Point-of-Care Creatinine Testing for the Detection and Monitoring of Chronic Kidney Disease

Horizon Scan Report 0038
March 2014

Clinical Question:

In the primary care setting, what is the accuracy and utility of creatinine point-of-care (POC) tests in the detection and monitoring of Chronic Kidney Disease (CKD), compared to standard practice using laboratory blood tests?

Current Practice and Advantages over Existing Technology:

a) **Screening for CKD by detection of elevated creatinine levels:**
Existing Technology: Blood samples sent from General Practice (GP) for analysis in local hospital laboratory. Results subsequently sent back to GP typically within 24 hours. Depending on significance of result, this may or may not be communicated to the patient by letter, telephone or in person.
Benefits of creatinine POC testing: Rapid (within minutes) result of creatinine level allowing immediate feedback of result to patient.

b) **Dose adjustment of prescribed medications in patients with renal impairment:**
Existing Technology: Typically, the most recent recorded renal function test is used to assist medication dose adjustment.
Benefits of creatinine POC testing: Up-to-date renal function allowing immediate dose reduction of medications which require dose adjustment due to renal impairment if necessary (1).

c) **Monitoring of CKD**
Existing Technology: Patients attend GP or hospital for blood tests to monitor renal function.

Benefits of creatinine POC testing: Home testing would allow monitoring of renal function in comfort of own home. This might be particularly useful in patients with end stage renal failure requiring renal replacement therapy. Speed and ease of testing may allow more frequent monitoring, and earlier detection and thus management of deteriorating renal function (2).

d) Detection of acute on chronic renal failure and acute kidney injury (AKI)

Existing Technology: Blood samples sent from GP for analysis in local hospital laboratory. Results subsequently sent back to general practice typically within 24 hours. Depending on significance of result, this may or may not be communicated to the patient by letter, telephone or in person.

Benefits of POC creatinine testing: Rapid knowledge of renal function, facilitating referral of patients to secondary care (emergency department or clinic) if necessary.

Details of Technology:

The table in Appendix 1 provides an overview of the ten creatinine POC devices identified.

Creatinine POC devices allow rapid measurement of creatinine levels. The devices analyse whole blood, serum, plasma, or a combination of these, and require very small sample volumes. The Nova Statsensor (Nova Biomedical, USA) requires only 1.2 microlitres of blood for analysis; as such, fingerprick blood collection is sufficient. The time taken to generate a result varies between 30 seconds (Nova Statsensor) and 12 minutes (Piccolo Xpress). Despite this variation, all analysis times are far shorter than the time taken for conventional creatinine results generated by laboratory testing.

Both the Nova Statsensor and i-STAT are hand-held devices and could therefore be used in the home environment. The other appliances, by virtue of their table-top design, would be better suited to a primary care setting.

Two of the principle methods of measuring creatinine in blood/serum/plasma are the Jaffe method (alkaline picrate method) and enzymatic methods. The Jaffe method was developed in the 19th century and is traditionally used in hospital laboratories. It is based upon the colour change that occurs when creatinine is mixed with picric acid in an alkaline solution. There have been concerns over the accuracy of the picric acid method, as multiple compounds can interfere with the reaction, thus generating an inaccurate result. Subsequently, enzymatic methods have been developed in an attempt to reduce these inaccuracies, and have been found to be more accurate (3), and are replacing the picrate methods used in laboratories. Most of the creatinine POC devices employ enzymatic methods, although of note, the Pentra C200 uses the picric acid reaction.

In an attempt to standardise the various methods and appliances for creatinine measurement, some of the devices are IDMS (Isotope Dilution Mass Spectrometry) aligned, such as the Piccolo Xpress. Other devices are IDMS traceable (see table).

Patient Group and Use:
- Screening for CKD in high risk patients.
- Monitoring renal function in patients with known CKD.
- Adjustment of doses of renal excreted medication in patients with CKD.
- Detection of relapse in post renal transplant patients.
- Detection of AKI and acute-on-chronic renal failure in unwell patients presenting to GP.

