CREJ2

Creatinine Jaffe Gen.2

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08057532190	08057532500	Creatinine Jaffé Gen.2 (2500 tests)	System-ID 2047 001	**cobas c** 303, **cobas c** 503

Materials required (but not provided):

10759350190	Calibrator f.a.s. (12 x 3 mL)	Code 20401	
03121313122	Precinorm PUC (4 x 3 mL)	Code 20240	
03121291122	Precipath PUC (4 x 3 mL)	Code 20241	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 20391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 20391	
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 20392	
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 20392	
08063494190	Diluent NaCl 9 % (123 mL)	System-ID 2906 001	

English

System information

CREJ2: ACN 20470 (Serum/plasma)

CREJ2U: ACN 20471 (Urine)

Intended use

In vitro test for the quantitative determination of creatinine in human serum, plasma and urine on **cobas c** systems.

Summary

Creatinine measurements, performed with this assay, in human serum, plasma and urine are used as an aid in diagnosis and monitoring of renal disease and in monitoring of renal dialysis. Creatinine measurements are also used for the calculation of the fractional excretion of other urine analytes (e. g., albumin, α-amylase).

Creatinine is a break-down product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). It is freely filtered by the glomeruli and, under normal conditions, is not reabsorbed by the tubules to any appreciable extent. A small but significant amount is also actively secreted. Its concentration is thus, inversely related to glomerular filtration rate (GFR).[1,2]

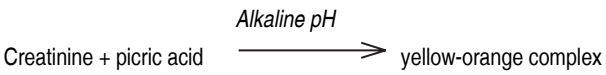
The assay of creatinine in serum or plasma is the most commonly used test to assess renal function. Chronic kidney disease is a worldwide problem that carries a substantial risk for cardiovascular morbidity and death. Current guidelines define chronic kidney disease as kidney damage or decreased glomerular filtration rate (GFR) (less than 60 mL/min per 1.73 m^2) for three months or more.[2,3]

Since a rise in blood creatinine is observed only with marked damage of the nephrons, it is not suited to detect early stage kidney disease. A considerably more sensitive test and better estimation of glomerular filtration rate (GFR) is given by the creatinine clearance test based on creatinine's concentration in urine and serum or plasma, and urine flow rate. For this test a precisely timed urine collection (usually 24 hours) and a blood sample are needed. However, since this test is prone to error due to the inconvenient collection of timed urine, mathematical attempts to estimate GFR (eGFR) based only on the creatinine concentration in serum or plasma have been made.[4] Among the various approaches suggested, three have found wide recognition: the Cockroft and Gault, the Modification of Diet in Renal Disease (MDRD) Study equation and the CKD-EPI (Chronic Kidney Disease Epidemiology) equation. While the Cockcroft and Gault equation was derived from data in which serum creatinine was measured with the conventional Jaffé method, the MDRD study equation measured serum creatinine using the Jaffé method calibrated to an isotope dilution mass spectrometry (IDMS).[5,6] These estimates of GFR are useful during monitoring of renal dialysis.[7,8] In children, the Bedside Schwartz formula should be used.[9,10,11]

In addition to the diagnosis and treatment of renal disease and the monitoring of renal dialysis, creatinine measurements are used for the calculation of the fractional excretion of other urine analytes (e. g., albumin, α-amylase). Numerous methods were described for determining creatinine. Automated assays established in the routine laboratory include the Jaffé alkaline picrate method in various modifications, as well as enzymatic tests.[2]

Test principle[12,13,14]

This kinetic colorimetric assay is based on the Jaffé method. In alkaline solution, creatinine forms a yellow-orange complex with picrate. The rate of dye formation is proportional to the creatinine concentration in the specimen. The assay uses "rate-blanking" to minimize interference by bilirubin. To correct for non-specific reaction caused by serum/plasma pseudo-creatinine chromogens, including proteins and ketones, the results for serum or plasma are corrected by -26 µmol/L (-0.3 mg/dL).



Reagents - working solutions

R1	Potassium hydroxide: 900 mmol/L; phosphate: 135 mmol/L; pH ≥ 13.5; preservative; stabilizer
R3	Picric acid: 38 mmol/L; pH 6.5; non reactive buffer

R1 is in position B and R3 is in position C.

