

# Point-of-care neutrophil gelatinase-associated lipocalin (NGAL) tests

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## Clinical Question:

In the primary care setting, what is the accuracy and utility of neutrophil gelatinase-associated lipocalin (NGAL) point-of-care tests to predict, diagnose, and manage kidney diseases?

## Background, Current Practice and Advantages over Existing Technology:

### *Background:*

The burden of ill health from both acute kidney injury (AKI) and chronic kidney disease (CKD) is being increasingly recognised. Publication of the second part of the Renal National Service Framework (NSF) (1) and the subsequent NICE Clinical Practice Guideline for early identification and management of adults with chronic kidney disease (CKD) in primary and secondary care (CG73) (2) emphasised the change in focus in renal medicine from treatment of established kidney disease to earlier identification and prevention of kidney disease.

Rapid detection and early intervention in AKI can significantly improve outcomes, while early detection and management of chronic disease risk factors can reduce long-term deterioration in renal function. A number of renal tubular damage-specific biomarkers have emerged in recent years, offering the opportunity to diagnose AKI earlier, as well as facilitating differential diagnosis of structural and functional kidney injury and predicting outcomes. A small polypeptide, neutrophil gelatinase-associated lipocalin (NGAL), is one of the most promising and best-studied AKI biomarkers. NGAL, also known as lipocalin-2 or siderocalin, was discovered in 2003 (3) (4). The expression of NGAL was predominantly in proliferating and regenerating tubular epithelial cells, which suggested a role in repair. Siderophores, small iron-containing molecules, are the major ligand for NGAL and are involved in cellular growth and survival through iron transport and supply. In addition, NGAL enhances the delivery of iron and helps protect kidney tubule cells by upregulating haem oxygenase-1 (5). The majority of NGAL, secreted by injured renal tubule epithelial cells, is in a 25kDa monomeric form. In contrast, neutrophils have been claimed to release NGAL primarily as a 45kDa homodimer, i.e. two NGAL monomers linked by a disulfide bridge. It also exists as a 135-kDa heterodimer, covalently conjugated with gelatinase (6).

NGAL is easily detected in blood and urine due to its small size and resistance to degradation. It can be measured non-invasively using routine laboratory analysers as well as some point of care devices. Furthermore, NGAL concentration in both urine and plasma rises rapidly in a dose-dependent

manner that is proportional to the degree of acute kidney damage (7) and is detectable at a point where injury is still potentially limitable and reversible. It adds value on top of baseline clinical risk assessment providing physicians the opportunity to intervene early in order to limit the extent of renal injury. Therefore, NGAL may enable prospective diagnostic and prognostic stratification in the primary care setting.

### ***Current Practice and Advantages over Existing Technology:***

#### **a) Acute kidney Injury**

AKI refers to a sudden loss of kidney function and it is associated with significant morbidity and mortality as well as significant health care costs. In current clinical practice, serum creatinine is used as a marker of rapid changes in glomerular filtration rate and the consensus diagnosis of AKI depends on the detection of an acute rise in creatinine and/or oliguria (8).

However, this traditional biomarker has several important limitations. Creatinine is a product of muscle breakdown and therefore several non-renal factors also influence its concentrations, compromising its performance as a surrogate marker; including age, gender, muscle mass, muscle disease, metabolism and diet (9). Further, creatinine is a suboptimal indicator of acute changes in kidney function as studies have shown that over 50% of renal function may be lost before creatinine rises are detectable above the upper reference limit and it is of particular concern that it might not be useful until steady state equilibrium has been reached, which may not occur until days after injury (10) (11). Therefore, it is possible that early renal dysfunction could go undetected. Since creatinine cannot be considered an early marker of AKI, is not reliable in detecting AKI in patients during the early phases, during which there is greater potential to reverse renal injury.

NGAL overcomes the shortcomings of creatinine as a conventional marker of AKI. Creatinine and urinary output are markers of kidney function whereas NGAL is a direct marker of structural kidney injury. During health, there are only low levels of NGAL detectable in urine. Immediately following acute kidney injury, NGAL is substantially upregulated in the distal part of the nephron leading to increased urinary and plasma NGAL levels. Reduced reabsorption from the proximal tubule in the setting of tubular injury may also potentiate the increased NGAL levels in urine (5) (12). NGAL is detectable two to three hours following injury (13) (14).

#### **b) Chronic Kidney Disease**

As mentioned, AKI is increasingly acknowledged as a prelude to CKD (15). Diagnosis of CKD has been facilitated by the introduction of equations for estimated glomerular filtration rate (eGFR) (16) and CKD classifications by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) and the Kidney Disease: Improving Global Outcomes (KDIGO) (17) (18). Early intervention in patients with CKD is believed to improve the prognosis by addressing chronic vascular disease risk factors and supporting lifestyle change. Following this, early identification of those likely to progress to end stage renal disease (ESRD) has become increasingly important. Existing measures such as eGFR and proteinuria help with this stratification (19). However, proteinuria also has limitations as a surrogate marker of CKD progression and of treatment effect (20). As such, new improved biomarkers are required for CKD progression and CVD risk.

Conventional renal function measures, such as the serum creatinine level, cannot identify early renal damage or predict renal disease progression. Several recent studies have identified that serum and

urinary NGAL levels are a marker of kidney disease and severity in CKD (21). This suggests that NGAL level may reflect active renal damage that underlies this chronic impairment condition. A cross-sectional study carried out by Malyszko et al., comparing 80 non-diabetic kidney transplant patients with CKD stages 2 to 4 to healthy volunteers, reported that serum NGAL is a sensitive marker of kidney injury, especially in advanced CKD and post-kidney transplantation patients (22). In a longitudinal study of a cohort of 96 patients with CKD stage 4 and above over a median follow-up period of 18.5 months, baseline serum and urinary NGAL were predictors of eGFR decline and were associated with the severity of CKD (21).

