The NGAL Test for early diagnosis of acute kidney injury

Medtech innovation briefing
Published: 4 February 2014

www.nice.org.uk/guidance/mib3

Summary

Effectiveness

- Three published observational studies involving a total of 46 patients were identified.

- It is not clear whether the clinical utility of The NGAL Test is at least equivalent to current diagnostic methods.

Adverse events and safety

The current clinical evidence has not measured any outcomes relating to patient safety and no adverse events have been reported.

Costs and resource use

- The average cost is £24 per NGAL Test.

- One study assessed the cost effectiveness of a different urinary neutrophil gelatinase-associated lipocalin (NGAL) biomarker for diagnosing acute kidney injury after cardiac surgery in patients in the UK compared with current diagnostic methods.

- The NGAL strategy was more cost effective than current practice in the base case and sensitivity analysis. However this evidence is of uncertain value because it only looked at urinary NGAL.

Technical factors

The NGAL test is intended to be used with an automated clinical chemistry analyser by qualified laboratory staff.

Key points

The NGAL Test (BioPorto) is intended to be used for detecting acute kidney injury. It got its CE mark in January 2011. Current NICE guidance (NICE guideline on acute kidney injury) recommends using serum creatinine or urine output to detect acute kidney injury. Estimated glomerular filtration (eGFR) may also be used for children and young people. The NGAL Test has been compared with serum creatinine and eGFR testing in clinical studies.

There is limited clinical evidence and statistical information from 3 published observational studies involving a total of 46 patients. The evidence is inconclusive on whether the clinical utility of The NGAL Test is at least equivalent to current diagnostic methods (that is, monitoring of serum creatinine, blood urea nitrogen and urine output).

No publicly available reports were found on how using The NGAL Test would affect resource use. One study assessed the cost effectiveness of a different urinary neutrophil gelatinase-associated lipocalin (NGAL) biomarker for diagnosing acute kidney injury after cardiac surgery in patients in the UK compared with current diagnostic methods. The NGAL strategy was more cost effective than current practice in the base case and sensitivity analysis. Both urine and plasma samples can be used with The NGAL Test, so this evidence is of uncertain value because it only looked at urinary NGAL. There is no

research comparing the use of urine and plasma samples, but which is better probably depends on the clinical setting and population. For example, many patients with acute kidney injury stop passing urine, so a plasma sample may then be preferred.

Introduction

Acute kidney injury is common; it is seen in 13% to 18% of all people admitted to hospital. It increases both morbidity and mortality, although how often acute kidney injury is the cause is difficult to assess because it can often be a symptom of an underlying condition.

Acute kidney injury is generally subdivided into 4 types:

- pre-renal – in which the kidneys are structurally intact but the body is responding to severe fluid loss or hypotension

- intrinsic – in which ischaemic, inflammatory, cytotoxic or physical injury has damaged the kidney

- post-renal – in which mechanical urological obstruction prevents urine being passed

- acute-on-chronic – in which chronic kidney disease is already present.

Acute kidney injury is usually temporary and treatable. However, sometimes it is not completely reversible and can increase the risk of future acute kidney injury. Severe acute kidney injury can lead to, or may already be associated with, multi-organ failure; emergency treatment, dialysis and extended care may be needed, and mortality rates can be high.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The NGAL Test reagent kit, calibrator kit and control kit, manufactured by BioPorto, got its CE marking on 31 January 2011. It is classed as an in vitro diagnostic device.

Intended use

The NGAL Test is a laboratory test used to determine the level of a chemical known as neutrophil gelatinase-associated lipocalin (NGAL) in human urine and blood. Increased concentrations of NGAL may be caused by acute kidney injury. The NGAL Test could potentially therefore be used in the NHS to diagnose acute kidney injury.

Setting and intended user

The NGAL Test is promoted to be used in:

- intensive care for monitoring

- the emergency room as a triage tool

- cardiopulmonary bypass surgery for monitoring

- renal transplantation for predictive evaluation

- nephrotoxicity assessment using intravenous contrast agents.

It is intended to be used with an automated clinical chemistry analyser by qualified laboratory staff (BioPorto 2013).

Description

The NGAL Test is designed as a standard clinical laboratory test and can be used with most clinical chemistry analysers. The amount of NGAL present in samples of a patient's blood or urine is measured using a particle-enhanced turbidimetry laboratory technique. This involves quantifying the particles present in solution by measuring the reduction in transmitted light intensity through the sample. The assay takes about 10 minutes.

NGAL is a protein normally present in low levels in several human tissues. Its expression is greatly increased as a human immune response to inflammation and injury to epithelia (Cowland and Borregaard 1997).

In a person who is healthy, NGAL is filtered out of blood plasma by the glomeruli when it passes through the kidneys. NGAL is then reabsorbed back into blood plasma in the tubules. However, kidney inflammation in acute kidney injury can cause expression of NGAL directly into the urine (Tsigou et al. 2013) because there is a reduction in the glomeruli filtration rate and an increase in NGAL expression from the liver and lungs. This means that an accumulation of NGAL in blood plasma, with increased concentrations in plasma and urine, could indicate acute kidney injury.

Increased concentrations of NGAL can present earlier than other biomarkers used to detect acute kidney injury. Other conditions such as infection, hypertension, inflammation, anaemia and hypoxia can also cause increased concentrations of NGAL in urine and plasma (Tsigou et al. 2013), although not at the levels associated with acute kidney injury. Guidelines defining acute kidney injury use measurements of serum creatinine, urine output and, for children and young people, estimated glomerular filtration rate (eGFR), but do not include a definition of acute kidney injury based on measurement of NGAL.

