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Assessment of the Nova StatSensor whole blood point-of-care creatinine analyzer for the measurement of kidney function in screening for chronic kidney disease

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Abstract

Background: Point-of-care testing for creatinine using a fingerprick sample and resultant estimated glomerular filtration rate has potential for screening for chronic kidney disease in community settings. This study assessed the applicability of the Nova StatSensor creatinine analyzer for this purpose.

Methods: Fingerprick samples from 100 patients (63 renal, 37 healthy volunteers; range 46–962 μmol/L) were assayed using two StatSensor analyzers. Lithium heparin venous plasma samples collected simultaneously were assayed in duplicate using the isotope dilution mass spectrometry-aligned Roche Creatinine Plus enzymatic assay on a Hitachi Modular P unit. Method comparison statistics and the ability of the StatSensor to correctly categorise estimated glomerular filtration rate above or below 60 mL/min were calculated pre- and post-alignment with the laboratory method.

Results: StatSensor 1 creatinine results (y) were much lower than the laboratory (y=0.75x + 10.2, average bias –47.3, 95% limits of agreement –208 to +113 μmol/L). For estimated glomerular filtration rates above or below 60 mL/min, 100% and 87% of results respectively agreed with the laboratory estimated glomerular filtration rate (79% and 96% post-alignment). StatSensor 2 statistics were similar. The 95% limits of agreement between StatSensor creatinine results were –35 to +34 μmol/L.

Conclusions: Isotope dilution mass spectrometry alignment of the StatSensor will identify most patients with estimated glomerular filtration rate < 60 mL/min, but there will be many falsely low estimated glomerular filtration rate results that require laboratory validation. Creatinine results need improvement.

Keywords: chronic kidney disease; creatinine; estimated glomerular filtration rate; POCT; renal function.

Introduction

Chronic kidney disease (CKD) has a prevalence of approximately 16% and 13% in Australian and American environments, respectively (1, 2). The disease is usually silent and progressive, and end-stage renal disease is placing increasing burdens on health care budgets, with increasing numbers of patients requiring dialysis (3). Early signs of CKD include proteinuria, increased blood pressure and reduced glomerular filtration rate (GFR) (4). GFR can be estimated (eGFR) using laboratory measurements of serum creatinine, and considerable international efforts have been made to align creatinine results to isotope dilution mass spectrometry (IDMS) equivalent standards (5). In addition, simplified equations to convert serum creatinine results to eGFR based on age, gender, and ethnic background have now been adopted (5–7).

Although efforts to align the calibration of laboratory creatinine estimations are well-advanced (8), there can be valid reasons for measuring creatinine in non-laboratory situations. These include screening programs for CKD to facilitate the early detection and follow-up of at-risk patients. Recently, Kidney Health Australia conducted a targeted community-based program for CKD risk called Kidney Evaluation for You (KEY). This pilot program was the first program for CKD risk assessment undertaken in the primary health care setting in Australia (9). The KEY study used the i-STAT point-of-care testing (POCT) analyzer (Abbott Point-of-Care Inc., Princeton, NJ, USA) for measuring creatinine, with subsequent calculation of eGFR. However, the i-STAT device required a venous whole blood sample of approximately 100 μL, which is less ideal than a fingerprick sample for a screening situation. In addition, i-STAT has been reported to produce higher creatinine results than the Roche enzymatic creatinine assay (Roche Diagnostics, Sydney, Australia) (10).

A recently released point-of-care device from Nova Biomedical (Waltham, MA, USA) that measures creatinine using just 1.2 μL of whole blood and converts creatinine results...
to eGFR has been actively promoted to fill a niche in the POCT market. We evaluated the performance of this device against the IDMS-aligned Roche enzymatic creatinine assay, and assessed the potential use of the Nova device for detecting silent kidney disease in the community. The results of this study are also relevant for radiology patients using potentially nephrotoxic contrast media (11) and in other POCT environments.

Materials and methods

Ethics approval

Ethics approval to conduct this study was obtained from the Flinders Clinical Research Ethics Committee (application number 222/08).

Patient samples

One hundred subjects (48 males and 52 females) participated in the study; 63 were patients attending either the renal clinic or dialysis clinic at the Renal Unit, Flinders Medical Centre (FMC), and 37 subjects were healthy volunteers.