### **Details of Technology:**

A variety of assays and platforms are currently available for the measurement of NGAL in both urine and blood. A comparison of commercially available rapid diagnostic tests we identified is included in Table 1 (23). Additional laboratory tests, two of which are currently only licenced for research purposes, are detailed in Table 2. We identified four clinical analytical platforms that are CE-marked and launched for diagnostic use in Europe that deliver a result in less than 1 hour. All are yet to obtain FDA approval for diagnostic use in the USA. They include the following:

- Alere Triage NGAL Test (Alere Ltd)
- ARCHITECT Urine NGAL assay (Abbott Diagnostics)
- The NGAL Test™ (BioPorto)
- NGAL Rapid ELISA Kit 037 (BioPorto)

Three of the aforementioned tests, the ARCHITECT Urine NGAL assay (Abbott Diagnostics), The NGAL Test™ (BioPorto) and the NGAL Rapid ELISA Kit 037 (BioPorto), are tests requiring laboratory-based analysers. These are therefore not suitable for use as point-of-care NGAL assays. It is worth noting that, although The NGAL Test™ is not a point-of-care test, it provides results in just 10 minutes and thus addresses the demand for fast NGAL results. The test can be run on most automated clinical chemistry analysers; however the delays associated with obtaining results from a laboratory setting, limit its use as a triage tool. Presently, the only commercially available point-of-care NGAL test we identified is the Alere Triage® NGAL test. This test is a fluorescence-based immunoassay that can process a single sample in conjunction with the Alere Triage® Meter, a portable fluorescence spectrometer. The assay works with EDTA-anticoagulated blood or plasma samples and contains an NGAL-specific monoclonal antibody conjugated to a fluorescent nanoparticle, NGAL antigen immobilized on a solid phase, and stabilisers. In order to perform the test several drops of blood or plasma are added to the sample port of the device and the fluid move through a filter, which separates any blood cells. The plasma flows down the diagnostic lane by capillary action and reconstitutes the fluorescent labelled antibodies. The presence of NGAL prevents binding of the particles to the solid phase so that the NGAL concentration is inversely proportional to the fluorescence detected. The results, which can be measured in the range of 60 to 1,300 ng/ml, are available in approximately 15 minutes on the meter screen and as a print out.

**Table 1: Table of available clinical diagnostic NGAL tests**

Product	Brand	Method	Sample	Sample Volume (µL)	Analysis Time	Measurement Range	Analyser	Availability
<b>AlereTriage® NGAL test</b>	Biosite Inc/Alere	Point-of-care fluorescence immunoassay	EDTA anti- coagulated whole blood or plasma sample	150-250 µL	15 mins	15-1300 ng/mL	Alere Triage® MeterPro	CE marked (not available in USA)
<b>ARCHITECT Urine NGAL assay</b>	Abbott Diagnostics	Chemiluminescentmicrop article immunoassay (CMIA)	Urine	50 µL	35 mins	10–1500 ng/mL	ARCHITECT analyzer	CE marked (not available in USA)
<b>The NGAL Test™</b>	Bioporto	Particle-enhanced turbidimetric immunoassay (PETIA)	Urine, EDTA plasma and heparin Plasma	5 µL	10 mins	25–5000 ng/mL	<ul style="list-style-type: none"> <li>• Roche Cobas c501/c502 (Cobas 6000)</li> <li>• Roche Hitachi Modular P</li> <li>• Hitachi 917</li> <li>• Beckman Coulter UniCel DxC</li> <li>• Beckman Coulter (Olympus) AU640</li> <li>• Abbott Architect</li> <li>• Abbott Aeroset</li> <li>• Siemens ADVIA 1800</li> <li>• Siemens ADVIA 2400</li> <li>• Siemens Dimension Vista</li> </ul>	CE marked (pending Food and Drug Administration approval for diagnostics use in the USA)
<b>NGAL Rapid ELISA Kit</b>	Bioporto	ELISA	urine, serum, plasma, tissue extracts or culture media	10 µL/well	<1 hour	2–2000 pg/mL	-	CE marked but not sold in the UK for diagnostic use (USA approved for research only)

**Table 2: Table of laboratory NGAL tests available for research purposes**

Product	Brand	Method	Sample	Sample Volume (µl)	Analysis Time	Measurement Range	Analyser	Availability
<b>NGAL ELISA kit (BIO92)</b>	Argutus Medical	ELISA	Urine, serum, cell culture supernatant	100 µL/well	3.5 hours	0.4–1000 ng/mL	-	For research use only
<b>Human NGAL monomer specific ELISA Kit</b>	Bioporto	ELISA	Urine, EDTA plasma and Li-Heparin plasma	100 µL/well	<4 hours	10-1000 pg/mL	-	For research use only
<b>Lipocalin-2/NGAL ELISA</b>	R&D/BioVendor	ELISA	Urine, plasma or serum	5–10 µL/well	3.5 hours	0.3–1000 ng/mL	-	For research use only
<b>Human NGAL ELISA Kit (HK330)</b>	Hycult Biotech	ELISA	cell culture medium, plasma and urine	100 µl/well	3.5 hours	0.4-100 ng/ml	-	For research use only

This emerging diagnostic technology could benefit patients in primary care at risk of AKI and CKD patients undergoing frequent kidney monitoring. If validated and accepted, NGAL point-of-care testing could help GPs detect renal impairment and CVD risk faster in these patients. This will ensure optimal management of these patients and a timely referral when required. Age and gender are critical determinants of NGAL concentration. Using a creatinine-based AKI definition and a standardized timing of NGAL measurement in relation to the occurrence of renal insult, a meta-analysis published in 2009 including data from 19 publications with 2538 patients reported that NGAL was substantially better at indicating acute kidney injury in children than in adults (24). A substantially lower occurrence of concomitant disease states in children may offer an explanation of why NGAL seems to perform better in children than in adults.