Alternative NHS options

Serum creatinine measurement is the recommended method for detecting and measuring acute kidney injury (NICE 2013). Measurement of urine output and eGFR can also be used. For each of these measurement methods, there are established ranges that define acute kidney injury: the recognised criteria of risk, injury, failure, loss of kidney function, and end-stage renal failure (RIFLE) (Bellomo et al. 2004); Acute Kidney Injury Network (AKIN 2007); and Kidney Disease Improving Global Outcomes (KDIGO 2012). However, there are limitations to standard methods. Serum creatinine values vary with age, sex, diet, muscle mass, drug intake and exercise and are affected by a compromised glomerular filtration. It can take up to 24 hours for changes in creatinine concentrations to become detectable. Urine output is an inconsistent measure because it is affected by non-renal factors such as bleeding, and there can be practical difficulties in measuring it accurately. eGFR is not considered appropriate in certain groups, including people with severe malnutrition, obesity or other extreme body size; exceptional dietary intake, such as a vegetarian diet or creatinine supplements; a skeletal muscle disease; paraplegia; high muscle mass; or an amputation (KCAT 2013).

The NGAL Test is one of a group of newer biomarkers that have been proposed for detecting acute kidney injury. The others include cystatin C, kidney injury molecule-1, interleukine-18 and fatty-acid binding proteins. None of the newer biomarkers are in clinical use in the NHS.

NICE is aware of the following CE marked diagnostic tests that appear to fulfil a similar function to The NGAL Test:

- the NGAL Rapid ELISA Kit 037CE (BioPorto)

- the ARCHITECT Urine NGAL assay (Abbott Diagnostics)

- the Alere Triage NGAL Test (Alere Ltd).

Costs and use of the technology

Information on the cost of using the technology and alternative treatment options was sourced from the manufacturer and the literature (Shaw et al. 2011). Shaw et al. used a cost of £16 (inflated to 2012 prices) for the combined tests of serum creatinine, blood urea nitrogen and urine output. A cost of £27 (inflated to 2012 prices) was used for a urinary NGAL test. However, blood urea nitrogen is not used routinely in the UK and Shaw et al. did not provide the source of the costs, so these estimates should be treated with caution. The cost of testing for serum creatinine (by the Jaffe method) alone is around £2 per test.

The average cost per test of The NGAL Test is estimated to be £24, assuming the test reagent kit, controls and standards can be used for about 100 patients. The individual components needed for the test are The NGAL Test Reagent kit (£1,770), the calibrator kit (£213) and the control kit (£417). The lifespan of the technology is thought to be 24 months from manufacturing, with open vial stability and on board stability of 30 days. At 2°C to 8°C, the calibrator and control kits have a shelf life of 24 months from manufacture and an open vial stability of 4 weeks. There are no costs available for service, maintenance or training with The NGAL Test or alternative options. It is estimated that The NGAL Test or alternative options will be used about 4 times in cardiac surgery patients (Shaw et al. 2011) and might be used more often in other clinical settings like monitoring intensive care unit patients.

A nephrologist is needed to interpret NGAL, serum creatinine, blood urea nitrogen and urine output measurements, but the staff time is not expected to be more than for current

tests.

Likely place in therapy

The technology is intended to be used in the detection phase of the identification stage of the NICE pathway on acute kidney injury.

The NGAL Test is not used in clinical practice in any hospitals in the UK, but it is being used in research projects in some institutions.

Specialist commentator comments

Measurement of serum creatinine was stated as the primary method of detecting acute kidney injury. A lack of clinical evidence was the main reason given by some clinicians for not currently using The NGAL Test in clinical practice. Some clinicians reported using the test for research purposes, but none reported using it in clinical practice in the UK.

Evidence review

Clinical and technical evidence

The evidence available for The NGAL Test (BioPorto) relating to acute kidney injury was limited to 3 observational studies, summarised in tables 1, 2 and 3.

Table 1 Summary of prospective observational study (Jeong T-D et al. 2012)

Study component	Description
Objectives/ hypotheses	To evaluate whether plasma and urinary NGAL concentrations are useful early markers of AKI developing during and after liver transplantation surgery.
Study design	Prospective observational

Study component	Description
Setting	- Patients were recruited before liver transplantation. Baseline urine and blood samples were collected before surgery. Follow-up samples were collected 2, 4, 10, 16, 24, 30, 40 and 48 hours after reperfusion. - The Jaffe kinetic method was used to measure the concentrations of sCr and uCr on the Toshiba 200FR autoanalyser. - uNGAL was measured using the ARCHITECH Urine NGAL assay, a chemiluminescent microparticle immunoassay from Abbott diagnostics. - pNGAL was measured using The NGAL Test, a particle enhanced turbidimetric immunoassay from BioPorto. The analyser used was not stated. - uNGAL was corrected for volume output by normalisation relative to uCr because the volume of urine can affect the result (corrected uNGAL).
Inclusion/ exclusion criteria	- This study recruited 19 adult patients between April and June 2010 who were having living-related liver transplantation. - Exclusion criteria: - Patients under 18 years old - Patients having cadaveric liver transplantation - Patients with a history of diabetes and who were likely to have had renal injury before liver translation - Patients who had simultaneous liver and kidney transplantation.
Variables	Early diagnosis of AKI using corrected uNGAL and pNGAL.
Statistical methods	This study used the mean plus or minus standard deviation to report the results, and did comparisons using the chi-squared test, Mann–Whitney U test and Wilcoxon signed rank test. Statistical significance was defined as $p < 0.05$.

Study component	Description
Results	Using RIFLE criteria, 11 out of 19 patients (57.9%) were diagnosed with AKI after reperfusion. Baseline sCr values were within normal range, and there was no statistically significant difference between the AKI group and the non-AKI group. AKI group: • The mean and standard deviations for the time taken before an increase of 50% was seen in the sCr' corrected uNGAL and pNGAL were 26.0 plus or minus 15.4, 7.0 plus or minus 10.6 and 7.3 plus or minus 5.8 hours respectively. • All 11 patients with AKI experienced a 50% increase or more from baseline in corrected uNGAL. In 8 of these patients, the uNGAL concentration increased before the sCr. In 3, the 2 concentrations increased at the same time. • In 8 out of 11 patients, pNGAL increased 50% or more. • Receiver operating curve analysis for uNGAL found the area under the curve, indicating the predictive ability at 2 hours after reperfusion to be 0.693 (95% CI 0.443 to 0.944), and for pNGAL 0.682 (95% CI 0.415 to 0.949). Non-AKI group: • Mean and standard deviations for the time taken before an increase of 50% was seen in sCr; corrected uNGAL and pNGAL were not reported for this group. • 7 out of 8 patients without AKI had increases 50% or more from baseline on both corrected uNGAL and pNGAL.