Capillary whole blood specimens were obtained from each subject and immediately analyzed in singlicate with two Nova StatSensor creatinine devices using the same reagent strip lot number. A venous whole blood specimen anticoagulated with lithium heparin (Greiner blood tube, Greiner Labortecnik GmbH, Cat No 456083; Kremsmuenster, Austria) was obtained from each subject at the same time and sent to the pathology laboratory at FMC, Adelaide, South Australia. In the laboratory, the venous whole blood sample was centrifuged (4500 g for 5 min) and a plasma sample aliquoted for duplicate laboratory analysis.

Test method

The Nova Biomedical StatSensor creatinine meter measured creatinine in 1.2 μL of whole blood in 30 s. The sample was added to a reagent strip which was inserted into the device prior to sample application. In the reagent strip, creatinine is converted to hydrogen peroxide in an enzymatic cascade involving creatinase, creatinine oxidase and sarcosine oxidase. The signal generated from H2O2 was detected amperometrically. Calibration was factory-encoded into the reagent strip.

Fingerprick analyses were conducted according to manufacturer directions by a non-laboratory operator trained by Nova Biomedical.

Comparison method

Creatinine was also measured in the laboratory by assaying plasma from each patient in duplicate using the IDMS-aligned Roche Creatinine Plus enzymatic assay (Cat No 1775685) with a Hitachi Modular P unit. The performance of this assay has been validated vs. both the IDMS reference method and international reference materials (SRM 967) (12–15).

Table 1 Nova StatSensor day-to-day method imprecision (n = 20).

<table>
<thead>
<tr>
<th>QC</th>
<th>Target</th>
<th>Acceptable range</th>
<th>Mean Device 1</th>
<th>Mean Device 2</th>
<th>SD Device 1</th>
<th>SD Device 2</th>
<th>CV% Device 1</th>
<th>CV% Device 2</th>
<th>Range Device 1</th>
<th>Range Device 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low QC</td>
<td>84</td>
<td>44–124</td>
<td>99.6</td>
<td>100.8</td>
<td>8.89</td>
<td>8.97</td>
<td>8.9</td>
<td>8.9</td>
<td>83–123</td>
<td>84–123</td>
</tr>
<tr>
<td>Mid QC</td>
<td>173</td>
<td>115–230</td>
<td>199.6</td>
<td>195.5</td>
<td>17.31</td>
<td>16.09</td>
<td>8.7</td>
<td>8.2</td>
<td>157–237</td>
<td>158–232</td>
</tr>
<tr>
<td>High QC</td>
<td>531</td>
<td>398–663</td>
<td>605.4</td>
<td>601.0</td>
<td>32.65</td>
<td>31.28</td>
<td>5.4</td>
<td>5.2</td>
<td>543–665</td>
<td>532–668</td>
</tr>
</tbody>
</table>

Creatinine units are μmol/L. Devices 1 and 2 are two separate Nova analyzers. Acceptable range is that stated by the manufacturer.

Imprecision

Imprecision (coefficient of variation, CV%) for creatinine measurements on the Nova StatSensor device was assessed in three ways. Within-run and day-to-day imprecision were calculated using repeated analysis (n = 10 and 20, respectively) of three levels of Nova StatSensor quality control (QC) material (Cat No 43921-3; QC lot numbers 5008340241, 5008100242 and 5008344243 for within-day and 5009037241, 5009037242 and 5009043243 for day-to-day). Between-device imprecision was calculated from the difference between results obtained on the same samples analyzed on the two Nova devices (using the equation $s = \sqrt{\frac{d^2}{2n}}$, where $s = \text{standard deviation}$, $d = \text{difference between individual results on the two devices}$ and $n = \text{number of duplicates (98 in this data set)}$ and CV% = \frac{s}{m} \times 100$ where $s = \text{standard deviation and } m = \text{mean creatinine concentration}$).

Linearity

Linearity of the Nova analyzers was assessed by increasing the creatinine concentration of a base pool of lithium heparin anticoagulated venous whole blood (58 μmol/L) by 100 μmol/L using a concentrated solution of creatinine prepared from National Institute of Standards and Technology Standard Reference Material (NIST SRM) 914a (NIST, United States Department of Commerce). By mixing the base pool and the spiked sample in various ratios, whole blood samples were prepared in which the base pool was supplemented with 100, 250, 500, 750 and 1000 μmol/L of creatinine. All samples were assayed with both Nova 1 and Nova 2 analyzers, and linearity assessed using Clinical and Laboratory Standards Institute (CLSI) EP6-A guidelines (16) (see Statistical analyses).

