The ARCHITECT and Alinity urine NGAL assays, urine NephroCheck test, and urine and plasma BioPorto NGAL tests to help assess the risk of acute kidney injury for people who are being considered for admission to critical care

Produced by **Aberdeen HTA Group**

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Contribution of authors

Miriam Brazzelli (Reader on Research) planned the systematic review of the clinical evidence contributed to the statistical analyses and interpreted the results; Magaly Aceves Martins, Mari Imamura, Clare Robertson (Research Fellows) selected relevant papers from the literature, performed data extraction and risk of bias assessment of all included studies; Amudha Poobalan contributed to the data extraction and risk of bias assessment of included studies; Lorna Aucott (senior statistician) conducted the statistical analyses; Elisabet Jacobsen (Research Assistant) reviewed the evidence on the cost-effectiveness of the biomarkers under investigation, contributed to the acquisition of input data and to the economic evaluation under the supervision of

Dwayne Boyers (Health Economist); Dwayne Boyers developed the economic model, conducted cost-effectiveness analyses and interpreted the results, Graham Scotland (Reader on Research) provided senior advice and guidance on the development of the economic model. Paul Manson (Information Specialist) developed and ran the literature searches, retrieved full-text copies of the selected papers and provided information support throughout the project; Callum Kaye (Consultant in Anaesthetics and Intensive Care Medicine) and Simon Sawhney (Clinical Lecturer in Nephrology) provided expert advice and guidance on the clinical aspects of this assessment. Miriam Brazzelli oversaw and co-ordinated all aspects of this assessment. All authors contributed to the writing of this draft report.

Abstract

Background

Acute kidney injury (AKI) is a serious complication that typically occurs in the context of an acute critical illness or during a postoperative period. Earlier detection of AKI may facilitate strategies to preserve renal function, prevent further progression of kidney disease, and reduce mortality. Currently, AKI diagnosis relies on a rise in serum creatinine levels and/or a fall in urine output; however, creatinine is an imperfect marker of kidney function. There is interest in the performance of novel biomarkers used in conjunction with existing clinical assessment, such as NephroCheck, ARCHITECT urine NGAL, and urine and plasma BioPorto NGAL immunoassays. If reliable, these biomarkers may enable earlier identification of AKI and enhance management of those with a modifiable disease course.

Objectives

To evaluate the role of these biomarkers for assessing the risk of AKI in critically ill patients who are considered for admission to critical care.

Data sources

We searched major electronic databases, conference abstracts and ongoing studies up to June 2019.

Methods

Systematic review and meta-analysis to evaluate the performance of these biomarkers for detection of AKI and prediction of other relevant clinical outcomes. Random effects models were adopted to combine evidence. A decision tree was developed to evaluate costs and QALYs accrued due to changes in short-term (up to 90 days) outcomes and a Markov model used to extrapolate results over a lifetime horizon.

Results

56 studies, mainly prospective cohorts, with a total of 17967 participants were included in the clinical effectiveness review. There were no studies addressing the clinical impact of the use of biomarkers over patient outcomes compared with

standard care. The main sources of bias across studies were a lack of information on blinding and the optimal threshold for NGAL. In addition, for prediction studies the reporting of statistical details was limited. In general, the included studies were considered applicable to the remit of this assessment.

While summary estimates from the conducted meta-analyses appeared to show the potential ability of these biomarkers to detect and predict the course of AKI, there were limited data to establish any causal link with hard clinical outcomes. Moreover, confidence in these findings has to be tempered by the heterogeneity, as demonstrated by the large confidence and prediction regions in the HSROC plots.

The probability of cost-effectiveness at an ICER < £20,000 per QALY gained for scenarios where the NGAL biomarkers are assumed equally effective as NephroCheck in preventing AKI ranged from 0% to 15% (NephroCheck); 0-55% (BioPorto uNGAL); 0-2% (ARCHITECT uNGAL) and 0-48% (BioPorto pNGAL). When it is assumed that the NGAL biomarkers cannot avert AKI, but only reduce its severity, the cost-effectiveness of NephroCheck improves, but remains highly uncertain with a probability ranging from 0% to 99% across 15 scenario analyses.

Limitations

Cost-effectiveness results should be interpreted cautiously considering the heterogeneity observed in the diagnostic analyses, the unknown impact of NGAL-guided treatment, and the uncertain causal links between changes in AKI status and changes in health outcomes.

Conclusions

Current evidence is insufficient to make a full appraisal of the role and economic value of these biomarkers and determine whether they provide cost-effective improvements in clinical outcomes of AKI patients.

Future work

Future studies should evaluate the targeted use of these biomarkers within specific patient populations and the clinical impact of their routine use on patient outcomes and management.

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List of abbreviations

ACEi	Angiotensin-converting enzyme inhibitors
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
APACHE III	Acute physiology and chronic health evaluation III
ARBs	Angiotensin receptor blockers
AUC	Area under the curve
AUC-ROC	Area under the receiver operating characteristics
BNF	British National Formulary
CCT	Controlled clinical trial
CCU	Critical care unit
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CPB	Cardiopulmonary bypass
CVI	Cumulative vasopressor index
CysC	Cystatin C
DAM	Decision-analytic modelling
DAP	Diagnostic assessment programme
DM	Diabetes mellitus
EAG	External assessment group
ED	Emergency department
eGFR	Estimated glomerular filtration rate
EQ-5D-3L	3-level EQ-5D
EQ-5D-5L	5-level EQ-5D
ESRD	End-stage renal disease
FN	False negative
FP	False positive
FP	False positive
HD	Haemodialysis
HR	Hazard ratio
HRQOL	Health-related quality of life

HRS	Hepatorenal syndrome
HSROC	Hierarchical summary receiver operating curve
HT	Hypertension
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IDI	Integrated discrimination improvement
IGFBP-7	Insulin-like growth factor-binding protein
INR	International normalized ratio
ITU	Intensive treatment unit
KDIGO	Kidney Disease: Improving Global Outcome
LIMS	Laboratory Information Management Systems
LOS	Length of stay
MELD	Model for end stage liver disease
NA	Not applicable
NEWS	National Early Warning Score
NGAL	Neutrophil gelatinase-associated lipocalin
NHS	National health service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRI	Net reclassification improvement
OR	Odds ratio
p.a.	Per annum
PD	Periotoneal dialysis
PICU	Paediatric intensive care unit
pNGAL	Plasma neutrophil gelatinase-associated lipocalin
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROBAST	Prediction model Risk Of Bias ASsessment Tool
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal social services research unit
QALY	Quality adjusted life year

QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies, version 2
RACHS	Risk adjustment for congenital heart surgery
RCT	Randomised controlled trial
RIFLE	Risk, Failure, Loss of kidney function, End-stage disease
ROC	Receiver operating characteristics
ROSC	Return of spontaneous circulation
RR	Relative risk
RRT	Renal replacement therapy
SAPS III	Simplified acute physiology score III
sCr	Serum creatinine
SEM	Standard error of the mean
SHARP	Study of Heart and Renal Protection
SOFA	Sequential organ failure assessment
TIMP-2	Tissue inhibitor of metalloproteinase-2
TP	True positive
uL-FABP	Urinary liver-type fatty acid-binding protein
uNGAL	Urine neutrophil gelatinase-associated lipocalin
UTI	Urinary tract infection
WTP	Willingness to pay

Plain English summary

Among people who are very ill or have received surgery, the kidneys may suddenly stop to work properly. This is known as acute kidney injury (AKI). AKI can progress to serious lasting kidney problems and can be fatal. At present, the level of creatinine (a waste product filtered by the kidneys) in the blood or urine is used by health professionals to decide whether AKI is present. However, creatinine levels are not a precise indicator and they can take hours or even days to rise – this may lead to delays in AKI recognition. Novel biomarkers may help health professionals recognise the presence of AKI earlier and treat patients more promptly. This work evaluates existing evidence for biomarker utility with respect to clinical usefulness and cost.

We reviewed the current evidence on the use of these biomarkers for assessing the risk of AKI in people who are very ill and assessed whether they are of good value for the NHS. We assessed the ARCHITECT urine NGAL, urine and plasma BioPorto NGAL and urine NephroCheck biomarkers.

We checked studies published up to June 2019 and found 36 relevant studies (17,967 patients). Most studies were conducted outside the UK and investigated people already admitted to critical care. We combined the results of the studies and found that NephroCheck and NGAL biomarkers might potentially be useful in identifying AKI or pre-empting AKI in some circumstances. However, studies differed in patient characteristics, clinical setting, and the way biomarkers were used. This could explain why the number of people correctly identified and missed by the biomarkers varied across studies. Hence, we do not completely trust our pooled results.

When we looked at costs for the NHS we found that AKI is associated with substantial cost, but there was insufficient good quality evidence to decide which biomarker (if any) offered the best value for money to the NHS.

Scientific summary

Background

Acute kidney injury (AKI) is a common and serious complication that typically occurs in the context of an acute critical illness or during a postoperative period. It is associated with prolonged hospital stay, increased morbidity and increased mortality. AKI is a challenging clinical problem for hospitalised patients. Earlier detection of kidney injury may facilitate the adoption of strategies to preserve renal function and prevent further progression of kidney disease.

Currently, AKI diagnosis relies on a rise in serum creatinine levels and/or a fall in urine output. Despite its widespread use in the monitoring of kidney health and disease, creatinine is an imperfect marker of kidney function because its level in the blood is not solely dependent on kidney function, and changes in creatinine lag behind reductions in kidney function. The limitations of creatinine assessment have led to the search for novel biomarkers which may detect kidney damage or kidney stress earlier and more reliably.

Biomarker tests for AKI include NGAL (neutrophil gelatinase-associated lipocalin), which can be measured using a sample of urine or blood. NGAL is released from neutrophils and is induced by inflammation, indicating tubular injury. Another recent biomarker for AKI is NephroCheck, which tests for the presence of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) in the urine. Both TIMP-2 and IGFBP7 are cell-cycle arrest proteins and used as markers of cellular stress in the early phase of tubular cell injury. Both NephroCheck and NGAL immonoassays are intended to be used in conjunction with existing clinical care. This assessment focuses specifically on the ARCHITECT and Alinity urine NGAL assays (Abbott), the BioPorto urine and plasma NGAL tests (BioPorto Diagnostics), and the NephroCheck test (Astute Medical).

If these biomarkers demonstrated the ability to identify patients at risk of AKI early, they could have the potential to enhance current AKI management by enabling timely measures to prevent progression of kidney injury, and by informing decisions about

the ‘step down’ of low risk patients to a lower level of hospital care, reducing the use of hospital resources. The remit of this work was to evaluate the clinical and cost-effectiveness of biomarker use in the evaluation of patients not in critical care, but who might be considered for admission to critical care.

Objectives

The aim of this project was to summarise the current evidence on the clinical and cost-effectiveness of the NephroCheck test, the ARCHITECT and Alinity Urine NGAL assays, the BioPorto urine and plasma NGAL tests to assess the risk of AKI in critically ill, hospitalised, patients (adults and children) who are considered for admission to critical care.

There are several components to this project that fall within the scope of the following research questions:

1. Do the novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?
2. Do the novel biomarkers predict the development of future events (e.g., AKI, mortality, need for long-term renal replacement therapy) in critically ill people at risk of developing AKI who are considered for admission to critical care?
3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill patients at risk of developing AKI who are considered for admission to critical care and whose management is guided by the novel biomarkers (e.g. reduction in events rates of mortality and long-term renal replacement therapy)?
4. Does routine use of novel biomarkers affect costs to the NHS, length or quality of life (i.e. Quality Adjusted Life Years or QALYs), or cost-effectiveness measured as incremental cost per QALY gained for critically ill people who are considered for admission to critical care?

Methods

Assessment of clinical effectiveness

Comprehensive electronic searches were undertaken to identify relevant reports of published studies up to June 2019.

The population of interest was critically ill people at risk of developing AKI who are considered for admission to critical care. Studies were eligible for inclusion only if they enrolled at least 100 participants at risk of AKI. The biomarkers under investigation were the NephoCheck test (Astute Medical), the ARCHITECT and Alinity Urine NGAL assays (Abbott), the urine and plasma BioPorto tests (BioPorto Diagnostics), all used in conjunction with existing care. At present, there is no universally accepted reference standard for diagnosing AKI. The relevant comparator for this assessment was existing clinical criteria for monitoring serum creatinine and urine output in conjunction with clinical judgement, and in line with current clinical classification systems (RIFLE, paediatric-modified RIFLE, AKIN and KDIGO) (see NICE Clinical Guidance 169 on the prevention, detection and management of AKI).

The outcomes of interest were: detection of AKI, prediction of AKI, prediction of mortality, prediction of the need for long-term renal replacement therapy (RRT) and prediction of developing chronic kidney disease (CKD) over 90 days post-AKI.

The quality of included studies was assessed using the QUADAS-2 and PROBAST tools.

Assessment of cost-effectiveness

The impact of biomarker diagnostic accuracy on short-term costs and QALYs up to 90-days was modelled using a decision tree. As there is no evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, 90-day mortality or development of CKD), it was necessary to use a linked evidence approach that relied on observational associations to infer how prevention of AKI, or reduction in its severity may affect changes in health outcomes. These associations necessitate causal assumptions, but while a causal link between AKI and poor outcomes is plausible, the extent of this causal relationship is uncertain and controversial. These hypothesised links are tested extensively in sensitivity analysis.

The surviving proportion from each decision tree pathway at 90 days entered a Markov model (starting age = 63) with six mutually exclusive health states (out-patient follow up, CKD stages 1-4, end stage renal disease [ESRD] without dialysis,

ESRD with dialysis, transplantation and death). The cohort can enter the Markov model in the outpatient or CKD states with the starting proportions dependent on the experience of AKI up to 90 days.

NHS perspective costs (2018 values) in the first 90 days included the cost of the diagnostic biomarkers, the costs of implementing an additional three days of a KDIGO care bundle for test-positive patients, detailed costs over the initial hospital period including days in ICU, on ward and need for acute RRT. Costs over the longer-term Markov phase included follow-up costs post-discharge, costs of CKD, ESRD costs, cost of long-term dialysis treatment, transplantation, immunosuppressant costs and post-transplant follow-up costs.

Health state utility values, based on EQ-5D data obtained from the literature, were combined with mortality estimates for each health state to calculate QALYs. For the acute stage, utilities were applied to the level of hospital care required (ICU, hospital ward, or discharged). An additional utility decrement was applied for the proportion of the cohort receiving acute RRT. For the chronic phase health state utility values were applied to CKD, ESRD, and ESRD with dialysis. It was assumed that after recovery from a transplant, utility reverted back to that of the outpatient post-discharge state. All utilities were adjusted for UK age- and sex-specific general population norms.

The model captured the cumulative cost and QALY implications of transitions through the health states in annual cycles over a life-time horizon from an NHS perspective. All future costs and QALYs were discounted at 3.5% per annum. All analyses were reported probabilistically.

Results

Assessment of clinical effectiveness

A total of 56 studies were included in the systematic review of clinical effectiveness evidence. The majority were prospective cohort studies. No studies addressing the impact of the routine use of the biomarkers on clinical outcomes of critically ill people considered for admission to critical care were identified. Of the 56 included studies, 46 enrolled only adults, 8 only children and 2 both adults and children. The

total number of participants was 17,967 of which 16,247 were adults (average age range from 49 to 77 years) and 1720 were children (average age range from 1 day to 5 years). The 46 studies that focused on an adult population assessed patients after cardiac surgery (n=12), non-surgical cardiac care (n=4), major abdominal surgery (n=1), hepatobiliary surgery (n=1), patients admitted to ICUs (n=16), patients with liver disease (n=5, mainly cirrhosis), sepsis (n=2), CKD (n=2) and patients presenting to the emergency department (n=3). Of the eight studies that focused on children, 6 studies assessed children (including neonates) undergoing cardiac surgery and 2 children admitted to a paediatric ICU or neonatal ICU. The two studies that assessed both adults and children included patients undergoing cardiac surgery.

For the purpose of the statistical and cost-effectiveness analyses the participants were grouped into three categories according to the clinical setting reported in the included studies: patients undergoing cardiac surgery, patients undergoing major non-cardiac surgery, and patients admitted to critical care (mixed patient population).