Study component	Description
Conclusions	• The authors concluded that corrected uNGAL may be more useful than sCr for early diagnosis of AKI. • They concluded that, while there was no consensus on which of corrected uNGAL or pNGAL is the superior marker, their results showed it to be corrected uNGAL, despite previous studies finding the better marker to be pNGAL. • Finally, they noted that this study only included a few patients, and so additional, larger studies are needed.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; pNGAL, plasma neutrophil gelatinase-associated lipocalin; RIFLE, risk injury failure loss end stage renal disease; sCr, serum creatinine; uCr, urinary creatinine; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

Table 2 Summary of prospective observational study (Di Nardo et al. 2013)

Study component	Description
Objectives/ hypotheses	To look at whether sepsis could have an impact on the sensitivity of sNGAL, uNGAL and CysC for AKI diagnosis in critically ill children.
Study design	Single-centre prospective observational cohort study.

Study component	Description
Setting	• This study was done in a tertiary paediatric hospital on 2 groups of patients, one from the PICU, and the other from elective ambulatory surgery. For group A, blood and urine samples were those taken for the scheduled daily examinations in the PICU. For group B, the blood and urine samples were obtained from the perioperative examinations. • Serum and urine biomarkers were obtained. • Paediatric severe sepsis was diagnosed according to the definitions of the American College of Chest Physicians. • AKI was defined using the pRIFLE criteria. • uNGAL was measured using The NGAL Test from BioPorto and analysed on the ADVIA 2400 Chemistry System from Siemens. • sNGAL was measured using an alternative BioPorto assay. • sCysC and uCysC were measured using a method from Siemens.
Inclusion/ exclusion criteria	• Group A – 11 children admitted consecutively to the PICU with severe sepsis at admission. • Group B – 10 healthy patients scheduled for elective ambulatory surgery without sepsis or AKI (control group matched by age, body surface area and body weight).
Variables	Evaluate levels of sNGAL, uNGAL, sCysC and uCysC in children with severe sepsis, with and without AKI.
Statistical methods	• Continuous variables were reported using the median and interquartile range, and examined using the Mann–Whitney test. • Categorical variables were examined using the chi-squared test. • Biomarker level variability is assessed using 2-way ANOVA.

Study component	Description
Results	• Four patients from group A were found to have AKI as well as severe sepsis by the pRIFLE criteria. All 4 patients with severe sepsis and AKI died, but no patients with sepsis without AKI died (OR 0.007, 95% CI 0.001 to 0.4; p=0.0009). • The study found that, in patients with sepsis with or without AKI, the pooled median levels (presented here with interquartile ranges) were significantly increased: for uNGAL 300.8 (15.05 to 5,952) vs 26.59 (11.5 to 543.6) nanogram/dl (p=0.0019); for sCysC 1.27 (0.8 to 2.12) vs 0.56 (0.38 to 0.99) mg/dl (p<0.0001); and for uCysC 0.4 (0.04 to 2.9) vs 0.04 (0.04 to 0.38) mg/dl (p=0.0038). There was no significant difference between the median sNGAL levels of the 2 groups: 169.7 (101.9 to 532.5) vs 237.9 (55.81 to 641.9) nanogram/ml (p=0.59).
Conclusions	• The authors concluded that sNGAL did not appear to be a specific predictor of AKI in patients with sepsis. The 3 other biomarkers – uNGAL, sCysC and uCysC – were significantly increased in children with sepsis and AKI, and were considered more specific biomarkers. • Small sample size was noted and the authors suggested that larger multicentre studies are needed to confirm the results.

Abbreviations: AKI, acute kidney injury; analysis of variance, ANOVA; CI, confidence interval; OR, odds ratio; PICU, paediatric intensive care unit; pRIFLE, paediatric modified risk injury failure loss end stage renal disease; sCysC, serum Cystatin C; sNGAL serum neutrophil gelatinase-associated lipocalin; uCysC, urinary Cystatin C; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

Table 3 Summary of prospective observational study: Lippi et al. (2012a)

Study component	Description
Objectives/ hypotheses	To assess acute variations in NGAL and creatinine after doing strenuous exercise.

Study component	Description
Study design	Prospective observational study.
Setting	- The patients ran a 60 km ultra marathon. For 36 to 48 hours before the trial, they did no strenuous exercise. Blood and urine samples were taken 20 minutes before the athletes warmed up, after 8 hours of fasting, and 10 minutes after they finished the run. - Creatinine and albumin were assessed by the Jaffe method on a Beckman Coulter AU5800. - The eGFR was calculated using the equation developed and validated by Levey et al. (2007). - sNGAL and uNGAL were measured using The NGAL Test, on a Beckman Coulter AU5800.
Inclusion/ exclusion criteria	The study recruited 16 white men who had done an endurance training regime for the previous 3 to 10 years. Exclusion criteria: - Acute or chronic disease of any sort - Intake of medications, including antioxidants or nicotine.
Variables	Variation in uCr, sCr, uNGAL, sNGAL, eGFR and uNGAL/uCr ratio between pre- and post-run blood and urine tests.
Statistical methods	Statistical analysis was done using Analyse-it for Excel. Data were presented using medians and interquartile ranges, and statistical significance was set at $p<0.05$.