Accuracy

The accuracy of creatinine results obtained with each Nova StatSensor device was compared to the mean of duplicate creatinine results from the IDMS-aligned laboratory method using Passing-Bablok linear regression analysis (17). Differences between results were graphed against the Roche enzymatic assay using a modified Bland-Altman difference plot (18).

eGFR on the Nova StatSensor, calculated automatically from the measured creatinine using the modification of diet in renal disease (MDRD) equation (factor 186), was also plotted against eGFR from the laboratory method, calculated by the laboratory information system (LIS) from the measured creatinine using the standardised MDRD equation (factor 175). The ability of the Nova StatSensor to correctly categorise eGFR above or below 60 mL/min was then assessed by calculation of sensitivity, specificity, positive and negative predictive values.
Table 2  Method correlation statistics for the Nova (y) vs. the IDMS-aligned Roche enzymatic creatinine method (x) before and after IDMS alignment.

<table>
<thead>
<tr>
<th>Nova (y)</th>
<th>Creatinine concentration, ( \mu \text{mol/L} )</th>
<th>PB slope (95% CI)</th>
<th>PB intercept (95% CI)</th>
<th>r</th>
<th>Mean (x) (range)</th>
<th>Mean (y) (range)</th>
<th>Mean bias (95% CI)</th>
<th>95% Limits of agreement</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factory calibration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nova 1</td>
<td>&lt; 150</td>
<td>0.96 (0.82–1.11)</td>
<td>–3.5 (–14.5 to 7.5)</td>
<td>0.83</td>
<td>82.6 (46–144)</td>
<td>75.2 (32–131)</td>
<td>–7.3 (–11.0 to –3.6)</td>
<td>–35.9 to 21.2</td>
<td>62</td>
</tr>
<tr>
<td>Nova 2</td>
<td>&lt; 150</td>
<td>0.92 (0.77–1.06)</td>
<td>2.4 (–9.1 to 12.8)</td>
<td>0.84</td>
<td>82.6 (46–144)</td>
<td>75.9 (31–125)</td>
<td>–6.7 (–10.3 to –3.1)</td>
<td>–34.8 to 21.3</td>
<td>62</td>
</tr>
<tr>
<td>Nova 1</td>
<td>All</td>
<td>0.75 (0.70–0.79)</td>
<td>10.2 (6.2 to 17.4)</td>
<td>0.97</td>
<td>217.0 (46–962)</td>
<td>169.6 (32–566)</td>
<td>–47.3 (–63.6 to –31.1)</td>
<td>–207.7 to 113.0</td>
<td>100</td>
</tr>
<tr>
<td>Nova 2</td>
<td>All</td>
<td>0.74 (0.69–0.79)</td>
<td>14.0 (8.0 to 20.5)</td>
<td>0.97</td>
<td>209.8 (46–962)</td>
<td>163.4 (31–545)</td>
<td>–46.5 (–63.6 to –29.3)</td>
<td>–213.7 to 120.8</td>
<td>98</td>
</tr>
<tr>
<td><strong>After recalibration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nova 1</td>
<td>&lt; 150</td>
<td>1.31 (1.12–1.51)</td>
<td>–19.9 (–36.0 to –5.7)</td>
<td>0.83</td>
<td>82.6 (46–144)</td>
<td>86.8 (29–161)</td>
<td>4.2 (–0.2 to 8.7)</td>
<td>–30.1 to 38.5</td>
<td>62</td>
</tr>
<tr>
<td>Nova 2</td>
<td>&lt; 150</td>
<td>1.25 (1.08–1.44)</td>
<td>–12.3 (–27.4 to 0.3)</td>
<td>0.84</td>
<td>82.6 (46–144)</td>
<td>87.6 (28–153)</td>
<td>5.0 (0.8 to 9.3)</td>
<td>–27.5 to 37.6</td>
<td>62</td>
</tr>
<tr>
<td>Nova 1</td>
<td>All</td>
<td>1.00 (0.94–1.06)</td>
<td>–0.4 (–5.7 to 9.1)</td>
<td>0.97</td>
<td>217.0 (46–962)</td>
<td>212.6 (29–741)</td>
<td>–4.3 (–14.5 to 5.9)</td>
<td>–105.2 to 96.5</td>
<td>100</td>
</tr>
<tr>
<td>Nova 2</td>
<td>All</td>
<td>0.99 (0.93–1.05)</td>
<td>4.5 (–3.7 to 12.7)</td>
<td>0.97</td>
<td>209.8 (46–962)</td>
<td>204.3 (28–713)</td>
<td>–5.5 (–16.4 to 5.3)</td>
<td>–111.3 to 100.3</td>
<td>98</td>
</tr>
</tbody>
</table>
After alignment of the Nova StatSensor results to the laboratory creatinine method, this process was repeated, now using an eGFR factor of 175 for the Nova StatSensor.

