Intended Use: The ECREA method is an *in vitro* diagnostic test for the quantitative measurement of creatinine in human serum, plasma and urine on the Dimension Vista® System. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for other urine analytes.

Summary: This creatinine method measures creatinine enzymatically. Enzymatic creatinine methods are reported to be less susceptible to interference than Jaffe methods from non-creatinine substances.[1]

Serum and plasma creatinine concentrations, freely filtered by the glomerulus, are inversely related to glomerular filtration rate (GFR).[2] Therefore, both blood and urine creatinine measurements are used to assess kidney function and in the diagnosis and treatment of renal diseases. Creatinine is also useful in monitoring effectiveness of renal dialysis.

Additionally, calculated creatinine clearance values may be used to establish effective therapeutic dosing levels of pharmaceuticals.[3]

Principles of Procedure: In a coupled enzyme reaction, creatininase hydrolyzes creatinine to creatine, which is hydrolyzed by creatinase to sarcosine. Sarcosine oxidase hydrolyzes sarcosine to glycine, formaldehyde, and peroxide. The peroxide and a chromogen in the presence of peroxidase form a colored end product that is proportional to the amount of creatinine in the sample. The colored reaction product is measured at 540 and 700 nm.

$$\text{Creatinine} + H_2O \xrightarrow{\text{Creatininase}} \text{Creatine}$$

$$\text{Creatine} + H_2O \xrightarrow{\text{Creatinase}} \text{Sarcosine} + \text{Urea}$$

$$\text{Sarcosine} + H_2O + O_2 \xrightarrow{\text{Sarcosine oxidase}} \text{Glycine} + HCHO + H_2O_2$$

$$H2O2 + \text{4-aminophenazone} + \text{HTIB}^{**} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine chromogen} + H2O + HI$$

**HTIB is 2,4,6-triiodo-3-hydroxybenzoic acid.

Reagents

Wells[a]	Form	Ingredient	Concentration[b]	Source
1 – 2		HCl	0.5 N	
		ECREA Reagent 1		
3 – 6[c]	Liquid	TAPS buffer: (3-[[tris(hydroxymethyl)methyl] amino] propanesulfonic acid)	30 mmol/L	
		creatinase	>333 µkat/L	Bacterial
		sarcosine oxidase	>33 µkat/L	Bacterial
		HTIB (2,4,6-triiodo-3-hydroxybenzoic acid)	5.9 mmol/L	
		ECREA Reagent 2		
9 – 12[c]	Liquid	TAPS buffer: (3-[[tris(hydroxymethyl)methyl] amino] propanesulfonic acid)	50 mmol/L	
		creatininase	>500 µkat/L	Bacterial
		horseradish peroxidase	≥16.7 µkat/L	
		4-aminophenazone	2.0 mmol/L	
		potassium hexacyanoferrate (II)	163 µmol/L	

a. Wells are numbered consecutively from the wide end of the cartridge.
b. Nominal value per well in a cartridge.
c. Wells 3 – 12 contain buffers and preservatives.

Risk and Safety:

H290
P390

Warning!

May be corrosive to metals.

Absorb spillage to prevent material damage.

Contains: Hydrochloric acid

Safety data sheets (MSDS/SDS) available on www.siemens.com/diagnostics

Precautions: Used cuvettes contain human body fluids; handle with appropriate care to avoid skin contact or ingestion.

For *in vitro* diagnostic use.

Reagent Preparation: All reagents are liquid and ready to use.

Store at: 2 – 8 °C

Expiration: Refer to carton for expiration date of individual unopened reagent cartridges. Sealed wells on the instrument are stable for 30 days.

Open well stability: 3 days for wells 1 – 12

Specimen Collection and Handling: Recommended specimen types: serum, lithium/sodium heparin plasma, and urine.

Grossly hemolyzed samples should not be used with the ECREA method.

Serum and plasma can be collected using recommended procedures for collection of diagnostic blood specimens by venipuncture.[4]

Follow the instructions provided with your specimen collection device for use and processing.[5]

For serum, complete clot formation should take place before centrifugation. Serum or plasma should be physically separated from cells as soon as possible with a maximum limit of two hours from the time of collection.[6] Separated serum/plasma samples should be stored at 2 – 8 °C and analyzed within 48 hours. For longer storage, samples should be frozen at or below -20 °C.[6]

Urine creatinine measurements require no special patient preparation for specimen collection. Use recommended procedures when collecting, transporting, and preserving random and timed urine specimens.[7] Random or 24-hour urine collections require no preservatives. Specimens preserved with 6N hydrochloric acid, boric acid, and sodium fluoride are acceptable. Other preservatives were not tested.