Importance:

CKD is a common condition describing impairment of renal function with an annual incidence rate of 1,701 per million population in the UK (4). The incidence increases with age, and due to the ageing population, it is an ever-increasing problem. It is typically stratified into severity on the basis of the GFR (Glomerular Filtration Rate), which can be calculated using serum creatinine. (See table 1)

Table 1 Stages of CKD as defined in the NICE clinical guideline (5)

Stage*	GFR (ml/min/1.73 m^2)	Description
1	90 or more	Normal or increased GFR, with other evidence of kidney damage
2	60-89	Slight decrease in GFR, with other evidence of kidney damage
3A	45-59	Moderate decreases in GFR, with or without other evidence of
3B	30-44	kidney damage
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure
*Use the suffix (p) to denote the presence of proteinuria when staging CKD (recommendation 1.2.1)		

As CKD is irreversible, frequently progressive and tends to present insidiously, NICE has placed emphasis on early detection through screening of at-risk groups such as patients with hypertension and diabetes (5).

Early recognition of CKD may enable the initiation of preventative measures that halt or slow the progress of CKD (6), together with the ensuing complications such as cardiovascular disease. This is particularly noteworthy, as 30% of people with advanced kidney disease are referred late to nephrology services from both primary and secondary care, and more than 2% of the NHS budget is spent on renal replacement therapy, namely dialysis and transplantation (5).

Previous Research:

Accuracy compared to existing technology:

The majority of studies reviewed have found creatinine POC devices to be rapid and reliable alternatives to laboratory testing. However, some studies have noted a tendency of certain devices to underestimate renal impairment (7, 8, 9), as well as poor inter-device concordance (10) and as such have recommended employing of these devices with caution.

A German study (11) compared creatinine levels measured by two separate Nova Statsensor devices against values generated by the laboratory Jaffe method in 401 consecutive patients scheduled for contrast-enhanced CT scans. The hand-held devices were found to have a mean sensitivity of 77.42%

and a mean specificity of 94.71% for detecting patients with a serum creatinine over 106 µmol/L (1.2 mg/dl) was determined by the authors as the cut-off of normal renal function). Excellent inter-device agreement was found (p < 0.0001).

The ABL800 FLEX (Radiometer), i-STAT and the Nova Statsensor were compared with a reference laboratory plasma creatinine assay in 266 patients scheduled for CT examination, requiring a creatinine or eGFR measurement before contrast administration (12). Concordance was defined as the percentage of all results falling into the correct eGFR category, calculated from their plasma creatinine (i.e., eGFR <60 or ≥60 mL/min/1.73 m^2). The Radiometer analyser displayed the best overall concordance with plasma creatinine (93%). The i-STAT demonstrated lower overall concordance (87%) but it had the best sensitivity (97%) for the detection of plasma eGFR less than 60 mL/min/1.73m2. The Nova Statsensor had the lowest overall concordance (79%) with laboratory plasma creatinine assays. This concordance increased to 80% following implementation of the StatSensor device offset function, which allows users to match whole blood to plasma creatinine values.

A further study found that the ABL800 FLEX performed well with acceptable precision when measuring creatinine values (13). In this Australian study, creatinine values generated by the Radiometer POC device and standard laboratory analysis were compared in 650 paired samples involving 125 patients admitted to ITU. Creatinine POC results were found to correlate well with creatinine values generated in the central laboratory (R² = 0.991, p < 0.001).

The i-STAT and IRMA TRUpoint analysers were compared with both Jaffe and enzymatic creatinine methods in a hospital laboratory in an American study (14). This involved 49 consecutive patients requiring creatinine measurement prior to chemotherapy. Statistically significant agreement was found for both POC analysers compared to both laboratory methods. The concordance was better for the i-STAT using modification of diet in renal disease (MDRD) estimation of GFR and TRUpoint using MDRD or Cockcroft-Gault (CG) estimation of GFR [κ 0.6–1.0] than for the i-STAT using the CG estimation[κ<0.6] (kappa measure of agreement).

In an American study (10) creatinine values generated by four separate Nova Statsensor devices were compared with laboratory values measured using the Roche Modular enzymatic method in 119 intensive care and oncology patients. Significant differences in results were found to be generated by the four different meters (p<0.0035). Almost a quarter of the samples in this study had creatinine values that differed by 44 µmol/L (0.5 mg/dL) or more between the Nova StatSensor and the enzymatic method (27 of 119); poorer concordance was observed at creatinine values over 177 µmol/L (2.00 mg/dL).