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:

Danger

H314	Causes severe skin burns and eye damage.

Prevention:

P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.

Response:

P301 + P330 + P331	IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P303 + P361 + P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water.

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P304 + P340 + P310	IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/ doctor.
P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.

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

Reagent handling

Ready for use

Storage and stability

Shelf life at 15-25 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	26 weeks

Specimen collection and preparation[15]

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.

Serum.

Plasma: Li-heparin and K_2-EDTA plasma.

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.

Urine.

Collect urine without using additives. If urine must be collected with a preservative for other analytes, only hydrochloric acid (14 to 47 mmol/L urine, e.g. 5 mL 10 % HCl or 5 mL 30 % HCl per liter urine) or boric acid (81 mmol/L, e.g. 5 g per liter urine) may be used. If stabilizers are added to the sample, the sample index feature must not be used.

Stability in *serum/plasma:*[16]	7 days at 15-25 °C
	7 days at 2-8 °C
	3 months at (-15)-(-25) °C

Freeze only once.

Stability in *urine* (without preservative):[16]	2 days at 15-25 °C
	6 days at 2-8 °C
	6 months at (-15)-(-25) °C

Freeze only once.

Stability in *urine* (with preservative):	3 days at 15-25 °C
	8 days at 2-8 °C
	3 weeks at (-15)-(-25) °C

Freeze only once.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

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.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Test definition

Reporting time	10 min	
Wavelength (sub/main)	570/505 nm	
Reagent pipetting		Diluent (H_2O)
R1	10 µL	58 µL
R3	13 µL	23 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	7.5 µL	–	–
Decreased	7.5 µL	20 µL	80 µL
Increased	7.5 µL	–	–

Application for urine

Test definition

Reporting time	10 min	
Wavelength (sub/main)	570/505 nm	
Reagent pipetting		Diluent (H_2O)
R1	10 µL	58 µL
R3	13 µL	23 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	7.5 µL	4 µL	96 µL
Decreased	7.5 µL	1.5 µL	135 µL
Increased	7.5 µL	4 µL	96 µL

For further information about the assay test definitions refer to the application parameters setting screen of the corresponding analyzer and assay.

Calibration

Application for serum/plasma (ACN 20470)

Calibrators	S1: H_2O
	S2: C.f.a.s.
Calibration mode	Linear
Calibration frequency	Automatic full calibration - after reagent lot change
	Full calibration - every 8 weeks on-board - as required following quality control procedures

Application for urine (ACN 20471)

Transfer of calibration from serum/plasma application (ACN 20470)

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

Traceability: This method has been standardized against ID/MS.

Quality control

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

Serum/plasma:	PreciControl ClinChem Multi 1, PreciControl ClinChem Multi 2
Urine:	Precinorm PUC, Precipath PUC

The control intervals and limits should be adapted to each laboratory's individual requirements. It is recommended to perform quality control always after lot calibration and subsequently at least every 26 weeks.

Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

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

Calculation

cobas c systems automatically calculate the analyte concentration of each sample in the unit µmol/L (mg/dL, mmol/L, mg/L).

Conversion factors:	µmol/L x 0.0113 = mg/dL
	µmol/L x 0.001 = mmol/L
	µmol/L x 0.113 = mg/L

Limitations – interference

Criterion: Recovery within ± 10 % of initial value at a creatinine concentration of 80 µmol/L (0.90 mg/dL) in serum/plasma and 2.5 mmol/L (28.3 mg/dL) in urine.

Serum/plasma

Icterus (*CREJ2*):[17] No significant interference up to an I index of 5 for conjugated bilirubin and 10 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 86 µmol/L or 5 mg/dL; approximate unconjugated bilirubin concentration: 171 µmol/L or 10 mg/dL).

Hemolysis:[17] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[17] No significant interference up to an L index of 800. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Pyruvate: No significant interference from pyruvate up to a concentration of 0.3 mmol/L (2.6 mg/dL).

Glucose: No significant interference from glucose up to a concentration of 25 mmol/L (450 mg/dL).