**Importance:**

Acute kidney injury is common; it is seen in 13–18% of all people admitted to hospital. Its complications include progression to more severe kidney injury (requiring renal replacement therapy), CKD, and death. AKI is also known to have effects on the cardiovascular, respiratory, hepatic, and neurological systems (25). The incidence of AKI and, in particular, the most severe form of AKI (as defined by dialysis requirement) has risen over the past several years (26) and the serious and far reaching consequences of AKI highlight the need for early detection.

In the case of AKI, early recognition is of critical importance to the timely introduction of measures to reverse injury or prevent further damage and progression towards chronically lowered eGFR post recovery. Testing and then establishing protocols for monitoring AKI using NGAL may achieve this.

CKD is a progressive loss of renal function and is subdivided into stages 1-5, based on stable eGFR measurements and, for early stages, evidence of structural renal disease (imaging abnormalities, proteinuria). Most people with CKD only develop symptoms in advanced stages (stages 4-5) and, therefore, early CKD is rarely detected outside of opportunistic blood sampling for other reasons. CKD is predictive of increased all-cause and cardiovascular mortality (27) (28). Cardiovascular disease (CVD) is a major comorbidity and primary cause of mortality in CKD patients. Similar to AKI, early diagnosis and appropriate classification of CKD is crucial in order to ensure better management of CKD and its associated CVD and in slowing progression to End Stage Renal Disease (ESRD).

Concerning the prevalence of CKD in England, a cross sectional point prevalence study of more than 130,000 adults in primary care suggested an age-standardised prevalence of stages 3-5 CKD of 8.5% (29). In a second study, the Quality Improvement in CKD (QICKD) study, which also took place in primary care, suggested a prevalence of 6.8% for stage 3–5 CKD, which equates to approximately 3 million adults. The 2010 Health Survey for England, a smaller study using a stratified sample of adults from the community suggested an overall prevalence for CKD stage 3-5 of 6% in men and 7% in women. It also showed a strong age gradient with less than 1% of men and women in the 16-24 age category having CKD stage 3-5 whereas the numbers were much higher in the age 75 and over category (29% in men and 35% in women).

The financial burden of CKD on the NHS is increasing rapidly, with particularly high costs relating to renal replacement therapy (RRT) and cardiovascular complications (30) for people with ESRD. The cost of CKD to the NHS was estimated at about £450 million in 2002 growing to about £1.5 billion in 2009–10. This represented almost 1.5% of all NHS spending in 2009-10. More than half this sum was spent on RRT, with excess CVD events (strokes and myocardial infarctions) accounting for almost £200 million (30). The majority of these late-stage CKD patients have either been diagnosed or referred later than appropriate. Consequently, the objectives of current NICE CKD guidelines are moving towards timely and appropriate CKD detection and CVD risk assessment in order to reduce the risk of hospitalisation, ESRD and of CVD events (31).

## **Previous Research:**

### ***Accuracy compared to existing technology***

The clinical NGAL assays have been tested in various clinical settings, however we did not identify any studies performed in primary care.

#### NGAL for the prediction of acute kidney injury after cardiac surgery

The studies listed in Table 3 have investigated the utility of NGAL to predict AKI in cardiac surgery patients; this setting presents the advantage that the time point of injury is known. Most of these studies showed NGAL both in the blood and urine to be a good early predictor of AKI, although areas under the receiver operating characteristic curves (AUC) have varied between 0.65-0.998 for urine and 0.64-0.98 in plasma (Table 3). There was a significant increase in NGAL levels measured by Western blotting, ELISA, and the clinical platforms (Abbott ARCHITECT and Triage® NGAL device) just hours after surgery, both in the urine and in blood with AUC-ROC of 0.61-0.99 for the urine NGAL and 0.56-0.96 for the plasma NGAL. These studies also confirmed a delay of between 1-3 days in the diagnosis of AKI using serum creatinine alone.

Mishra et al. were first to show the utility of both serum and urine NGAL for early detection of AKI in a paediatric population of 71 children undergoing cardiac surgery of whom 20 developed AKI. NGAL levels at 2 hours after the procedure were found to be powerful predictors of AKI with AUC for urine NGAL of 0.998 and plasma NGAL of 0.91 (32). In another study of 120 children undergoing cardiopulmonary bypass (CPB), 45 developed AKI and the NGAL concentration measured using the Triage® NGAL device was found to triple within two hours of the procedure. Multivariate analysis showed that plasma NGAL concentration at two hours after injury was the most powerful independent predictor of AKI. Using a cut off value of 150 ng/mL, AUC was 0.96, sensitivity was 84% and specificity was 94% for prediction of AKI (33). There was also a strong correlation between two hour NGAL measurement and change in creatinine concentrations, duration of AKI and length of hospital stay (33). In addition, the 12 hour measurement of plasma NGAL also strongly correlated with mortality (33). Similarly, a prospective study by Bennett et al. in 196 children undergoing CPB found that urinary NGAL measurements at 2, 4 and 6 hours after the procedure predicted severity and duration of AKI, length of hospital stay, requirement for renal replacement therapy and mortality (34).