NGAL was the most commonly studied biomarker (41/56 studies; 37 studies used urine NGAL assays and 4 plasma NGAL assays). NephroCheck was assessed in 8 studies. Seven studies provided data on more than one assay (6 studies on urine NGAL and plasma NGAL assays and 1 study on NephroCheck, urine NGAL and plasma NGAL assays). Among the NGAL studies, 24 used the urine NGAL ARCHITECT platform (Abbott) and 20 used the urine NGAL BioPorto Diagnostics assay. All 11 plasma NGAL studies used the BioPorto Diagnostics assay. No studies used the NGAL Alinity platform (Abbott).

The main source of bias across diagnostic studies was the lack of information on blinding and of a common threshold for NGAL. Among prediction studies, the risk of bias for the analysis domain was unclear in 58% of studies and high in 42%. In particular, the statistical prediction models differed between studies and often were not sufficiently detailed. In general, the included studies were considered applicable to the remit of this assessment.

With regard to the detection of AKI, the results of the meta-analyses of sensitivity and specificity estimates suggest that the biomarkers under investigation may potentially

have a role in the detection of AKI in patients already admitted to critical care. There were too few studies assessing patients after cardiac surgery or major non-cardiac surgery. The urine NephroCheck test at a common threshold of 0.3 ng/mL^2/1000 had the higher pooled sensitivity (0.83) but the worst pooled specificity (0.51), while the uNGAL ARCHITECT and the BioPorto uNGAL tests had slightly lower pooled sensitivity estimates (0.70 and 0.72, respectively) but better pooled specificity estimates (0.72 and 0.87 respectively). The urine NGAL BioPorto pooled sensitivity was similar to that of plasma NGAL BioPorto (0.72 versus 0.76), whilst the pooled specificity was better for urine NGAL BioPorto (0.87 versus 0.67). NGAL thresholds varied across studies. The biomarkers had a similar performance across all clinical settings:

- NephroCheck pooled sensitivity and specificity were 0.75 and 0.61, respectively;
- uNGAL ARCHITECT pooled sensitivity and specificity were 0.67 and 0.72, respectively;
- uNGAL BioPorto pooled sensitivity and specificity were 0.73 and 0.83, respectively;
- pNGAL BioPorto pooled sensitivity and specificity were 0.76 and 0.67, respectively, with pNGAL BioPorto showing the higher sensitivity (0.76) and uNGAL BioPorto the higher specificity (0.83).

While summary estimates from these meta-analyses appeared to show some diagnostic usefulness of the use of the biomarkers, confidence in these findings has to be tempered by the considerable heterogeneity observed across studies and demonstrated by the large confidence and prediction regions in the HSROC plots.

Moreover, for studies with a low prevalence of AKI (low number of AKI events) the relationship between sensitivity and specificity estimates appeared to be quite different from that of studies for which prevalence was higher.

For prediction of relevant clinical outcomes, only a limited number of studies were available for each biomarker in each clinical setting and this hampered the possibility to perform pooled analyses. Moreover, details of the methodology used for the statistical models in individual studies were scant.

Similarly, while there was an indication that the addition of biomarkers to existing clinical models might improve the prediction of relevant clinical outcomes, studies varied substantially in terms of study characteristics and of statistical methods used to assess prediction hindering any reliable conclusion.

In general, all included studies varied considerably in terms of clinical setting, NGAL threshold levels, time of sample collection, definition of AKI, time of AKI diagnosis, number of AKI events, assay platforms. Therefore, we have limited confidence in the validity and reliability of our findings.

Results of the cost-effectiveness model (including sensitivity analyses)

Published data show that NephroCheck-guided implementation of a KDIGO care bundle has potential to avert AKI. However, no such data exist for the NGAL tests. Therefore, two base case analyses were considered. Base case 1 can be considered an optimistic scenario for the NGAL biomarkers assuming that all NGAL tests are equally effective as NephroCheck in terms of the potential to avert AKI. Base case 2 can be considered a more conservative analysis. It assumes, in the absence of evidence to suggest otherwise, that only NephroCheck can avert AKI, but that all tests have the potential to reduce AKI severity if it occurs.

Fifteen scenario analyses were conducted for each potential base case, ranging from a set of optimistic assumptions where biomarker-guided care bundles led to substantial improvements in health outcomes (need for ICU, hospital length of stay, CKD, mortality) to a set of more conservative assumptions where changing of AKI status had no effect on health outcomes.

ICERs were highly uncertain, and subject to wide variation depending on the set of scenarios chosen. The probability of cost-effectiveness at an ICER < £20,000 per QALY gained for scenarios where all NGAL biomarkers were assumed equally effective as NephroCheck in preventing AKI ranged from 0% to 15% (NephroCheck); 0-55% (BioPorto urine NGAL); 0-2% (ARCHITECT urine NGAL) and 0-48% (BioPorto plasma NGAL). BioPorto urine NGAL was usually the test associated with the greatest probability of cost-effectiveness, albeit highly uncertain, when compared

to standard care only. This was because the BioPorto urine NGAL biomarker was estimated to have slightly better diagnostic test accuracy data from the meta-analysis and incurred slightly lower test costs compared with the comparators. However, there was substantial uncertainty in diagnostic accuracy information, driven by substantial study heterogeneity. The cost-effectiveness results should therefore be interpreted cautiously.

When it was assumed that NGAL biomarkers could not avert AKI, but could only reduce its severity, the cost-effectiveness case for NephroCheck improved substantially, whilst remaining highly uncertain with a probability of cost-effectiveness ranging from 0% to 99% across the explored scenarios.

Discussion

Strengths, limitations of the analyses and uncertainties

The methods used to conduct this assessment were detailed, thorough and in line with current methodological standards. We identified a large volume of potentially relevant literature, which required significant screening resources and adoption of additional inclusion criteria to ensure that the assessment remained feasible and timely.

The main limitations of the clinical effectiveness assessment are summarised below:

i) Considerable clinical and statistical heterogeneity in the diagnostic and prediction analyses;
ii) Use of an imperfect reference standard for detection of AKI (clinical assessment based on serum creatinine and urine output);
iii) Variation in the use of the NGAL assays and lack of a common threshold for identification of AKI;
iv) Uncertainty regarding the best timing of biomarker measurements;
v) Variation in AKI prevalence across studies with very low number of AKI events in some studies;
vi) Lack of data on the impact of the routine use of the biomarkers on health outcomes over current clinical assessment.

The majority of the included studies were conducted outside the UK and assessed hospitalised patients admitted to critical care, with large variation in delivery of

critical and intensive care medicine across the world. There is great uncertainty on how well findings of studies that are predominantly based in intensive care, non-UK and heterogenous, could be applied to a UK clinical scenario of people at risk of AKI who do not currently receive critical care.

With regard to the economic modelling, we identified three key areas of uncertainty, which mirror those identified for the clinical effectiveness assessment and limit the robustness of the cost-effectiveness results:

i) Lack of direct evidence on the impact of the use of the biomarkers on health outcomes;
ii) Heterogeneity in the diagnostic accuracy data (including uncertainty in the prevalence of AKI in a broad, poorly defined population);
iii) Uncertainty around the impact of an NGAL-guided implementation of a KDIGO care bundle on the frequency and severity of AKI.

Given these uncertainties, the results of the cost-effectiveness modelling were largely speculative and should be interpreted with caution. Whilst we conducted extensive probabilistic analyses for all scenario analyses, these may still not capture the full magnitude of uncertainty faced in the implementation of these biomarkers in clinical practice.

Generalisability of the findings

Due to the limitations listed above, it is unclear how the findings of this assessment can be generalised to current UK practice.

Conclusions

Future studies should evaluate the targeted use of the biomarkers within specific clinical populations and circumstances were there is potential for benefit with a plausible and feasible intervention. They should focus on the assessment of the impact of routine biomarker use on a reduction in mortality, major clinical adverse events, modification of clinical care, and resource utilization.

There is also a need to harmonise the methods and platforms for collection, handling and storage of urine and plasma biomarker samples as well as reporting of biomarkers concentrations (units of measurement).

Study registration

This study is registered as PROSPERO CRD42019147039

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1 Objectives

The overall objective of this assessment was to summarise the current evidence on the clinical and cost-effectiveness of using NephroCheck test, ARCHITECT and Alinity urine NGAL, and urine and plasma BioPorto NGAL immunoassays to help assess the risk of AKI in critically ill hospitalised patients who are considered for admission to critical care. AKI is still a challenging clinical problem for hospitalised patients especially for those in need of critical care. Earlier detection of kidney injury may facilitate the adoption of strategies to preserve renal function and prevent further progression of kidney disease.

There are several components to this assessment that fall within the scope of the following research questions:

1. Do novel biomarkers (NephroCheck test, ARCHITECT and Alinity Urine NGAL assays, urine and plasma BioPorto NGAL tests) accurately detect emerging AKI in critically ill people who are considered for critical care? (re
2. Do the novel biomarkers (NephroCheck test, ARCHITECT and Alinity Urine NGAL assays, urine and plasma BioPorto NGAL tests) predict the development of future events (e.g., AKI, mortality, need for long-term renal replacement therapy) in critically ill people at risk of developing AKI who are considered for admission to critical care?
3. Does the use of novel biomarkers (NephroCheck test, ARCHITECT and Alinity Urine NGAL assays, urine and plasma BioPorto NGAL tests) lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care? (i.e., reduction in events rates – such as mortality and long-term renal replacement therapy - among patients whose management is guided by the novel biomarkers)
4. Does routine use of novel biomarkers (NephroCheck test, ARCHITECT and Alinity Urine NGAL assays, urine and plasma BioPorto NGAL tests) affect costs to the NHS, length or quality of life (i.e. Quality Adjusted Life Years, QALYs), or cost-effectiveness measured as incremental cost per QALY gained for critically ill people who are considered for admission to critical care?

In brief, the main objectives of this assessment are the following:

- To determine the diagnostic accuracy, prognostic accuracy and clinical impact of the use of novel biomarkers (NephroCheck test, ARCHITECT and Alinity Urine NGAL assays, urine and plasma BioPorto NGAL tests) for the assessment of acute kidney injury in critically ill patients (adults and children) who are being assessed for admission to critical care.
- To develop an economic model to assess the cost-effectiveness of the use of novel biomarkers (NephroCheck test, ARCHITECT and Alinity Urine NGAL assays, urine and plasma BioPorto NGAL tests) for the assessment of acute kidney injury in critically ill patients (adults and children) who are considered for admission to critical care.

2 Background and definition of the decision problem

Health problem

Acute kidney injury (AKI) is a common and serious complication that typically occurs in the context of an acute critical illness or during a postoperative period. It is associated with prolonged hospital stay, severe morbidity and increased mortality.[1, 2] Delayed identification of AKI contributes to worse outcomes.[3]

To pre-empt or avoid lasting consequences of AKI, early detection may be beneficial. Traditionally, AKI diagnosis relies on a rise in serum creatinine levels and/or a fall in urine output. Despite its widespread use in the monitoring of kidney health and disease, creatinine is an imperfect marker of kidney function because its level in the blood is not solely dependent on kidney function, and changes in creatinine lag behind when kidney function reduces in AKI.[4] When kidney function suddenly falls, even if a reduction in renal excretion occurs instantly, it can take hours or sometimes days for the level to creatinine to rise in the blood sufficiently for AKI to be diagnosed according to current international definitions. Moreover, in response to stress or even kidney damage, the kidneys have reserve capacity and can compensate so that kidney function is maintained. For this reason, in some clinical settings significant kidney damage can occur without AKI being apparent from changes in blood creatinine. In other settings, such as during a temporary reduction in blood flow to kidneys, rises in creatinine and a reduction in urine can occur, even when no significant damage has occurred. These limitations related to the use of creatinine assessment have led to the search for novel biomarkers that may detect kidney damage or kidney stress earlier and more reliably.

Biomarker tests for AKI include the NGAL test (neutrophil gelatinase-associated lipocalin), which can be measured using a sample of urine or blood.[5] NGAL is released from neutrophils and is induced by inflammation, indicating tubular injury.[4] One limitation of NGAL is that it is produced throughout the body making it difficult to distinguish systemic inflammation from localised renal inflammation.[4] Novel NGAL tests include the ARCHITECT and Alinity Urine NGAL assays (Abbott), the

BioPorto NGAL plasma test (BioPorto Diagnostics) and the BioPorto NGAL urine test (BioPorto Diagnostics).

Another biomarker for AKI is the NephroCheck test (Astute Medical), a combination of two urinary biomarkers, the tissue inhibitor of metalloproteinase-2 (TIMP-2) and the insulin-like growth factor-binding protein 7 (IGFBP-7). Both TIMP-2 and IGFBP7 are cell-cycle arrest proteins that are released into urine as markers of cellular stress in the early phase of tubular cell injury due to a variety of insults (e.g., toxins, drugs, oxidative stress and inflammation), which lead to AKI[6]. The US Food and Drug Administration has approved these combined biomarkers to assess the risk of AKI in critically ill patients.[4]

These novel biomarkers have been developed to detect early damage or stress in the kidneys. If reliable use of these biomarkers can be demonstrated, they may enable earlier identification of AKI, and, therefore, early management of those with a modifiable disease course - with potential for downstream benefits in patients' clinical outcomes. If demonstrated, the ability of these novel biomarkers for early detection of AKI could have the potential to improve current AKI management by enabling timely measures that could prevent progression to more severe kidney injury as well as by informing decisions about the 'step down' of low risk patients to a lower level of hospital care, reducing the use of hospital resources.

The purpose of this assessment is to review the current evidence on the diagnostic accuracy, prognostic accuracy, impact on clinical outcomes and cost-effectiveness of novel biomarkers (NephroCheck test, ARCHITECT and Alinity Urine NGAL assays, BioPorto NGAL plasma test and BioPorto NGAL urine test) for the assessment of AKI in critically ill patients who are considered for critical care admission.

Aetiology, pathology and prognosis

AKI ranges from minor loss of kidney function to complete kidney failure. In current practice, reduced kidney function is identified by elevated serum creatinine levels and/or reduced urine output.

There are many causes of acute kidney injury[7], including:

Pre-renal: Reduced oxygen delivery to the kidneys, caused by:

- low blood volume (after bleeding, excessive vomiting or diarrhoea and severe dehydration),
- reduced blood flow from the heart (potentially caused by sepsis or heart/liver failure)
- damage to blood vessels which can be caused by inflammation or blockages within the kidneys
- medications that affect blood flow to the kidneys

Intrinsic/Renal: Damage to the kidney potentially caused by drugs, infections or contrast agents

Post-renal: A blockage preventing drainage from the kidneys (potentially caused by an enlarged prostate, a tumour in the pelvis or kidney stones).

Incidence and/ or prevalence

Major surgery is a significant risk factor for the development of acute kidney injury[4]. In general, incidence of post-operative AKI depends on the type surgery. Rates of AKI after cardiac surgery have been reported to range from 8% to 40% according to the patient populations[4]. Recent meta-analyses have reported a pooled incidence of AKI in patients admitted to intensive care after abdominal surgery of 13.4% (95% CI 10.9% to 16.4%)[8] and after major trauma of 24% (95% CI 20% to 29%)[7] and 21% (95% CI 16.5% to 24.9%).[9]

The incidence of AKI for all major, non-cardiac surgery patients and trauma patients can be as high as 50% (e.g., liver transplant patients). In a retrospective cohort of over 27,000 patients the incidence of AKI defined according to the RIFLE criteria was 37%.[10, 11]

Impact of health problem

People with AKI have a higher mortality and longer hospital stay.[1, 2] In addition, acute kidney injury is associated with a higher risk of developing chronic kidney disease

(CKD) and need for long term dialysis. The risk of CKD increases with severity of acute kidney injury. More severe acute kidney injury has also been associated with increased mortality, length of hospital stay and use of intensive care services, in addition to a reduced chance of renal recovery.[1, 2] People with more severe acute kidney injury (and a greater loss of renal function) are more likely to need temporary renal replacement therapy.

