NICE advice

Point-of-care creatinine tests before contrast-enhanced imaging

Medtech innovation briefing
Published: 18 January 2018
nice.org.uk/guidance/mib136

Summary

- The 7 **technologies** described in this briefing are point-of-care (POC) creatinine tests used to measure kidney function before contrast-enhanced imaging.
- The **innovative aspects** are that the tests give results from whole blood, blood plasma or blood serum samples in about 9 minutes or less. This helps to inform a decision on whether to proceed with contrast-enhanced imaging in people without a recent creatinine test result.
- The intended **place in therapy** would be as an alternative to current laboratory-based creatinine testing in people needing contrast-enhanced imaging.
- The **key points from the evidence** summarised in this briefing are from 7 observational studies with a total of 3,859 participants. Most of the included studies show that POC creatinine tests correlate very well with laboratory-based reference tests with acceptable specificity and sensitivity.
- **Key uncertainties** around the evidence and technology are that there is no published evidence of effectiveness for several of the devices in this briefing and only 1 of the studies was conducted in the UK. Some of the devices included in the evidence were susceptible to variation in creatinine levels compared with laboratory reference tests. Specificity and sensitivity were not always reported and some devices included in this briefing are not represented in the evidence.

- The **cost** of the products included in this briefing range from £4,995 to £35,000 (excluding VAT) without consumables. The **resource impact** would most likely be an increase in cost to the NHS, which could be offset by reduced incidences of cancelled scans and contrast-induced acute kidney injury (CI-AKI).

This briefing describes technologies that fulfil a similar purpose. During development, every effort was made to identify and include relevant technologies but others may not have been identified, or key information was unavailable.

The technologies

POC creatinine tests allow rapid measurements of creatinine levels using very small samples of whole blood, serum, plasma or a combination of these. The devices used for these tests are either handheld or table-top and need blood from either finger-prick or venous/arterial samples. The method of analysis can vary with some devices using test cartridges and some using test strips.

The focus of this briefing is POC creatinine testing to assess kidney function in people who are scheduled to have contrast-enhanced imaging. Testing is important because contrast materials such as iodine or gadolinium can cause kidney injury, particularly in high-risk patients and those with known kidney dysfunction. If patients do not have a recent creatinine measurement, their imaging may be cancelled and rescheduled. Alternatively, they may have unenhanced imaging – which is less reliable – or the planned contrast agent may be given, risking kidney injury. Current practice varies; a recent UK survey estimated that up to 20% of hospitals only check creatinine levels before imaging in people known to be at high risk of kidney injury (Harris et al. 2016).

The alkaline picrate (Jaffe) method is used for most current laboratory creatinine testing but can be affected by other compounds or by delayed processing leading to incorrect reporting. Enzymatic methods are designed to reduce these inaccuracies and are used in all but 1 of the POC devices summarised in this briefing.

All the technologies included in this briefing have received regulatory approval under the European Union 98/79/EC in-vitro diagnostics annex III directive and are described in table 1.

Table 1 List of included devices and specifications

Device	Analyser	Sample type/volume	Analysis time	Laboratory test method	eGFR	Creatinine measurable range micromole/litre
Nova StatSensor (Nova Biomedical)	Handheld	Whole blood, 1.2 microlitres finger-prick sample	30 seconds	Enzymatic	Yes	27–1,056
i-STAT 1 (Abbott)	Handheld	Whole blood, 65 microlitres	2 minutes	Enzymatic	No	18–1,768
i-STAT Alinity (Abbott)	Handheld	Whole blood, 65 microlitres	2 minutes	Enzymatic	Yes	18–1,768
ABL90 FLEX PLUS (Radiometer)	Table-top	Whole blood, plasma, serum, 65 microlitres	35 seconds	Enzymatic	Yes	10–1,800
ABL800 FLEX (Radiometer)	Table-top	Whole blood, plasma, serum, 125–250 microlitres	1 minute	Enzymatic	Yes	10–1,800
Pentra C200 (Horiba)	Table-top	Serum or plasma, 9 microlitres	8.5 minutes	Picric acid	No	18–2,000
Dri-chem NX500 (Fujifilm)	Table-top	Serum or plasma, 10 microlitres, finger-prick samples can be used	5 minutes	Enzymatic	No	18–2,122
Abbreviations: eGFR, estimated glomerular filtration rate.						