In a retrospective observational study involving 879 patients post coronary artery bypass graft surgery of whom 8.6% of patients developed AKI, plasma NGAL levels measured immediately after CPB were higher in patients who subsequently developed AKI than in those who did not, but using a cut-off of 353.5 ng/mL had a low sensitivity of only 38.7% (35).

More recently, as part of the multicentre TRIBE (Translational Research Involving Biomarkers and Endpoints) study, Parikh et al. prospectively assessed the utility of NGAL in 1219 adults undergoing coronary artery bypass grafting and/or valvular surgery cardiac surgery (36) and 311 children undergoing surgery for congenital cardiac lesions (37). Postoperative blood samples were collected at the time of admission to the Intensive Care Unit and then daily for 5 days. Urine was collected four times during the first postoperative day and then daily until day 5. In both groups NGAL in urine and blood peaked within 6 hours of ICU arrival, which was well before increases in serum creatinine (24–72 hours postoperative). NGAL measurement significantly improved risk prediction over the clinical models alone. Multivariate analysis revealed that both plasma and urine NGAL are associated with a risk of AKI and with longer length of hospital stay, longer intensive care unit stay, and higher risk for RRT or death. In the adult population, urine NGAL had a sensitivity of 46% and a specificity of 81%, at a cutoff point of 102 ng/mL. Plasma NGAL had a sensitivity of 50% and a specificity of 82% at a cutoff point of 293 ng/mL. Plasma but not urine NGAL improved the AUC of the clinical model (36). In the paediatric population, the accuracy of urine NGAL for diagnosis of severe AKI was moderate, with areas under the curve of 0.71. The addition of urinary NGAL measurement also improved risk prediction over clinical models alone (measured by net reclassification improvement and integrated discrimination improvement). In this population, urine NGAL, but not plasma NGAL, was associated with subsequent AKI and poor outcomes (37).

Krawczeski et al. recently investigated the importance of timing of NGAL measurement. They investigated four AKI biomarkers in the urine of 220 children, without other pre-existing major comorbidities, at several time points after CPB. NGAL, IL-18, L-FABP, and KIM-1 were measured at 2, 6, 12, and 24 hours after CPB and urine NGAL was the first to rise in AKI patients, even at the first 2 hour measurement. In addition, NGAL maintained the best predictive performance at all time points (AUC 0.90, 0.91, 0.90, and 0.87 at 2, 6, 12, and 24 hours, respectively) (38). In a further study, NGAL was investigated as an early biomarker of AKI after neonatal and paediatric CPB. in 374 patients before and at intervals after surgery. NGAL levels were found to be significantly increased in patients with AKI at 2 hours after CPB (for every 10 ng/mL increase in 2-hour plasma NGAL, the odds of AKI increased by 47% and for every 10 ng/mL increase in 2-hour urine NGAL threshold, the odds of AKI increased by 32%) and remained elevated at all points. The 2-hour plasma and urine NGAL measurements correlated strongly with length of hospitalisation (correlation coefficient being 0.35 for plasma and 0.44 for urine,  $P < 0.0001$ ) as well as severity (correlation coefficient 0.64 for plasma and 0.65 for urine,  $P < 0.0001$ ) and duration of AKI (correlation coefficient 0.28 for plasma and 0.37 for urine,  $P < 0.0001$ ).



**Table 3: Studies investigating plasma and urine NGAL for the prediction of acute kidney injury after cardiac surgery.**

Reference	Sample Population	AKI definition	NGAL assay	Biofluid	AUC-ROC	NGAL cut-off ng/ml	Sensitivity %	Specificity %
Mishra 2005 (32)	71 children	RIFLE creatinine R or worse	Western blot, ELISA (Antibodyshop)	Urine Plasma	0.998 0.91	>50 >50	100 50	98 100
Wagener 2006 (39)	81 adults	RIFLE creatinine R or worse	ELISA (Antibody Shop)	Urine	0.74 (3 hours) 0.80 (18 hours)	>210	73	78
Koyner 2010 (40)	123 adults	AKIN criteria (stage 3)	ELISA (Antibody Shop)	Urine	0.88 (6 hours)	-	-	-
Koyner 2008 (41)	72 adults	≥25% creatinine rise or RRT within first 3 days	ELISA (Antibody Shop)	Urine	0.71	>300	67	62
Han et al 2009 (42)	90 adults	>0.3 mg/dL or 2-3-fold creatinine rise within first 3 days	ELISA (Antibody Shop)	Urine	0.65	>460	71	39
Krawczeski et al 2011 (43)	374 children	AKIN or ≥50% creatinine rise within 48hrs	ELISA (Antibody Shop)	Plasma Urine	0.94 0.88	Neonates >100 Non-neonates >50	90 85	88 86
Krawczeski et al 2011 (38)	220 children	≥50% creatinine rise during first 48 h	ELISA (Antibody Shop)	Urine	0.92	-	88	83
Tuladhar et al 2009 (44)	50 adults	>0.5 mg/dL creatinine rise	ELISA (Antibody Shop)	Urine Plasma	0.96 0.85	>390 >430	90 80	78 67
Prabhu et al. (45)	30 adults	RIFLE creatinine R or worse	ELISA (Antibody Shop)	Plasma	0.98	>230	100	91
Heise et al. 2011 (46)	50 adults	AKIN criteria	ELISA (Rapid Kit) (BioPorto)	Urine	0.77	>20	82	78
Che et al. 2010 (47)	30 adults	RIFLE creatinine R or worse	ELISA (R&D Systems)	Urine	0.85	>50	84	80
Xin et al. 2008 (48)	33 adults	>50% creatinine first 48 hrs or urine output <0.5 ml/kg/hr for <6hr	ELISA (Antibody Shop)	Urine	0.88	>250	81	78
Bennett 2008 (34)	196 Children	RIFLE creatinine R or worse	ARCHITECT	Urine	0.95	>100	82	90
Parikh 2011 (36)	1219 adults	RRT or doubling in creatinine	ARCHITECT Triage® point of care device (Biosite Inc.)	Urine Plasma	0.67 0.70	>100 >290	46 50	81 82
Parikh et al. 2011 (37)	311 children	RRT or doubling in creatinine	ARCHITECT Triage® point of care device (Biosite Inc.)	Urine Plasma	0.71 0.56	>70 >260	42 27	85 81
Tuladhar et al 2009 (44)	50 adults	>0.5 mg/dL creatinine rise	ELISA (Antibody Shop)	Urine Plasma	0.96 0.85	>390 >430	90 80	78 67
Dent 2007 (33)	120 children	RIFLE creatinine R or worse	Triage® point of care device (Biosite Inc.)	Plasma	0.96	>150	84	94
Perry 2010 (35)	879 adults	RIFLE creatinine R or worse	Triage® point of care device (Biosite Inc.)	Plasma	0.64 (after surgery) 0.74 (on day 3)	>350	39	82
Haase-Fielitz 2009 (7)	100 adults	RIFLE creatinine R or worse	Triage® point of care device (Biosite Inc.)	Plasma	0.80-0.89	>150	79	78