Measurement of disease

Several tools are available for determining the stage of AKI. The NICE Clinical Knowledge Summary[12] on acute kidney injury outlines a summarised staging system for acute kidney injury in adults based on the RIFLE (Risk, Failure, Loss of kidney function, End-stage disease),[13] AKIN (Acute Kidney Injury Network)[14] and KDIGO (Kidney Disease: Improving Global Outcome)[15] systems (see Table 1 below). A patient's acute kidney injury should be staged by the criterion, and a classification of stage 1 or above indicates acute kidney injury.

Table 1 Summary of the staging system for acute kidney injury in adults (based on the KDIGO, RIFLE and AKIN systems)

Criteria	Stage	Definition
KDIGO[15]	1	Creatinine rise of 26 micromol or more within 48 hours OR Creatinine rise of 50–99% from baseline within 7 days* (1.50–1.99 x baseline) OR Urine output** < 0.5 mL/kg/h for more than 6 hours
	2	100–199% creatinine rise from baseline within 7 days* (2.00–2.99 x baseline) OR Urine output** < 0.5 mL/kg/hour for more than 12 hours
	3	200% or more creatinine rise from baseline within 7 days* (3.00 or more x baseline) OR Creatinine rise to 354 micromol/L or more with acute rise of 26 micromol/L or more within 48 hours or 50% or more rise within 7 days OR Urine output** < 0.3 mL/kg/hour for 24 hours or anuria for 12 hours
RIFLE[13]	R	≥ 1.5- and < 2-fold increase from baseline SCr or ≥ 25% fall in GFR from baseline or urine output < 0.5 ml/kg/hour for ≥ 6 and < 12 hours
	I	≥ 2- and < 3-fold increase from baseline SCr or ≥ 50% fall in GFR from baseline or urine output < 0.5 ml/kg/hour for ≥ 12 hours and < 24 hours
	F	≥ 3-fold increase from baseline SCr or ≥ 75% fall in GFR from baseline or SCr ≥ 4 mg/dl with an acute rise of ≥ 0.5 mg/dl or urine output < 0.3 ml/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours
	L	Complete loss of renal function for > 4 weeks
	E	End-stage renal disease
AKIN[14]	1	Increase in SCr of ≥ 0.3 mg/dl (≥ 26.4 μmol/l) or increase in SCr to ≥ 150–200% (1.5- to 2-fold) of baseline value or urine output < 0.5 ml/kg/hour for ≥ 6 and < 12 hours

Criteria	Stage	Definition
	2	Increase in SCr to > 200–300% (> 2- to 3-fold) of baseline value or urine output < 0.5 ml/kg/hour for ≥ 12 hours and < 24 hours
	3	Increase in SCr to > 300% (3-fold) of baseline value or SCr ≥ 4.0 mg/dl (≥ 354 μmol/l) with an absolute increase of ≥ 0.5 mg/dl (≥ 44 μmol/l) or initiation of RRT or urine output < 0.3 ml/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours
* The rise is known (based on previous blood tests) or presumed (based on history) to have occurred within 7 days. ** Measurement of urine output may not be practical in a primary care population, but can be considered in a person with a catheter.		

Source: NICE Clinical knowledge summaries on acute kidney injury (2018)[12]

Description of the technologies under assessment

The NephroCheck test, the ARCHITECT and Alinity Urine NGAL assays, the NGAL plasma test and the NGAL urine test may help to assess AKI in critically ill people who are considered for admission to critical care in hospital. These tests may be able to detect kidney injury earlier than methods currently used for monitoring kidney function.

The NeproCheck test

The NephroCheck test (Astute Medical, Inc., USA) measures the level of 2 biomarkers in urine, the TIMP-2 (tissue inhibitor of metalloproteinase 2) and IGFBP-7 (insulin-like growth factor binding protein 7), to assess risk of moderate to severe acute kidney injury (defined as per KDIGO guidelines) in the subsequent 12 hours. The test result must be used in conjunction with clinical evaluation and results of other tests such as serum creatinine and urine output.

The concentrations of TIMP-2 and IGFBP-7 are used to calculate an AKIRisk score (the concentrations of each [ng/ml] multiplied together and divided by 1,000). A score of 0.3 or less indicates a low risk of developing *moderate to severe* AKI within 12 hours of assessment, while a score of greater than 0.3 indicates a high risk of developing *moderate to severe* AKI within 12 hours of assessment[5].

When used with the Astute 140 Meter,NephroCheck test system consists of the following components:

- Astute140 Meter Kit (a benchtop analyser)
- Astute140 Electronic Quality Control device
- NephroCheck Test Kit (includes a single-use NephroCheck test cartridge and reagents)
- NephroCheck Liquid Control kit
- NephroCheck Calibration Verification kit

A fresh or thawed urine sample (mixed with reagent) is added to a single-use test cartridge, which is then inserted into an Astute140 Meter for incubation and result calculation. Preparation takes 3 to 5 minutes and results of NephroCheck are available in about 20 minutes. In the NHS, the Astute 140 Meter would be used in a laboratory and not at the point of care.

The test can also be run on the VITROS 3600 immunodiagnostic System and on the VITROS 5600 Integrated System clinical chemistry analysers. All systems generate a single numerical result (the AKIRisk score).

[redacted]

For surgical patients the NephroCheck test is recommended to be administered 2 to 4 hours after surgery. As NephroCheck exhibits a characteristic rise and fall after various exposures, a second administration of the test within the first 24 hours may be considered in patients with an ongoing risk of developing AKI.

In the UK, Nephrocheck test is marketed for people aged over 21 years old.

Neutrophil gelatinase-associated lipocalin (NGAL) assays

ARCHITECT and Alinity Urine NGAL assays

The ARCHITECT Urine NGAL assay (Abbot, Germany) is a chemiluminescent micro particle immunoassay for the quantitative determination of NGAL in human urine. NGAL can be used as a marker of kidney injury.

ARCHITECT Urine NGAL assay might be used as follows:

- Early detection of acute kidney injury;
- Provides a measure of the severity of acute kidney injury;
- Predicts the requirement for renal replacement therapy;
- Helps differentiate acute kidney injury from chronic kidney disease and dehydration.

For diagnostic purposes, the test results should be used in conjunction with clinical assessment and the results of any other testing that has been done (including serum creatinine and urine output). In addition, if the NGAL results are inconsistent with clinical assessment and other test results, additional testing can be done to confirm the NGAL results.

The test could be used daily until a diagnosis is made or treatment for acute kidney injury is initiated.

The expected range for the assay (for people without kidney injury) is less than or equal to 131.7 ng/ml, based on the 95th percentile from specimens from non-hospitalised donors, but results from individual laboratories may vary and the manufacturer recommends that each laboratory should determine its own reference range based upon the particular locale and population characteristics. The test has no age restrictions in use.

The assay is run on the ARCHITECT system (i1000SR, i2000, i2000SR, ci4100, ci8200 or ci16200) in a laboratory. The throughput of the system is up to 200 tests per hour, and the time to first result is 36 minutes.

In addition to the ARCHITECT Urine NGAL Reagent Kit, the following materials are also needed:

- ARCHITECT Urine NGAL Calibrators
- ARCHITECT Urine NGAL Controls or other control material
- ARCHITECT i pre-trigger solution
- ARCHITECT i trigger solution
- ARCHITECT i wash buffer
- ARCHITECT i reaction vessels
- ARCHITECT i sample cups
- ARCHITECT i septum
- ARCHITECT i replacement caps

The Abbott NGAL assay is also available for use on Alinity immunoassay analyser, The reagents for the Alinity and ARCHITECT NGAL assays are the same.

The BioPorto NGAL Test (using urine or plasma)

The BioPorto NGAL Test (BioPorto Diagnostics, Denmark) is particle-enhanced turbidimetric immunoassay for the quantitative determination of NGAL in human urine, EDTA plasma and heparin plasma on automated clinical chemistry analysers. NGAL measurements may be useful in pre-empting the diagnosis of acute kidney injury, which may lead to acute renal failure. Urinary NGAL can serve as an early marker of acute kidney injury after cardiopulmonary bypass surgery and both urinary and plasma levels of NGAL provide an early indication of acute renal injury in unselected patients in intensive care.

The NGAL test is intended to be used alongside monitoring of serum creatinine and urine output (not as a stand-alone test) and the significance of any raised NGAL level should be interpreted in the light of a patient's clinical features.

The NGAL test can be administered as a single measurement but also as a serial measurement to detect any further development of acute kidney injury during hospitalisation, or any improvement in the clinical condition. In patients admitted to

intensive care the test can be used to predict stage 2/3 AKI or as a negative predictive marker to rule out the presence of acute kidney injury.

To indicate the presence of acute kidney injury, NGAL concentration in an isolated sample of urine and/or EDTA plasma should exceed 250 ng/mL. This threshold has been chosen to minimise the risk of an unacceptably high proportion of false positive results.

The assay can be run on clinical chemistry analyser systems from Roche (Cobas, Modular P), Siemens (ADVIA), Abbott (AEROSET, ARCHITECT) and Beckman Coulter (Olympus AU) in a laboratoty. The assay time is 10 minutes.

In addition to the NGAL Test Reagent Kit, the following materials are also needed:

- The NGAL Test Calibrator Kit
- The NGAL Test Control Kit
- 0.9% w/v aqueous sodium chloride solution as zero calibrator
- Analyzer-specific reagent containers

At present, the test has no age restrictions on use. [redacted]

Identification of important sub-groups

The primary scope of this assessment is the optimisation of current secondary care of critically ill patients, to decide whether the use of novel biomarkers would improve detection of AKI and consequently the current care pathway. The relevant population considered in this assessment is critically ill people at risk of developing AKI (i.e., who are having their serum creatinine and urine output monitored) who are being assessed for possible admission to critical care. In most studies conducted outside UK, critically ill participants are usually admitted to critical or intensive care due to the variation in intensive care ultilisation across the world. The following patient subgroups have been identified as particularly relevant for the purpose of this assessment.

Relevant subgroups include:

- Type of surgery (e.g., major vascular/cardiac surgery, major non-vascular surgery, trauma, solid organ transplant)
- Type of setting (e.g., post-surgery care, cardiac care, intensive or critical care, emergency department)
- Type of sample media (i.e., urine, blood plasma)
- People with a different underlying risk of AKI (e.g., people with chronic kidney disease, sepsis, hip fracture, major trauma, chronic liver disease)
- People with or without urinary infection and other inflammatory conditions (tests may perform differently in these populations)

Relevant comparator

Novel biomarkers need to be compared for incremental advantage over standard approaches to measuring kidney function. As discussed earlier, AKI diagnosis traditionally relies on a rise in serum creatinine levels and/or fall in urine output. Creatinine has limitations as a biomarker because it depends on the total body muscle mass, which varies between individual people. Some creatinine is also eliminated from the body by mechanisms other than filtering by the kidneys, which can be influenced by a variety of medications, including some commonly used antibiotics. In an illness where kidney function suddenly falls (AKI), there may be a lag of hours to days before creatinine levels in the blood rise to a level sufficient for AKI to be diagnosed according to current international definitions. In addition, in response to stress or even kidney damage, the kidneys have reserve capacity and can compensate so that kidney function is maintained. For this reason, in some clinical settings significant kidney damage can occur without AKI being apparent from changes in blood creatinine. In other settings, such as during a temporary reduction in blood flow to kidneys, rises in creatinine and a reduction in urine can occur, even when no significant damage has occurred.

Care pathway

The NICE clinical guideline on acute kidney injury[16] recommends measuring serum creatinine and comparing with baseline for adults, children and young people with acute illness if risk factors for the condition are likely or present. Risk factors include

sepsis, hypovolemia and deteriorating early warning scores (using a paediatric version for children and young people). NHS England and NHS Improvement have endorsed the National Early Warning Score (NEWS) for use in acute and ambulance settings. An updated version of the score (NEWS2)[17] was published in December 2017. The score should not be used in children (under 16 years) or pregnant women.

The NICE guideline further recommends monitoring serum creatinine regularly in all adults, children and young people with or at risk of acute kidney injury. The guideline development group did not wish to define 'regularly' because this would vary according to clinical need, but recognised that daily measurement was typical while in hospital.

An **AKI algorithm** to help with detection and diagnosis of the condition has been endorsed by NHS England[18]. In some hospitals the algorithm has been integrated into Laboratory Information Management Systems (LIMS) to help identify potential cases of acute kidney injury from laboratory data in real time.

The **KDIGO Clinical Practice Guideline for Acute Kidney Injury**[19] highlights the importance of screening patients who have had an exposure that may cause acute kidney injury (such as sepsis or trauma) and that high-risk patients should continue to be monitored until risk subsides. The guideline states that intervals of checking serum creatinine is a matter of clinical judgement, but suggest as a general rule that high risk in-patients should have serum creatinine measured at least daily and more frequently after an exposure. Critically ill patients should also have urine output monitoring.

For adults who are at risk of acute kidney injury, the NICE AKI guideline[16] also recommends that systems are in place to recognise and respond to oliguria (urine output less than 0.5 ml/kg/hour).

For children and young people who are at risk of acute kidney injury, the guideline recommends:

- measure urine output
- record weight twice daily to determine fluid balance

- measure urea, creatinine and electrolytes
- think about measuring lactate, blood glucose and blood gases.

Further detail on these recommendations, and further recommendations on the ongoing assessment of the condition of patients in hospital, can be found in section 1.2 of the NICE clinical guideline on AKI.[16]

The NICE guideline recommends diagnosing acute kidney injury in line with the RIFLE[13] (or paediatric-modified RIFLE – pRIFLE),[20] AKIN[14] or KDIGO[15] definitions, by using any of the following criteria:

- a rise in serum creatinine of 26 micromol/litre or greater within 48 hours
- a 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days
- a fall in urine output to less than 0.5 ml/kg/hour for more than 6 hours in adults and more than 8 hours in children and young people
- a 25% or greater fall in eGFR in children and young people within the past 7 days.

There are no direct therapies for treating acute kidney injury. Care focuses on optimising hemodynamics and fluid status, avoiding nephrotoxic treatments, and carrying out investigations to identity and resolve the underlying cause as quickly as possible. In general, the goal of care is to prevent any further kidney injury and stop worsening of the underlying illness; in particular, to prevent mortality or renal progression to a stage where renal replacement therapy is needed.

The **NICE clinical guideline on AKI**[16] highlights the importance of identifying the cause, or causes, of acute kidney injury and has recommendations on the use of urinalysis and ultrasound for this purpose.

The **KDIGO Clinical Practice Guideline for Acute Kidney Injury**[19] also recommends prompt evaluation of people with acute kidney injury to determine the cause. Identifying possible reversible causes of the condition is highlighted as important to reduce severity of the condition.

The NICE clinical guideline on AKI[16] has recommendations on managing acute kidney injury (section 1.5); covering removing urological obstruction, pharmacological management, renal replacement therapy and referral to nephrology services. **The KDIGO Clinical Practice Guideline for Acute Kidney Injury**[19] recommends staging severity of acute kidney injury with serum creatinine and urine output, and to manage the condition according to stage and cause. General management principles for people at high risk of acute kidney injury (or with the condition) are to:

- discontinue nephrotoxic agents if possible,
- monitor volume status and perfusion pressure,
- consider functional haemodynamic monitoring,
- monitor serum creatinine and urine output,
- avoid hyperglycaemia,
- consider alternatives to radiocontrast procedures.

Further actions should only be considered at higher stages of acute kidney injury, such as renal replacement therapy. Dosages of drugs may also need to be adapted because of reduced kidney function. The KDIGO guideline also has more detailed guidance on the prevention and treatment of acute kidney injury (section 3). This includes haemodynamic monitoring and support, glycemic control and nutritional support, the use of diuretics and vasodilator therapy.

In UK clinical practice the NephroCheck test and NGAL assays are likely to be used for the assessment of AKI in people who are considered for admission to critical care rather than in patients already admitted to critical care. It is worth pointing out that the NephroCheck test, the ARCHITECT and Alinity Urine NGAL assays, the NGAL plasma test and the NGAL urine test would not replace serum creatinine and urine output monitoring but they would be used alongside current monitoring to facilitate earlier detection of kidney injury and prompt adoption of strategies to prevent further progression of kidney disease.