Study component	Description
Results	Post run: sCr increased by 38% (IQR 14% to 66%) uCr increased by 78% (IQR 21% to 158%) eGFR decreased by 31% (14% to 44%) sNGAL increased 1.6 fold (IQR 1.3 to 2.0 fold) uNGAL increased 7.7 fold (IQR 1.9 to 37.3 fold) nNGAL/uCr ratio increased 2.9 fold (IQR 1.6 to 25.8 fold) 6/16 athletes met the AKIN criteria for AKI. No significant relationship was found between pre-exercise sNGAL and uNGAL concentrations (r −0.147; p=0.564) or between sNGAL and uNGAL/uCr ratio (r −0.110; p=0.673). Likewise, no significant relationship was found between the same categories post exercise (r 0.085; p=0.746 and r 0.192; p=0.460). No significant correlation was found between the pre- and post-exercise variation in sNGAL and either uNGAL (r 0.025; p=0.925) or uNGAL/uCr ratio (r 0.016; p=0.950), or between sCr and either uNGAL (r 0.248; p=0.338) or uNGAL/uCr ratio (r 0.254; p=0.325). A highly significant correlation was found between the pre- and post-exercise changes of sCr and sNGAL (r −0.813; p<0.001).
Conclusions	The authors concluded that there is evidence that strenuous physical exercise increases NGAL and creatinine concentration, which may indicate AKI.

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; IQR, interquartile range; r, sample correlation coefficient; sCr, serum creatinine; sNGAL serum neutrophil gelatinase-associated lipocalin; uCr, urinary creatinine; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

Jeong et al. (2012) (see table 1) used 2 separate NGAL test methods – the Abbott ARCHITECT NGAL assay for urinary neutrophil gelatinase-associated lipocalin (NGAL), and The NGAL Test from BioPorto for plasma NGAL. Consequently, the results for plasma NGAL are those of interest.

In this study, 11 of the 19 patients were diagnosed with acute kidney injury by the risk, injury, failure, loss of kidney function, and end-stage renal failure (RIFLE) criteria, using an increase of greater than 50% from baseline in serum creatinine as the formal definition of

onset of acute kidney injury. This is one of the recommended criteria in NICE's guideline on acute kidney injury for defining the onset of acute kidney injury, but may present later than other criteria such as an increase of 26 micromol/litre. This could cause some of the patients in the study to be defined incorrectly as not having acute kidney injury.

The authors acknowledged that there are no established criteria for diagnosing acute kidney injury using a NGAL test, so they defined the onset of acute kidney injury as the point at which the level of NGAL in either plasma or urine had risen by greater than 50%. Of the 11 patients with acute kidney injury, 8 had an increase in plasma NGAL of greater than 50% with the increase occurring before the increase in serum creatinine in 7 of these patients. However, out of the 8 patients who were not diagnosed with acute kidney injury by the RIFLE criteria, 7 of these also experienced an increase in plasma NGAL of greater than 50%. Sensitivity, specificity, positive predictive values and negative predictive values were not reported.

Di Nardo et al. (2013) (see table 2) also investigated both urinary NGAL and serum NGAL with 2 different NGAL test methods. The NGAL Test was used to measure urinary NGAL while an ELISA NGAL kit, also from BioPorto, was used to measure serum NGAL. The ELISA NGAL kit is outside of the scope of this briefing.

The study included 11 paediatric patients with severe sepsis admitted consecutively to the paediatric intensive care unit, of which 4 were diagnosed with acute kidney injury using paediatric RIFLE criteria. Ten paediatric patients who were having elective surgery were recruited to form a control group.

A statistically significant difference (p=0.0019) was found in urinary NGAL levels between patients with sepsis and acute kidney injury (median 300.8 nanogram/dl, interquartile range 15.05 to 5,952) and those with sepsis without acute kidney injury (median 26.59 nanogram/dl, interquartile range 11.5 to 543.6). No statistically significant difference was found in the urinary NGAL levels between the group of patients with sepsis without acute kidney injury and the control group (p>0.05). The study did not report a comparison between urinary NGAL levels in patients with sepsis with acute kidney injury and the control group. Therefore it is not possible to draw a conclusion about this.

Lippi et al. (2012a) (see table 3) measured urinary NGAL, corrected urinary NGAL and serum NGAL using The NGAL Test in 16 athletes to examine whether strenuous physical exercise could cause acute kidney injury.

Within this study, 6 of the 16 athletes were diagnosed with post-run acute kidney injury using the acute kidney injury network criteria. This is one of the methods recommended in NICE's guideline on acute kidney injury for detecting acute kidney injury. However, the results for these 6 athletes were not separated from the group results, and so it is not possible to conclude which results were related to those athletes who were diagnosed with acute kidney injury. The result from 1 athlete with a high baseline serum NGAL (but not urinary NGAL), which increased more after the run, was considered anomalous with an explanation that this may have been due to a high leukocyte count, which was normal in all the other athletes.

In addition, 3 technical validations were identified, summarised in tables 4, 5 and 6.

Table 4 Summary of technical validation (Kift et al. 2012)

Study component	Description
Objectives/ hypotheses	To do an independent technical validation and comparison of 5 commercially available urinary NGAL assays, 2 CE marked in vitro diagnostics and 3 research-use only ELISAs.
Study design	Technical Validation.

Study component	Description
Setting	The CE marked assays were the ARCHITECT uNGAL assay, Abbott, and The NGAL Test, BioPorto. These were analysed on the i2000SR ARCHITECT analyser and the Siemens ADVIA 1800 respectively. The research-only use assays were the Human NGAL ELISA kit, Hycult Biotech, the human NGAL ELISA kit 036, BioPorto, and the Quantikine Human Lipocalin-2/NGAL Immunoassay, R&D systems. Validation stages: • Low- and high-quality control, using both manufacturer and internal samples • Parallelism • Recovery • Selectivity • Limit of quantitation • Haemoglobin interference • High-dose hook effect • Inter-assay comparisons.
Inclusion/ exclusion criteria	• Mid-stream urine samples were obtained from several patient groups from St James's University Hospital in Leeds in 2011. • Patient backgrounds: • AKI, diagnosed using AKIN criteria – 25 • Renal cancer – 10 • Benign urological conditions e.g. renal stones or UTI – 10 • Diabetic albuminuria – 13 • Healthy volunteers – 10.