### NGAL in critically ill and septic patients

In contrast with cardiac surgery patients, critically ill patients suffering from AKI and those admitted from the emergency department have a timing of renal insult that is generally not entirely clear. This makes it difficult to interpret an elevated NGAL result, in particular in the presence of sepsis. Studies concerning critically ill and septic patients are presented in Table 4.

Wheeler et al. conducted a multicentre observational cohort study involving 143 critically ill children in America with systemic inflammatory response syndrome (SIRS) or septic shock admitted to paediatric intensive care units (PICU) (49). Serum NGAL was measured during the first 24 hours of admission to the PICU. There was a significant difference in serum NGAL between healthy children (median 80 ng/mL), critically ill children with SIRS (median 107.5 ng/mL), and critically ill children with septic shock (median 302 ng/mL). Serum NGAL was also significantly increased in critically ill children with AKI (median 355 ng/mL) compared to those without AKI (median 186 ng/mL). AUC of serum NGAL on admission to the PICU for the prediction of AKI was 0.677 with an optimal cut off value of 139 ng/mL. Zappitelli et al. (50) carried out a prospective cohort study of 140 critically ill mechanically ventilated children. Serum creatinine was collected daily for up to 14 days, and urine was collected once daily for up to 4 days for urinary NGAL measurement. A significant rise (16 times) in levels of urine NGAL occurred 48 hours earlier than a 50% increase in serum creatinine levels. Urine NGAL levels increased in a stepwise fashion with worsening RIFLE class. The AUC for urine NGAL for predicting AKI in was 0.78.

Martensson et al. studied the impact of inflammation on NGAL concentrations in plasma and urine in patients with SIRS, severe sepsis and septic shock with and without AKI (51). In this cohort of 45 adult patients, 27 patients with SIRS, severe sepsis, or septic shock without AKI and 18 patients with septic shock and concomitant AKI were included. Plasma and urine were analysed twice daily for NGAL levels and both plasma (AUC 0.85) and urine NGAL (AUC 0.86) were good predictors of AKI developing within the subsequent 12 hours. However, the ability of plasma NGAL to predict AKI (AUC 0.67) compared to urine NGAL (AUC 0.86) in patients with septic shock was less robust.

Bagshaw et al. showed similar results in a prospective observational study involving 83 critically ill patients with septic and non-septic AKI. Specimens for blood and urine NGAL were collected at enrolment, 12, 24 and 48 hours (52). Septic AKI patients displayed the highest concentrations of both plasma and urine NGAL when compared with those with non-septic AKI. Urine NGAL remained higher in septic compared with non-septic AKI at 12 and 24 hours. Plasma NGAL showed reasonable discrimination for AKI progression (AUC 0.71) and renal replacement therapy (AUC 0.78). Although urine NGAL performed less well (AUC 0.70 and 0.70 respectively), peak urine NGAL predicted AKI progression better in non-septic AKI. The multiple insults and higher baseline NGAL levels in these patients may be a confounding factor that may add to the heterogeneity of the results in the critical care setting.

In one of the largest recent studies, De Gues et al. carried out a prospective cohort study consisting of 632 consecutive adult patients admitted to ICU. Plasma and urine NGAL were measured at ICU

admission and predicted the development of severe AKI similarly to eGFR. However, when patients with eGFR<60 mL/min/1.73 m<sup>2</sup> were excluded, plasma (AUC 0.75) and urine NGAL (AUC 0.79) displayed diagnostic superiority over serum creatinine (AUC 0.65) and eGFR (AUC 0.67) for predicting AKI (53). Thus, the accuracy of NGAL in predicting AKI is highest in patients with normal kidney function before the acute illness.