Two other devices, IRMA TRUpoint (Lifehealth) and Piccolo Xpress (Abaxis), were identified but no additional information was made available so they are not described elsewhere in this briefing.

The innovation

The devices are designed to provide results from whole-blood samples in about 9 minutes or less at the POC, compared with at least 1 hour for laboratory testing. This is intended to reduce the incidence of cancelled scans while minimising the risk of kidney injury.

Current NHS pathway

The NICE guideline on preventing, detecting and managing acute kidney disease states that before offering iodinated contrast agents to adults for non-emergency imaging, testing for chronic kidney disease should be done using estimated glomerular filtration rate (eGFR) results or by checking an eGFR result taken in the past 3 months. The eGFR is calculated from the creatinine value, corrected for age, ethnicity and sex, and has been suggested as a better measure of kidney function compared with serum creatinine levels alone (Levey et al. 2003). In the NHS, eGFR is calculated using the abbreviated chronic kidney disease epidemiology collaboration (CKD-EPI) equation. The eGFR value is presented as ml/minute/1.73 m^2 and falls into one of 6 stages indicating the severity of kidney damage. The result from calculating the eGFR and creatinine levels will inform the decision on the dose of contrast materials used to avoid CI-AKI or whether to proceed with the contrast-enhanced imaging. If the eGFR calculation is greater than 30 then the scan can go ahead.

Current care pathways involve sending a blood sample, usually taken by a phlebotomist, to a laboratory for testing. Most laboratory devices will use the Jaffe method for determining creatinine levels. The results can take between 60 minutes and 24 hours. The levels of creatinine and eGFR help to decide whether to continue with the imaging procedure and, if so, will determine the dose of contrast agent and any prophylactic treatment against potential adverse effects.

Population, setting and intended user

The devices included in this briefing would be used at the POC for anyone without a recent creatinine result having either planned or emergency contrast-enhanced imaging. It would be particularly useful for people at high risk of kidney disease such as those with diabetes, people taking metformin and older people. The devices would be used by radiographers in a secondary- or tertiary-care setting. Users would need additional training of between 30 minutes and 1 day, depending on their previous skill level and the device used.

Costs

The devices cost from £4,995 to £35,000, with each individual creatinine test costing between £0.17 and £4.75. Devices vary in price because of their size – some are large table-top machines – but also because of their functionality as some can perform multiple tests.

Table 2 Cost of POC creatinine devices (excluding VAT)

Device	Device cost	Estimated cost per creatinine test strip/ cartridge	Additional information and costs
Nova StatSensor	£4,995 Includes docking station, mains power lead, spare battery, network cable and workstation	£3.95	Quality-control agent level 1, 4-ml vial (need 4 per year): £9.00 Quality-control agent level 3, 4-ml vial (need 4 per year): £9.00 Service cost after year 1: £800 (optional cost)
i-STAT 1	£5,500 Includes handheld analyser, printer kit, downloader/rechargeable battery, electronic simulator and cables	£3.75–£4.75 Depends on volume of use	Service cost per year (first year free): £850 (optional cost) Quality-control agent unknown
i-STAT Alinity	£6,500 Includes handheld analyser, printer kit, downloader/rechargeable battery, electronic simulator and cables	£3.75–£4.75 Depends on volume of use	Service cost per year (first year free): £850 (optional cost) Quality-control agent unknown
ABL90 FLEX PLUS	£10,000 Includes power cord	£1.83 (based on 15 tests per day for 365 days)	Quality-control agent unknown