Study component	Description
Variables	Determined which assays display satisfactory performance for the validation tests.
Statistical methods	Modified Bland–Altman plots, Passing–Bablok analysis.
Results	- ARCHITECT uNGAL assay, Abbott – satisfactory performance for all parameters tested. - The NGAL Test, BioPorto – problems with limit of quantification. Kift et al. found the lower limit of quantification to be 150 nanogram/ml, which was higher than the manufacturer-stated lower limit of 25 nanogram/ml. - Human NGAL ELISA kit, Hycult – issues with many parameters. - Human NGAL ELISA kit 036, BioPorto – issues with parallelism. - Quantikine Human Lipocalin-2/NGAL Immunoassay, R&D systems – satisfactory performance for all parameters tested. - Inter assay NGAL comparison: - Only 22 of the 68 samples were above the lower limit of quantification for The NGAL Test, which limited the inter-assay NGAL comparison. For these 22 samples, with the higher concentrations of NGAL, there was good agreement found between the BioPorto ELISA, the Abbott and The NGAL Test, although no figures were reported.

Study component	Description
Conclusions	• The assays produced by Abbott and R&D Systems performed acceptably throughout all stages of the validation, and produced comparable results. • The BioPorto assays were broadly comparable but had a bias towards higher concentrations. • Markedly different results were obtained using the Hycult assay. • There was variation in the results between the 5 different commercially available assays, and it is important to identify the type of assay used within studies when interpreting their results.

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ELISA, enzyme-linked immunoassay; NGAL, neutrophil gelatinase-associated lipocalin; UTI, urinary tract infection.

Table 5 Summary of technical validation (Seo et al. 2013)

Study component	Description
Objectives/ hypotheses	To evaluate the precision and reportable range of results in comparison to a widely used point of care test.
Study design	Performance evaluation.
Setting	• The comparison was done between The NGAL Test from BioPorto diagnostics measured on the Hitachi 7600 Clinical Analyser and the Triage NGAL Test. This used plasma submitted for routine haemoglobin A1c testing. • The 2 tests were evaluated for precision by taking measurements 4 times a day over 5 days. • The reportable range was measured using high and low NGAL concentration plasmas mixed in different proportions.

Study component	Description
Inclusion/ exclusion criteria	• 129 adults (63 men) • Exclusion criteria: • History of administration to hospital or surgery in last 6 months • Chronic disease • Glucose level less than 50 ml/dl or more than 126 mg/dl • Aspartate aminotransferase level more than 36 U/litre • Haemoglobin level less than 11 g/dl • White blood cell count less than 3,000 /ml or more than 15,000 /ml • Blood urea nitrogen level less than 5 mg/dl or more than 25 mg/dl • Creatinine level less than 0.5 mg/dl or more than 1.4 mg/dl.
Variables	Comparison of the precision and reportable range of results of The NGAL Test to a point of care device.
Statistical methods	Only stated method was that Analyse-it for Microsoft Excel was used.

Study component	Description
Results	Precision: • Low NGAL-level quality control materials had a total coefficient of variation of 3.3% with a within run coefficient of variation of 2.8%. • High NGAL-level quantity control materials had a total coefficient of variation of 1.8% with a within run coefficient of variation of 1.4%. Reportable range: BioPorto specify the analytical measurement range to be 25 to 5,000 nanogram/ml. The author measured the analytical range from 57 to 3,182 nanogram/ml and found the coefficient of correlation equal to 0.999 within the range tested. Coefficient of determination: The comparison between The NGAL Test and the Triage NGAL Test found the coefficient of determination to be $r^2=0.791$. No confidence intervals were reported. The paper noted that the correlation improved when the highest 8 results were removed from the analysis ($r^2=0.959$), but no justification for removing these results was given.
Conclusions	The results were compared with the Triage NGAL point of care test, using results reported by Dent et al. (2007). The coefficients of variation for The NGAL Test from BioPorto were much lower than that for Triage NGAL Test, showing there is less variation in results for The NGAL Test between test runs. Additionally, the reportable range of the Triage NGAL Test was reported as 60 to 300 nanogram/ml, narrower than The NGAL Test and significantly reducing the use at higher NGAL concentrations.

Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin.

Table 6 Summary of technical validation (Lippi et al. 2012b)

Study component	Description
Objectives/ hypotheses	To evaluate an NGAL immunoassay and compare it with the Abbott ARCHITECT NGAL.
Study design	Technical validation/Comparison study.

Study component	Description
Setting	• This study examined the within- and between-run imprecision as well as the linearity of The NGAL Test in comparison to the results published by Cavalier et al. (2011) and Grenier et al. (2010) on the Abbott ARCHITECT NGAL. • The imprecision studies used 3 urine samples with low, intermediate and high NGAL concentrations (approximately 200, 600 and 800 nanogram/ml). Both imprecision studies were analysed using 20 sequential runs, using identical reagent lot and calibration curve. • Linearity was done by serially diluting a patient with a high NGAL concentration at fixed ratios, and using an additional urine sample of a patient with a low NGAL concentration. This covered the range 20 to 800 nanogram/ml, which was considered to cover the most clinically significant range of concentrations. • A comparison study was done on the urine of 70 patients randomly selected from those needing urinalysis referred from the emergency department. Each sample was tested within 2 hours of collection using both The NGAL Test and ARCHITECT. The samples displayed a broad range of NGAL values. • Results of The NGAL Test were analysed on the Beckman Coulter AU5822.
Inclusion/ exclusion criteria	70 patients who needed urinalysis presenting consecutively to the emergency department.
Variables	Comparison study, comparing the results of The NGAL Test to the Abbott ARCHITECT NGAL.
Statistical methods	Statistical evaluation was done with Analyse-it for Microsoft Excel.