**Table 4: Studies investigating the use of plasma and urine NGAL critically ill and septic patients**

Clinical Setting	Reference	Sample Population	AKI definition	NGAL assay	Biofluid	AUC-ROC	NGAL cut-off ng/ml	Sensitivity %	Specificity %	
15 PICUs	Wheeler 2008 (49)	143 Septic Children	SCr >2 mg/dL, BUN > 100 mg/dL or need for RRT	ELISA (Antibody shop)	Plasma	0.68	>140	86	40	Prediction of AKI
General ICU	Martensson et al (51)	45 adults	RIFLE and AKIN	RIA	Urine Plasma	0.86 0.85	>70 ng/mg uCrea >120	71 83	100 86	Prediction on AKI
General ICU	Zappitelli 2007 (50)	140 Children	pRIFLE	ELISA	Urine	0.78	>1.5 ng/mg uCrea	54	97	Prediction of AKI
General ICU	Cruz 2010 (54)	301 adults	RIFLE R or worse	Triage® point of care device (Biosite Inc.)	Plasma	0.78	>150	73	81	Prediction of AKI and AKI severity
General ICU	De Geus 2011 (53)	632 adults	RIFLE F	Triage® point of care device (Biosite Inc.)	Urine Plasma	0.75 0.79	>250	82	70	Prediction of Severe AKI
Two adult ICUs	Bagshaw 2010 (52)	82 adults with AKI septic vs. non septic	RIFLE R or worse	ARCHITECT <sub>2</sub> Triage	Urine Plasma	0.70 0.77	≥150 ≥280	69 75	60 76	Prediction of AKI progression and RRT
General ICU	Siew et al. 2009 (10)	451 adults	AKIN	ELISA (Antibody shop)	Urine	0.71	-	78	70	Prediction of AKI and AKI severity
ICU patients with multiple trauma	Makris et al 2009 (55)	31 adults	RIFLE creatinine R or worse	ELISA (Rapid Kit, BioPorto)	Urine	0.98	>25	91	95	Prediction of AKI
General ICU	Constantin et al. 2010	88 adults	RIFLE creatinine R or worse	Triage® point of care device (Biosite Inc.)	Plasma	0.92	>155	82	97	Prediction of AKI
General ICU	Royackers et al 2012 (56)	140 adults	RIFLE R	ELISA (R&D) Systems	Plasma Urine	0.53 0.48	-	-	-	Prediction of AKI and RRT
General ICU	Ramprasad et al (57)	194 adults	RIFLE R	The NGAL Test™, Bioport o	Plasma Urine	0.77 0.79	400 ng/ml 350 ng/ml	60 58	85 84	Prediction of AKI

## NGAL in the Emergency Department

A single-centre prospective study involving 635 patients admitted to an Emergency Department assessed the use of NGAL for emergency admissions (58). A single measurement of urinary NGAL was obtained at presentation and patients were separated into diagnostic groups according to currently used criteria: normal kidney function, intrinsic AKI, prerenal azotemia, and non-progressive CKD. At a cut-off level of urine NGAL of 130  $\mu\text{g/g}$  of creatinine, intrinsic AKI could be distinguished from the other clinical groups, with an AUC of 0.95, sensitivity of 99% and specificity approaching 100%. Furthermore, a urinary NGAL level of more than 130  $\mu\text{g/g}$  was highly predictive of adverse clinical outcomes, including need for nephrology consultation, dialysis and admission to the ICU.

These findings have been corroborated in a large, multicenter prospective cohort of 1635 patients admitted to an Emergency Department (59). At a cutoff concentration of 104 ng/ml, urine NGAL measured on admission predicted AKI (AUC 0.81; specificity 81%), the severity and duration of AKI, and a composite outcome of dialysis initiation or death during hospitalization. Net risk classification also improved when urinary NGAL was added to clinical risk-prediction models (59). In another multicentre cohort study involving 661 adult patients, Shapiro et al. investigated the diagnostic accuracy of plasma NGAL for the prediction of AKI in the emergency department (60). In this study a plasma NGAL level of more than 150 ng/ml, measured using the rapid POC Triage<sup>®</sup> NGAL assay at the time of presentation to the Emergency Department, predicted AKI within the first three days of hospitalisation, with a sensitivity of 96% and an AUC of 0.82.

These results were validated by a recent prospective study by Soto et al. involving 616 patients admitted from the Emergency Department who had plasma NGAL levels measured, using the Triage<sup>®</sup> NGAL assay, at five different time points (at presentation then 6, 12, 24, and 48 hours from admission) to better understand how NGAL would perform over 48 hours (61). Following admission GFR was estimated and patients were separated into one of four diagnostic groups: normal kidney function (GFR greater than 60 ml/min per 1.73 m<sup>2</sup> and no increases in serum creatinine during the hospital stay), stable CKD (stably reduced estimated GFR <60 ml/min per 1.73 m<sup>2</sup> before admission and <25% change from baseline during the hospitalization), transient azotaemia (new-onset increase in serum creatinine that satisfied any grade of RIFLE) or AKI (defined according to the RIFLE and AKIN criteria). NGAL levels were highest in the AKI group (146–174 ng/ml) and increased with AKI severity (207–244 ng/ml for AKIN stage >2). The ability of plasma NGAL to predict AKI (AUC 0.77–0.82 at different time points) improved with increasing severity of AKI (AUC 0.85–0.89 AKIN>2). Plasma NGAL values taken at 12 hours after hospitalisation reliably distinguished intrinsic AKI from transient azotaemia (AUC 0.73) and CKD (AUC 0.82). Plasma NGAL also discriminated AKI from normal function and transient azotaemia (AUC 0.85 and 0.73, respectively).