Urines (random or 24-hour collections) should be stored at 2 – 8 °C and analyzed within 4 days. Freeze urines for longer storage.[8] Urine specimens should be free of particulate matter.

The purpose of specimen storage information is to provide guidance to users; however, users may validate their own procedures for storing patient samples.

Procedure

Materials Provided

ECREA Flex® reagent cartridge, Cat. No. K1270A

Materials Required But Not Provided

ECREA CAL, Cat. No. KC270
Quality control materials

Test Steps

Sampling, reagent delivery, mixing, and processing are automatically performed by the Dimension Vista® System. For details of this processing, refer to your Dimension Vista® Operator's Guide.

Test Conditions

Sample Volume	(delivered to the cuvette)	2.7 µL
Reagent 1 Volume		50 µL
Reagent 2 Volume		54 µL
Temperature		37.0 °C
Reaction time		7.7 minutes
Wavelength		540 and 700 nm
Type of Measurement		Bichromatic endpoint

Calibration

Calibration Material	ECREA CAL, Cat. No. KC270
Calibration Scheme	3 levels, n = 5
Units	mg/dL [µmol/L][d]
Unit conversion	mg/dL x 88.4 = [µmol/L]
Typical Calibration Levels	Level 1 (System water): 0.0 mg/dL [0.000 µmol/L] Level 2 (Calibrator A): 0.95 mg/dL [83.98 µmol/L] Level 3 (Calibrator B): 20.0 mg/dL [1768 µmol/L]
Calibration Frequency	Every 90 days for any one lot Calibration interval may be extended based on acceptable verification of calibration.
A new calibration is required:	• For each new lot of Flex® reagent cartridges • After major maintenance or service, if indicated by quality control results • As indicated in laboratory quality control procedures • When required by government regulations

d. Système International d'Unités [SI units] are in brackets.

Quality Control

Follow government regulations or accreditation requirements for quality control frequency. At least once each day of use, analyze two levels of a quality control (QC) material with known creatinine concentrations. Follow your laboratory internal QC procedures if the results obtained are outside acceptable limits.

Results: The instrument calculates the concentration of creatinine in mg/dL [µmol/L] using the calculation scheme described in your Dimension Vista® Operator's Guide.

Calculated result applications available in the Dimension® EasyLink™ Informatics System:

Creatinine clearance (mL/min) = (U (mg/dL) x V (mL/min))/(S (mg/dL))

where U = urine creatinine in mg/dL
V = urine volume in mL/min
S = serum creatinine in mg/dL

An estimated glomerular filtration rate (eGFR) can be calculated using Dimension Vista® ECREA results and one of the following Modification of Diet in Renal Disease (MDRD) equations:

IDMS-Traceable MDRD eGFR Equation for use with ECREA method:

$$GFR\ (mL/min/1.73m^2) = 175 \times (ECREA, mg/dL)^{-1.154} \times (Age)^{-0.203} \times 1.210\ (\text{if African American}) \times 0.742\ (\text{if female})\ (\text{conventional units})$$

$$GFR\ (mL/min/1.73m^2) = 175 \times (ECREA\ \mu mol/L / 88.4)^{-1.154} \times (Age)^{-0.203} \times 1.210\ (\text{if African American}) \times 0.742\ (\text{if female})\ (\text{SI units})$$

Use of equations such as those shown above to report estimated GFR should be limited to adults over the age of 18 who are of average body composition and are not experiencing rapidly changing kidney function status.[9]

Estimation of GFR using mathematical equations such as the MDRD eGFR is NOT recommended when patients have: extremes of age or body size, severe malnutrition or obesity, skeletal muscle diseases, paraplegia or quadriplegia, limb amputations, vegetarian diets, pregnancy, rapidly changing kidney function, prior to dosing drugs with significant toxicity that are excreted by kidneys, or any other condition in which the patient does not have stable kidney function. Such patients may need measurement of clearance instead of estimation.[9]

Clinical practice guidelines with limitations for use of the MDRD Study equation for reporting eGFR can be found on the KDOQI and NKDEP websites.[9, 10, 11] Any future refinements in the recommended MDRD equation(s) would also be published there.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

Analytical Measurement Range (AMR): Serum/plasma 0.14 – 20.0 mg/dL [12.4 – 1770 µmol/L]
Urine 2.80 – 400 mg/dL [0.25 – 35.4 mmol/L]

This is the range of analyte values that can be measured directly from the specimen without any dilution or pretreatment that is not part of the usual analytical process and is equivalent to the assay range.

- Serum or plasma samples with results in excess of 20.0 mg/dL [1770 µmol/L] should be repeated on dilution.

