

Elecsys CYFRA 21-1

| | | | |
|--------------|-------------|-----|--------------------|
| REF | | | SYSTEM |
| 07299966190* | 07299966500 | 300 | cobas e 402 |
| 07299966214* | | | cobas e 801 |

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

English

System information

| | |
|------------|-------------------------------|
| Short name | ACN (application code number) |
| CYFRA | 10030 |

Please note

The measured CYFRA 21-1 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 CYFRA 21-1 assay method used. CYFRA 21-1 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 CYFRA 21-1 assay procedure used while monitoring therapy, then the CYFRA 21-1 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 fragments of cytokeratin 19 in human serum and plasma.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Cytokeratins are structural proteins forming the subunits of epithelial intermediary filaments. Twenty different cytokeratins have so far been identified, CYFRA 21-1 which is a fragment of cytokeratin 19, being the most prominent one. Intact cytokeratin polypeptides are poorly soluble, but soluble fragments like CYFRA 21-1, are frequently released into the blood of cancer patients and can be detected in serum.¹ Although being expressed in different organs, its major occurrence is in the lung. CYFRA 21-1 can be considered as the biomarker of choice for non-small cell lung cancer (primarily for squamous cell and large cell carcinoma subtypes).^{2,3,4,5,6} In adenocarcinoma of the lung, a combination of CYFRA 21-1 and Carcinoembryonic antigen (CEA) has been found to be the most useful.^{7,8}

The main indication for CYFRA 21-1 is monitoring the course of NSCLC.⁹ Successful therapy is accompanied by a rapid decrease of serum levels to the normal range.^{9,10}

Increased CYFRA 21-1 levels have also been described in non-malignant diseases (i.e. pneumonia, sepsis)^{11,12,13} and renal dysfunction.¹⁴ Therefore evaluation of renal function (i.e. by measuring serum creatinine levels) should be considered in cases of high CYFRA 21-1 levels that are not consistent with the diagnostic and clinical characteristics of the patient.

With the use of two specific monoclonal antibodies (KS 19.1 and BM 19.21), the Elecsys CYFRA 21-1 assay measures a fragment of cytokeratin 19 having a molecular weight of approximately 30000 Da.¹⁵

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, a biotinylated monoclonal cytokeratin 19-specific antibody, and a monoclonal cytokeratin 19-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)₃²⁺)

Reagents - working solutions

The **cobas e** pack is labeled as CYFRA.

- M Streptavidin-coated microparticles, 1 bottle, 13.2 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-cytokeratin 19-Ab~biotin, 1 bottle, 19.7 mL:
Biotinylated monoclonal anti-cytokeratin 19 antibody (KS 19.1; mouse) 1.5 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.
- R2 Anti-cytokeratin 19-Ab~Ru(bpy)₃²⁺, 1 bottle, 18.8 mL:
Monoclonal anti-cytokeratin 19 antibody (BM 19.21; mouse) labeled with ruthenium complex 2 mg/L; phosphate buffer 100 mmol/L, pH 7.2; 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.

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).

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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, K₂-EDTA and K₃-EDTA plasma.

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ± 0.3 ng/mL + coefficient of correlation ≥ 0.95 .

Stable for 7 days at 20-25 °C, 30 days at 2-8 °C, 6 months at -20 °C (± 5 °C). Freeze only once.

It is recommended that the samples be mixed by careful swirling or by placing on a roller mixer (maximum 5 minutes). Homogenization of samples using electric vibration mixers must be limited to a maximum of 5 seconds. Longer mixing times lead to lower values being found.

Contamination of the sample with saliva leads to falsely elevated results.

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] 11820974322, CYFRA 21-1 CalSet, for 4 x 1.0 mL
- [REF] 11776452122, PreciControl Tumor Marker, for 4 x 3.0 mL or
- [REF] 07360070190, PreciControl Lung Cancer, 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 CYFRA 21-1 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

For quality control, use PreciControl Tumor Marker or PreciControl Lung Cancer.