The concept of NGAL cutoff values was also re-examined in the study by Soto et al. A distinct plasma NGAL cut-off for differentiating between AKI and non-AKI could not be identified. Instead, the authors identified a grey zone of plasma NGAL concentrations (97 to 133 ng/mL) that was associated with a moderate risk for AKI. Patients who had plasma NGAL concentrations above 133 ng/mL were found to have a 10-fold greater risk of AKI. Therefore, patients who are at risk for AKI according to clinical presentation would benefit from point-of-care plasma NGAL measurements and could be triaged and managed as having true intrinsic AKI. Patients whose plasma NGAL levels fall within the

‘grey zone’ and who have clinical AKI risk factors should also be considered at high risk for intrinsic AKI.

Di Somma et al conducted a multicentre prospective cohort study involving 665 patients admitted to hospital from the Emergency Department in the period from November 2008 to April 2009. They evaluated the utility of POC blood NGAL measurement as an aid in the early risk diagnosis for AKI. NGAL and serum creatinine were determined at presentation, 6, 12, 24 and 72 hours after hospitalisation. The physician, while blinded to NGAL results, determined the clinical certainty of AKI. The physician’s initial judgement lacked sensitivity and specificity, incorrectly predicting a diagnosis of AKI in 27% of the cohort, while missing 20% of those with confirmed AKI. The AUC for blood NGAL obtained at presentation in the AKI group was 0.80. However, when NGAL was added to the physician’s initial clinical judgement, the AUC was increased to 0.90 and this was significantly greater than the AUC for eGFR obtained at presentation (AUC 0.78). In the net reclassification improvement analysis, the model obtained by combining NGAL with the physician’s initial clinical judgement compared to the model combining serum creatinine with the physician’s initial clinical judgement, resulted in a 32.4% improvement. Using a cutoff of 150 ng/ml and two serial NGAL measurements (at presentation and at 6 hours), AKI could be ruled out within 6 hours of patients’ arrival with a negative predictive value of 98%. On the other hand, an NGAL cut-off of 400 ng/ml was very specific for deciding on a diagnosis of AKI. Admission NGAL was also most strongly predictive of in-hospital mortality at a cut off above 400 ng/ml (AUC 0.76).

**Table 5: Studies investigating the use of plasma and urine NGAL in the Emergency Department.**

Reference	Sample Population	AKI definition	NGAL assay	Biofluid	AUC-ROC	NGAL cut-off ng/ml	Sensitivity %	Specificity %	Outcome
Di Somma et al 2013 (62)	665 adults	RIFLE creatinine R or worse	Triage® point of care device (Biosite Inc.)	Plasma	0.80	>150 and >400	62 37	78 97	- Prediction of AKI - Prediction of RRT and mortality
Nickolas et al 2008 (58)	635 adults	RIFLE creatinine R or worse	Immunoblotting	Urine	0.95	130	90	100	Diagnosis of intrinsic AKI (versus prerenal AKI, stable CKD or normal function)
Nickolas et al 2012 (59)	1635 adults	RIFLE creatinine R or worse	ARCHITECT ELISA	Urine	0.81	>100	68	81	Diagnosis of intrinsic AKI (versus prerenal AKI, stable CKD or normal function)
Soto et al 2013 (61)	616 adults	1.5-fold increase or ≥0.3mg SCr rise (unresolved after 3 days)	Triage® point of care device (Biosite Inc.)	Plasma	0.85	>150	80	86	- Predicts AKI - AKI vs. prerenal azotemia and CKD - Predicts AKI severity
Shapiro et al (60) 2010	661 adults with suspected sepsis	>0.5 mg/dL SCr rise or RRT within 72hr	Triage® point of care device (Biosite Inc.)	Plasma	0.82	>150	96	51	Prediction of AKI

## NGAL in prediction of contrast nephropathy

NGAL has also been shown to be useful as a biomarker of AKI in other settings. In a small cohort of 26 non-diabetic patients with normal serum creatinine, undergoing coronary angiography, a 25% increase in urine NGAL from baseline (measured using an ELISA) was found to be predictive of contrast nephropathy (defined as 25% increase in serum cystatin C), with a sensitivity of 80% and specificity of 83%. On the contrary, serum creatinine did not change significantly after the angiography (13). Another study assessed 91 children with congenital heart disease undergoing elective cardiac catheterisation and angiography with contrast administration. The authors found that significant elevation of NGAL in urine and plasma within 2 hours of predicted contrast induced nephropathy. Detection using serum creatinine was only possible after 6-24 hours (14).

**Table 6: Studies investigating the use of plasma and urine NGAL in prediction of contrast nephropathy**

Reference	Sample Population	AKI definition	NGAL assay	Biofluid	AUC-ROC	NGAL cut-off ng/ml	Sensitivity %	Specificity %
Hirsch 2007 (14)	91 Children	50% increase in SCr from baseline	ELISA	Urine Plasma	0.92 0.91	100	73	100
Bachorzewska-Gajewska 2006 (13)	26 adults	25% increase in serum cystatin C	ELISA (Antibody Shop)	Urine Plasma	- -	-	68 80	76 83

It should be noted that the diagnostic ability of NGAL in these clinical studies is dependent on the gold standard used to detect the diagnostic outcome. Using a diagnosis of AKI based on creatinine may not be an accurate measure of kidney injury, particularly considering the aforementioned disadvantages. To avoid this problem, some studies have tried to differentiate between intrinsic and prerenal AKI based on clinical criteria e.g. recovery of creatinine when haemodynamic changes are corrected (59) (63). In these studies, the AUC-ROC ranged from 0.81-0.95, suggesting that NGAL may be better at identifying intrinsic nephron damage than predicting AKI based on conventional criteria. These studies are limited by the fact that clinical criteria were used rather than biopsy results to diagnose intrinsic damage.

