CREATININE/CREA

Creatinine is measured amperometrically. Creatinine is hydrolyzed to creatine in a reaction catalyzed by the enzyme creatinine amidohydrolase. Creatine is then hydrolyzed to sarcosine in a reaction catalyzed by the enzyme creatine amidinohydrolase. The oxidation of sarcosine, catalyzed by the enzyme sarcosine oxidase, produces hydrogen peroxide (H_2O_2). The liberated hydrogen peroxide is oxidized at the platinum electrode to produce a current which is proportional to the sample creatinine concentration.

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

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

$$\text{Sarcosine} + O_2 + H_2O \xrightarrow{\text{Sarcosine Oxidase}} \text{Glycine} + \text{Formaldehyde} + H_2O_2$$

$$H_2O_2 \longrightarrow O_2 + 2H^+ + 2e^-$$

See below for information on factors affecting results. Certain substances, such as drugs, may affect analyte levels *in vivo*.[1]

If results appear inconsistent with the clinical assessment, the patient sample should be retested using another cartridge.

INTENDED USE

The test for creatinine, as part of the i-STAT® System, is for the quantitative determination of creatinine in whole blood on the i-STAT handheld.

Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.

Contents

Each i-STAT cartridge contains one reference electrode (when potentiometric sensors are included in the cartridge configuration), sensors for the measurement of specific analytes, and a buffered aqueous calibrant solution that contains known concentrations of analytes and preservatives. For cartridges that contain a sensor for the measurement of creatinine, a list of reactive ingredients is indicated below:

Reactive Ingredient	Biological Source	Minimum Quantity
Creatinine	N/A	158.4 µmol/L
Creatine Amidinohydrolase	*Actinobacillus* spp.	0.01 IU
Creatinine Amidohydrolase	Microbial	0.02 IU
Sarcosine Oxidase	Microbial	0.001 IU

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Metrological Traceability

The i-STAT System test for creatinine measures creatinine amount-of-substance concentration in the plasma fraction of arterial, venous, or capillary whole blood (dimension μmol L^{-1}) for *in vitro* diagnostic use. Creatinine values assigned to i-STAT's controls and calibration verification materials are traceable to the U.S. National Institute of Standards and Technology (NIST) standard reference material SRM967. i-STAT System controls and calibration verification materials are validated for use only with the i-STAT System and assigned values may not be commutable with other methods. Further information regarding metrological traceability is available from Abbott Point of Care Inc.

Expected Values

Test/Abbreviation	Units*	Reportable Range	Reference Range
Creatinine/Crea	mg/dL	0.2 – 20.0	0.6 – 1.3[2]
	μmol/L	18 – 1768	53 – 115

To convert a creatinine result from mg/dL to μmol/L, multiply the mg/dL value by 88.4.

The i-STAT reference ranges for whole blood listed above are similar to reference ranges derived from serum or plasma measurements with standard laboratory methods.

The reference range programmed into the analyzer and shown above is intended to be used as a guide for the interpretation of results. Since reference ranges may vary with demographic factors such as age, gender and heritage, it is recommended that reference ranges be determined for the population being tested.

* The i-STAT System can be configured with the preferred units.

Clinical Significance

Elevated levels of creatinine are mainly associated with abnormal renal function and occur whenever there is a significant reduction in glomerular filtration rate or when urine elimination is obstructed. The concentration of creatinine is a better indicator of renal function than urea or uric acid because it is not affected by diet, exercise, or hormones.

The creatinine level has been used in combination with BUN to differentiate between prerenal and renal causes of an elevated urea/BUN.

Performance Characteristics

The typical performance data summarized below were collected in health care facilities by professionals trained in the use of the i-STAT System and comparative methods. Clinical settings vary and some may require different performance characteristics to assess renal function status than others (e.g., medication dosing, intravenous contrast use, and outpatient clinic). If deemed necessary by a health care facility, performance data should be obtained in specific clinical settings to assure patients' needs are met.