Chapter 3 Assessment of clinical effectiveness

Systematic review methods

Identification of studies

Comprehensive electronic searches were conducted to identify relevant reports of published studies. Highly sensitive search strategies were developed, to include index terms, free-text words, abbreviations and synonyms, to combine biomarkers and AKI. The electronic databases Ovid MEDLINE, Ovid EMBASE, Web of Science Core Collection, HTA Database, CINAHL and CENTRAL were searched, with no restriction on date or publication type. Full details of the search strategies are presented in Appendix 1. The searches were undertaken during the period of 17 May to 10 June 2019.

Additionally, we searched the following sources for ongoing or unpublished studies: ClinicalTrials.gov (www.clinicaltrials.gov/), WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch) and WHO Global Index Medicus (www.who.int/library/about/The Global Index Medicus/en/). Furthermore, websites of relevant professional organisations and health technology agencies, as well as appropriate clinical experts, were consulted to obtain any additional potentially relevant reports. The reference lists of all included studies were perused to identify further potentially relevant studies. We also considered evidence provided by the manufacturers of the biomarkers included in this assessment (Astute Medical, Abbott and BioPorto Diagnostics).

Inclusion and exclusion criteria

Inclusion and exclusion criteria for each of the clinical effectiveness questions considered in this assessment are summarised in Table 2 below. Only studies that fulfilled these criteria were deemed suitable for inclusion.

Table 2 Eligibility criteria for the systematic review

Research question	**1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?**	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**
Population and setting	Critically ill patients (adults and children) at risk of AKI in an unselected hospitalised population (medical or surgical hospital admissions) in the following settings: • general hospital • emergency department • post-surgery or post-operative care • intensive or critical care, e.g. ICU (intensive care unit), CCU (critical care unit), ITU (intensive treatment unit), and paediatric intensive care unit (PICU) Patients who had established AKI before being admitted to intensive or critical care and those who were managed in the community setting were excluded. While the eligible patient population is an unselected critically ill population considered for admission to critical care, the following	Critically ill patients (adults and children) at risk of AKI in an unselected hospitalised population (medical or surgical hospital admissions) in the following settings: • general hospital • emergency department • post-surgery or post-operative care • intensive or critical care, e.g. ICU (intensive care unit), CCU (critical care unit), ITU (intensive treatment unit), and paediatric intensive care unit (PICU) Patients who had established AKI before being admitted to intensive or critical care and those who were managed in the community setting were excluded. While the eligible patient population is an unselected critically ill population considered for admission to critical care, the following	Critically ill patients (adults and children) at risk of AKI in an unselected hospitalised population (medical or surgical hospital admissions) in the following settings: • general hospital • emergency department • post-surgery or post-operative care • intensive or critical care, e.g. ICU (intensive care unit), CCU (critical care unit), ITU (intensive treatment unit), and paediatric intensive care unit (PICU) Patients who had established AKI before being admitted to intensive or critical care and those who were managed in the community setting were excluded. While the eligible patient population is an unselected critically ill population considered for admission to critical care, the following subgroups

Research question	1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?	2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?	3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?
	subgroups were identified to be particularly at risk of developing AKI: • People undergoing major cardiac or cardiovascular surgery • People undergoing major non-cardiac or non-vascular surgery • People undergoing major trauma surgery • People undergoing solid organ transplant (except kidney) • People undergoing hip replacement • People with sepsis • People with chronic kidney disease (CKD) • People with chronic liver disease • People with a serious (non-surgical) acute cardiac event or emergency, e.g. myocardial infarction Exclusion:	subgroups were identified to be particularly at risk of developing AKI: • People undergoing major cardiac or cardiovascular surgery • People undergoing major non-cardiac or non-vascular surgery • People undergoing major trauma surgery • People undergoing solid organ transplant (except kidney) • People undergoing hip replacement • People with sepsis • People with chronic kidney disease (CKD) • People with chronic liver disease • People with a serious (non-surgical) acute cardiac event or emergency, e.g. myocardial infarction Exclusion:	were identified to be particularly at risk of developing AKI: • People undergoing major cardiac or cardiovascular surgery • People undergoing major non-cardiac or non-vascular surgery • People undergoing major trauma surgery • People undergoing solid organ transplant (except kidney) • People undergoing hip replacement • People with sepsis • People with chronic kidney disease (CKD) • People with chronic liver disease • People with a serious (non-surgical) acute cardiac event or emergency, e.g. myocardial infarction Exclusion:

Research question	**1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?**	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**
	• People with other clinical conditions or illnesses. • People assessed immediately after a kidney transplant (within 365 days of index test). • Preterm infants and low birth weight babies	• People with other clinical conditions or illnesses. • People assessed immediately after a kidney transplant (within 365 days of index test). • Preterm infants and low birth weight babies	• People with other clinical conditions or illnesses. • People assessed immediately after a kidney transplant (within 365 days of index test). • Preterm infants and low birth weight babies
Biomarkers under investigation	• the NephoCheck test (Astute Medical) • the ARCHITECT and Alinity Urine NGAL assays (Abbott) • the BioPorto NGAL urine test (BioPorto Diagnostics) • the BioPorto NGAL plasma test (BioPorto Diagnostics) All used in conjunction with existing care The primary timepoint for biomarker measurement was immediately after surgery or on admission to critical or intensive care. When multiple measurements were reported,	• the NephoCheck test (Astute Medical) • the ARCHITECT and Alinity Urine NGAL assays (Abbott) • the BioPorto NGAL urine test (BioPorto Diagnostics) • the BioPorto NGAL plasma test (BioPorto Diagnostics) All used in conjunction with existing care The primary timepoint for biomarker measurement was immediately after surgery or on admission to critical or intensive care. When multiple measurements were reported, we	AKI care initiated according to the results of the biomarkers under investigation (the NephoCheck test, ARCHITECT and Alinity Urine NGAL assays, BioPorto NGAL urine test, BioPorto NGAL plasma test).

Research question	**1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?**	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**
	we selected the time closest to the primary timepoint. Exclusion • Solid tissue (not fluid) biomarkers or imaging modalities for detection of AKI • Biomarkers that used different assays than those listed above or did not specify the details of the assay	selected the time closest to the primary timepoint. Exclusion • Solid tissue (not fluid) biomarkers or imaging modalities for detection of AKI • Biomarkers that used different assays than those listed above or did not specify the details of the assay	
Reference standard/ Comparator	At present, there is no universally accepted reference standard for the diagnosis of AKI. The current methods for detecting or predicting AKI are in line with the RIFLE (or paediatric-modified RIFLE), AKIN and KDIGO classification systems, which are based on the assessment of serum creatinine levels and urine output alongside clinical judgement (see NICE Clinical Guidance 169	Existing clinical criteria for the monitoring of serum creatinine and urine output used in conjunction with clinical judgement (reference standard)	AKI care initiated according to standard clinical practice (existing clinical criteria without biomarkers).

Research question	**1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?**	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**
	on prevention detection and management of AKI).		
Outcomes	Detection of AKI (using measures of accuracy – i.e., sensitivity and specificity)	• Mortality • Need for long-term renal replacement therapy (RRT) • Chronic kidney disease (CKD) >90 days post-AKI At abstract screening, studies that did not report any of the above selected outcomes were excluded.	Clinical outcomes: • Mortality • AKI-associated morbidity (e.g., chronic kidney disease/end stage renal disease, other organ failure) Patient-reported outcome: • Health-related quality of life Intermediate outcomes may include: • Incidence of AKI (and severity/stage of condition) • Incidence/duration of acute renal replacement therapy within 7 days • Incidence of chronic kidney disease-related renal replacement therapy post AKI

Research question	**1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?**	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**
			• Length of stay in critical/intensive care • Length of stay in hospital • Length of AKI episode • Incidence of hospital readmission post-discharge • Impact of test result on clinical decision making • Impact on steady state estimated glomerular filtration rate at 90 days • Time to test results • Equivalence of biomarkers (e.g., the NGAL assays)
Study design	• Any cross-sectional study which investigates the diagnostic accuracy of a single biomarker (NephroCheck test or NGAL test) against the reference standard in the same study population • Any fully paired direct comparison (observational or randomised direct comparison) in which one of the	Prospective studies reporting: • prognostic accuracy for the specified outcomes (e.g. sensitivity, specificity, ROC curve, AUC) • sufficient information to complete a two-by-two contingency table for the specified outcomes (i.e. true positives, false positives, negatives and true negatives); as a minimum, the number of disease	• Randomised controlled trials • Prospective cohort studies with a concurrent comparison group Exclusion: • Studies with <100 participants • Pilot studies or studies of preliminary results only

Research question	1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?	2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?	3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?
	biomarkers under investigation (NephroCheck test or NGAL test) is compared with another biomarker in the same study population against the reference standard Exclusion: • Studies with <100 participants • Pilot studies or studies of preliminary results only • Case reports • Conference abstracts or proceedings • Studies published in language other than English • Studies with insufficient information to complete a two-by-two contingency table	positives (number of participants with AKI) and disease negatives (number without AKI) • a statistical prediction model for the specified outcomes Exclusion: • Studies with <100 participants • Pilot studies or studies of preliminary results only • Case reports • Conference abstracts or proceedings • Studies published in language other than English	• Case reports • Conference abstracts or proceedings • Studies published in language other than English

Study selection and data extraction

A screening tool was developed to assist study selection and data extraction (Appendix 2). One reviewer (CR) screened the titles and abstracts identified by the search strategies for inclusion or exclusion. A second reviewer (MI) double-checked all non-selected citations. As many relevant information was not available from the titles or abstracts (e.g., information about the immunoassay used and type of analyses) of the reports identified by the literature searches, our selection approach was over-inclusive. Full-text copies of all potentially relevant reports were retrieved and assessed for inclusion by one reviewer (MAM, MI or CR). A second reviewer (MAM, MI or CR) double checked 20% of the reports. Any disagreement was resolved by discussion or referred to a third reviewer (MB).

One reviewer (MAM, MB, MI, AP or CR) extracted data from each eligible study using a form developed and piloted for the purpose of this assessment. Where multiple publications of the same cohort of participants were identified, the publication with the most complete or suitable data set was considered as the primary source of information. Any uncertainty related to the data extraction process was discussed among reviewers and resolved by consensus.

From each study, data were extracted as follows:

1. Characteristics of studies: first author, year of publication, study centre, country, inclusion and exclusion criteria, method of participant enrolment.
2. Characteristics of study participants: age, gender, target condition, setting, number of participants enrolled, number of participants analysed, number excluded from analysis, main reasons for exclusion.
3. Characteristics of the biomarkers (e.g., manufacturer, detection method, threshold, timing of the measurement).
4. Characteristics of the reference standard (i.e., creatinine and urine output criteria for AKI).
5. Outcome data:
    - Data on the diagnostic performance of the biomarkers for detection of AKI (absolute number of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) cases; sensitivity and specificity values; area under the receiver-operating characteristic curve - AUC).

- Data on the prediction of development of AKI, worsening of AKI, mortality, renal replacement therapy and CKD as provided by the study authors (e.g., AUC values, odds ratio or hazard ratio, length of follow up).
- Data on the clinical utility of the biomarkers (impact of the use of the biomarkers on clinical outcomes) as reported by study authors (e.g., number of events and number of participants for each relevant binary outcome; mean, standard deviation and number of participants for each relevant continuous outcome).

Assessment of risk of bias

Validated tools were used to assess the risk of bias of the included studies according to their study design. We used the QUADAS-2 tool[21] to assess the risk of bias of studies assessing the diagnostic and prognostic accuracy of the biomarkers under investigation. The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of 'low', 'high' or 'unclear' risk of bias, and the first three in terms of concerns regarding 'low', 'high' or 'unclear' applicability.

We used the Prediction model Risk Of Bias ASsessment Tool (PROBAST)[22], which is structured into four domains (participants, predictors, outcome and analysis) to assess the risk of bias and applicability of prediction model studies.

A single reviewer (MAM, MB, MI, AP or CR) assessed the risk of bias of each of the included studies. Any uncertainty was discussed among reviewers and resolved by consensus.

No other types of study design were identified.

Data synthesis and analysis

For each assay, for each study we calculated sensitivity, specificity and prevalence values from the reported numbers of TP, FP, FN and TN cases. If studies did not provide 2x2 data, these were derived from the sensitivity and specificity estimates,

where given. We entered diagnostic data into Review Manager software (RevMan version 5.3, Nordic Cochrane Centre, Copenhagen), [23] to produce forest plots of sensitivity and specificity estimates together with their 95% confidence intervals (CIs).

Where appropriate we performed meta-analysis of each pair of sensitivity and specificity estimates from each included study for each relevant assay. Since reported threshold levels for a positive test differed across studies, we conducted random effects meta-analyses using the Hierarchical Summary ROC (HSROC) model[24, 25] implemented in STATA® (METANDI command)[26] to estimate summary values for sensitivity and specificity. The model takes into account both these measures of accuracy and their correlation, assumes that accuracy and thresholds vary between studies and incorporates both within- and between-studies variability. We constructed a summary ROC using the HSROC model, produced sensitivity and specificity summary estimates and hence a summary operating point, and calculated the 95% confidence and prediction regions. In accordance with the STATA requirements, we performed meta-analyses when data from four or more studies were available. For studies that reported multiple thresholds, we selected only one threshold to be included in the analysis. We performed separate meta-analyses for each biomarker, clinical setting, mode of sampling (urine, plasma) and type of patient population (adults, children). To inform the economic model, we also performed separate meta-analyses for each biomarker across all clinical settings.

For each biomarker, heterogeneity was assessed by visual inspection of the forest plots of sensitivity and specificity estimates and of the size of the prediction region in the HSROC plots.

When possible, we performed meta-analyses of AUC values using a random-effects model to measure the performance of each biomarker for the prediction of each relevant outcome (i.e., AKI, mortality, RRT and CKD). We assessed the proportion of between-study variation in the AUC-ROC due to heterogeneity rather than sample error using the prediction interval. We considered an AUC >0.70 as indicative of a useful risk predictor.