Statistical analyses

Statistical analyses, including assessment of linearity, were performed using the statistical package Analyse-it (clinical laboratory version 2.21).

Results

Imprecision

Within-run and day-to-day imprecision averaged 3.3% and 8.9%, respectively, at 100 μmol/L creatinine, and 2.8% and 5.3% at 600 μmol/L creatinine for the two StatSensor analyzers (Table 1). For the laboratory assay, year-long imprecision (approx. 1200 QC data points) was 1.9% and 1.4% at similar low and high concentrations of creatinine. The imprecision of the Roche enzymatic assay was consistent with data reported during the use of this method to develop the IDMS-aligned 175 MDRD equation (14).

Between-device imprecision was 7.8% (all concentrations, n=98), 7.8% for creatinine <150 μmol/L (n=62), and 6.2% for creatinine >150 μmol/L.

The StatSensor creatinine day-to-day imprecision did not meet either the desirable or minimum analytical goal for imprecision derived from biological variation criteria (CV <2.2% and 3.2%, respectively) (19), or the criteria required to keep the analytical error in eGFR calculations below 10% (5). The laboratory assay met both these requirements.

Linearity

Minor deviations from linearity were observed and are shown in parenthesis after the addition of 100 (−3.9%), 250 (5.4%), 500 (5.5%), 750 (2.0%) and 1000 (−3.3%) μmol/L creatinine to a base pool of blood containing 58 μmol/L creatinine. The CLSI EP6-A linearity protocol measures the degree to which a curve (polynomial line of best fit) approximates a straight line.

Initial method comparison

Creatinine concentrations in the samples tested ranged from 46 to 962 μmol/L by the laboratory method. Table 2 summarises the method correlation statistics for the Nova StatSensor device vs. the IDMS-aligned Roche enzymatic method, split by creatinine concentration.

Using a factory-based calibration, StatSensor 1 (y) produced slightly lower results than the IDMS-aligned Roche enzymatic assay (x) for 62 samples with creatinine concentrations <150 μmol/L (y = 0.96x − 3.5, average bias −7.3, 95% limits of agreement −36 to +21 μmol/L). For 100 samples spanning the full concentration range, the StatSensor results were much lower (y = 0.75x + 10.2, average bias −47.3, 95% limits of agreement −208 to +113 μmol/L). Patients on dialysis had significantly lower StatSensor creatinine results compared with the Roche enzymatic assay, as shown in Figure 1A. Similar findings have been reported at a recent conference (20–22), with interference from creatine and urea described in one abstract (20), while the effect of hemocrit was ruled out as a cause of discordant results in another study (21).

Because of the underestimation of creatinine, eGFR results from StatSensor 1 were incorrectly categorised as >60 mL/min for 7/53 patients (false normal results). There were no false abnormal results (eGFR ≤60 mL/min) (Figure 2A and Table 3).

StatSensor 2 had very similar summary statistics, indicating a consistent factory calibration and analytical performance for the two instruments (n=98 pairs, average bias between StatSensors 0.7 μmol/L, two samples had insufficient volume for assay on both devices). However, as illus-
Figure 2 Plot of eGFR results (mL/min) from Nova StatSensor 1 vs. the laboratory Roche enzymatic method. (A) Using the StatSensor factory encoded calibration. (B) Following recalibration to the Roche enzymatic assay.

Figure 3, for individual samples, there was more variation in results than expected between the two POC analyzers (95% limits of agreement –35 to +34 μmol/L for all samples and –16 to +17 μmol/L for samples with laboratory creatinine <150 μmol/L).

**Correction of observed method bias**

Using the Passing-Bablok slope and intercept factors, the significant overall negative bias observed across the full creatinine concentration range with the factory-calibrated Nova 1 device was corrected using a reciprocal recalibration equation: Nova (recalibrated) = [Nova (factory calibration) × 1.3333] – 13.53 μmol/L. Method comparison statistics post-recalibration are provided in Table 2.