Study component	Description
Results	Imprecision: • The NGAL Test had a within run imprecision coefficient of variation between 1.0% and 2.3%, and a between-run imprecision coefficient of variation between 1.2% and 2.0%. This was concluded to be comparable or better than reported results for the Abbott ARCHITECT and the Biosite Triage from Cavalier et al. (2011) and Grenier et al. (2010). • The linearity of The NGAL Test was described as 'excellent' (linear regression analysis r=1.000; p<0.001). The comparison study found a highly significant agreement between the results obtained using The NGAL Test and the Abbott ARCHITECT, with a mean bias of 65% (95% CI 49% to 81%). • The analytical accuracy of The NGAL Test when compared with the values reported in the literature for the Abbott ARCHITECT found an area under the curve of 0.993 (p<0.001), with sensitivity of 100% and specificity of 98%.
Conclusions	The authors concluded that there were many benefits with The NGAL Test, such as fast turnaround time, low imprecision, optimal linearity in the most clinically significant range and a wide dynamic range.

Abbreviations: CI, confidence interval; NGAL, neutrophil gelatinase-associated lipocalin.

Kift et al. (2013) compared the analytical performance of 5 commercially available assays, including 2 CE marked assays (the Abbott ARCHITECT and The NGAL Test), as well as 3 research-only assays. This study found that The NGAL Test performed well for all tests except for the limit of quantification, which was found to be 150 nanogram/ml, when the manufacturer had stated that it was 25 nanogram/ml in the application notes (see table 4).

Lippi et al. (2012b) evaluated the imprecision and linearity of The NGAL Test from BioPorto. In addition, they compared The NGAL Test with the Abbott ARCHITECT NGAL (see table 5).

The imprecision and linearity results from The NGAL Test were compared with results found in the literature from papers by Cavalier et al. (2011) and Grenier et al. (2010) for the

Abbott ARCHITECT NGAL and the Biosite Triage. The methods used by Cavalier et al. (2011) varied slightly from the methods used by Lippi et al. (2012b), so it is not certain whether the comparison between results was valid.

The results showed a good correlation between The NGAL Test and the ARCHITECT, but also a mean bias towards The NGAL Test of 65%.

Seo et al. (2013) compared The NGAL Test from BioPorto with the Biosite Triage NGAL Test, which is a point of care assay (see table 6). The precision coefficients of variation for The NGAL Test were found to be less than 5% compared with less than 14% for the Biosite Triage precision, as reported by Dent et al. (2007). Seo et al. claimed that 'Plasma used in The NGAL Test was more reliable than that of urine' (in the Triage Test).

Seo et al. found that the results of the Triage NGAL Test correlated better with those obtained using The NGAL Test for NGAL concentrations of less than 500 nanogram/ml. Between 500 nanogram/ml and 1300 nanogram/ml (the upper limit of quantification for the Triage test), the results were not linearly correlated.

Costs and resource consequences

Extrapolations from academic studies suggest that there may be as many as 360,000 admissions of people with a diagnosis of acute kidney injury in the UK annually (HSJ supplement 2011). The NGAL Test can be done in a standard laboratory and can be run on most automated clinical chemistry analysers, suggesting that there would be no need to change service organisation or delivery if the test is adopted.

No published evidence on resource consequences of The NGAL Test was identified. Only 1 study (Shaw et al. 2011), which assessed the cost effectiveness of a different NGAL as a biomarker in general rather than specific use of The NGAL Test was identified and included in the review. The study assessed the cost effectiveness of urinary NGAL to diagnosis acute kidney injury after cardiac surgery compared with current diagnostic methods (that is, monitoring of serum creatinine, blood urea nitrogen and urine output).

A decision model was created from the societal perspective using a base case to depict a typical patient in the UK without a history of chronic kidney disease (67-year-old man) having coronary artery bypass graft surgery and admitted to the intensive care unit immediately after the procedure. Cost per quality-adjusted life-year (QALY) was used as the relevant measure for the economic evaluation. A 25% improvement in outcomes from

acute kidney injury because of early diagnosis, based on NGAL levels, was assumed in the model. This was varied to 12.5% and 50% levels in the sensitivity analysis. Probabilities and costs were obtained from literature sources and also from expert opinion when data were not available.

The base-case analysis showed an expected cost of £4,244 and 11.86 QALYs for the NGAL strategy compared with £4,672 and 11.76 QALYs for current practice. The cost-effectiveness ratio, presented in the study, was £358 per QALY for NGAL compared with £396 per QALY for current practice. The NGAL strategy dominated (was more effective and less expensive than) current practice and the conclusions remained the same for the sensitivity analysis with therapeutic effect size. Probabilistic sensitivity analyses showed that the NGAL strategy was cost effective for 100% of the 1,000 patient simulations. The results therefore suggested that using urinary NGAL is likely to economically beneficial because acute kidney injury is diagnosed earlier, which appears to result in lower than expected costs.

The results of Shaw et al. (2011) need to be considered with caution because of gaps in the information presented or potential weaknesses in the study design. It is difficult to identify the respective literature source and expert opinion used in the model because the presentation of the parameter estimates was not clearly described. Specifically, the cost estimates used were arbitrary. The serum creatinine test cost estimate was £15 and the urinary NGAL test cost estimate was £25, which were not based on accepted sources such as National Health Service tariffs. There was zero cost assigned to urine output measurement, but this could include measurement costs in terms of time and nursing staff. There was uncertainty surrounding these estimates. The authors did the appropriate sensitivity analysis to account for this but this did not mitigate the study limitation. Secondly, the authors claimed that the study used a societal perspective for evaluation, but they did not consider indirect and opportunity costs that may be associated with acute kidney injury and its potential sequelae in patients who survive hospitalisation and develop some of the long-term complications associated with chronic and end-stage renal disease. Thirdly, the model was based on data from coronary artery bypass graft surgery patients only, and it is very likely that it underestimated overall surgical mortality and the likelihood of developing acute kidney injury because these are likely to be higher for other cardiac procedures. Finally, the model assessed the cost effectiveness of NGAL as a biomarker in general rather than specific use of The NGAL Test.

Adoption of The NGAL Test based only on study results for urinary NGAL biomarker testing is not reliable because The NGAL Test can use both urine and plasma samples, not just

urine samples, for the assay procedure.