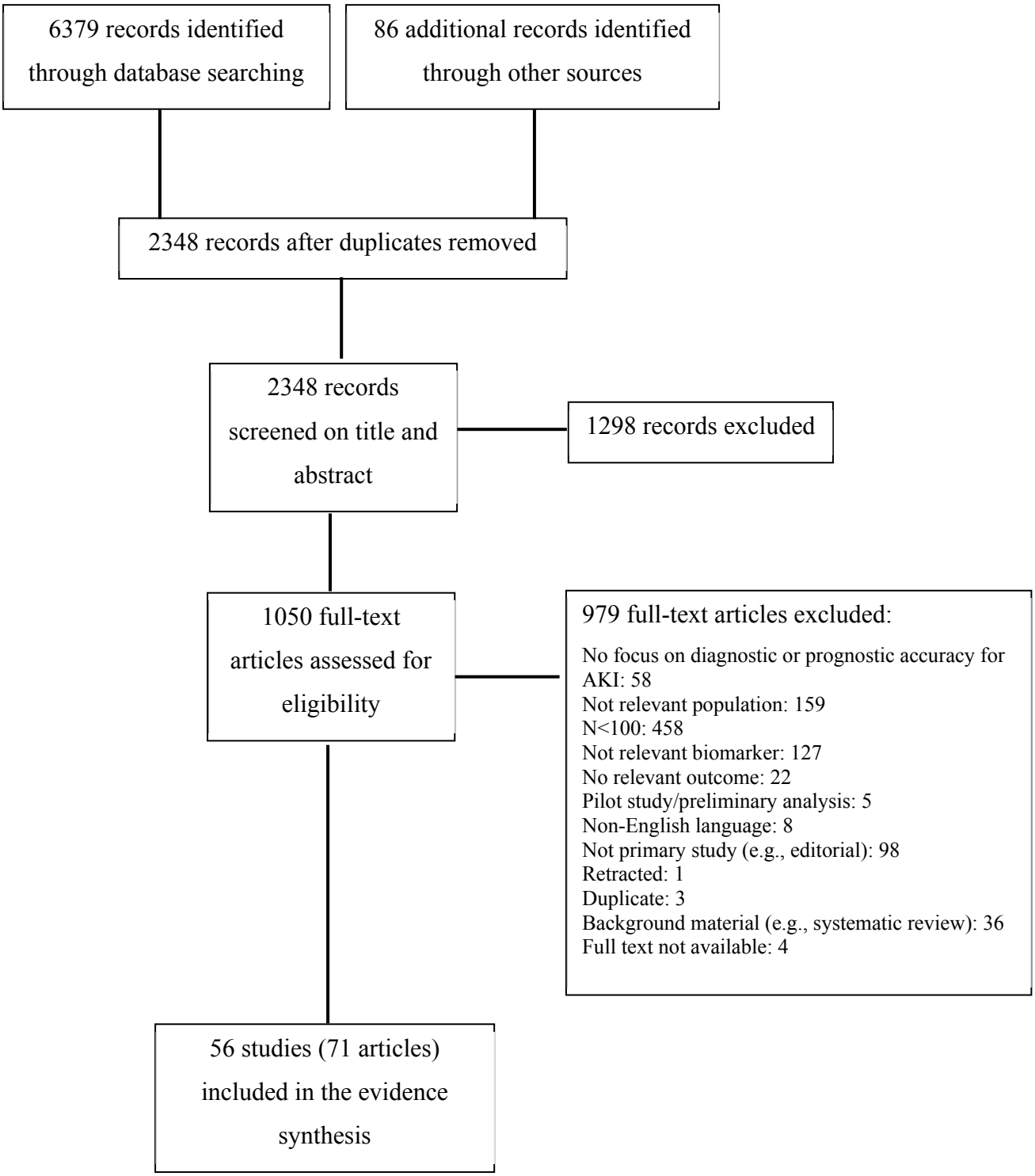
STATA® software version 15.0 (StataCorp LP, College Station, TX, USA)[27] was used for all statistical analyses. Graphs were made using either STATA or Review Manager software version 5.3 (Nordic Cochrane Centre, Copenhagen).[23]

Results of the assessment of clinical effectiveness

Literature searches results

The literature searches identified 6379 records and 86 additional records were identified in either trial registers (i.e., EU Clinical Trials Register, International Clinical Trials Registry Platform, Clinical Trials.gov) and other literature collections (i.e., HTA Database, WHO Global Index Medicus) for a total of 6465 retrieved records. After de-duplication, 2348 records were screened for relevance. Of these, 1050 were considered potentially relevant and selected for full text assessment. Four articles could not be obtained. Of the 1046 records retrieved and assessed in-depth, 71 met our inclusion criteria. After excluding secondary or multiple publications, we selected 56 studies for inclusion in the systematic review of effectiveness. Figure 1 (PRISMA diagram) shows the flow of studies through the selection process. The bibliographic details of the studies retrieved for full-text assessment and subsequently excluded together with the main reasons for their exclusion are presented in Appendix 7.

Figure 1 PRISMA flow diagram of selected studies



Overview of included studies

General characteristics of the 56 included studies and their associated references are provided in Table 3 for the adult population and in Table 4 for the child population. The majority of studies were cohort studies. In 46 studies data were collected prospectively, in one study data were collected prospectively but analysed retrospectively, in one study data were collected retrospectively, and in eight studies information on data collection was unclear. Fifty-three studies provided suitable data on the use of the biomarkers for detection or prediction of AKI in critically ill patients admitted to hospital, 16 studies provided information on prediction of mortality in critically ill patients at risk of AKI, and eight on prediction of RRT. No studies provided suitable data for prediction of CKD.

No randomised controlled trials (RCTs) or controlled clinical trials (CCTs) were identified; no studies provided data on the incremental value of the use of the biomarkers compared with standard clinical care.

Of the 56 included studies, 36 involved a single centre and 13 multiple centres. Seven studies did not provide this information. Twenty seven studies were conducted in Europe (4 in the UK, 6 in Germany, 3 in Italy, 3 in Spain, 2 in France, 2 in Greece, 2 in Denmark, 1 in the Netherlands, 1 in Belgium, 1 in Finland, 1 in Norway, and 1 in Switzerland); 15 in North America (12 in the US, 2 in the US and Canada, and 1 in Canada); 9 in Asia (3 in Japan, 3 in South Korea, 2 in Thailand, and 1 in China); and one in Australia. One study did not provide clear information on the geographical location.

NGAL was the most common studied biomarker (41/56 studies; 37 studies used urine NGAL assays and four plasma NGAL assays). NephroCheck was assessed in eight studies. Seven studies provided data on more than one assay (6 studies on urine NGAL and plasma NGAL assays and 1 study on NephroCheck, urine NGAL and plasma NGAL assays). Among the NGAL studies, 24 used the urine NGAL ARCHITECT platform, Abbott and 20 the urine NGAL BioPorto Diagnostics assay. All 11 plasma NGAL studies used the BioPorto Diagnostics assay. No studies used the NGAL Alinity platform, Abbott.

Of the 56 included studies, 46 enrolled only adults, 8 only children and 2 both adults and children. The total number of pariticipants was 17,967 of which 16,247 were adults (average age range from 49 to 77 years) and 1720 were children (average age range from 1 day to 5 years). Of the 46 studies that focused only on adults, 12 studies assessed patients after cardiac surgery, 4 studies patients requiring non-surgical cardiac care, 1 study patients undergoing major abdominal surgery, 1 study patients undergoing hepatobiliary surgery, 16 studies patients admitted to ICUs, 5 studies patients with liver disease (mainly cirrhosis), 2 studies patients with sepsis, 2 studies patients with CKD and 3 studies patients admitted to the emergency department. Of the eight studies that focused on children, 6 assessed children (including neonates) undergoing cardiac surgery and 2 children admitted to a paediatric ICU or neonatal ICU. The two studies that assessed both adults and children included patients undergoing cardiac surgery. For the purpose of the clinical and cost-effectiveness analyses the participants were grouped into three categories according to the clinical setting reported in the included studies: patients undergoing cardiac surgery, patients undergoing major non-cardiac surgery, and patients admitted to critical care (mixed patient population). The latter includes critically ill patients presenting to the emergency department and participants admitted to ICU or considered for critical care for various medical conditions or after surgery (but the studies did not specify which type of surgery or did not provide separate results for medical and surgical ICU particants).

Table 3 General characteristics of included studies - adult population

First author, year of publication, country, associated publications	Assay	Target population (setting)	Mean age (range or SD)	Sample size	AKI events	AKI Definition	Timeframe for AKI diagnosis
Cummings 2019[28], USA	NephroCheck, Astute Medical	Cardiac Surgery (Atorvastin for AKI cardiac surgery study)	67 (58, 75) *	400	14	KDIGO stage 2/3	Within 48 hours of surgery
Oezkur 2017[29], Germany	NephroCheck, Astute Medical	Cardiac Surgery (CABG, valve surgery or surgery of the thoracic aorta)	AKI 65 (59, 73) No AKI 71 (64,76) *	150	35	KDIGO	Within 48 hours of surgery
Beitland 2016[30], Norway	NephroCheck, Astute Medical	Critical care - mixed population (out-of-hospital cardiac arrest)	AKI 60 (13) No AKI 60 (14)	195	88	KDIGO	Within 3 days of admission
Bihorac 2014[31], USA	NephroCheck, Astute Medical	Critical care - mixed population (ICU/ITU)	63 (17)	408	71	KDIGO stage 2/3	Within 12 hours of admission
Di Leo 2018[32], Italy • Xie 2019[33]	NephroCheck, Astute Medical	Critical care - mixed population (ICU/ITU)	68 (51, 78) *	719	234	KDIGO	Within 24 hours of admission
Gayat 2018[34], France and Belgium	NephroCheck, Astute Medical	Critical care - mixed population (ICU, mainly sepsis)	65 (54, 75) *	200	Unclear	KDIGO	Within 48 hours of admission
Hoste 2014[35], USA	NephroCheck, Astute Medical	Critical care - mixed population (ICU/ITU)	AKI (stage 2/3) 64 (54, 75); No AKI (stage 0/1) 65 (54, 78) *	153	27	KDIGO stage 2/3	Within 12 hours of admission
Kashani 2013[36], North America (21 sites) and Europe (15 sites)	NephroCheck, Astute Medical	Critical care - mixed population (ICU/ITU)	64 (53, 73) *	728	101	KDIGO stage 2/3	Within 12 hours of biomarker measurement (biomarker

							measurement occurred within 18 hours of ICU admission)
Kimmel 2016[37], Germany • Kimmel 2016[38]	NephroCheck, Astute Medical uNGAL, BioPorto & pNGAL BioPorto	Critical care - mixed population (emergency department)	63 (14)	298	46	KDIGO (modified version) stage 2/3	Within 12 hours of sample collection
Parikh 2011[39], North America • Parikh 2013[40] • Koyner 2015[41] • Coca 2014[42] • Brown 2019[43] • Coca 2016[44] • Zhang 2015[45] • Greenberg 2018[46]	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (CABG or valve surgery)	71 (10)	1200	60	Acute dialysis or doubling of sCr (consistent with RIFLE stage 1 or AKIN stage 2)	AKI developed at a median of 3 days after surgery (IQR 2 to 4 days)
Albert 2018[47], Germany	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (open-heart surgery with CPB)	70 (61,77)	101	15	RIFLE	NR
Garcia-Alvarez 2015[48], Spain	uNGAL, ARCHITECT, Abbott	Cardiac Surgery	AKI 74 (68, 80); No AKI 69 (59, 76) *	288	104	sCr ≥200% from baseline or eGFR <50% from baseline	Within 7 days of surgery
Liebetrau 2013[49], Germany	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (CABG and/or valve replacement with the use of extracorporeal circulation)	AKI 74 (8) No AKI 68 (11)	141	47	KDIGO stage 2/3	Within 4 days of surgery

Thanakitcharu 2014[50], Thailand	uNGAL, ARCHITECT, Abbott	Cardiac Surgery	51 (15.6)	130	46	Increase in sCr ≥0.3mg/dL within 48 h	Within 48 hours of surgery
Cullen 2014[51], UK	uNGAL, ARCHITECT, Abbott	Non-cardiac surgery (major abdominal surgery)	68 (11)	109	16	AKIN	NR
Asada 2016[52], Japan	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (ICU/ITU)	AKI 62 (48, 74) No AKI 63 (51,73)	133	31	KDIGO	Within 7 days of admission
Collins 2012[53], USA	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (acute heart failure)	NR	399	20	Increase in sCr ≥0.3mg/dL or RIFLE	Worsening renal function at 12 to 24 hours and 72 to 96 hours
Dupont 2012[54], USA	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (acute decongestive heart failure)	NR	141	35	Increase in sCr ≥0.3mg/dL	Within 48 hours of admission
Isshiki 2018[55], Japan	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (ICU/ITU)	62 (51,73) *	148	33	KDIGO	Within 7 days of admission
Kokkoris 2012[56], Greece	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (ICU/ITU)	AKI 63 (50, 81) No AKI 49 (35, 66) *	100	36	RIFLE	Within 7 days of admission
Martensson 2015[57], Australia	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (ICU/ITU)	Mild AKI 69 (59,74) Severe AKI 68 (54,76) No AKI 62 (48,72) *	102	28	RIFLE	NR
Nickolas 2012[58], USA and Germany	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (emergency department)	64 (19)	1635	96	RIFLE	Within 24 hours of admission

Park 2017[59], USA	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (CKD)	59 (11)	2466	NR	Unclear	NR
Pipili 2014[60], Greece	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (mechanically ventilated patients admitted to the ICU)	64 (18)	106	44	RIFLE	NR
Treeprasertsuk 2015[61], Thailand	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (cirrhosis)	57 (15)	121	35	AKIN	Within 24 hours of admission
Haase 2014[62], Germany • Albert 2018[47]	uNGAL, ARCHITECT, Abbott & pNGAL BioPorto	Cardiac Surgery (open-heart surgery with CPB)	72 (65,77)	100	23	RIFLE	NR
Schley 2015[63], Germany	uNGAL, BioPorto & pNGAL BioPorto	Cardiac Surgery	70 (10)	110	37	AKIN	Within 72 hours of surgery
Jaques 2019[64], Switzerland	uNGAL, BioPorto & pNGAL BioPorto	Critical care - mixed population (cirrhosis)	58 (10)	105	55	AKIN	Within 7 days of admission
De Loor 2017[65], Belgium	uNGAL, BioPorto	Cardiac Surgery (CPB)	69 (61, 76) *	203	95	KDIGO	NR
Tidbury 2019[66], UK	uNGAL, BioPorto	Cardiac Surgery	AKI 73 (54-87); No AKI 75 (59-85) **	125	54	RIFLE	NR
Yang 2017[67], China	uNGAL, BioPorto	Cardiac Surgery (Atorvastin for AKI cardiac surgery study)	46 (15)	398	164	Acute dialysis or doubling of sCr consistent with KDIGO stage 2 and 3 criteria	NR

Cho 2014[68], South Korea	uNGAL, BioPorto	Non-cardiac surgery (hepatobiliary surgery)	57 (12)	131	10	AKIN	Within 5 days of admission
Ariza 2016[69], Europe	uNGAL, BioPorto	Critical care - mixed population (liver disease)	Acute-on-Chronic Liver Failure 57 (11) No Acute-on-Chronic Liver Failure 57 (12)	716	NR	NR	NR
Barreto 2014[70], Spain	uNGAL, BioPorto	Critical care - mixed population (cirrhosis)	58 (12)	132	65	AKIN	An increase in serum creatinine of $\geq$0.3 mg/dl or $\geq$50% over the baseline value obtained in the previous 48–72 hours.
Cho 2013[71], South Korea	uNGAL, BioPorto	Critical care - mixed population (ICU medical or surgical)	AKI 65.4 (14.8) No AKI 60.4 (17.4)	145	54	AKIN	Within 24 hours of surgery
Doi 2014[72], Japan • Doi 2011[73]	uNGAL, BioPorto	Critical care - mixed population (ICU/ITU)	AKI 66 (55,73) No AKI 65 (53, 74) *	339	131	RIFLE	NR
Hjortrup 2015[74], Denmark	uNGAL, BioPorto & pNGAL BioPorto	Critical care - mixed population (ICU/ITU sepsis)	66 (57, 75) *	151	91	KDIGO	Within 48 hours of admission
Matsa 2014[75], UK	uNGAL, BioPorto & pNGAL BioPorto	Critical care - mixed population (ICU/ITU medical or surgical)	60 (15)	194	59	RIFLE	Within 72 hours of admission

Nickolas 2008[76], USA	uNGAL, BioPorto	Critical care - mixed population (emergency department)	60 (18)	635	30	RIFLE	NR
Nisula 2015[77], Finland • Nisula 2014[78]	uNGAL, BioPorto	Critical care - mixed population (post-operative)	62 (50,73) *	855	379	KDIGO	NR
Smith 2013[79], UK	uNGAL, BioPorto	Critical care - mixed population (CKD)	69 (12)	158	40	KDIGO	NR
Tecson 2017[80], USA	uNGAL, BioPorto & pNGAL BioPorto	Critical care - mixed population (ICU/ITU)	AKI (stage2/3) 68 (56, 74); No AKI (stage 0/1) 63 (54,73) *	245	33	KDIGO stage 2/3	Within 8 days of admission
Verna 2012[81], USA	uNGAL, BioPorto	Critical care - mixed population (cirrhosis)	56 (49, 62)	118	52	Increase in sCr >1.5 and 0.3 mg/dL from baseline value	NR
Zelt 2018[82], USA	pNGAL, BioPorto	Cardiac Surgery (major elective cardiac surgery requiring CPB)	67 (61,73) *	178	35	AKIN	Within 48 hours of surgery
Itenov 2017[83], Denmark	pNGAL, BioPorto	Critical care - mixed population (ICU/ITU)	67 (60, 76) *	454	87	KDIGO	NR
Lee 2018[84], South Korea	pNGAL, BioPorto	Critical care - mixed population (comatose cardiac arrest survivors treated with therapeutic hypothermia)	59 (50, 71) *	279	111	KDIGO stage 3	Within 7 days of return of spontaneous circulation
Marino 2015[85], Italy	pNGAL, BioPorto	Critical care - mixed population (sepsis)	77 (72, 83) *	101	49	RIFLE	Within 7 days of admission