StatSensor 1 eGFR results were then recalculated using the 175 MDRD equation and replotted against the IDMS-aligned laboratory eGFR (Figure 2B). Once Nova StatSensor 1 was recalibrated to the laboratory assay, eGFR ≥60 mL/min was correctly identified vs. the laboratory assay for 37/47 patients (79%). There were 10 false abnormal results. An eGFR <60 mL/min was identified correctly for 51/53 patients (96%). There were two false normal results (Table 3).

However, both before and after recalibration, we were concerned by the number of StatSensor creatinine results showing poor agreement with the laboratory method (Figure 1). Predialysis results from one patient were omitted from graphs and statistical calculations because of very inconsistent results (lab 541,538: Nova, factory calibration 186,154 μmol/L).

**Discussion**

Screening programs for early detection of CKD are increasing important because the burden of the disease continues to rise globally, and many risk factors, such as hypertension, smoking and obesity can be readily modified (3). In the US, the Kidney Early Evaluation Program (KEEP) provides such a national screening agenda (23). As part of KEEP, creatinine (and eGFR) is measured at a central laboratory and results are returned to patients at a later date. POCT for creatinine confers particular advantages for the CKD screening process as participants can be provided with immediate feedback on their kidney function during their community assessment. In Australia, the recent KEY study combined POCT for creati-
Table 3 Predictive values for Nova StatSensor vs. Roche Hitachi enzymatic assay using an eGFR cut-off value of 60 mL/min to detect reduced kidney function.

<table>
<thead>
<tr>
<th>Device</th>
<th>Calibration</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PV (+ve test), %</th>
<th>PV (−ve test), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nova 1</td>
<td>Factory calibration</td>
<td>86.8</td>
<td>100.0</td>
<td>100.0</td>
<td>87.0</td>
</tr>
<tr>
<td>Nova 2</td>
<td>Factory calibration</td>
<td>82.4</td>
<td>100.0</td>
<td>100.0</td>
<td>83.9</td>
</tr>
<tr>
<td>Nova 1</td>
<td>Post lab recalibration</td>
<td>96.2</td>
<td>78.7</td>
<td>83.6</td>
<td>94.9</td>
</tr>
<tr>
<td>Nova 2</td>
<td>Post lab recalibration</td>
<td>92.2</td>
<td>78.7</td>
<td>82.6</td>
<td>90.2</td>
</tr>
</tbody>
</table>

Positive test (reduced kidney function) eGFR < 60 mL/min; negative test eGFR ≥ 60 mL/min.

Analysis of creatinine results and falsely low results for patients undergoing dialysis requires further investigation. Imprecision (8.9%) exceeded established criteria at creatinine concentrations < 150 μmol/L. For detecting eGFR < 60 mL/min, the Nova StatSensor recorded a 13% (7/53) false normal rate, meaning these patients with stage 3 CKD would be missed.

Once Nova StatSensor 1 was recalibrated to the IDMS-aligned Roche enzymatic Hitachi assay, the number of false normal results decreased to 4% (2/53). However, 21% (10/47) of results were now incorrectly classed as abnormal (i.e., eGFR < 60 mL/min). For community-based programmes and hospital use, we consider that with recalibration this instrument will identify most patients with eGFR < 60 mL/min, but there will be many falsely low eGFR results that will require laboratory validation and contribute to unnecessary stress among patients.

Throughout the evaluation period, some further problems were experienced with the StatSensor method. These included poor reproducibility with certain batches of QC material (not used in the imprecision studies) and instability with different reagent strip lot numbers.

In summary, the Nova StatSensor did not measure creatinine as well as expected, and we believe that the assay needs urgent improvement. Using the factory calibration, 18% of creatinine results below 150 μmol/L differed by more than 20 μmol/L from the Roche enzymatic assay, and 62% of results above 150 μmol/L differed by more than 20%. Many samples had large differences in creatinine results compared to the IDMS-aligned laboratory method (Figure 1); this is concerning given international efforts to standardise creatinine results (5). Despite this, it could still be useful as a screening test for CKD in community and other settings, as the risk of missing CKD stage 3 with recalibration of the instrument was < 5% in this study.

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Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research support provided by Nova Biomedical played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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