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 either in ng/mL or µg/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 | ≤ 1112 µmol/L or ≤ 65 mg/dL |
| Hemoglobin | ≤ 0.621 mmol/L or ≤ 1000 mg/dL |
| Intralipid | ≤ 1500 mg/dL |
| Biotin | ≤ 205 nmol/L or ≤ 50 ng/mL |
| Rheumatoid factors | ≤ 1200 IU/mL |

Criterion: For concentrations of 0.1-1 ng/mL the deviation is ± 0.1 ng/mL. For concentrations > 1 ng/mL the deviation is ± 10 %.

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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 CYFRA 21-1 concentrations up to 2000 ng/mL.

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 | 120 |
| Cyclophosphamide | 1000 |
| Cisplatin | 225 |
| 5-FU | 500 |
| Methotrexate | 1000 |
| Tamoxifen | 50 |
| Mitomycin | 25 |
| Carboplatin | 1000 |
| Etoposide | 400 |
| Paclitaxel | 265 |
| Clotrimazole | 0.3 |
| Dexamethasone | 20 |
| Leucovorin | 750 |
| Melphalan | 15 |
| Tarceva | 150 |

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

0.1-500 ng/mL (defined by the Limit of Blank and the maximum of the master curve). Values below the Limit of Blank are reported as < 0.1 ng/mL. Values above the measuring range are reported as > 500 ng/mL (or up to 1000 ng/mL for 2-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.1 ng/mL

Limit of Detection = 0.3 ng/mL

Limit of Quantitation = 0.5 ng/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 $n \geq 60$ 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 determined to be the following:

Limit of Blank = 0.069 ng/mL

Limit of Detection = 0.125 ng/mL

For Limit of Quantitation ≥ 4 human serum samples were measured over 5 days with 5 replicates on 1 analyzer. With an intermediate precision CV of ≤ 20 % the Limit of Quantitation was 0.324 ng/mL.

Dilution

Samples with CYFRA 21-1 concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:2 (either automatically by the analyzer or manually). The concentration of the diluted sample must be > 225 ng/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.

Expected values

Normal CYFRA 21-1 values are expected to be ≤ 2.37 ng/mL.

The following table shows the results of three separate cohorts. The first study represents the distribution of expected results from 240 apparently healthy men and women equally divided into smokers and nonsmokers. The second study represents the distribution of expected results from 195 benign disease conditions other than cancers, and the third study represents the distribution of expected results from different cancers, including lung cancer.

| Elecsys CYFRA 21-1 distribution of values by cohort | | | | | | |
|---|------------------|----------------|----------------|-----------------|-----------------|-------------|
| | No. of sub-jects | 0.3-2.37 ng/mL | 2.38-5.0 ng/mL | 5.01-20.0 ng/mL | 20.01-100 ng/mL | > 100 ng/mL |
| Apparently healthy | 240 | | | | | |
| All normals | 240 | 228 | 12 | 0 | 0 | 0 |
| Nonsmokers | 120 | 111 | 9 | 0 | 0 | 0 |
| Smokers | 120 | 117 | 3 | 0 | 0 | 0 |
| Normal females | 125 | 119 | 6 | 0 | 0 | 0 |
| Nonsmokers | 63 | 59 | 4 | 0 | 0 | 0 |
| Smokers | 62 | 60 | 2 | 0 | 0 | 0 |
| Normal males | 115 | 109 | 6 | 0 | 0 | 0 |
| Nonsmokers | 57 | 52 | 5 | 0 | 0 | 0 |
| Smokers | 58 | 57 | 1 | 0 | 0 | 0 |
| Benign conditions | 195 | | | | | |
| Benign lung disease | 75 | 70 | 5 | 0 | 0 | 0 |
| CHF ^{b)} | 40 | 29 | 11 | 0 | 0 | 0 |
| Benign kidney disease | 40 | 8 | 24 | 8 | 0 | 0 |
| Benign liver disease | 40 | 35 | 4 | 1 | 0 | 0 |
| Cancer | 440 | | | | | |
| Lung cancer | 120 | 53 | 33 | 27 | 5 | 2 |
| Bladder cancer | 40 | 13 | 9 | 12 | 5 | 1 |
| Breast cancer | 40 | 32 | 5 | 3 | 0 | 0 |
| Cervical cancer | 40 | 28 | 11 | 1 | 0 | 0 |