Precision data were collected in multiple sites following the protocol recommended by Abbott Point of Care. The means, SDs and CVs from 20 replicates at each site were averaged. The average statistics are presented below.

Method comparison data were collected using CLSI guideline EP9-A.[3] Venous blood samples, collected in lithium or sodium heparin Vacutainer® tubes, and arterial blood samples, collected in blood gas syringes, were analyzed in duplicate on the i-STAT System. A portion of each specimen was centrifuged, and the separated plasma was analyzed on the comparative method.

Deming regression analysis[4] was performed on the first replicate of each sample. In the method comparison table, n is the number of specimens in the data set, Sxx and Syy refer to the estimates of imprecision based on the duplicates of the comparative and the i-STAT methods respectively, Sy.x is the standard error of the estimate, and r is the correlation coefficient.*

*The usual warning relating to the use of regression analysis is summarized here as a reminder. For any analyte, "if the data are collected over a narrow range, the estimate of the regression parameters is relatively imprecise and may be biased. Therefore, predictions made from these estimates may be invalid."[4] The correlation coefficient, r, can be used as a guide to assess the adequacy of the comparative method range in overcoming this problem. As a guide, the range of data can be considered adequate for r >0.975.

Precision Data (mg/dL)

Aqueous Control	Mean	SD	%CV
Level 1	4.33	0.131	3.0
Level 3	0.81	0.039	4.8

Method Comparison (mg/dL)

	Roche Integra 800	Beckman LX20	J & J Vitros 950	Dade Dimension RxL
n	30	58	31	36
Sxx	0.029	0.141	0.04	0.04
Syy	0.112	0.143	0.12	0.06
Slope	0.929	0.960	0.948	0.964
Int't	0.237	0.022	0.206	0.100
Syx	0.204	0.261	0.165	0.123
Xmin	0.4	0.7	0.5	0.5
Xmax	10.3	20.0	7.2	5.7
r	0.997	0.996	0.991	0.986

Cartridge Comparison

The performance characteristics of the sensors are equivalent in all cartridge configurations. System difference analysis was performed on 39 patient samples using the i-STAT CHEM8+ and i-STAT Crea cartridges. In the 0.42-2.50 mg/dL range, the average difference was -0.01. In the 2.50-9.08 mg/dL range, the average difference was -0.04.

Factors affecting results*

Interference studies were based on CLSI guideline EP7-A2.[5] Test concentrations used were as per the CLSI guideline unles otherwise indicated.

When added to a plasma pool the following substances (at the concentrations indicated) were found to interfere with the i-STAT Creatinine assay:

Substance	Test Concentration (mmol/L)	Interference
Acetaminophen	1.32	Increased i-STAT creatinine results. See Note below.
Acetylcysteine	10.2	Increased i-STAT creatinine results. See Note below.
Ascorbate	0.34	Increased i-STAT creatinine results by up to 0.3 mg/dL.
Bromide (*therapeutic*)	2.5 [6,7,8]	Increased i-STAT creatinine results. See Note below.
Creatine	0.382	Increased i-STAT creatinine results by up to 0.3 mg/dL. See Note below.
Glycolic Acid	10.0	Decreased i-STAT creatinine results. Use another method.
Hydroxyurea	0.92	Increased i-STAT creatinine results. Use another method.
Nithiodote (sodium thiosulfate)	16.7[13]	Increased i-STAT creatinine results. See Note below.