Shephard *et al* (9) evaluated the potential reliability of the Nova Statsensor, with a view to determining its applicability to screening for CKD in the community. In this Australian study, creatinine values obtained using the Nova Statsensor with capillary blood samples were compared to laboratory values from paired venous blood samples in 100 patients (63 attending renal/dialysis clinic and 37 healthy volunteers). They found a 13% (7/53) false normal rate for detecting eGFRs < 60

mL/min using the Nova Statsensor compared to standard laboratory methods, meaning that these patients with CKD stage 3 would be missed in screening.

Creatinine values generated by the Nova Statsensor were highly correlated with central laboratory values (p < 0.0001) in a Japanese study (7). This involved comparing eGFRs calculated from creatinine values generated by the Nova Statsensor with laboratory measurements, in 113 patients scheduled to undergo contrast enhanced CT and MRI scans. They noted that the mean eGFR was higher with the POC results compared to laboratory results (p<0.0001). This was also demonstrated by Schnabl *et al* (8); creatinine values generated by the Nova Statsensor and laboratory analysis in 161 patients (non-, pre- and post-dialysis patients) were compared. Good concordance (R^2=0.9328) between POC values and laboratory values was found, but the creatinine values measured with the Nova Statsensor were consistently lower than those measured using standard laboratory techniques. Nonetheless, the authors concluded that the device provided reliable measurement across a clinically relevant range.

Impact compared to existing technology:

POC testing could facilitate early diagnosis of CKD via screening programmes, as well as follow-up of patients at high risk (9). A screening programme by "KEY" (Kidney Evaluation for You) targeted individuals at high risk of CKD and performed POC analysis (6). In this Australian initiative, of 402 individuals recruited, 20.4% had CKD. The authors argue that an early CKD diagnosis could allow targeted preventative measures that might reduce morbidity or facilitate management of patients with progressive kidney failure. The POC pathology testing (including creatinine POC testing) was well received by participants; 99% found it convenient and 96% felt that the immediate results and feedback helped them in understanding their condition. One big benefit of POC testing over standard laboratory analysis cited by the authors is the ability to inform participants instantly of their results and facilitate shared decision making for future management.

It is feasible that this approach could be translated into a primary care initiative with an annual (or more frequent) POC creatinine test for high risk patients, as part of 'Healthy Heart' check-ups for example, with immediate action on significant results.

Geerts *et al* evaluated use of creatinine POC testing in a community pharmacy setting in the Netherlands (1). 46 individuals underwent POC creatinine testing, with subsequent dose adjustment of medications excreted via the kidneys in the context of elevated creatinine levels. More than half of the patients who underwent POC testing had mild-to-moderate renal impairment. In a questionnaire given to patients after POC testing, asking patients to rate their experience on a five point Likert scale (1=bad, 5=good), a mean score of four or more was attained for each question. Creatinine POC testing in a GP surgery could make for safer prescribing and reduced morbidity, theoretically reducing prescription of medications excreted via the kidneys without up-to-date renal function.

Creatinine POC analysis, particularly the use of hand-held devices, allows for rapid analysis of creatinine in the home environment. This in turn could allow faster diagnosis and management of serious conditions, such as Haemolytic Uraemic Syndrome which can present with recurrent renal

failure, in turn leading to better prognosis (2). This could also be of benefit in cases of end stage renal failure requiring renal replacement therapy. Home testing of creatinine may lead to more frequent renal function analysis due to its convenience and simplicity. Twenty outpatients of a Paediatric Nephrology Unit and dialysis patients were randomly selected together with six healthy volunteers (n=26) in a Dutch study (2). Creatinine values generated by two POC machines (Reflotron plus and i-STAT) were compared with standard laboratory methods. 62% of results fell within +/- 20 µmol/L of laboratory results for the Reflotron and 77% of results for the i-STAT. The authors found POC analysis at home to be an acceptable alternative to laboratory testing.

The utility of POC systems in plasma creatinine estimation in critically ill patients with acute kidney injury was reported in an Australian study (13). By extension of this, in the primary care setting, creatinine POC estimation could be used as a screening tool in acutely unwell patients (with or without CKD) with dehydration illness (for example an elderly patient with diarrhoea or vomiting) to help triage those who require admission, from those who could be managed as an outpatient. However, some have warned against the use of creatinine in screening for acute kidney injury, describing it as an unreliable marker in this context, despite its frequent use to this end (15). They instead state that creatinine determination performs better in detecting deterioration of kidney function in patients with stable CKD.

