# Elecsys CA 19-9

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| REF | | Σ | SYSTEM |
|---|---|---|---|
| 07027028190*<br>07027028214* | 07027028500 | 300 | **cobas e** 402<br>**cobas e** 801 |

* Some kits shown may not be available in all countries.

## English

### System information

| Short name | ACN (application code number) |
|---|---|
| CA 19-9 | 10019 |

**Please note**

The measured CA 19-9 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 CA 19-9 assay method used. CA 19-9 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. If there is a change in the CA 19-9 assay procedure used while monitoring therapy, then the CA 19-9 values obtained upon changing over to the new procedure must be confirmed by parallel measurements with both methods.

### Intended use

Immunoassay for the in vitro quantitative determination of CA 19-9 in human serum and plasma.

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

### Summary

Measurements of carbohydrate antigen 19-9 (CA 19-9) performed with this assay in human serum and plasma are used in conjunction with other procedures to aid in the diagnosis, prognosis and management of pancreatic and other gastrointestinal cancers.

CA 19-9 (carbohydrate antigen 19-9 or sialylated Lewis (a) antigen) belongs to the large family of mucinous markers. It is normally present in small amounts in serum as a carbohydrate-rich glycoprotein associated primarily with mucin.[1] Elevated concentrations have been found under several physiological and clinical conditions.[1,2] In relation to malignant diseases, increased CA 19-9 levels have been reported in multiple cancer types, such as pancreatic, colorectal, gastric, hepatocellular and hepatobiliary cancers.[1] Benign diseases associated with increased CA19-9 serum levels include acute and chronic pancreatitis, liver cirrhosis, cholangitis and obstructive jaundice.[1, 2,3,4] The common underlying mechanism for elevations in non-malignant conditions could include inflammatory hypersecretion by epithelial cells or leakage of biliary mucins carrying the epitope of CA 19-9 into serum.[1] Notably, approximately 6 % of the Caucasian population and about 22 % of non-Caucasican population belongs to the Lewis (a-/b-) blood group, lacking the antigenic determinant CA 19-9 and will therefore not release CA 19-9 even when a malignancy is present.[1]

In view of the above findings, CA 19-9 is not useful for screening for malignancies in asymptomatic individuals.[5,6,7,8] Most expert groups cautiously recommend measurement of CA 19-9 in the initial work-up of patients presenting with suspected pancreatic cancer.[6] Although CA 19-9 levels are of limited sensitivity for small pancreatic cancers, nearly 80 % of patients with advanced pancreatic cancer report increased serum levels of CA 19-9.[7] CA 19-9 can be used as a serum marker to measure the disease burden and prognosis of pancreatic cancer, to potentially guide treatment decisions, and to monitor treatment and disease course.[5,6,7,8,9]

CA 19-9 has shown clinical utility in the diagnosis, prognosis and monitoring of hepatobiliary cancers, including cholangiocarcinoma.[10,11,12,13,14] In colorectal cancer, CA 19-9 is described as a possible emerging marker for postoperative disease monitoring, in conjunction with carcinoembryonic antigen (CEA).[15,16,17,18,19]

### Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample, a biotinylated monoclonal CA 19-9-specific antibody, and a monoclonal CA 19-9-specific antibody labeled with a ruthenium complex[a)] form a sandwich complex.
- 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 is labeled as CA19-9.

M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-CA 19-9-Ab~biotin, 1 bottle, 18.8 mL:
Biotinylated monoclonal anti-CA 19-9 antibody (mouse) 3 mg/L, phosphate buffer 100 mmol/L, pH 6.5; preservative.

R2 Anti-CA 19-9-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 21.0 mL:
Monoclonal anti-CA 19-9 antibody (mouse) labeled with ruthenium complex 4 mg/L; phosphate buffer 100 mmol/L, pH 6.5; preservative.

### 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 mist or vapours. |
| 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. |
| P362 + P364 | Take off contaminated clothing and wash it before reuse. |
| **Disposal:** | |
| P501 | Dispose of contents/container to an approved waste disposal plant. |

# Elecsys CA 19-9

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Product safety labeling follows EU GHS guidance.

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

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

**Reagent handling**

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

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: | |
|---|---|
| unopened at 2-8 °C | up to the stated expiration date |
| on the analyzers | 16 weeks |

**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.

Li-heparin, $K_2$-EDTA and $K_3$-EDTA plasma.

Do not use sodium citrate plasma.

Criterion: Slope 0.9-1.1 + coefficient of correlation ≥ 0.95.

Stable for 14 days at 2-8 °C, 5 days at 20-25 °C, 3 months at -20 °C (± 5 °C). Freeze only once.

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 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.

**Materials required (but not provided)**

- REF 11776215122, CA 19-9 CalSet, for 4 x 1.0 mL
- REF 11776452122, PreciControl Tumor Marker, for 4 x 3.0 mL
- REF 07299001190, Diluent Universal, 36 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

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.

**Calibration**

Traceability: This method has been standardized against the Enzymun-Test CA 19-9 method.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

*Calibration frequency:* Calibration must be performed once per reagent lot using 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

**Quality control**

Use PreciControl Tumor Marker or other suitable controls for routine quality control procedures.

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 (either in U/mL or kU/L).