  Autodilution (AD): The autodilute sample volume is 13 µL (dilution factor = 4) for serum/ plasma. Refer to your Dimension Vista® Operator's Guide.

  Manual Dilution: Dilute with Reagent grade water to obtain results within reportable range. Enter dilution factor on the instrument. Reassay. Resulting readout is corrected for dilution.
- Urine samples with results in excess of 400 mg/dL [35.4 mmol/L] are above assay range and should be repeated on dilution.

  Predilution of urine: The ECREA method performs a predilution of urine samples. The prediluted sample volume is 10 µL (dilution factor = 20).

  Autodilution of urine: The autodilute sample volume for urine is 20 µL (dilution factor = 40). Refer to your Vista® Operator's guide.

  Manual Dilution for urine: Where larger dilutions are required; dilute with Reagent grade water to obtain results within the measuring range. Enter dilution factor on the instrument. Reassay. Resulting readout is corrected for dilution. Refer to your Dimension Vista® Operator's Guide.
- Serum/plasma samples with results less than 0.14 mg/dL [12.4 µmol/L] will be reported as "less than 0.14 mg/dL [12.4 µmol/L]" by the instrument.
- Urine samples with results less than 2.80 mg/dL [248 µmol/L] will be reported as "less than 2.80 mg/dL [248 µmol/L]" by the instrument.

Limitations of Procedure

The instrument reporting system contains flags and comments to provide the user with information regarding instrument processing errors, instrument status information and potential errors in ECREA results. Refer to your Dimension Vista® Operator's Guide for the meaning of report flags and comments. Any report containing flags and/or comments should be addressed according to your laboratory's procedure manual and not reported.

Interfering substances

The ECREA method was evaluated for interference according to CLSI/NCCLS EP7-A2.[12] Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Bias exceeding 10% is considered interference.

Hemoglobin at 600 mg/dL [0.37 mmol/L] decreases ECREA results by 10% at 1.02 mg/dL [90.2 µmol/L] ECREA.
Bilirubin (unconjugated) at 40 mg/dL [707 µmol/L] decreases ECREA results by 19% at 1.01 mg/dL [89.3 µmol/L].
Bilirubin (conjugated) at 40 mg/dL [707 µmol/L] decreases ECREA results by 16% at 1.01 mg/dL [89.3 µmol/L].
Lipemia at 3000 mg/dL [33.9 mmol/L] increases ECREA by 25% at 1.01 mg/dL [89.3 µmol/L].

Blood samples from patients with Waldenstrom's Macroglobulinemia contain monoclonal IgM that can produce falsely elevated results.[13]

Expected Values:

Serum/plasma[14]
Males: 0.67 – 1.17 mg/dL [59.2 – 104 µmol/L]
Females: 0.51 – 0.95 mg/dL [45.1 – 84 µmol/L]

Random Urine[14]
Males: 40.0 – 278 mg/dL [3.54 – 24.6 mmol/L]
Females: 29.0 – 226 mg/dL [2.56 – 20.0 mmol/L]

24 Hour Urine Excretion[15]
Males: 0.87 – 2.41 g/day [7.7 – 21.3 mmol/day]
Females: 0.67 – 1.59 g/day [5.9 – 14.1 mmol/day]

Each laboratory should establish its own expected values for ECREA as performed on the Dimension Vista® System.

Maximum Observed Repeatability

The expected maximum observed standard deviations for repeatability (within-run precision) using n = 5 replicates at the following creatinine concentrations are:

ECREA concentration	Acceptable SD Maximum
1.02 mg/dL [90 µmol/L]	0.12 mg/dL [11 µmol/L]
6.09 mg/dL [538 µmol/L]	0.29 mg/dL [26 µmol/L]

A system malfunction may exist if the acceptable SD maximum is exceeded.

Specific Performance Characteristics

The following data represent typical performance for the Dimension Vista® System.

Precision[16, e]

	Mean		Standard Deviation (%CV)	
Material	**mg/dL**	**[µmol/L]**	**Repeatability**	**Within-Lab**
Serum Pool 1	0.61	[53.72]	0.02 [1.54] (2.9)	0.03 [2.38] (4.4)
Serum Pool 2	1.57	[139.22]	0.02 [1.94] (1.4)	0.04 [3.29] (2.4)
Liquichek™ Control				
Level 1	0.79	[70.20]	0.02 [1.71] (2.4)	0.03 [2.67] (3.8)
Level 2	5.81	[513.97]	0.05 [4.34] (0.8)	0.10 [8.87] (1.7)
Urine Pool 1	112	[9917]	1.8 [162] (1.6)	3.2 [278] (2.8)
Urine Pool 2	282	[24945]	3.5 [311] (1.2)	8.6 [764] (3.1)
Liquichek™ Urine Control				
Level 1	64.1	[5666]	1.6 [139] (2.5)	2.6 [225] (4.0)
Level 2	150	[13246]	2.7 [242] (1.8)	4.9 [437] (3.3)

e. CLSI/NCCLS EP5-A2 was used. During each day of testing, two separate runs, with two test samples, for each test material, were analyzed for 20 days.