Guidelines and Recommendations:

NICE (5) has placed emphasis on screening of at-risk groups for CKD, namely those with diabetes, hypertension, cardiovascular disease or structural kidney problems, patients with a family history of stage 5 CKD, and those patients suffering from multisystem disease with the potential for renal involvement (such as Systemic Lupus Erythematosus). NICE guidelines also state that the IDMS (isotope dilution mass spectrometry)-traceable simplified MDRD (modification of diet in renal disease) equation should be used to estimate GFR, using creatinine assays with calibration traceable to a standardised reference material. Ideally specific assays (e.g. enzymatic), should be used.

There are no guidelines in existence about the use of creatinine POC devices.

Research Questions:

1) Determine the accuracy of creatinine POC devices in the primary care setting.

2) Assess the cost-effectiveness of creatinine POC devices in primary care and community settings.

3) To delineate the clinical needs from the clinician and patient perspectives for POC creatinine testing in the primary care setting.

Suggested next step:

1) Studies to assess the accuracy of creatinine POC measurement in primary care settings against traditional laboratory methods.

2) Study to determine the needs in different clinical situations and settings within primary care, e.g. urgent care/out-of-hours, screening, diabetes clinics etc.

3) Study to assess feasibility of training patients requiring renal replacement therapy to use creatinine POC devices at home.

4) Study to assess impact of use of creatinine POC devices in conjunction with Healthy Heart clinics and Diabetes clinics ('at-risk' groups) in detection of CKD.

Expected Outcomes:

Creatinine POC devices allow the ability to rapidly generate creatinine values. If used in the primary care setting, they would be expected to facilitate screening of CKD, in line with NICE guidance, as well as monitoring of patients with known CKD or End stage renal failure. Hand-held devices used in the home setting appear to be a convenient and hassle-free alternative to GP/hospital visits for venepuncture, in those patients requiring (frequent) renal function monitoring. Patients could keep a record of their creatinine values, much in the same way that diabetics record their blood glucose results, encouraging patients to take control of their own health.

References:
1.   Geerts AFJ, De Koning FHP, De Vooght KMK, Egberts ACG, De Smet PAGM, van Solinge WW. Feasibility of point-of-care creatinine testing in community pharmacy to monitor drug therapy in ambulatory elderly patients. *Journal of Clinical Pharmacy & Therapeutics*. *2013*; 38(5): 416-422.
2.   Schenk PW, Cransberg K, Wolff ED, de Rijke DB. Point-of-care creatinine testing in children at risk for sudden deterioration of renal function. *Clinical Chemistry & Laboratory Medicine*. *2007*; 45(11): 1536-1541.
3.   Qiu L, Guo X, Zhu Y, Shou W, Gong M, Zhang L, Han H, Quan G, Xu T, Li H, Li X. Effect of picric acid and enzymatic creatinine on the efficiency of the glomerular filtration rate predicator formula. *Clinical Laboratory.* *2012*; 59(5-6):511-22.
4.   Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *American Journal of Kidney Diseases. 2003*; 42(4):677-84.
5.   http://www.nice.org.uk/nicemedia/live/12069/42117/42117.pdf NICE clinical guideline 73.
6.   Mathew TH, Corso O, Ludlow M, Boyle A, Cass A, Chadban SJ, Joyner B, Shephard M, Usherwood T. Screening for chronic kidney disease in Australia: a pilot study in the community and workplace. *Kidney International – Supplement*. 2010; *(*116): S9-16.
7.   Morita S, Suzuki K, Masukawa A, Ueno E. Assessing renal function with a rapid, handy, point-of-care whole blood creatinine meter before using contrast materials. *Japanese Journal of Radiology*. *2011*; 29(3): 187-193.
8.   Schnabl KL, Bagherpoor S, Diker P, Cursio C, Dubois J, Yip PM. Evaluation of the analytical performance of the Nova StatSensor creatinine meter and reagent strip technology for whole blood testing. *Clinical Biochemistry*. *2010*; 43(12): 1026-1029.
9.   Shephard M, Peake M, Corso O, Shephard A, Mazzachi B, Spaeth B, Barbara J, Mathew T. Assessment of the Nova StatSensor whole blood point-of-care creatinine analyzer for the measurement of kidney function in screening for chronic kidney disease. *Clinical Chemistry & Laboratory Medicine*. *2010*; 48(8): 1113-1119.
10.   Straseski JA, Lyon ME, Clarke W, Dubois JA, Phelan LA, Lyon AW. Investigating interferences of a whole-blood point-of-care creatinine analyzer: comparison to plasma enzymatic and definitive creatinine methods in an acute-care setting. *Clinical Chemistry*. *2011*; 57(11): 1566-1573.
11.   Haneder SA. Gutfleisch A, Meier C, Brade J, Hannak D, Schoenberg SO, Becker CR, Michaely HJ. Evaluation of a handheld creatinine measurement device for real-time determination of serum creatinine in radiology departments. *World journal of radiology*. *2012 July*; 4(7): 328-334.