ABL800 FLEX	£15,000 Includes power cord	£1.83 (based on 15 tests per day per year)	Quality-control agent unknown
Pentra C200	£35,000	£0.17	Control agent, 10×5 ml: £121.99 Calibrants, 10×3 ml: £237.88 Service costs (includes all parts, labour, transport and helpline access): £5,242
Dri-chem NX500	£8,500 with plasma filter £6,000 without plasma filter function Both of these include the power cable	£1.23	Pipette tip: £0.16 each 0.5-ml tube: £0.23 each Quality-control agent high level: £11.97 quality-control low level Quality-control agent low level: £11.97 Optional plasma filter for whole-blood samples (negates need for centrifuge): £2.50

Costs of standard care

The unit cost of laboratory tests for blood/serum/plasma creatinine is £1.29 based on 2015/16 reference costs code DAPS04 (Department of Health 2016).

Resource consequences

Using POC creatinine tests would add initial costs compared with standard laboratory-based methods. This includes an increased cost per test and the need to redesign care pathways and develop decision algorithms for specified creatinine levels. These additional costs could be offset if POC testing reduced the number of cancelled scans or the incidence of contrast-induced kidney injury. An NHS service evaluation stated that these POC tests could be beneficial to the NHS because of early diagnosis of chronic kidney disease (CKD) and reduced visits to GPs for testing. However, these savings would be minimal as CKD is a chronic condition.

There would be minimal practical difficulties as some of the devices are handheld and only need a small charging station. The table-top devices take up more space, which could be a minimal change. All devices including docking and charging stations would need power and ethernet sockets. More storage may be needed for the consumables, but this would unlikely be a significant change. Staff training would be needed to ensure that radiographers can use the POC test correctly and are up-to-date with all regulatory and quality-assurance requirements. Additional resources may be needed for participation in external quality-assurance schemes.

A US-based study showed that, after implementing POC creatinine/eGFR testing in a radiology department, the waiting time for results reduced from an average of 1 hour 54 minutes to 5 minutes; rescheduled scans reduced from 7.3% to 0%; and the volume of contrast materials used was reduced in 25% of patients (Nowacek and McClintock, 2015).

Based on information provided by companies, the individual POC creatinine-testing technologies are currently used in up to 35 NHS trusts.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Kidney disease occurs more frequently in males, people over the age of 60, and those of African-Caribbean family origin. Sex, age and race are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods guide. This briefing includes the most relevant/best publicly-available evidence relating to the clinical and cost effectiveness of the technologies. The literature search strategy, evidence selection methods and detailed data extraction tables are available on request by contacting mibs@nice.org.uk.

Published evidence

There are 7 studies summarised in this briefing with a total of 3,859 participants. Six studies used a comparative within-subject design comparing POC testing with a standard laboratory method. There was also 1 case-control study. Table 3 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

No relevant published evidence was identified for 4 of the 8 included technologies (ABL90 FLEX PLUS, Pentra C200, Piccolo Xpress or Dri-chem NX500).

The sample sizes of 2 of the included studies are small compared with the others and so results from these studies should be interpreted with caution. The studies generally lack a description of where the samples were recruited or why the patients needed a contrast-enhanced scan. The outcomes reported are limited and only 3 of the studies reported the specificity and sensitivity of the POC devices compared with laboratory-based reference tests. Correlation analysis was used in the other studies, which may be performed because creatinine is a continuous variable. It should be noted that studies have used different equations for calculating eGFR with some not including family origin as a variable. This could produce different results to those calculated under the same conditions in a different study.

Only 1 of the studies included was conducted in the UK but 2 studies reported outcomes directly related to possible changes in the NHS care pathway. However, there may be an issue in the creatinine cut-offs used. Most radiology departments use 1.6 mg/dl to distinguish between normal and elevated creatinine, whereas the included studies use cut-off values in the range 0.7 mg/dl to 10 mg/dl, making their results potentially less relevant to the NHS. Evidence comparing POC devices with current methods in an NHS setting with large samples would be beneficial.