Liquichek™ is a trademark of Bio-Rad Laboratories, Irvine, CA 92618.

Method Comparison[17]
Regression Statistics[f]

Comparative Method	Slope	Intercept	Correlation Coefficient	n
Serum/Plasma		**mg/dL [µmol/L]**		
Roche/Hitachi CREA-plus	1.029	-0.177 [-15.60]	1.000	130[g]
Urine		**mg/dL [mmol/L]**		
Roche/Hitachi CREA-plus	1.057	-6.109 [-539]	0.999	126[h]

f. CLSI/NCCLS EP9-A2 was used. The method used to fit the linear regression line was orthogonal (total least squares).
g. The range of 130 serum and plasma values in the correlation study was 0.57 – 19.9 mg/dL [50.1 – 1759 µmol/L].
h. The range of 126 urine values in the correlation study was 8.2 – 391 mg/dL [726 – 34564 mmol/L].

Specificity

Hemoglobin, Icterus, Lipemia (HIL) Interference

The ECREA method was evaluated for interference according to CLSI/NCCLS EP7-A2.[12] Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Bias exceeding 10% is considered interference.

Substance Tested	Substance Concentration		Creatinine mg/dL [µmol/L]	Bias* %
Hemoglobin	600 mg/dL	[0.37 mmol/L]	1.02 [90.2]	>10
(hemolysate)	500 mg/dL	[0.31 mmol/L]		<10
Bilirubin	40 mg/dL	[684 µmol/L]	1.01 [89.3]	-19
(unconjugated)	30 mg/dL	[513 µmol/L]		<10
Bilirubin	40 mg/dL	[684 µmol/L]	1.01 [89.3]	-16
(conjugated)	30 mg/dL	[513 µmol/L]		<10
Lipemia	3000 mg/dL	[33.9 mmol/L]	1.01 [89.3]	25
(Intralipid®)	1000 mg/dL	[11.3 mmol/L]		<10

Intralipid® is a registered trademark of Fresenius Kabi AG, Bad Homburg, Germany
***Analyte results should not be corrected based on this bias.**

Non-Interfering Substances – Blood

The following substances do not interfere with the ECREA method when present in serum and plasma at the concentrations indicated. Inaccuracies (biases) due to these substances are less than 10% at ECREA method concentrations of 1.00 mg/dL [88.4 µmol/L].

Substance	Test Concentration	SI Units
Acetaminophen	20 mg/dL	1324 µmol/L
Amikacin	8 mg/dL	137 µmol/L
Ampicillin	5.3 mg/dL	152 µmol/L
Ascorbic acid	6 mg/dL	342 µmol/L
Benzyl alcohol (in heparin)	1%	1%
Caffeine	6 mg/dL	308 µmol/L
Carbamazepine	3 mg/dL	127 µmol/L
Cefazolin	1.5 mg/dL	133 µmol/L
Cephalexin	1.5 mg/dL	133 µmol/L
Cephaloridine	1.5 mg/dL	133 µmol/L
Cephalothin	1.5 mg/dL	133 µmol/L
Cephradine	1.5 mg/dL	133 µmol/L
Chloramphenicol	5 mg/dL	155 µmol/L
Chlordiazepoxide	1 mg/dL	33 µmol/L
Chlorpromazine	0.2 mg/dL	6 µmol/L
Cholesterol	500 mg/dL	13 mmol/L
Cimetidine	2 mg/dL	79 µmol/L
Creatine	25 mg/dL	1907 µmol/L
Dextran 40	6000 mg/dL	1500 µmol/L
Diazepam	0.5 mg/dL	18 µmol/L
Digoxin	6.1 ng/mL	9.4 nmol/L