12.   Korpi-Steiner NL, Williamson EE, Karon BS. Comparison of three whole blood creatinine methods for estimation of glomerular filtration rate before radiographic contrast administration. *American Journal of Clinical Pathology. 2009*; 132(6): 920-926.

13.   Udy A, O'Donoghue S, D'Intini V, Healy H, Lipman J. Point of care measurement of plasma creatinine in critically ill patients with acute kidney injury. *Anaesthesia. 2009*; 64(4): 403-407.

14.   Nichols JH, Bartholomew C, Bonzagi A, Garb JL, Jin L. Evaluation of the IRMA TRUpoint and i-STAT creatinine assays. *Clinica Chimica Acta. 2007*; 377(1-2): 201-205.

15.   Soni SS, Ronco C, Katz N, Cruz DN. Early diagnosis of acute kidney injury: The promise of novel biomarkers. *Blood Purification*. 2009; 28(3): 165-174.

This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford
Authors: Oghenekome Gbinigie, Matthew Thompson, Christopher P. Price, Carl Heneghan, Annette Plüddemann
Contact details: Dr. Annette Plüddemann; Email: dec@phc.ox.ac.uk

Appendix 1: Table of available devices

Product	Manufacturer/ Location	Blood type analysed	Sample Volume	Analysis Time	CE Mark	FDA approved	Hand-held/Table-top	Detection Range (μmol/L)	Measurement Method (Enzymatic/ Picric acid)	Method Principle	IDMS Aligned/ traceable
Nova Statsensor	Nova Biomedical, USA	Whole blood	1.2μl	30 seconds	Yes	Yes	Hand-held	27-1056	Enzymatic	Amperometic Biosensor	Unknown
i-STAT	Abbott, USA	Whole blood, plasma, serum	65 μl	2 minutes	Unknown	Yes	Hand-held	18-1768	Enzymatic	Amperometic Biosensor	Traceable
ABL800 FLEX	Radiometer, Denmark	Whole blood, plasma, serum	Syringe - 250 μl Capillary – 125 μl	1 minute	Yes	Yes	Table-top	10-2000	Enzymatic	Amperometic Biosensor	Traceable
IRMA TRUpoint	ITC, USA	Whole blood	200 μl	2.6 minutes	Unknown	Yes	Table-top	18-1061	Enzymatic	Amperometic Biosensor	None
Pentra C200	Horiba, France	Serum or plasma	9 μl	8.5 minutes	Yes	Unknown	Table-top	18-2000	Picric Acid	Colorimetric	Traceable
Piccolo Xpress	Abaxis, USA	Whole blood, plasma, serum	100 μl	12 minutes	Yes	Yes	Table-top	18-1768	Enzymatic	Indicator Absorbance	Aligned
Reflotron Plus	Roche, Germany	Whole blood	30 μl	2 minutes	Yes	Yes	Table-top	44.5-884	Enzymatic	Dye Reflectance	Unknown
Dri-Chem 4000	Fuji Film, Japan	Serum or plasma	10 μl	5 minutes	Yes	Unknown	Table-top	18-2122	Enzymatic	Dye Absorbance	Traceable
Stat Profile CCX	Nova Biomedical, USA	Whole blood, plasma, serum	120 μl	2.5 minutes	Yes	Yes	Table-top	18-1768	Enzymatic	Amperometic Biosensor	Unknown
Stat Profile pHOx Ultra	Nova Biomedical, USA	Whole blood, plasma, serum	150 μl	2 minutes	Yes	Yes	Table-top	18-1768	Enzymatic	Amperometic Biosensor	Unknown