Strengths and limitations of the evidence

The evidence is limited to 3 observational studies, and 3 technical validations. No published randomised controlled trials investigating The NGAL Test were identified during the literature search. Additionally, no ongoing clinical trials specifying the use of The NGAL Test have been found. However, some UK trials are due to start in 2014 that will evaluate The NGAL Test in different clinical settings, including urology, intensive care units and accident and emergency units (BioPorto: personal communication [2014]).

Relevance to NICE guidance programmes

Use of The NGAL Test is not currently planned into any NICE guidance programme.

References

Bellomo R, Ronco C, Kellum JA et al. (2004) Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Critical Care 8(4): R204–12

BioPorto, Instructions for use: The NGAL Test Reagent Kit Ref ST001CA. Available online at http://ngal.com/media/43899/st001ca_ifu_ivd.pdf (last accessed 06/11/2013)

Cavalier E, Bekaert A-C, Carlisi A et al. (2011) Neutrophil gelatinase-associated lipocalin (NGAL) determined in urine with the Abbott Architect or in plasma with the Biosite triage? The laboratory's point of view. Clinical Chemistry and Laboratory Medicine 49(2): 339–41

Cowland JB, Borregaard N (1997). Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. Genomics 45(1): 17–23

Dent CL, Ma Q, Dastrala S et al. (2007) Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Critical Care 11: R127

Di Nardo M, Ficarella A, Ricci Z et al. (2013) Impact of severe sepsis on serum and urinary biomarkers of acute kidney injury in critically ill children: an observational study. Blood Purification 35: 172–6

Grenier FC, Ali S, Syed H et al. (2010) Evaluation of the ARCHITECT urine NGAL assay: assay performance, specimen handling requirements and biological variability. Clinical Biochemistry 43: 615–20

Health Service Journal Supplement on acute kidney injury. (2011) available at http://www.hsj.co.uk/Journals/2/Files/2011/6/23/ HSJ_Supplement_acutekidneyinjur_23june.pdf

Jeong T-D, Kim S, Lee W et al. (2012) Neutrophil gelatinase-associated lipocalin as an early biomarker of acute kidney injury in liver transplantation. Clinical Transplantation 26: 775–81

KCAT, Chronic Kidney Disease (CKD) & eGFR. Available online at http://www.aacb.asn.au/ documents/item/1199 (last accessed 20/12/2013)

KDIGO (Kidney Disease Improving Global Outcomes). Clinical practice guideline for acute kidney injury, (2012). Kidney International Supplements Vol. 2, Issue 1.

Kift RL, Messenger MP, Wind TC et al. (2012) A comparison of the analytical performance of five commercially available assays for neutrophil gelatinase-associated lipocalin using urine. Annals of Clinical Biochemistry 50: 236–44

Levey AS, Coresh J, Greene T et al. (2007) Chronic kidney disease epidemiology collaboration. Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clinical Chemistry 53: 766–72

Lippi G, Sanchis-Gomar F, Salvagno GL et al. (2012a) Variation of serum and urinary neutrophil gelatinase associated lipocalin (NGAL) after strenuous physical exercise. Clinical Chemistry and Laboratory Medicine 50(9): 1585–9

Lippi G, Aloe R, Storelli A et al. (2012b) Evaluation of NGAL Test, a fully-automated neutrophil gelatinase-associated lipocalin (NGAL) immunoassay on Beckman Coulter AU 5822. Clinical Chemistry and Laboratory Medicine 50(9): 1581–4

Mehta RL, Kellum JA, Shah SV et al. (2007) AKIN (Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury). Critical Care 11(2): R31

NICE (CG169) Acute kidney injury: Prevention, detection and management of acute kidney injury up the point of renal replacement therapy, (August 2013). National Institute for Health and Care Excellence.

Seo Y, Lee W, Hun Kwon O. (2013) Performance evaluation of BioPorto diagnostics' neutrophil gelatinase-associated lipocalin assay on automated clinical chemistry analyzer Hitachi 7600. Journal of Laboratory Medicine and Quality Assurance 35: 23–8

Shaw AD, Chalfin DB, Kleintjens J. (2011) The economic impact and cost-effectiveness of urinary neutrophil gelatinase-associated lipocalin after cardiac surgery. Clinical Therapeutics 33(11): 1713–25

Tsigou E, Vasiliki P, Demponeras C et al. (2013) Role of new biomarkers: Functional and structural damage. Critical Care Research and Practice, Article ID 361078, 13 pages.

Search strategy and evidence selection

Search strategy

The following databases were searched with the stated search criteria.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) 1946 to Present and Embase 1974 to 2013 November 01

For clinical evidence:

1. Acute kidney injury/ or AKI.mp.

2. Acute renal failure/ or ARF.mp.

3. Reduced urine output.mp.

4. Glomerular filtration rate/

5. Creatinine/

6. or/1-5

7. NGAL.mp.

8. Neutrophil gelatinase-associated lipocalin.mp.

9. Bioporto.mp. = 40

10. LCN2.mp.

11. Lipocalin2.mp.

12. or/7-12

13. Serum creatinine.mp.

14. Urination/

15. (Urine output or urine volume).mp.

16. Jaffe.mp.

17. Enzyme assays/

18. or/13-17

19. 6 and 12 and 18

20. limit 19 to English language

21. limit 20 to human

For economic evidence:

1. Acute kidney injury.mp.

2. AKI.mp.

3. Acute renal failure.mp.

4. ARF.mp.

5. Reduced urine output.mp.

6. Glomerular filtration rate.mp.

7. Creatinine.mp.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. NGAL.mp.

10. Neutrophil gelatinase-associated lipocalin.mp.

11. Bioporto.mp.

12. LCN2.mp.

13. Lipocalin2.mp.

14. 9 or 10 or 11 or 12 or 13

15. cost*.mp.

16. economic*.mp.