Table 3 Published evidence

Dimeski et al. 2013	
Study size, design and location	40 adults consisting of healthy laboratory staff and renal patients (proportions not reported). Repeated measure observational study. Australia.

Intervention and comparator(s)	Intervention: StatSensor and i-STAT. Comparator: Beckman DxC800 using the Jaffe method.
Key outcomes	Dopamine caused a significant over estimation of up to 338% for i-STAT compared with laboratory measurements. Dobutamine interference caused a small underestimation with the StatSensor of up to 27% compared with laboratory measurements but this was not significant. i-STAT creatinine levels correlated very highly with the laboratory results for different sample types (r=0.995 to 0.996). StatSensor levels also correlated with the laboratory results, but not as strongly (r=0.918 to 0.976). The StatSensor was less precise when testing creatinine levels in the same sample over separate days compared with the i-STAT (coefficient of variation 14.1% to 15.4% versus 4.9% to 5.6% respectively).
Strengths and limitations	Assessed both capillary and venous whole-blood samples. Small sample sizes used, especially for precision data.
Haneder et al. 2012	
Study size, design and location	401 patients referred for contrast-enhanced CT scanning. This was across 2 centres using a different comparator in each centre. Prospective observational study design. Germany.
Intervention and comparator(s)	Intervention: StatSensor. Comparators: Siemens Dimension RXL at centre 1 and the Olympus AU2700 at centre 2. Both used the Jaffe method.

Key outcomes	The StatSensor device slightly underestimated creatinine levels compared with a laboratory reference sample. In centre 1, across both StatSensor devices, the creatinine results correlated highly with the laboratory reference (r=0.93). In centre 2 across both StatSensor devices, the creatinine results correlated highly with the laboratory reference (r=0.84). After the addition of a correction factor to the original data from centre 1, the sensitivity of the StatSensor improved for detecting at-risk patients in device A and device B (those with >1.2 mg/100 ml serum creatinine levels) from 35.48% to 80.65% and 41.94% to 70.97% respectively. Acceptable specificity was also maintained (99.41% to 98.26% and 99.41% to 94.12%) and NPV improved from 89.42% to 96.57% and 90.37% to 94.67%.
Strengths and limitations	Large sample size. Corrected bias of different methods by using curve offset correction. Two different comparator devices.
Inoue et al. 2017	
Study size, design and location	233 blood samples were taken from patients scheduled to have contrast-enhanced CT scans. Of these, 123 patient blood samples were analysed without calibration alignment to reference method, and 110 samples were analysed after calibration alignment to reference method by linear regression offset correction. Three healthy volunteers were recruited to provide reference samples. Retrospective observational study. Japan.
Intervention and comparator(s)	Intervention was the StatSensor device. Comparator was the BM2250 analyser using the enzymatic method.

Key outcomes	In the non- and post-adjustment groups, mean creatinine levels were significantly lower when using the laboratory measurements compared with the StatSensor (0.8 mg/dl versus 0.94 mg/dl respectively). In both groups, the mean eGFR was higher when calculated using the comparator compared with the StatSensor (75.3 ml/min/1.73 m^2 versus 61.6 ml/min/1.73 m^2). In both groups serum creatinine values significantly correlated between the comparator and the StatSensor. Following curve offset adjustment, correlation of serum creatinine values to the comparator test improved. However, the eGFR correlation decreased in the adjusted samples, possibly because of the eGFR calculation also using age and sex as variables. The sensitivity, specificity, PPV, NPV and accuracy of StatSensor for detecting CI-AKI were 100%, 89%, 50%, 100% and 90.2% before and 100%, 96.3%, 33.3%, 100% and 96.4% following adjustment respectively.
Strengths and limitations	Corrected bias of different methods by using curve offset correction. Some samples were from healthy volunteers and from different sample sites.
Karamasis et al. 2017	
Study size, design and location	160 patients in the intervention group and 294 in a retrospective control group. All had ST-elevation myocardial infarction and needed contrast-enhanced imaging for percutaneous coronary intervention. Single centre: UK.
Intervention and comparator(s)	Intervention: pre-procedure creatinine testing using StatSensor. Comparator: laboratory-based testing in historical cohort.