AKI= Acute Kidney Injury; NephC= NephroCheck test; uNGAL= urine NGAL, pNGAL= plasma NGAL; KDIGO=Kidney Disease: Improving Global Outcomes; AKIN=Acute Kidney Injury Network; RIFLE=Risk, Injury, Failure; Loss, End-Stage Renal Disease; sCr =Serum creatinine; * Median (IQR);

Table 4 General characteristics of included studies - child population

First author, year of publication, country, linked publications	Assay	Population (setting)	Mean age (range or SD)	Sample size	AKI events	AKI Definition	Timeframe for AKI diagnosis
Parikh 2011[86], North America • Zappitelli 2015[87]	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (congenital cardiac lesions)	4 years (5)	311	53	Acute dialysis, or doubling of sCr from baseline	During hospital stay
Bojan 2014[88], France	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (CPB for surgical correction or palliation of congenital heart lesions)	<1 year	100	NR	AKIN	NR
Bennett 2013[89], USA	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (CPB for surgical correction or palliation of congenital heart lesions)	4 years	196	99	50% or greater increase in sCr from baseline within 72 hours	NR
Cantinotti 2012[90], Italy	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (cardiac surgery for correction/ palliation of congenital heart defects)	6 months (1, 49)	135	52	pRIFLE	NR
Alcaraz 2014[91], Spain	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (cardiac surgery, mainly CPB, for congenital cardiac lesions)	25 months (6.0-72.0)**	106	36	pRIFLE	Early AKI defined as renal dysfunction in the first postoperative 72 hours. Late AKI defined as occurring after the 4th postoperative day

Seitz 2013[92], NR	uNGAL, ARCHITECT, Abbott	Cardiac Surgery (CPB for surgical correction of congenital heart disease)	0 years (0-8)*	139	76	pRIFLE	NR
Zwiers 2015[93], Netherlands	uNGAL, ARCHITECT, Abbott	Critical care - mixed population (ICU/ITU)	27 days (1, 85)*	100	35	RIFLE	Within 48 hours of admission
Dong 2017[94], USA	uNGAL, BioPorto	Cardiac Surgery	AKI 4 years (0.[illegible]2.5); No AKI 5 years (4.1-5.9)	150	50	KDIGO	Within 72 hours of surgery
Lagos-Arevalo 2015[95], Canada	uNGAL, BioPorto	Critical care - mixed population (ICU/ITU)	AKI 5 years (6) No AKI 4.0 years (5)	160	70	KDIGO	NR
Yang 2017[67], China	uNGAL, BioPorto	Cardiac Surgery	Children 22 months (31 - Adults 46 years (15)	Children 323; Adults 39	Children 126; Adults 164	Acute dialysis or doubling of sCr consistent with KDIGO stage 2 and 3 criteria	NR

AKI= Acute Kidney Injury; NephC= NephroCheck test; uNGAL= urine NGAL, pNGAL= plasma NGAL; KDIGO=Kidney Disease: Improving Global Outcomes; AKIN=Acute Kidney Injury Network; pRIFLE=paediatric modified Risk, Injury, Failure; Loss, End-Stage Renal Disease; sCr =Serum creatinine; * Median (IQR);

Study quality

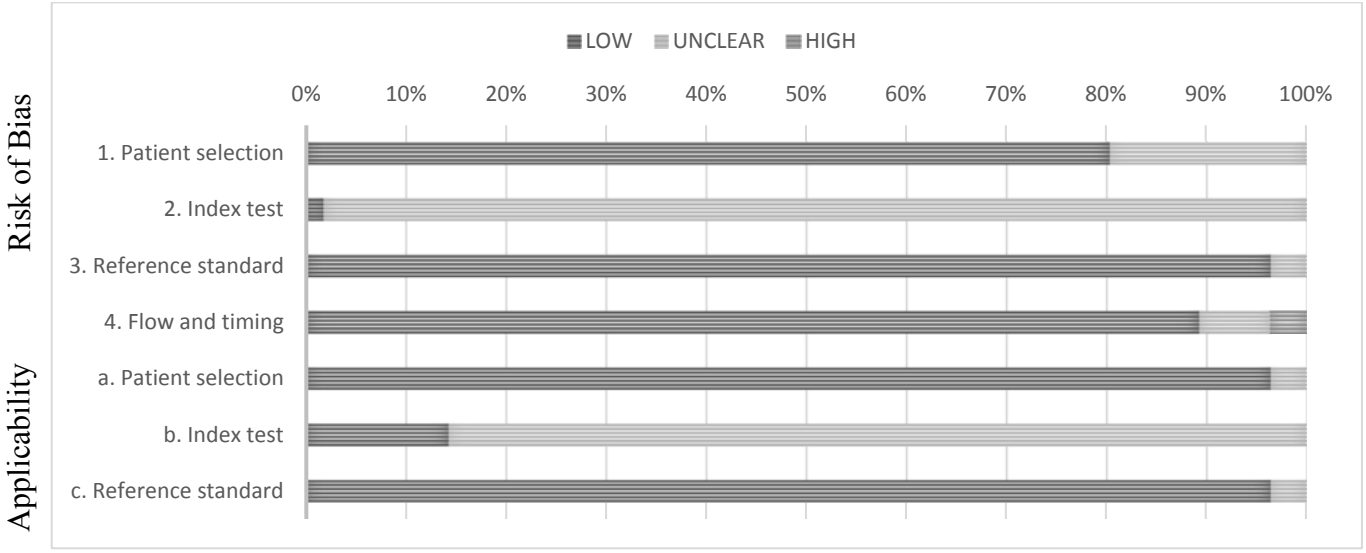
The risk of bias of studies assessing the accuracy of NephroCheck and NGAL assays in identifying people at risk of developing AKI was assessed using the QUADAS-2 tool. Results are summarised in Figure 2 below and in Table 42 in Appendix 10.

Eleven studies (20%) did not report sufficient information to determine whether a selection of patients could have introduced bias and these studies were assessed to be at unclear risk of bias.[52,51,34,62,74, 35,37,56, 84,57,96] The remaining studies were judged to be at low risk of bias for the patient selection domain.

The main potential source of bias across studies relates to blinding. Most studies (98%) were assessed at unclear risk of bias for the conduct and interpretation of the index test, either due to insufficient information or lack of clarity regarding whether the biomarkers results were interpreted without knowledge of the reference standard results (see Figure 2 below). The studies that used NephroCheck were judged at low risk of bias with regard to the interpretation of the test since all of them used a common threshold. However, for NGAL studies the threshold level was judged to be unclear as a common hreshold for NGAL has yet to be identified. While some studies alluded to the blinding of personnel performing the biomarker measurements to patients' clinical information, it was unclear whether the personnel were indeed blinded to sCr measurements (reference standard). With regard to whether the reference standard, its conduct or interpretation may have introduced bias, two studies (4%) were judged to be at unclear risk of bias because baseline sCr levels were determined by reviewing records of previous 12-month measurements.[56,58] The remaining studies (96%) were judged to be at low risk of bias for the reference standard domain.

Two studies (4%) were judged to be at high risk of bias in terms of the patient flow (e.g., attrition) because more than 50% of the participants were excluded from the analysis[64] or because the reporting of the patient selection and flow was poorly detailed.[52] Four studies (7%) were at unclear risk.[94,56,59,66] The remaining studies (89%) were considered to be at low risk of bias regarding the patient flow domain. Across studies there was not major concern that the patient population and the conduct and interpretation of reference standard were not applicable to the review

question. We observed an expected variation between studies in terms of characteristics of the index tests (biomarker assays) and clinical protocols. In particular, applicability of the index test to the review question was judged to be unclear in many studies mainly due to the variation with regard to the biomarker thresholds and timing of sample collections.



2 Risk of bias assessment of studies assessing the diagnostic performance of the biomarkers using the QUADAS-2 tool

The risk of bias of studies assessing the role of NephroCheck and NGAL assays for prediction of relevant clinical outcomes (worsening of AKI, mortality and RRT) was assessed using the PROBAST tool.[22] Results are summarised in Table 5 below.

Twelve prediction studies were assessed for risk of bias and applicability.[48,89,51,72,77,85,74,61,34,57,55,84] Three studies (25%) reported insufficient information to determine whether selection of patients could have introduced bias and these studies were judged to be at unclear risk of bias.[74,34,57] The remaining studies were judged to be at low risk of bias for this domain. No studies were judged to have made predictor assessments without the knowledge of outcome data and, therefore, the risk of bias for the predictors domain was judged to be unclear for all studies. The risk of bias in the outcome domain was unclear for all studies, mainly due to inadequate information to assess whether outcomes were determined without

knowledge of predictor information. The risk of bias for the analysis domain was unclear in 58% of studies and high in 42%.

The overall risk of bias was considered to be unclear for most studies (70%), mainly due to these studies being assessed as at high risk of bias in the analysis domain. The remaining studies were judged to be at unclear risk of bias.

Most studies were judged to be at low risk for applicability to the review question in each of the domain categories. Overall, applicability was judged to be at low risk of bias for 75% of the studies and at unclear risk for the remaining studies. In general, there was no major concern that the studies were not applicable to the research questions of this assessment. Summaries of the results are presented in Figures 3 and 4. The individual study level results are summarized in Appendix 8.

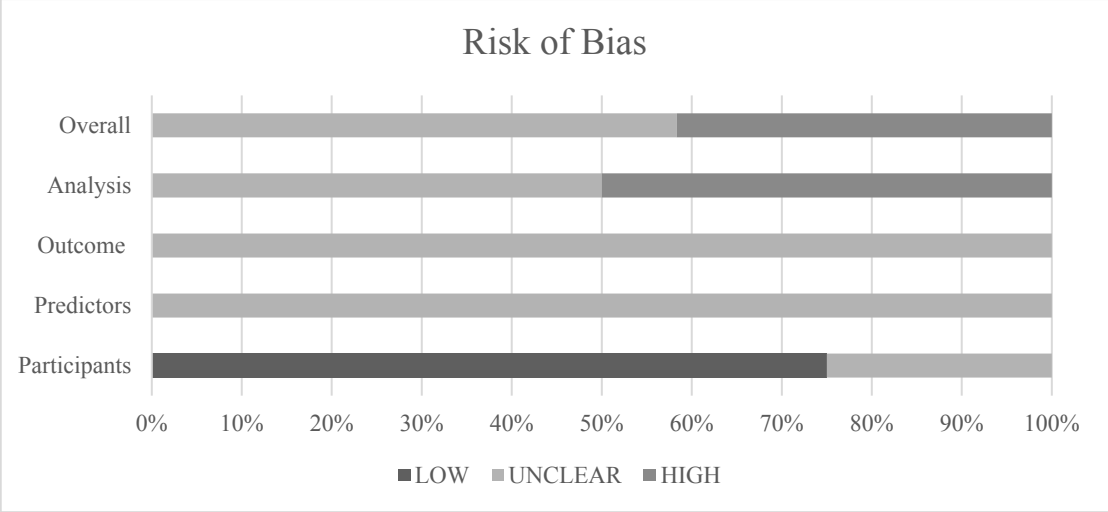


Figure 3 Risk of bias assessment of studies that assessed the role of biomarkers for prediction of relevant clinical outcomes using the PROBAST tool

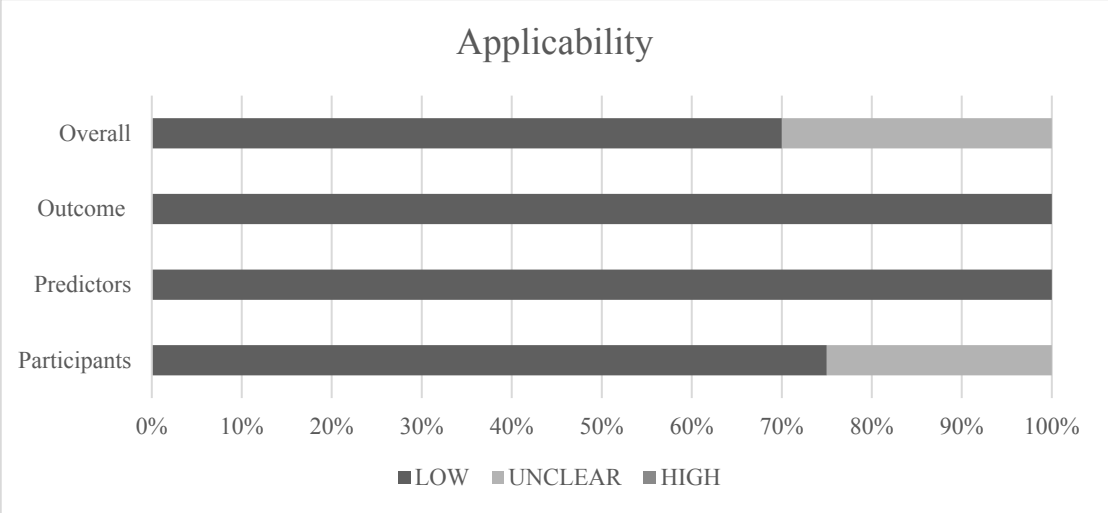


Figure 4 Applicability of prediction studies to the research questions using the PROBAST tool

Accuracy of the NephroCheck and NGAL assays for identifying AKI

We were able to extract or derive 2x2 data from 33 studies that assessed the performance of NephroCheck, urine NGAL ARCHITECT and urine and plasma BioPorto NGAL assays for identifying AKI in critically ill hospitalised patients. These studies are summarised below.

The summary estimates of accuracy and HSROC are provided separately for each assay, clinical setting, mode of sampling and type of patient population (adults,

children). We also present analyses across all settings. Studies that could not be combined in a meta-analysis (less than four) are summarised narratively.

NephroCheck urine assay (Astute Medical) - adult population

A summary of the diagnostic data for the seven studies that assessed the use of NephroCheck (Astute Medical) for detection of AKI in adults is presented in Table 5.

Table 5 Summary of diagnostic data for NephroCheck for detection of AKI - adult population

STUDY ID	Target Population (setting)	Assay	Timing of Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Oezkur 2017[29]	Cardiac Surgery	NephroCheck, Astute Medical	ICU-admission	0.3 ng/mL^2/1000	0.60	0.88	NR	0.19
Cummings 2019[28]	Cardiac Surgery	NephroCheck, Astute Medical	ICU admission	0.3 ng/mL^2/1000	0.31 (0.[illegible], 0.[illegible]1)	0.78 (0.74, 0.82)	0.68 (0.54, 0.81)	0.035
Kashani 2013[36]	Critical care - mixed population (ICU/ITU)	NephroCheck, Astute Medical	ICU admission	0.3 ng/mL^2/1000	0.89	0.50	0.8	0.14
Bihorac 2014[31]	Critical care - mixed population (ICU/ITU)	NephroCheck, Astute Medical	Within 24 h of admission to ICU	0.3 ng/mL^2/1000	0.92 (0.85, 0.98)	0.46 (0.41, 0.52)	0.82 (0.76, 0.88)	0.17
Hoste 2014[35]	Critical care - mixed population (ICU/ITU)	NephroCheck, Astute Medical	ICU admission	0.3 ng/mL^2/1000	0.89	0.53	0.79 (0.69, 0.88)	0.18
Kimmel 2016[38]	Critical care - mixed population	NephroCheck, Astute Medical	Admission to the internal medicine service	Between 0.3 and 2.0 ng/mL^2/1000	0.76 (0.63, 0.87)	0.53 (0.48, 0.57)	0.74 (0.66, 0.81)	0.15
Di Leo 2018[32]	Critical care - mixed population (ICU/ITU)	NephroCheck, Astute Medical	ICU admission	0.3 ng/mL^2/1000	0.56	0.54	0.63	0.34

Cardiac surgery

Two studies, Cummings 2019[28] and Oezkur 2017,[29] assessed the use of NephroCheck for detection AKI in patients after cardiac surgery (total 584 patients). Both studies used the same cut off point (0.3 ng/mL^2/1000). The study by Cummings et al. assessed a total of 400 cardiac patients soon after ICU admission. The sensitivity and specificity values were 0.31 (95% CI 0.09 to 0.61) and 0.78 (95% CI 0.74 to 0.82), respectively. The study was in any other ways consistent with other cardiac surgey cohorts but showed a low prevalence of AKI (4%). Only 14 participants developed AKI KDIGO stage 2 and 3. The study by Oezkur et al. assessed 184 patients immediately after cardiac surgery. The reported sensitivity and specificity values were 0.60 (95% CI 0.36 to 0.81) and 0.89 (95% CI 0.80 to 0.95), respectively. The prevalence of AKI was 19%. Table 5 shows a summary of the diagnostic data for the two studies and Figure 5 the forest plots of sensitivity and specificity.