Ascorbic acid: No significant interference from ascorbic acid up to a concentration of 5 mmol/L (88 mg/dL).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[18,19]

Exception: Antibiotics containing cephalosporin lead to significant false-positive values.[20,21] Cefoxitin causes artificially high creatinine results. Cyanokit (Hydroxocobalamin) may cause interference with results.

Values < 15 µmol/L (< 0.17 mg/dL) or negative results are reported in rare cases in children < 3 years and in elderly patients. In such cases use the Creatinine plus test to assay the sample.

Do not use Creatinine Jaffé for the testing of creatinine in hemolyzed samples from neonates, infants or adults with HbF levels ≥ 60 mg/dL for *CREJ2* applications.[22] In such cases, use the Creatinine plus test (≤ 600 mg/dL HbF) to assay the sample.

Estimation of the Glomerular Filtration Rate (GFR) on the basis of the Schwartz Formula can lead to an overestimation.[23]

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[24]

The presence of ketone bodies can cause artificially high results in serum and plasma.

Urine

Icterus: No significant interference up to a conjugated bilirubin concentration of 855 µmol/L or 50 mg/dL.

Hemolysis: No significant interference up to an H index of 1000 (approximate hemoglobin concentration of 621 µmol/L or 1000 mg/dL).

Glucose: No significant interference from glucose up to a concentration of 120 mmol/L (2162 mg/dL).

Urea: No significant interference from urea up to a concentration of 2100 mmol/L (12612 mg/dL).

Urobilinogen: No significant interference from urobilinogen up to a concentration of 676 µmol/L (40 mg/dL).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[19]

Exception: Cyanokit (Hydroxocobalamin) may cause interference with results.

High homogentisic acid concentrations in urine samples lead to false results.

The presence of ketone bodies can cause artificially high results in urine.

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

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SCCS Method Sheet. For further instructions, refer to the operator's manual.

Limits and ranges

Measuring range

Serum/plasma

15-2200 µmol/L (0.17-24.9 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.

Urine

0.375-55 mmol/L (4.2-622 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:3.6 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 3.6.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Serum/plasma (CREJ2)

Limit of Blank	= 15 µmol/L (0.17 mg/dL)
Limit of Detection	= 15 µmol/L (0.17 mg/dL)
Limit of Quantitation	= 15 µmol/L (0.17 mg/dL)

Urine (CREJ2U)

Limit of Blank	= 0.375 mmol/L (4.24 mg/dL)
Limit of Detection	= 0.375 mmol/L (4.24 mg/dL)
Limit of Quantitation	= 0.375 mmol/L (4.24 mg/dL)

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 a total error of 20 %. It has been determined using low concentration creatinine samples.

Expected values

µmol/L

Serum/plasma

Adults[25]

Females	44-80 µmol/L
Males	62-106 µmol/L

Children[26]

Neonates (premature)	25-91 µmol/L
Neonates (full term)	21-75 µmol/L
2-12 months	15-37 µmol/L
1- < 3 years	21-36 µmol/L
3- < 5 years	27-42 µmol/L
5- < 7 years	28-52 µmol/L
7- < 9 years	35-53 µmol/L
9- < 11 years	34-65 µmol/L
11- < 13 years	46-70 µmol/L
13- < 15 years	50-77 µmol/L

mmol/L

Urine

1st morning urine[25]

Females	2.47-19.2 mmol/L
Males	3.45-22.9 mmol/L

24-hour urine[27]

Females	7.0-14.0 mmol/24 h
Males	9.0-21.0 mmol/24 h

Creatinine clearance[27,28]	71-151 mL/min

Refer to reference for a prospective study on creatinine clearance in children.[29]

mg/dL

Serum/plasma

Adults[25]

Females	0.50-0.90 mg/dL
Males	0.70-1.20 mg/dL

Children[26]

Neonates (premature)	0.29-1.04 mg/dL
Neonates (full term)	0.24-0.85 mg/dL
2-12 months	0.17-0.42 mg/dL
1- < 3 years	0.24-0.41 mg/dL
3- < 5 years	0.31-0.47 mg/dL
5- < 7 years	0.32-0.59 mg/dL
7- < 9 years	0.40-0.60 mg/dL
9- < 11 years	0.39-0.73 mg/dL
11- < 13 years	0.53-0.79 mg/dL
13- < 15 years	0.57-0.87 mg/dL

Urine

1st morning urine[25]

Females	28-217 mg/dL
Males	39-259 mg/dL

24-hour urine[27]

Females	740-1570 mg/24 h
Males	1040-2350 mg/24 h

Creatinine clearance[27,28]	71-151 mL/min

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. These data represent the performance of the analytical procedure itself.