Key outcomes	In the study population as whole, the incidence of CI-AKI did not significantly differ between intervention and control groups. In a subset of patients with CKD, eGFR stage 3A or higher, the incidence of CI-AKI was reduced in the intervention group by 12% compared with the control group, but this was not significant. In a subset of patients with CKD, the intervention group also received a significantly reduced amount of contrast material compared with the control group. In a subset of patients without CKD, the incidence of CI-AKI and amount of contrast material received did not significantly differ between groups.
Strengths and limitations	Outcomes relate to NHS care pathway. Not randomised. No comparator device. Small subset sample sizes. Operators not blinded to treatment allocation. Study was funded by Nova Biomedical.
Korpi-Steiner et al. 2009	
Study size, design and location	266 adults having contrast-enhanced CT procedures. Observational study. US.
Intervention and comparator(s)	Interventions: i-STAT, StatSensor and ABL800 FLEX devices. Comparator: central laboratory methods using a Roche Cobas Integra 400 analyser and the enzymatic method.

Key outcomes	Imprecision tests using a sample with creatinine levels of 0.75 mg/dl showed that all the intervention tests slightly overestimated creatinine at low concentrations: mean recovery was higher for the StatSensor (134% of expected), compared with the ABL800 FLEX (120%) and i-STAT (106%). All intervention devices also underestimated creatinine levels at high concentrations, between 95% and 100% of the expected value when using samples between 2 mg/dl to 10 mg/dl. StatSensor consistently underestimated laboratory-measured creatinine levels. i-STAT systematically overestimated laboratory-measured creatinine levels and the ABL800 FLEX was very similar to laboratory-based measures. Whole-blood creatinine measured on the ABL800 FLEX showed the best correlation to measurements with the comparator (r=0.89). i-STAT had the best sensitivity (97%), but poorer specificity (84%) for prediction of eGFR <60 ml/min/1.73 m^2, the cut-off for diagnosis of CKD. The StatSensor device had the lowest concordance of eGFR measurements to the comparator, but has a slope and offset feature so this can be altered to improve performance.
Strengths and limitations	Clinical risk factors of patients was unknown. A few of the patients had severe renal insufficiency, which could have biased the results.
Lee-Lewandrowski et al. 2012	
Study size, design and location	2,646 patients needing contrast-enhanced imaging over a 6-month period based on average 441 patients per month. Observational study. US.
Intervention and comparator(s)	Intervention: i-STAT device. Comparator: central clinical laboratory methods using a Roche Cobas C501 device and the Jaffe method.

Key outcomes	Linear regression analysis showed very high agreement between results from the i-STAT and comparator devices (r^2=0.99). 2 imprecision tests using the i-STAT and samples known to have creatinine levels of 0.7 mg/dl and 4.4 mg/dl was 0% (perfect readings of 0.7 mg/dl) and 2.2% (slight overestimation of the concentration) respectively. 74% of patients tested had normal eGFR levels and were offered a scan. Of those with abnormal eGFR levels, 74% had scans with contrast agents and 26% without contrast.
Strengths and limitations	Outcomes relate to NHS care pathway. Large sample size. Part funded by Abbott Point of Care. Sample size is based on 3,087 creatinine tests done over a 7-month period.
Morita et al. 2011	
Study size, design and location	113 patients scheduled to have contrast-enhanced imaging. Prospective observational study. Japan.
Intervention and comparator(s)	Intervention was the StatSensor and the comparator was central laboratory measurement using the enzymatic method.
Key outcomes	The mean reported creatinine levels were lower when measured using the StatSensor compared with laboratory measurements (0.71 mg/dl versus 0.82 mg/dl). The mean reported eGFR levels were statistically higher when measured using StatSensor compared with laboratory measurements (81.2 ml/min/1.73 m^2 versus 71.2 ml/min/1.73 m^2). StatSensor and standard laboratory measurements were significantly correlated (r=0.74).
Strengths and limitations	Did not compare eGFR with actual GFR. Did not follow up patients.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; NPV, negative predictive values.	