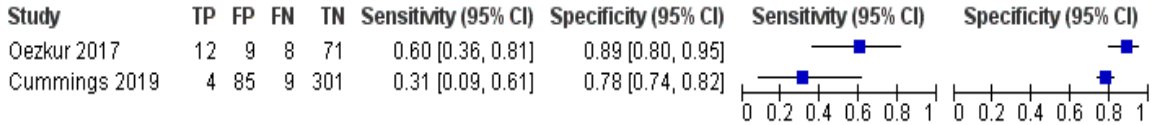


Figure 5 Forest plots of sensitivity and specificity for NephroCheck for detection of AKI in adults- cardiac surgery setting

No suitable NephroCheck data in other post-surgical settings (major non-cardiac surgery) were available from the included studies.

Critical care - mixed population

Six studies (2279 participants in total) assessed the use of NephroCheck for detection of AKI in hospitalised patients admitted to ICU or critical care for various clinical reasons. The cut off point used was consistent across studies (0.3 ng/mL^2/1000). Table 5 shows a summary of the diagnostic data for the six studies and Figure 6 the forest plots of sensitivity and specificity. Sensitivity values ranged from 0.64 to 0.92; specificity values form 0.46 to 0.56. The summary estimate of sensitivity was 0.83 (95% CI 0.72 to 0.91) and that of specificity 0.51 (95% CI 0.48 to 0.54). Figure 7 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions indicate a greater

degree of heterogeneity in sensitivity estimates than in specificity estimates between studies. Specificty estimates were low but reasonably homogeneous. It is worth noting that all the five studies were of moderate to small sample size (see Figure 6).

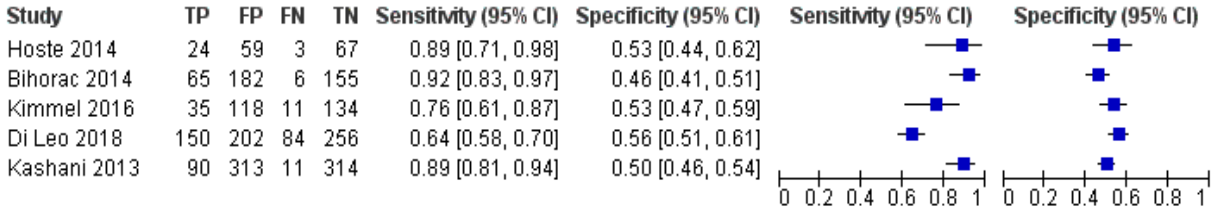


Figure 6 Forest plots of sensitivity and specificity for NephroCheck for detection of AKI in adults - critical care setting

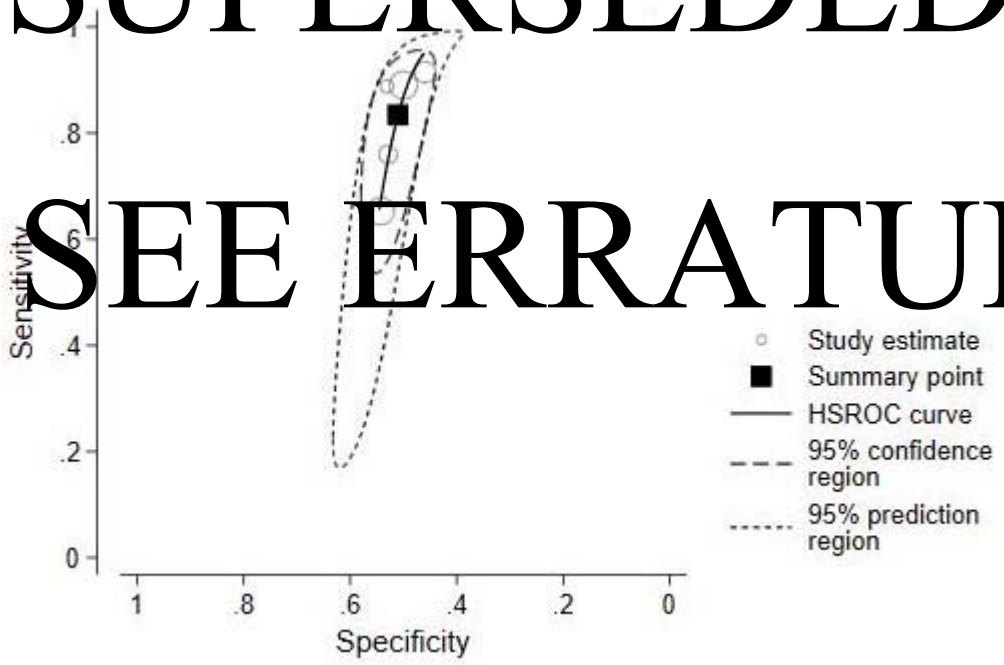


Figure 7 HSROC for NephroCheck studies - critical care setting

Figure 8 shows the forest plots of sensitivity and specificity estimates for all NephroCheck studies (2863 patients in total) across clinical settings. Sensitivity values ranged from 0.31 to 0.92 and specificity values from 0.46 to 0.89. Summary estimates for sensitivity and specificity were 0.75 (95% CI 0.58 to 0.87) and 0.61 (95% CI 0.49 to 0.72), respectively. Figure 9 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. The confidence

and prediction regions are large indicating considerable heterogeneity between studies. Across studies, estimates of specificity were generally low apart from two studies that showed higher estimates. Visual inspection of the forest and HSROC plots shows that the study by Cummings et al., is an outlier with a very different trend compared with the other studies (outlier).

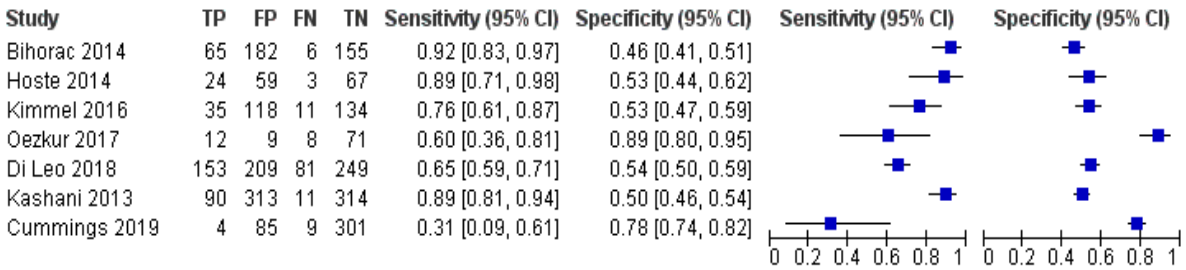


Figure 8 Forest plots of sensitivity and specificity for NephroCheck studies - all clinical settings

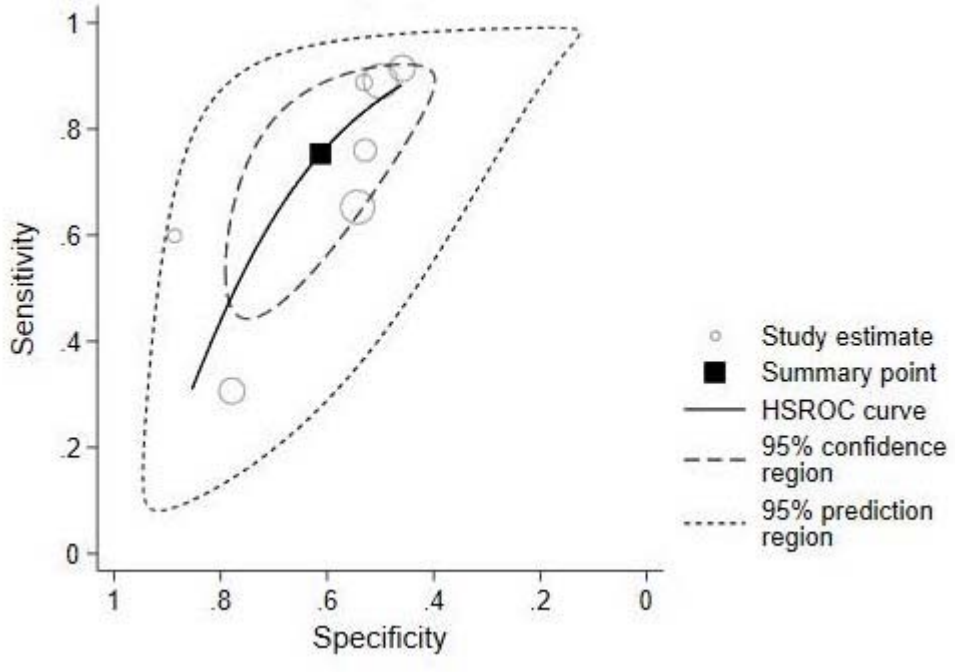


Figure 9 HSROC for NephroCheck studies - all clinical settings

There were no studies assessing the use of NephroCheck in children as this biomarker is recommended for adult use only (people ≥21 years).

Urine NGAL ARCHITECT assay (Abbott) - adult population

Cardiac surgery

Two studies, Parikh 2011[39] and Thanakitcharu 2014[50], provide test accuracy data on the use of uNGAL ARCHITECT for detection of AKI in patients who underwent cardiac surgery. The multicentre cohort study by Parikh et al. assessed a total of 1219 adults after cardiac surgery. The sensitivity and specificity values for the first urine sample collected soon after ICU admission were 0.46 (95% CI 0.33 to 0.59) and 0.81 (95% CI 0.79 to 0.83), respectively. The prevalence of AKI in the study was 5% similar to that observed earlier for the Cummings et al., study[28] that assessed the role of NephroCheck in 400 participants in the same clinical setting. The single centre study by Thanakitcharu et al. assessed 130 patients immediately after cardiac surgery. The sensitivity and specificity values for the urine sample collected immediately after surgery were 0.74 (95% CI 0.49 to 0.91) and 0.6 (95% CI 0.51 to 0.70), respectively. The prevalence of AKI in the study was 35%. Table 6 presents a summary of the diagnostic data for these two studies and Figure 10 shows the forest plot of sensitivity and specificity estimates.

Table 6 Summary of diagnostic accuracy data for urine NGAL ARCHITECT for detection of AKI in adults - the cardiac surgery setting

STUDY ID	Target population (setting)	Assay	Timing of Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Parikh 2011[39]	Cardiac Surgery	uNGAL, ARCHITECT, Abbott	ICU admission	>102 ng/mL	0.46	0.81	0.67	0.05
Thanakitcharu 2014[50]	Cardiac Surgery	uNGAL, ARCHITECT, Abbott	Immediately after surgery	>11.3 ng/mL	0.74	0.60	0.69 (0.52, 0.72)	0.35

Figure 10 Forest plots of sensitivity and specificity for urine NGAL ARCHITECT for detection of AKI in adults - cardiac surgery setting

No suitable urine NGAL ARCHITECT data in other post-surgical settings (major non-cardiac surgery) were available from the included studies.

Critical care - mixed population

Four studies (1998 patients in total) assessed the use of uNGAL ARCHITECT for detection of AKI in patients admitted to ICU or critical care for various clinical reasons. Cut off values varied across studies (see Table 7). In three studies, uNGAL levels were reported as ng/mL (per grams of urine) while in one study uNGAL levels were normalised by units of urine creatinine (per grams of creatinine). Prevalence of AKI ranged from 6% to 36% across studies. Table 7 shows a summary of the diagnostic data as reported by the six studies and Figure 11 the forest plots of sensitivity and specificity. Sensitivity values ranged from 0.63 to 0.78 and specificity values from 0.58 to 0.81. The summary estimate of sensitivity was 0.70 (95% CI 0.63 to 0.76) and that of specificity 0.72 (95% CI 0.63 to 0.80). Figure 12 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are very large indicating considerable heterogeneity in estimates of accuracy across studies, especially for specificity. The analysis appears to be dominated by the largest Nickolas et al.'s study,[58] which shows a small number of true positive cases and subsequently low sensitivity.

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Table 7 Summary of diagnostic data for urine NGAL ARCHITECT for AKI in the critical care setting (adult population)

STUDY ID	Target Population (setting)	Assay	Timing of Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Dupont 2012[54]	Critical care - mixed population (acute decongestive heart failure)	uNGAL, ARCHITECT, Abbott	48 h after admission	32 µg/g Cr	0.63	0.58	0.61	0.25
Kokkoris 2012[56]	Critical care - mixed population (ICU/ITU)	uNGAL, ARCHITECT, Abbott	ICU admission	58.5 ng/mL	0.78 (0.61, 0.90)	0.72 (0.59, 0.82)	0.74 (0.64, 0.82)	0.36
Nickolas 2012[58]	Critical care - mixed population (ICU/ITU)	uNGAL, ARCHITECT, Abbott	Admission to ED	104 ng/mL	0.68	0.81	0.81 (0.76, 0.86)	0.059
Treeprasertsuk 2015[61]	Critical care - mixed population (liver disease)	uNGAL, ARCHITECT, Abbott	Within 72 h after admission.	56 ng/mL	0.77	0.73	0.83 (0.76, 0.91)	0.29

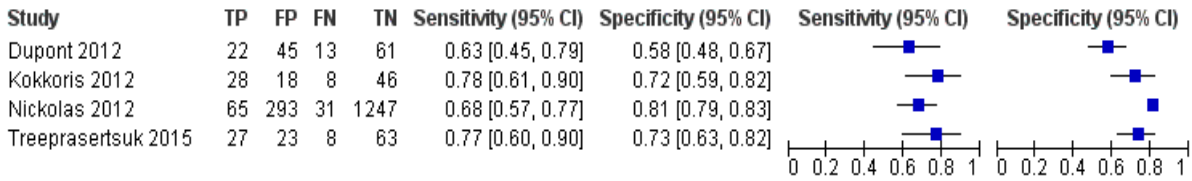


Figure 11 Forest plots of sensitivity and specificity for urine NGAL ARCHITECT for detection of AKI in adults - critical care setting

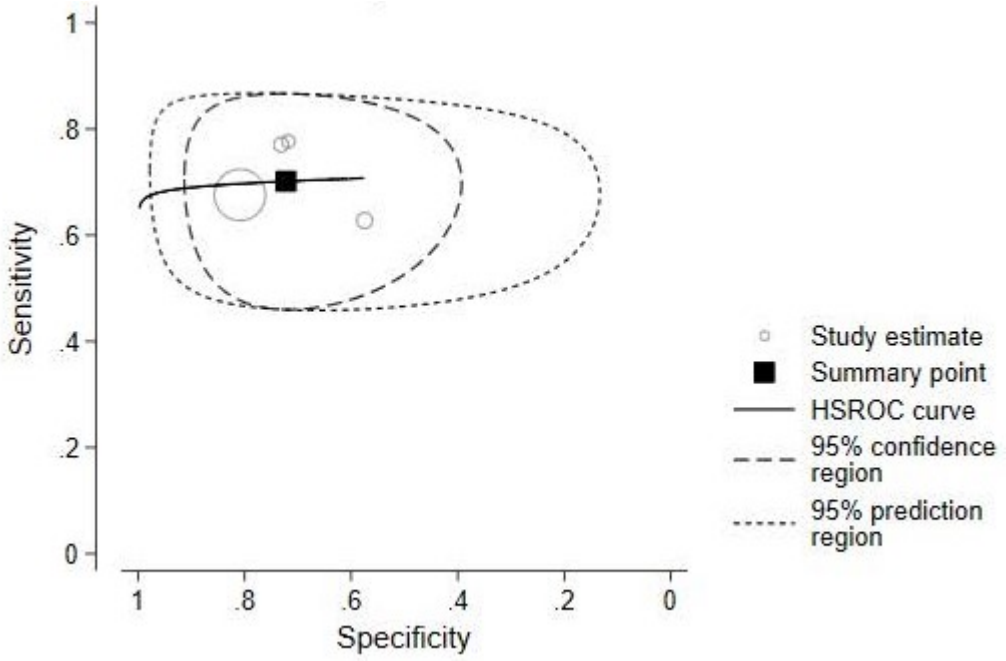


Figure 12 HSROC for urine NGAL ARCHITECT studies - clinical care setting (adult population)

Figure 13 shows the forest plots of sensitivity and specificity estimates for all uNGAL ARCHITECT studies (3347 patients in total) across all clinical settings. Sensitivity values ranged from 0.46 to 0.78 and specificity values from 0.58 to 0.81. Summary estimates for sensitivity and specificity were 0.67 (95% CI 0.58 to 0.76) and 0.72 (95% CI 0.64 to 0.79), respectively. Figure 14 shows HSROC with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are large indicating heterogeneity between studies.