Results obtained in individual laboratories may differ due to heterogenous sample materials, aging of analyzer components and mixture of reagents running on the analyzer.

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Serum/plasma (CREJ2)

Repeatability	*Mean*	*SD*	*CV*
	µmol/L	*µmol/L*	*%*
PCCC1[a)]	90.4	1.57	1.7
PCCC2[b)]	347	3.87	1.1
Human serum 1	48.2	1.40	2.9
Human serum 2	71.8	1.51	2.1
Human serum 3	480	4.15	0.9
Human serum 4	1064	12.0	1.1
Human serum 5	1791	20.6	1.2
Intermediate precision	*Mean*	*SD*	*CV*
	µmol/L	*µmol/L*	*%*
PCCC1[a)]	89.2	2.33	2.6
PCCC2[b)]	347	5.24	1.5
Human serum 1	48.2	1.64	3.4
Human serum 2	71.8	1.89	2.6
Human serum 3	480	7.59	1.6
Human serum 4	1064	16.1	1.5
Human serum 5	1791	30.0	1.7

a) PreciControl ClinChem Multi 1

b) PreciControl ClinChem Multi 2

Urine (CREJ2U)

Repeatability	*Mean*	*SD*	*CV*
	mmol/L	*mmol/L*	*%*
PN PUC[c)]	8.89	0.0922	1.0
PP PUC[d)]	4.56	0.0560	1.2

Human urine 1	1.19	0.0310	2.6
Human urine 2	2.41	0.0311	1.3
Human urine 3	22.5	0.210	0.9
Human urine 4	28.4	0.318	1.1
Human urine 5	49.7	0.480	1.0
Intermediate precision	*Mean*	*SD*	*CV*
	mmol/L	*mmol/L*	*%*
PN PUC[c)]	8.89	0.151	1.7
PP PUC[d)]	4.56	0.0824	1.8
Human urine 1	1.19	0.0341	2.9
Human urine 2	2.43	0.0398	1.6
Human urine 3	22.5	0.339	1.5
Human urine 4	28.4	0.417	1.5
Human urine 5	49.7	0.745	1.5

c) Precinorm PUC

d) Precipath PUC

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s).

Method comparison

Creatinine values for human serum, plasma and urine samples obtained on a **cobas c** 503 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Serum/plasma (CREJ2)

Sample size (n) = 71

Passing/Bablok[30]	Linear regression
y = 1.012x - 3.68 µmol/L	y = 1.010x - 3.19 µmol/L
τ = 0.980	r = 1.000

The sample concentrations were between 23.2 and 2133 µmol/L.

Urine (CREJ2U)

Sample size (n) = 72

Passing/Bablok[30]	Linear regression
y = 1.065x - 0.0368 mmol/L	y = 1.056x + 0.00514 mmol/L
τ = 0.984	r = 1.000

The sample concentrations were between 0.388 and 50.8 mmol/L.

Creatinine values for human serum, plasma and urine samples obtained on a **cobas c** 303 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Serum/plasma (CREJ2)

Sample size (n) = 70

Passing/Bablok[30]	Linear regression
y = 1.018x - 5.48 µmol/L	y = 1.015x - 4.42 µmol/L
τ = 0.968	r = 1.000

The sample concentrations were between 24.1 and 2114 µmol/L.

Urine (CREJ2U)

Sample size (n) = 69

Passing/Bablok[30]	Linear regression
y = 1.088x - 0.0452 mmol/L	y = 1.093x - 0.0846 mmol/L
τ = 0.984	r = 1.000

The sample concentrations were between 0.787 and 49.1 mmol/L.

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

CONTENT	Contents of kit
→	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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