### ***Impact compared to existing technology***

NGAL is not currently used in clinical practice in the UK. Numerous studies have addressed the potential clinical utility of NGAL in AKI (Tables 3 – 6). All studies combined include more than 10,000 patients.

### ***Health Economics:***

Only one study was identified, which assessed the cost effectiveness of using urinary NGAL for the diagnosis of AKI after cardiac surgery compared to current diagnostic methods (64). Shaw et al. created a decision model using a base case to represent a typical patient: A 67-year-old man, in the UK with no history of CKD, 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 measure for economic evaluation. A 25% improvement in outcomes from acute kidney injury

because of early diagnosis, based on NGAL levels, was assumed and this was varied to 12.5% and 50% levels in the sensitivity analysis (65).

The base case demonstrated expected costs of £4244 and 11.86 QALYs for the NGAL strategy compared with £4672 and 11.79 QALYs for the current methods. The cost-effectiveness ratio for the NGAL strategy was £358 per QALY compared with £396 per QALY for the standard practice. Cost-effectiveness increased with treatment effect of the therapy triggered by an elevated NGAL level. Probabilistic sensitivity analysis supported the NGAL strategy as the most cost-effective option for 100% of the 1000 patient simulations. Therefore, the results suggested that the use of urinary NGAL is likely to be economically beneficial since AKI is diagnosed earlier. It should be noted that, because this study was a decision analysis model incorporating a nonspecific treatment for AKI, model structural assumptions might have underestimated mortality and the likelihood of developing AKI. Indirect costs were also not explicitly factored. It is also difficult to clearly identify the literature source and expert opinion used due to lack of description of the parameter estimates.

### ***Guidelines and Recommendations***

Current NICE guidance (NICE clinical guideline 169) (8) recommends using serum creatinine or urine output to detect acute kidney injury, and do not include a definition of acute kidney injury based on measurement of NGAL. Estimated glomerular filtration (eGFR) may also be used for children and young people. 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) (66) (67) (18).

In 2014 the NICE Diagnostics Advisory Committee considered The NGAL Test™ (BioPorto). They concluded that more research was needed prior to adopting NGAL testing, but that this was certainly an area of significant clinical need (65).

### **Research Questions:**

- 1) What is the accuracy of rapid or point-of-care NGAL tests in primary care populations?
- 2) Could NGAL help improve targeted referral to secondary care when appropriate as opposed to current practice of relying upon clinical suspicion?
- 3) Could NGAL help improve diagnosis and targeted treatment of AKI in primary care where appropriate?
- 4) What is the cost: benefit ratio of implementing NGAL tests within primary care?
- 5) Could NGAL help to distinguish between nephrotoxicity due to medication and acute rejection in patients after renal transplantation?

### **Suggested next steps:**

Most studies on the clinical utility of NGAL have been conducted at secondary care level. More studies on the predictive value, suitability and utility of NGAL testing for AKI and CKD management



are required in primary care settings. With NGAL levels also indicative of CVD outcomes, it will be helpful to determine if this marker can simultaneously predict progressive CKD and CVD risk in high-risk patients in primary care. Both serum and urinary NGAL have been suggested as potential markers of renal function. As previously discussed, NGAL has multiple molecular forms, a dimeric form synthesized in neutrophils and the other monomeric form from kidney tubular epithelial cells (6). A clinical test method that can clearly distinguish between these two NGAL forms will undoubtedly be key to enhancing sensitivity for the purpose of monitoring renal and/or vascular integrity.

### **Expected outcomes:**

Overall, the aforementioned considerations support the view that measurement of tubule damage markers, such as NGAL, would add substantial value to a consistent approach to early AKI diagnosis. However, once biomarkers of tubule damage are fully established, markers of renal function, such as creatinine, are likely to remain relevant. Markers of glomerular filtration are valuable for diagnosing and quantifying loss of excretory function and prognosis, for example in the context of drug dosing or in the development or deterioration of CKD. Similarly, urine output will remain important for fluid balance and for monitoring the progress of patients on RRT.

Based on the current evidence both urine and plasma NGAL measurement improve the prediction of AKI risk over the clinical model alone and, regardless of clinical setting, NGAL correlates with severity of AKI and can predict poor outcomes. With regards to urine vs. plasma NGAL, the availability of biofluid and the assay used are likely to be the key determinants. In the primary care setting the only available point-of-care test, the AleréTriage® NGAL test, uses EDTA anti-coagulated plasma or whole blood. It is also worth noting that there is no general consensus regarding a specific cut-off value for NGAL above which AKI can be diagnosed. However, based on the available data, an NGAL value of less than approximately 100 ng/mL, measured on a routine clinical platform in urine or plasma, seems to be useful for ruling out AKI in those with normal baseline kidney function and a cut-off value of greater than 150 ng/mL can be used as diagnostic for AKI. Further cutoffs for blood and urine NGAL and their bedside utility are impending and will be determined according to the clinical setting, regulatory intended use guidelines, clinical assay standardization, and laboratory and POC system calibration.

The available data suggest that patients with stable CKD display low concentrations of NGAL similar to normal controls, but those with progressive CKD may exhibit higher concentrations that may approach those seen in prerenal states or even in mild forms of AKI. The lack of a gold standard AKI definition, the lack of specific cut-off values for NGAL and differences in clinical assay characteristics are additional limitations to the widespread use of NGAL in clinical practice at the present time.

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