	1.64	1.5
Human serum 5	252	2.90	1.2	3.15	1.3
Human serum 6	470	8.71	1.9	9.12	1.9
PC[b)] Anti-CCP 1	17.8	0.282	1.6	0.436	2.4
PC Anti-CCP 2	88.5	0.824	0.9	1.54	1.7

b) PC = PreciControl

Clinical sensitivity and specificity

In a cohort of 792 confirmed RA patients, 420 asymptomatic healthy individuals and 907 patients with other rheumatic and non-rheumatic

disorders an optimal cutoff of 17 U/mL was determined. At this cutoff the sensitivity was calculated to be 67.4 % with a specificity of 97.0 %. The area under the receiver operating characteristic (ROC) curve was 0.85.

The health status of 420 asymptomatic healthy volunteers (213 men, 207 women) was confirmed by a standard clinical chemistry and hematology profile and a brief medical examination. In particular, elevated CRP levels, elevated white blood cell counts and elevated uric acid levels were excluded for this group. A family history of rheumatic / autoimmune disorders was excluded through a medical questionnaire.

The group of established RA patients consisted of patients with unknown disease duration as well as patients with a known disease duration of more than 2 years or less than 2 years. Disease duration was measured from the time point of RA diagnosis by an experienced rheumatologist.

	N	Number of samples found positive with the Elecsys Anti-CCP assay	Sensitivity %
RA samples in total	792	534	67.4
RA, > 2 years	378	273	72.2

Clinical specificity

	N	Number of samples found negative with the Elecsys Anti-CCP assay	Specificity %
Non-RA samples in total	1327	1287	97.0
Healthy	420	416	99.0
Non-RA disease samples in total	907	871	96.0
Non-RA disease subsets:			
Connective tissue diseases	166	157	94.6
Vasculitides	47	43	91.5
Spondyloarthropathies	146	138	94.5
Other rheumatic diseases	108	106	98.1
Inflammatory bowel diseases	52	52	100
Non-rheumatic autoimmune diseases	31	29	93.5
Renal failure	31	30	96.8
Liver cirrhosis	26	24	92.3
Infectious diseases	300	292	97.3

Method comparison

A subset of the sample collectives, used to determine the clinical performance of the Elecsys Anti-CCP assay was also used to compare the Elecsys Anti-CCP assay to a commercially available, second-generation anti-CCP microtiter plate ELISA assay. The respective assay was used according to the manufacturer's instructions given in the package insert. Using a cutoff of ≥ 17 U/mL for the Elecsys Anti-CCP assay the following results were obtained:*

N = 1606		Commercially available, second-generation anti-CCP assay	
		positive	negative
Elecsys Anti-CCP assay	positive	428	18
	negative	26	1134

	Total	Samples concordant in both assays	Concordance %	95 % confidence interval
Positive concordance	454	428	94.3	91.7-96.2
Negative concordance	1152	1134	98.4	97.5-99.1
Concordance in clinical subgroups				
Non-RA group	992	968	97.6	96.4-98.4
RA group	614	594	96.7	95.0-98.0
Concordance over all samples	1606	1562	97.3	96.3-98.0

* Representative data, results from individual laboratories might differ.

The obtained results were also used to perform a ROC (receiver operating characteristic) analysis. The area under the curve (AUC) for the Elecsys Anti-CCP assay was 0.86 (95 % confidence interval: 0.84-0.88) and 0.81 (95 % confidence interval: 0.79-0.84) for the commercially available, second-generation anti-CCP assay used in this method comparison, thus indicating that both assays are comparable with respect to their clinical differentiation.

a) A comparison of the Elecsys Anti-CCP assay, REF 07251670190 (**cobas e** 801 analyzer; y) with the Elecsys Anti-CCP assay, REF 05031656190 (**cobas e** 601 analyzer; x) gave the following correlation (U/mL):
Number of samples measured: 276

Passing/Bablok[19]	Linear regression
y = 1.001x + 0.248	y = 1.010x + 0.565
τ = 0.955	r = 0.990

The sample concentration were between 8.34 and 499 U/mL.

b) A comparison of the Elecsys Anti-CCP assay, REF 07251670190 (**cobas e** 402 analyzer; y) with the Elecsys Anti-CCP assay, REF 07251670190 (**cobas e** 801 analyzer; x) gave the following correlations (U/mL):

Number of samples measured: 124

Passing/Bablok[19]	Linear regression
y = 0.983x - 0.103	y = 0.962x + 2.25
τ = 0.987	r = 0.999

The sample concentrations were between 10.3 and 483 U/mL.

References

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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

Additions, deletions or changes are indicated by a change bar in the margin.

CE 0123

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