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Elecsys CYFRA 21-1 distribution of values by cohort

| | No. of sub-jects | 0.3-2.37 ng/mL | 2.38-5.0 ng/mL | 5.01-20.0 ng/mL | 20.01-100 ng/mL | > 100 ng/mL |
|----------------------|------------------|----------------|----------------|-----------------|-----------------|-------------|
| ESCC ^{c)} | 40 | 21 | 12 | 6 | 1 | 0 |
| GI tract cancer | 40 | 23 | 10 | 6 | 1 | 0 |
| Head and neck cancer | 40 | 29 | 11 | 0 | 0 | 0 |
| Prostate cancer | 40 | 37 | 1 | 2 | 0 | 0 |
| Ovarian cancer | 40 | 25 | 8 | 5 | 2 | 0 |

b) CHF = Congestive heart failure

c) ESCC = Esophageal squamous cell carcinoma

Clearly elevated CYFRA 21-1 concentrations can also be found in samples from patients with acute pneumonia, tuberculosis and interstitial pulmonary diseases. Concentrations above the reference range are also observed in cases of liver cirrhosis and renal failure.¹⁶

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 | | | | | |
|---------------------------------------|------------|---------------|------|------------------------|------|
| Sample | Mean ng/mL | Repeatability | | Intermediate precision | |
| | | SD ng/mL | CV % | SD ng/mL | CV % |
| Human serum 1 | 0.872 | 0.026 | 3.0 | 0.030 | 3.4 |
| Human serum 2 | 3.56 | 0.043 | 1.2 | 0.052 | 1.4 |
| Human serum 3 | 71.3 | 0.695 | 1.0 | 0.816 | 1.1 |
| Human serum 4 | 245 | 3.17 | 1.3 | 3.59 | 1.5 |
| Human serum 5 | 439 | 5.99 | 1.4 | 6.95 | 1.6 |
| PC ^{d)} Tumor Marker1 | 2.85 | 0.041 | 1.4 | 0.052 | 1.8 |
| PC Tumor Marker2 | 26.8 | 0.244 | 0.9 | 0.351 | 1.3 |
| PC Lung Cancer1 | 3.40 | 0.041 | 1.2 | 0.049 | 1.4 |
| PC Lung Cancer2 | 30.5 | 0.355 | 1.2 | 0.416 | 1.4 |

d) PC = PreciControl

Method comparison

a) A comparison of the Elecsys CYFRA 21-1 assay, [REF] 07299966190 (cobas e 801 analyzer; y) with the Elecsys CYFRA 21-1 assay, [REF] 11820966122 (cobas e 601 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 146

Passing/Bablok¹⁷ Linear regression

$$y = 1.02x - 0.290$$

$$\tau = 0.983$$

$$y = 1.07x - 2.33$$

$$r = 0.999$$

The sample concentrations were between 0.395 and 467 ng/mL.

b) A comparison of the Elecsys CYFRA 21-1 assay, [REF] 07299966190 (cobas e 402 analyzer; y) with the Elecsys CYFRA 21-1 assay,

[REF] 07299966190 (cobas e 801 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 171

Passing/Bablok¹⁷ Linear regression

$$y = 1.03x + 0.029$$

$$\tau = 0.978$$

$$y = 1.01x + 0.448$$

$$r = 1.00$$

The sample concentrations were between 0.106 and 455 ng/mL.

Analytical specificity

The monoclonal anti-cytokeratin 19 antibodies recognize a fragment of the cytokeratin 19 peptide. There is no cross-reactivity with cytokeratins 8 and 18.¹⁸

References

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For further information, please refer to the appropriate 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.

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 dialog.roche.com for definition of symbols used):

| | |
|---|---|
|  | Contents of kit |
|  | Analyzers/Instruments on which reagents can be used |
|  | Reagent |
|  | Calibrator |
|  | Volume for reconstitution |
|  | Global Trade Item Number |


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