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.

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

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

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

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

See below for information on factors affecting results. Certain substances, such as drugs, may affect analyte levels \textit{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 intended for use in the \textit{in vitro} quantification of creatinine in arterial, venous, or capillary whole blood.

**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:

- Creatinine
- Creatine Amidinohydrolase
- Creatinine Amidohydrolase
- Sarcosine Oxidase

**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 $\mu$mol L\(^{-1}\)) for \textit{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 SRM909b. 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 i-STAT Corporation.
Expected Values

<table>
<thead>
<tr>
<th>Test/Abbreviation</th>
<th>Units*</th>
<th>Reportable Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine/Crea</td>
<td>mg/dL</td>
<td>0.2 – 20.0</td>
<td>0.6 – 1.3²</td>
</tr>
<tr>
<td></td>
<td>µmol/L</td>
<td>18 – 1768</td>
<td>53 – 115</td>
</tr>
</tbody>
</table>

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 as follows: Duplicates of each control fluid were tested in the morning and in the afternoon on five days for a total of 20 replicates. The averaged statistics are presented below.

Method comparison data were collected using NCCLS guideline EP9-A<sup>4</sup>. Venous blood samples, collected in lithium or sodium heparin Vacutainer<sup>®</sup> 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<sup>5</sup> 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.*

Interference studies were based on NCCLS guideline EP7.<sup>6</sup>

*The usual warning relating to the use of regression analysis is summarized here as a reminder: For any analyte, “If the data is collected over a narrow range, the estimate of the regression parameters are relatively imprecise and may be biased. Therefore, predictions made from these estimates may be invalid”.<sup>4</sup> 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 if r>0.975.
Precision Data (mg/dL)

<table>
<thead>
<tr>
<th>Aqueous Control</th>
<th>Mean</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>4.7</td>
<td>0.08</td>
<td>1.7</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.76</td>
<td>0.05</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Method Comparison (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>Hitachi 917</th>
<th>J&amp;J Vitros</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>Sxx</td>
<td>0.045</td>
<td>0.035</td>
</tr>
<tr>
<td>Syy</td>
<td>0.087</td>
<td>0.109</td>
</tr>
<tr>
<td>Slope</td>
<td>1.002</td>
<td>1.005</td>
</tr>
<tr>
<td>Int’t</td>
<td>0.030</td>
<td>-0.109</td>
</tr>
<tr>
<td>Sy.x</td>
<td>0.110</td>
<td>0.229</td>
</tr>
<tr>
<td>Xmin</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Xmax</td>
<td>11.2</td>
<td>12.6</td>
</tr>
<tr>
<td>r</td>
<td>0.9987</td>
<td>0.9931</td>
</tr>
</tbody>
</table>

Factors Affecting Results*

<table>
<thead>
<tr>
<th>Interferent</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbate</td>
<td>11 mmol/L ascorbate will cause a 0.7 mg/dL increase in creatinine.</td>
</tr>
<tr>
<td>Bromide</td>
<td>100 mg/dL (12.5 mmol/L) bromide will increase creatinine by 0.8 mg/dL (71 µmol/L) from an initial creatinine concentration of 1.0 mg/dL (88 µmol/L).</td>
</tr>
</tbody>
</table>
| CO₂         | For Crea values below 2 mg/dL:  
  For $PCO_2$ values above 40 mmHg, the values are increased by 6.9% for every 10 mmHg  
  For $PCO_2$ values below 40 mmHg, the values are decreased by 6.9% for every 10 mmHg  
    $[Cr]_{actual} = [Cr]_{istat} \cdot \{ 1 - \left( 0.069 \times \left[ (PCO_2 - 40)/10 \right] \right) \} $  
  For Crea values above 2 mg/dL:  
  For $PCO_2$ values above 40, the values are decreased by 3.7% for every 10 mmHg  
  For $PCO_2$ values below 40, the values are increased by 3.7% for every 10 mmHg  
    $[Cr]_{actual} = [Cr]_{istat} \cdot \{ 1 - \left( 0.037 \times \left[ (40 - PCO_2)/10 \right] \right) \} $  
| Creatine    | 5 mg/dL creatine will cause a 0.20 mg/dL increase in Creatinine. |

For clinical situations in which creatine may be elevated, see note (1) below.
Hydroxyurea (Droxia®, Hydrea®) Hydroxyurea may cause significant errors in the measurement of creatinine with the i-STAT System. Use an alternative method to measure creatinine when patients have been administered hydroxyurea. See note (2) below for typical uses of this drug and note (3) below for details of the interference.

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. 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, thrombocytopenia, 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. For every 100 µmol/L hydroxyurea in the whole blood sample, creatinine will be increased by approximately 1.85 mg/dL (164 µmol/L), up to a whole blood hydroxyurea concentration of at least 921 µmol/L (maximum concentration tested). The magnitude of the bias is independent of the creatinine level over a range of at least 1.0 mg/dL (88 µmol/L) to 12.4 mg/dL (1096 µmol/L).

Acetaminophen up to 20 mg/dL (1.3 mmol/L), bicarbonate up to 40 mmol/L, bilirubin up to 20 mg/dL (342 µmol/L), calcium up to 5.0 mg/dL (1.25 mmol/L), dopamine up to 13 mg/dL (0.85 mmol/L), methyldopa up to 2.5 mg/dL (118.4 µmol/L), salicylate up to 77.5 mg/dL (4.34 mmol/L), sarcosine up to 1.0 mmol/L, and uric acid up to 20 mg/dL (1190 µmol/L) were tested and found not to interfere with creatinine results.

*It is possible that other interfering substances may be encountered. These results are representative and your results may differ somewhat due to test-to-test variation. The degree of interference at concentrations other than those listed might not be predictable.
References

Droxia and Hydrea are registered trademarks of Bristol-Myers Squibb Company, Princeton, NJ.
i-STAT is a registered trademark of i-STAT Corporation, East Windsor, NJ USA. Vacutainer is a registered trademark of Becton Dickinson and Company, Franklin Lakes, NJ USA. Vitros is a registered trademark of Ortho-Clinical Diagnostics, Rochester, NY.