Recent and ongoing studies

- ISRCTN62796844 – Streamlining cross-sectional imaging pathways (SCIPs): A feasibility and economic modelling study of POC creatinine testing in radiology. Trial was completed May 2017.
- SRCTN18805212 – Method comparison and bias estimation of POC creatinine test. Trial was completed August 2017.

Specialist commentator comments

Comments on this technology were invited from clinicians working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 5 of the experts have experience with POC creatinine devices.

Level of innovation

Four of the experts believed POC devices were very innovative as they can be used in the imaging room at any time and produce rapid results. Three felt the devices were a minor variation or a standard technology.

Potential patient impact

Four experts felt the less invasive and rapid nature of the POC tests are beneficial to people with pre-existing kidney problems and also older people, those with long-term conditions such as cancer and people having elective or urgent radiological procedures. All agreed this could lead to reduced waiting times, fewer cancelled scans, fewer hospital visits, better renal safety and an overall streamlining of the patient pathway. One expert reported that an evaluation had revealed a positive patient experience through POC tests.

Potential system impact

All experts felt POC tests could lead to improved efficiencies by enabling better deployment of resources and reducing lost capacity and administrative burden from having to turn people away who did not have recent creatinine test results. Same-day results would reduce the need for additional appointments for creatinine testing before imaging, lead to fewer cancelled or delayed procedures and increase patient throughput. The need for training radiology staff in POC testing was highlighted and 2 commentators thought that initially it could be an extra burden on staff.

Three experts thought that POC creatinine testing would be a replacement to central laboratory-based methods and 2 thought that it would be an addition. This would be considered a moderate change to the current NHS pathway for the detection of kidney disease or injury.

Opinion was split about the cost of introducing POC testing. Three experts felt that over time it would cost less or about the same as standard care as long as it was used to redesign the care pathway. Two commentators said that the associated cost benefits would be hard to quantify and POC testing may lead to more people being tested, and that a full economic evaluation would be needed. Other factors that would need to be considered were the costs for storage of consumables and the need for integration of POC results with the existing hospital reporting system. None of the experts were aware of any safety concerns or regulatory issues surrounding POC creatinine testing.

General comments

Three experts suggested that POC teams and pathology departments would need to cooperate when implementing POC creatinine testing to ensure safe reporting of results. POC creatinine tests must also use UK formulas as there is international variation in eGFR formulas.

Specialist commentators

The following clinicians contributed to this briefing:

- Beverly Snaith, clinical professor of radiography, University of Bradford and The Mid Yorkshire Hospitals NHS Trust. BEPoCC study, supported by 3 device manufacturers with loan equipment and consumables.
- Martine Harris, research radiographer, The Mid Yorkshire Hospitals NHS Trust. Has undertaken research supported by the 3 vendors who loaned POC equipment and consumables brokered by the Yorkshire and Humber Academic Health Science Network.
- Annette Thomas, director of WEQAS and POC testing clinical lead, Cardiff and Vale University Health Board. No conflicts of interests declared.
- Anne Dawnay, consultant clinical biochemist, Barts Health NHS Trust. No conflicts of interest declared.
- Emma James, POC testing team leader, Manchester University NHS Foundation Trust. Phone interview for Homburg & Partner. A payment of €300 made to UNICEF for this consultation on her behalf.

Development of this briefing

This briefing was developed for NICE by Cedar. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-2783-8