Substance	Test Concentration	SI Units
Dipyrone (metamizol)	5 mg/dL	150 µmol/L
D/L-proline	11.5 mg/dL	1017 µmol/L
Dobutamine	0.5 mg/dL	44 µmol/L
Erythromycin	6 mg/dL	82 µmol/L
Ethanol	400 mg/dL	86.8 mmol/L
Ethosuximide	25 mg/dL	1770 µmol/L
Furosemide	6 mg/dL	181 µmol/L
Gentamicin	1 mg/dL	21 µmol/L
Heparin	3 U/mL	3000 U/L
Ibuprofen	50 mg/dL	2425 µmol/L
Immunoglobulin G (IgG)	5.0 g/dL	50 g/L
Immunoglobulin M (IgM)	1.0 g/dL	10 g/L
Lidocaine	1.2 mg/dL	51.2 µmol/L
Lithium	2.2 mg/dL	3.2 mmol/L
N-acetyl-cysteine	45 mg/dL	276 µmol/L
N-ethylglycine	4.0 mg/L	3540 µmol/L
Nicotine	0.1 mg/dL	6.2 µmol/L
Penicillin G	25 U/mL	25000 U/L
Pentobarbital	8 mg/dL	354 µmol/L
Phenobarbital	10 mg/dL	431 µmol/L
Phenytoin	5 mg/dL	198 µmol/L
Primidone	4 mg/dL	183 µmol/L
Propoxyphene	0.2 mg/dL	4.9 µmol/L
Protein: Albumin	6 g/dL	60 g/L
Protein: Total	12 g/dL	120 g/L
Salicylic Acid	60 mg/dL	4.3 mmol/L
Theophylline	4 mg/dL	222 µmol/L
Triglyceride	3000 mg/dL	33.9 mmol/L
Urea	500 mg/dL	83 mmol/L
Uric Acid	20 mg/dL	1.2 mmol/L
Valproic Acid	50 mg/dL	3.5 mmol/L
Vancomycin	10.3 mg/dL	71 µmol/L

Non-Interfering Substances – Urine

The following substances do not interfere with the ECREA method when present in urine at the concentrations indicated. Inaccuracies (biases) due to these substances are less than 10% at ECREA method concentrations of 45.0 mg/dL [3978 µmol/L]

Substance	Test Concentration	SI Units
5% NaOH	5%	1.25 mol/L
6N HCl	6 N	6 mol/L
Acetone	1 g/dL	1.72 mmol/L

Substance	Test Concentration	SI Units
Albumin	500 mg/dL	5 g/L
Ascorbic acid	1.5 g/dL	60 g/L
Bilirubin unconjugated	2.0 mg/dL	34 µmol/L
Bilirubin, conjugated	2.0 mg/dL	34 µmol/L
Boric acid	1% w/v	162 mmol/L
Cefazolin	1.5 mg/dL	133 µmol/L
Cephalexin	1.5 mg/dL	133 µmol/L
Cephaloridine	1.5 mg/dL	133 µmol/L
Cephalothin	1.5 mg/dL	133 µmol/L
Cephradine	1.5 mg/dL	133 µmol/L
Dipyrone (metamizol)	5 mg/dL	150 µmol/L
D/L-proline	11.5 mg/dL	1017 µmol/L
Dobutamine	0.5 mg/dL	44 µmol/L
Ethanol	1.0 g/dL	217 mmol/L
Gamma globulin	0.5 g/dL	5 g/L
Glucose	2.0 g/dL	1.11 mol/L
Hemoglobin	115 mg/dL	0.07 mmol/L
Immunoglobulin M (IgM)	10 g/L	10 g/L
N-acetyl-cysteine	90 mg/dL	552 µmol/L
N-ethylglycine	10 mg/dL	884 µmol/L
Oxalic acid	100 mg/dL	110 mmol/L
Riboflavin	7.5 mg/dL	2.0 mmol/L
Sodium azide	1 % w/v	154 mmol/L
Sodium chloride	6 g/dL	10.3 mol/L
Sodium fluoride	1 % w/v	238 mmol/L
Urea	6.0 g/dL	10 mol/L
pH	1.8 – 12.9	1.8 – 12.9

Cross-reactivity

Creatine and pyruvate were evaluated for cross-reactivity in the presence of 1.0 mg/dL [88.4 µmol/L] of creatinine. The percent cross-reactivity was calculated as follows:

$$\% \text{ cross reactivity} = \frac{\text{measured analyte} - \text{control analyte (x units [SI])}}{\text{metabolite added}} \times 100$$

Substance	Unit	SI	% cross-reactivity
Creatine	25 mg/dL	1907 µmol/L	6.6
Pyruvate	6 mg/dL	684 µmol/L	3.2

Limit of Detection

The Limit of Detection (LoD) for the ECREA method is 0.14 mg/dL [12.4 µmol/L]. This value represents less than 5% of statistical false positives (α) and false negatives (β) and a Limit of Blank (LoB) of 0.07 mg/dL [6.19 µmol/L]. This is consistent with the guidelines of CLSI EP17-A.

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