17. 15 or 16

18. 8 and 14 and 17

19. limit 18 to english language

20. limit 19 to human

PUBMED

For clinical evidence:

(((((NGAL[All Fields] OR (("neutrophils"[MeSH Terms] OR "neutrophils"[All Fields] OR "neutrophil"[All Fields]) AND gelatinase-associated[All Fields] AND ("lipocalins"[MeSH Terms] OR "lipocalins"[All Fields] OR "lipocalin"[All Fields]))) OR Bioporto[All Fields]) OR LCN2[All Fields]) OR lipocalin2[All Fields]) AND ((((("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields]) OR ("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields] OR ("acute"[All Fields] AND "renal"[All Fields] AND "failure"[All Fields]) OR "acute renal failure"[All Fields])) OR (Reduced[All Fields] AND ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) AND output[All Fields])) OR ("glomerular filtration rate"[MeSH Terms] OR ("glomerular"[All Fields] AND "filtration"[All Fields] AND "rate"[All Fields]) OR "glomerular filtration rate"[All Fields])) OR ("creatinine"[MeSH Terms] OR "creatinine"[All Fields])) AND ((((((("serum"[MeSH Terms] OR "serum"[All Fields]) AND ("creatinine"[MeSH Terms] OR "creatinine"[All Fields])) OR ("urination"[MeSH Terms] OR "urination"[All Fields])) OR (("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) AND output[All Fields])) OR (("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) AND volume[All Fields])) OR Jaffe[All Fields]) OR (("metabolism"[Subheading] OR "metabolism"[All Fields] OR "me"[All Fields]) AND assays[All Fields]))

For economic evidence:

(((Acute kidney injury OR AKI OR Acute renal failure OR ARF OR Reduced urine output OR Glomerular filtration rate OR Creatinine)) AND (NGAL OR Neutrophil gelatinase-associated lipocalin OR Bioporto OR LCN2 OR Lipocalin2)) AND (cost* OR economic*)

Cochrane Database of Systematic Reviews: Issue 11 of 12, November 2013, and Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2013

For clinical evidence:

1. Acute kidney injury or AKI

2. Acute renal failure or ARF

3. Reduced urine output

4. Glomerular filtration rate

5. Creatinine

6. #1 or #2 or #3 or #4 or #5

7. NGAL or Neutrophil gelatinase-associated lipocalin

8. Bioporto

9. LCN2 or Lipocalin2

10. #7 or #8 or #9

11. Serum creatinine

12. Urination

13. Urine output or urine volume

14. Jaffe

15. Enzyme assays

16. #11 or #12 or #13 or #14 or #15

17. 6 and 10 and 16

For economic evidence

1. Acute kidney injury or AKI

2. Acute renal failure or ARF

3. Reduced urine output

4. Glomerular filtration rate

5. Creatinine

6. #1 or #2 or #3 or #4 or #5

7. NGAL or Neutrophil gelatinase-associated lipocalin

8. Bioporto

9. LCN2 or Lipocalin2

10. #7 or #8 or #9

11. cost*

12. economic*

13. #11 or #12

14. #6 and #10 and #13

Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHS EED), and Health Technology Assessment (HTA) databases

Only searched for economic evidence:

1. (Acute kidney injury OR AKI) OR (Acute renal failure OR ARF) OR (Reduced urine output) IN DARE, NHSEED, HTA FROM 1960 TO 2013

2. (Glomerular filtration rate) OR (Creatinine) IN DARE, NHSEED, HTA FROM 1960 TO 2013

3. #1 OR #2

4. (NGAL OR Neutrophil gelatinase-associated lipocalin) OR (Bioporto) OR (LCN2 OR Lipocalin2) IN DARE, NHSEED, HTA FROM 1960 TO 2013

5. (cost) OR (economic) IN DARE, NHSEED, HTA FROM 1960 TO 2013

6. #3 AND #4 AND #5

Clinicaltrials.gov

Only searched for clinical evidence

1. NGAL or neutrophil associated gelatinase lipocalin.

Evidence selection

For the clinical evidence:

Total number of abstracts: 1063

Duplicates: 194

Abstracts/full papers reviewed: 869

(Note: the nature of this literature review needed 2-stage reading of the full papers to first exclude many studies that used a different test for NGAL. Tests from different manufacturers and BioPorto's ELISA test for NGAL had to be excluded manually).

Exclusion criteria: case studies, editorials, letters, reviews, conference proceedings/abstracts, animal studies, and non-English language studies, not using The NGAL Test manufactured by BioPorto for detection of urinary or serum NGAL levels in relation to Acute Kidney Injury (particle enhanced turbidimetric immune assays were assumed to be the correct test).

Studies for Review: 6

For clinical trials:

Total number of studies: 102

76 of these studies were not relevant to acute kidney injury or used an alternative test to measure NGAL.

In the remaining 26 studies, it was not possible to identify the method used for NGAL measurement.

No studies were found that explicitly used The NGAL Test (BioPorto).

For the economic evidence:

Total number of abstracts: 84

Duplicates: 22

Abstracts reviewed: 62

Exclusion criteria: case studies, editorials, letters, reviews, conference proceedings/abstracts, animal studies, and non-English language studies

Studies for review: 1

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers, and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by the KITEC KHP External Assessment Centre (EAC). 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.

Project team

KITEC KHP EAC

Medical Technologies Evaluation Programme, NICE

Peer reviewers and contributors

- James Clinch, Technical Adviser, KITEC KHP.

- Elizabeth Morris, Technical Adviser, KITEC KHP.

- Muralikrishnan Radhakrishnan Kartha, Health Economist, KITEC KHP.

- Stephen Keevil, Centre Director, KITEC KHP.

- Cornelius Lewis, Centre Director, KITEC KHP.

Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

- Dr Ashley Garner, Principal Clinical Biochemist, Leeds Teaching Hospitals NHS Trust

- Dr Edmund Lamb, Consultant Clinical Scientist, East Kent Hospitals University NHS Foundation Trust

- Dr David Milford, Consultant Nephrologist, Birmingham Children's Hospital NHS Foundation Trust

- Dr Sheetal Bhojani, Paediatric Nephrology Trainee, NHS Greater Glasgow &Clyde

Update information

Minor changes since publication

February 2014: Minor maintenance.

ISBN: 978-1-4731-0460-0