The following substances are known not to significantly interfere with the i-STAT Creatinine assay at the stated test concentrations:

Substance	Test Concentration (mmol/L)
Acetaldehyde	0.045 [9]
Acetaminophen *(therapeutic)*	0.132 [9]
Acetylcysteine *(therapeutic)*	0.3 [10,11]
Bicarbonate	35.0
Bilirubin	0.342
Calcium Chloride	5.0
Dopamine	0.006
Formaldehyde	0.133 [9]
β–Hydroxybutyrate	6.0 [12]
Lactate	6.6
Methyldopa	0.071
Pyruvate	0.31
Salicylate	4.34
Uric Acid	1.4

Notes:

1) The normal range of creatine concentration in plasma is 0.17–0.70 mg/dL (13 – 53 µmol/L) in males and 0.35 – 0.93 mg/dL (27 – 71 µmol/L) in females.[9] Creatine may be elevated in patients using creatine supplements, experiencing muscle trauma or other primary or secondary myopathies, taking statins for hyperlipidemia control, or in patients with hyperthyroidism or a rare genetic defect of the creatine transporter protein.

2) Hydroxyurea is a DNA synthesis inhibitor used in the treatment of various forms of cancer, sickle cell anemia, and HIV infection. This drug is used to treat malignancies including melanoma, metastatic ovarian cancer, and chronic myelogenous leukemia. It is also used in the treatment of polycythemia vera, thrombocythemia, and psoriasis. At typical doses ranging from 500 mg to 2 g/day, concentrations of hydroxyurea in patients' blood may be sustained at approximately 100 to 500 µmol/L. Higher concentrations may be observed soon after dosing or at higher therapeutic doses.

3) Acetaminophen has been shown to interfere at a concentration proscribed by the CLSI guideline, 1.32 mmol/L, which represents a toxic concentration. Acetaminophen at 0.132 mmol/L, which represents the upper end of the therapeutic concentration, has been shown not to significantly interfere with i-STAT creatinine results.

4) Acetylcysteine has been tested at two levels: the CLSI recommended level and a concentration of 0.30 mmol/L. The latter is 3 times the peak plasma therapeutic concentration associated with treatment to reverse acetaminophen poisoning. APOC has not identified a therapeutic condition that would lead to levels consistent with the CLSI recommended level. Acetylcysteine at a concentration of 10.2 mmol/L increased i-STAT creatinine results, while acetylcysteine at a concentration of 0.3 mmol/L did not significantly interfere with i-STAT creatinine results.

5) Bromide has been tested at two levels: the CLSI recommended level and a therapeutic plasma concentration level of 2.5 mmol/L. The latter is the peak plasma concentration associated with halothane anesthesia, in which bromide is released. APOC has not identified a therapeutic condition that would lead to levels consistent with the CLSI recommended level. Bromide tested at concentrations of 2.5 and 37.5 mmol/L interfered with i-STAT creatinine results.

6) The dependence of the i-STAT creatinine with respect to Carbon Dioxide (CO_2) is as follows:

   For creatinine results ≤ 2.0 mg/dL, no correction for ***P***CO2 is required.
   For creatinine results > 2.0 mg/dL, the following correction applies:

   $$\mathbf{creatinine_{corrected} = creatinine * (1 + 0.0025 * (PCO2 - 40))}$$

7) Nithiodote (sodium thiosulfate) is indicated for the treatment of acute cyanide poisoning. The journal article titled "Falsely increased chloride and missed anion gap elevation during treatment with sodium thiosulfate" indicated that sodium thiosulfate could be used in the treatment of calciphylaxis indicating that "the highest concentration likely to be seen in plasma [is] after infusion of a 12.5 g dose of sodium thiosulfate pentahydrate. Assuming that the 12.5 g dose of sodium thiosulfate pentahydrate is distributed in a typical blood volume of 5 L with a hematocrit of 40%, the peak sodium thiosulfate plasma concentration expected is 16.7 mmol/L."[13]

*It is possible that other interfering substance may be encountered. The degree of interference at concentrations other than those listed might not be predictable.

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Abbott Point of Care Inc.
100 and 200 Abbott Park Road
Abbott Park, IL 60064 • USA

EC REP

Emergo Europe
Molenstraat 15
2513 BH The Hague
The Netherlands

CE IVD