**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 | ≤ 1130 µmol/L or ≤ 66 mg/dL |
| Hemoglobin | ≤ 0.621 mmol/L or ≤ 1000 mg/dL |
| Intralipid | ≤ 1500 mg/dL |
| Biotin | ≤ 409 nmol/L or ≤ 100 ng/mL |
| Rheumatoid factors | ≤ 1200 IU/mL |

Criterion: Recovery ± 4.5 U/mL of initial value for samples ≤ 30 U/mL and within ± 15 % of initial value for samples > 30 U/mL.

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.

There is no high-dose hook effect at CA 19-9 concentrations up to 500000 U/mL.

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*Pharmaceutical substances*
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special cancer drugs were tested. No interference with the assay was found.

*Special cancer drugs*

| Drug | Concentration tested mg/L |
|---|---|
| Doxorubicin | 75 |
| Cyclophosphamide | 1000 |
| Cisplatin | 225 |
| 5-Flourouracil | 500 |
| Methotrexate | 1000 |
| Tamoxifen | 50 |
| Mitomycin | 25 |
| Carboplatin | 1000 |
| Etoposide | 400 |
| Flutamide | 1000 |
| Taxol | 5.5 |

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**

2-1000 U/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 2 U/mL. Values above the measuring range are reported as > 1000 U/mL or up to 10000 U/mL for 10-fold diluted samples).

**Lower limits of measurement**

*Limit of Blank, Limit of Detection and Limit of Quantitation*

Limit of Blank = 1.5 U/mL

Limit of Detection = 2 U/mL

Limit of Quantitation = 9 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 95$^{th}$ 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 %.

An internal study was performed based on guidance from the CLSI, protocol EP17-A2. Limit of Blank and Limit of Detection were calculated to be the following:

Limit of Blank = 0.876 U/mL

Limit of Detection = 1.89 U/mL

For Limit of Quantitation ≥ 4 human serum samples were measured over 5 days with 5 replicates on one analyzer. With an intermediate precision of ≤ 20 % the Limit of Quantitation was 2.72 U/mL.

**Dilution**

Samples with CA 19-9 concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:10 (either automatically by the analyzer or manually). The concentration of the diluted sample must be > 50 U/mL.

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

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Note: The CA 19-9 antigen tends to aggregate.[20] This may lead to non-linear dilution behavior in certain individual samples.

**Expected values**

In samples from 381 healthy test subjects (n = 187) and blood donors (n = 194), the following values were obtained:

27 U/mL (95$^{th}$ percentile)

34 U/mL (97.5$^{th}$ percentile)

39 U/mL (99$^{th}$ percentile)

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, samples 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 | 4.00 | 0.106 | 2.7 | 0.119 | 3.0 |
| Human serum 2 | 8.69 | 0.143 | 1.6 | 0.150 | 1.7 |
| Human serum 3 | 21.0 | 0.235 | 1.1 | 0.287 | 1.4 |
| Human serum 4 | 34.1 | 0.405 | 1.2 | 0.435 | 1.3 |
| Human serum 5 | 498 | 5.90 | 1.2 | 7.15 | 1.4 |
| Human serum 6 | 910 | 11.6 | 1.3 | 15.7 | 1.7 |
| PreciControl TM[b)]1 | 22.2 | 0.278 | 1.3 | 0.361 | 1.6 |
| PreciControl TM2 | 89.9 | 0.999 | 1.1 | 1.15 | 1.3 |

b) TM = Tumor Marker

**Method comparison**

a) A comparison of the Elecsys CA 19-9 assay, REF 07027028190 (**cobas e** 801 analyzer; y) with the Elecsys CA 19-9 assay, REF 11776193122 (**cobas e** 601 analyzer; x) gave the following correlations (U/mL):

Number of serum samples measured: 198

| Passing/Bablok[21] | Linear regression |
|---|---|
| y = 0.968x - 0.359 | y = 0.960x + 0.213 |
| τ = 0.988 | r = 0.999 |

The sample concentrations were between 4.00 and 981 U/mL.

b) A comparison of the Elecsys CA 19-9 assay, REF 07027028190 (**cobas e** 402 analyzer; y) with the Elecsys CA 19-9 assay, REF 07027028190 (**cobas e** 801 analyzer; x) gave the following correlations (U/mL):

Number of serum samples measured: 117

| Passing/Bablok[21] | Linear regression |
|---|---|
| y = 0.971x - 0.221 | y = 0.975x - 0.760 |
| τ = 0.988 | r = 1.00 |

The sample concentrations were between 5.38 and 985 U/mL.

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**Analytical specificity**

The Elecsys CA 19-9 tumor marker assay is based on the monoclonal 1116-NS-19-9 antibody which is only available from Fujirebio Diagnostics, its licensees and its representatives. The performance characteristics of testing procedures using this antibody cannot be assumed for testing methods using other antibodies.

**References**


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For further information, please refer to the appropriate user guide or operator's manual for the analyzer concerned, the respective application sheets 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.

FUJIREBIO® Diagnostics, Inc.

CA 19-9 is a registered trademark of Fujirebio Diagnostics, Inc.

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.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

**Symbols**

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.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 for reconstitution |
| GTIN | Global Trade Item Number |
| Rx only | For USA: Caution: Federal law restricts this device to sale by or on the order of a physician. |



CE 0123


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