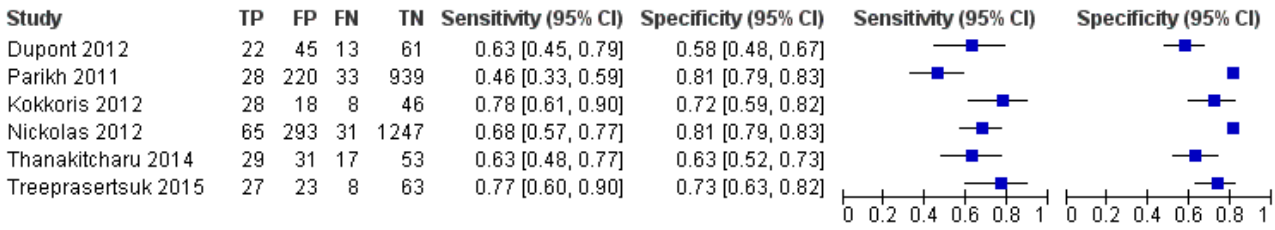


Figure 13 Forest plots of sensitivity and specificity for urine NGAL ARCHITECT for detection of AKI in adults across all clinical settings

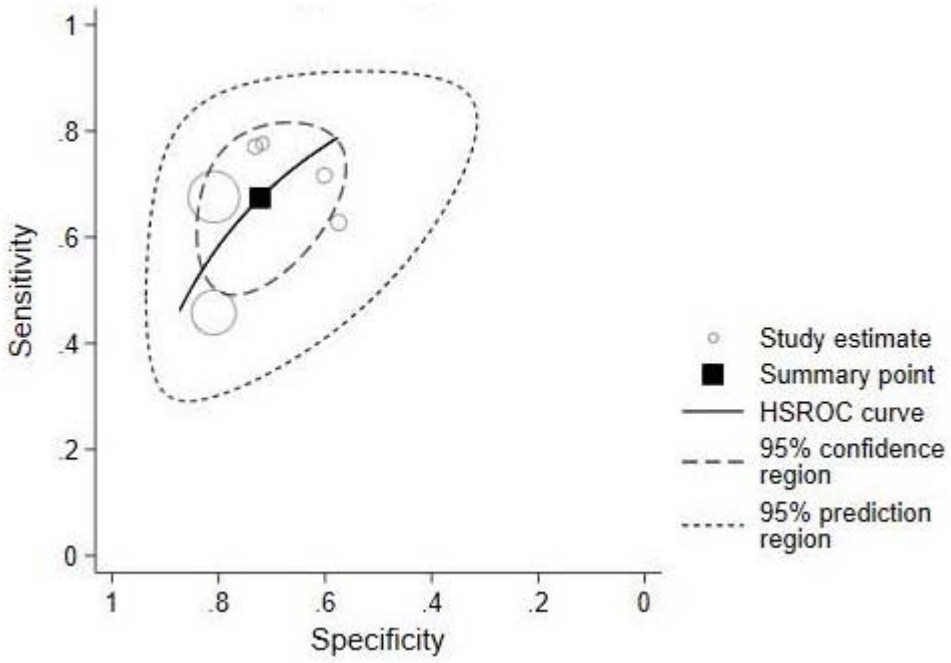


Figure 14 HSROC for urine NGAL ARCHITECT studies – all clinical settings (adult population)

Urine NGAL assay (BioPorto) - adult population

Cardiac surgery

One study, Yang 2017,[67] assessed the use of uNGAL (BioPorto) for detection of AKI in a total of 398 patients, who underwent cardiac surgery. uNGAL levels were normalised by units of urine creatinine (cut off 98 µg/g Cr). The sensitivity and specificity values for the urine sample collected 6 hours after surgery were 0.78 (95% CI 0.71 to 0.84) and 0.48 (95% CI 0.41 to 0.54), respectively. The prevalence of AKI in the study was 41%.

Non-cardiac surgery

One study, Cho 2014,[68] assessed the use of uNGAL (BioPorto) for detection of AKI in 131 patients undergoing hepatobiliary surgery. uNGAL cut off was 92.85 ng/mL. The sensitivity and specificity values for the urine sample collected just before surgery were 0.78 (95% CI 0.52 to 1.00) and 0.80 (95% CI 0.73 to 0.87), respectively. The prevalence of AKI in the study was 8%.

Critical care - mixed population

Six studies (1442 patients in total) assessed the use of uNGAL (BioPorto) for detection of AKI in patients admitted to ICU or critical care for various clinical reasons. Some studies reported absolute levels of uNGAL and others levels normalised to urine creatinine. The threshold varied across studies (see Table 9). Prevalence of AKI ranged from 5% to 49% across studies. Table 9 shows a summary of the diagnostic data for the six studies and Figure 15 the forest plots of sensitivity and specificity. Sensitivity values ranged from 0.58 to 0.90 and specificity values from 0.70 to 1.00. The summary estimate of sensitivity was 0.72 (95% CI 0.61 to 0.80) and that of specificity 0.87 (95% CI 0.66 to 0.96). Figure 16 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are large indicate heterogeneity between studies, especially for specificity.

Table 8 Summary of diagnostic data for urine NGAL (BioPorto) for AKI in the critical care setting (adult population)

STUDY ID	Target Population (setting)	Assay	Timing of Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Nickolas 2008[76]	Critical care - mixed population (ICU/ITU)	uNGAL, BioPorto	Admission to ED	130 µg/g Cr	0.90 (0.73, 0.98)	1.00 (0.99, 1.00)	0.95 (0.88, 1.00)	0.047
Cho 2013[71]	Critical care - mixed population (ICU/ITU)	uNGAL, BioPorto	ICU admission	NR	0.74	0.70	0.77 (0.69, 0.85)	0.37
Matsa 2014[75]	Critical care - mixed population (ICU/ITU)	uNGAL, BioPorto	ICU admission	350 ng/mL	0.58 (0.44, 0.70)	0.84 (0.75, 0.91)	0.79	0.38
Barreto 2014[70]	Critical care - mixed population (liver disease)	uNGAL, BioPorto	When the infection was detected	51 µg/g Cr	0.66	0.70	0.72 (0.64, 0.81)	0.49
Hjortrup 2015[74]	Critical care - mixed population (ICU/ITU)	uNGAL, BioPorto	ICU admission	582 ng/mL	0.75	0.77	0.71 (0.59, 0.82)	0.24
Tecson 2017[80]	Critical care - mixed population (ICU/ITU)	uNGAL, BioPorto	Within 48 hours of ICU admission	98 ng/mL	0.64 (0.45, 0.80)	0.81 (0.75, 0.86)	-	0.13

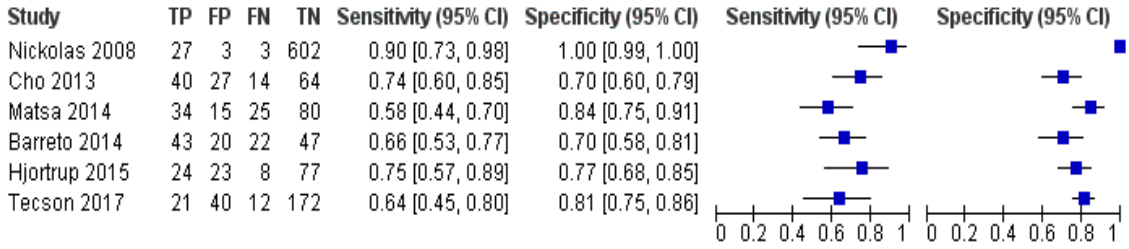


Figure 15 Forest plots of sensitivity and specificity for urine NGAL (BioPorto) for detection of AKI adults - critical care setting

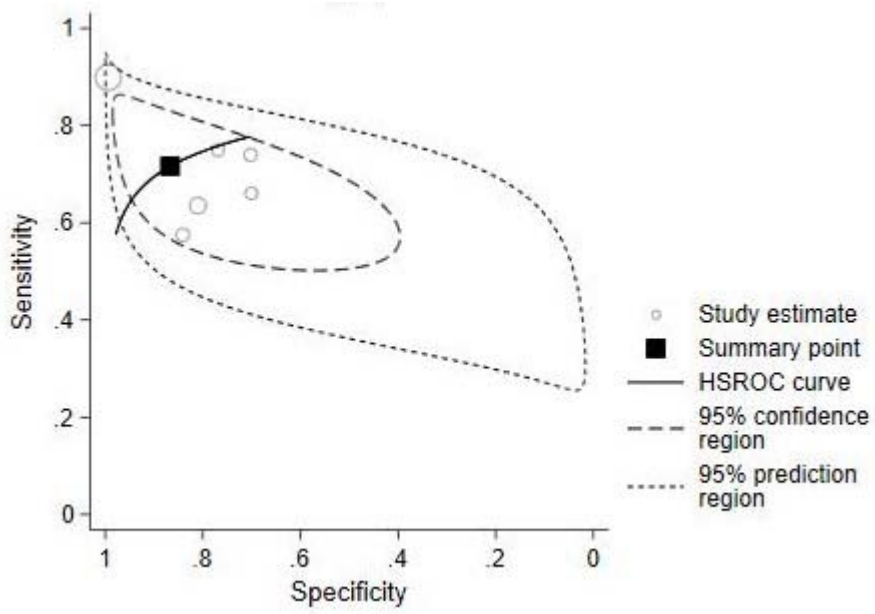


Figure 16 HSROC for urine NGAL (BioPorto) studies - critical care setting

Figure 17 shows the forest plots of sensitivity and specificity estimates for the eight studies (1971 patients in total) assessing uNGAL (BioPorto) for detection of AKI in adults across all clinical settings. Sensitivity values ranged from 0.58 to 0.90 and specificity values from 0.48 to 1.00. Summary estimates for sensitivity and specificity were 0.73 (95% CI 0.65 to 0.80) and 0.83 (95% CI 0.64 to 0.93), respectively. The HSROC together with the 95% confidence region for the summary operating point and the 95% prediction region is shown in Figure 18. The confidence and prediction regions are large indicating considerable heterogeneity between studies.

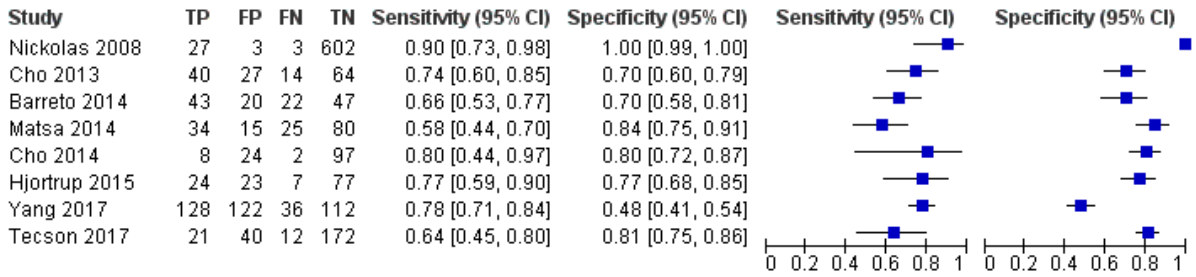


Figure 17 Forest plots of sensitivity and specificity for urine NGAL (BioPorto) for detection of AKI in adults across all clinical settings

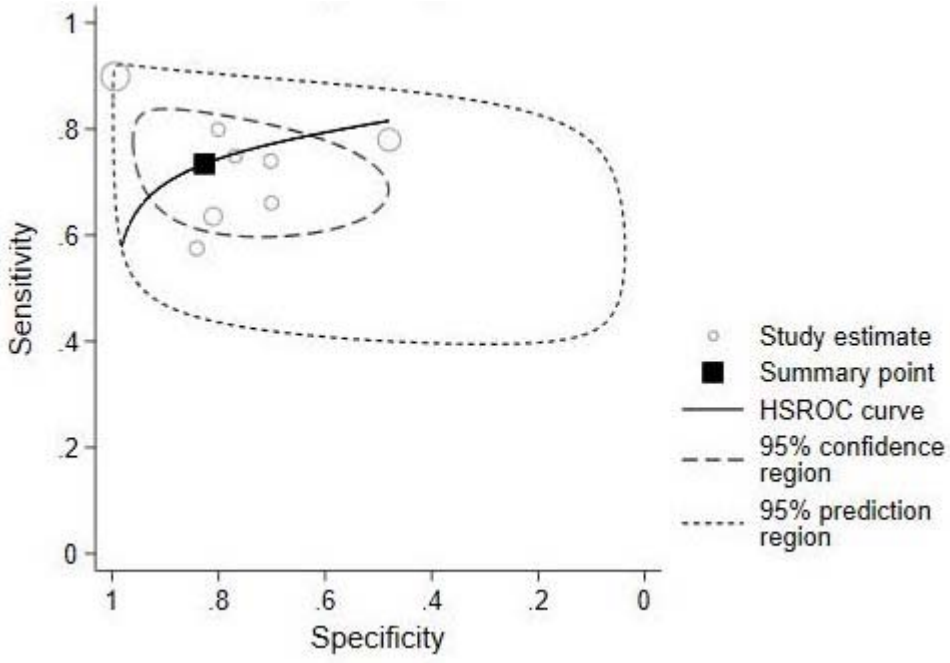


Figure 18 HSROC for urine NGAL (BioPorto) studies for detection of AKI in adults- all clinical settings

Urine NGAL assays (Abbott and BioPorto) critical care

Figure 19 shows the forest plots of sensitivity and specificity estimates for the 10 uNGAL (Abbott and BioPorto) studies (3441 patients in total) that assessed patients admitted to critical care. Sensitivity values ranged from 0.58 to 0.90 and specificity values from 0.58 to 1.00. Summary estimates for sensitivity and specificity were 0.71 (95% CI 0.64 to 0.77) and 0.82 (95% CI 0.67 to 0.90), respectively. Figure 20 shows the HSROC with 95% confidence region for the summary operating point and 95%

prediction region. The prediction region is large, especially for specificity, indicating heterogeneity across studies.

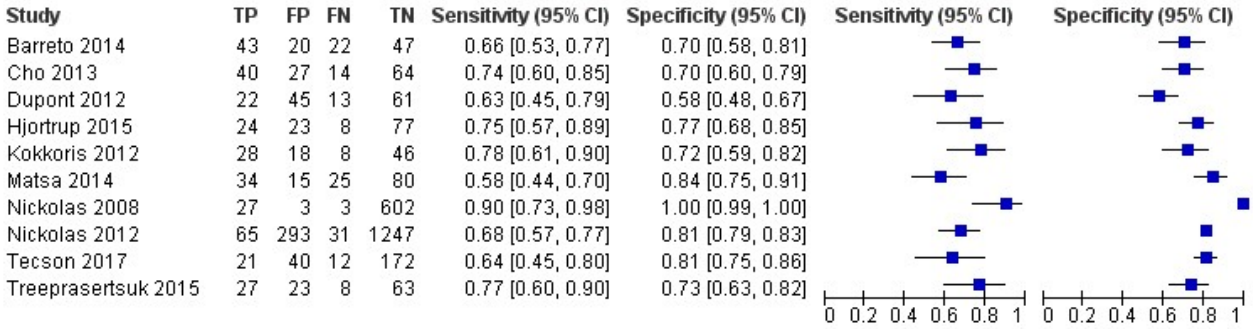


Figure 19 Forest plots of sensitivity and specificity for all urine NGAL assays (Abbott and BioPorto) for detection of AKI in adults admitted to critical care

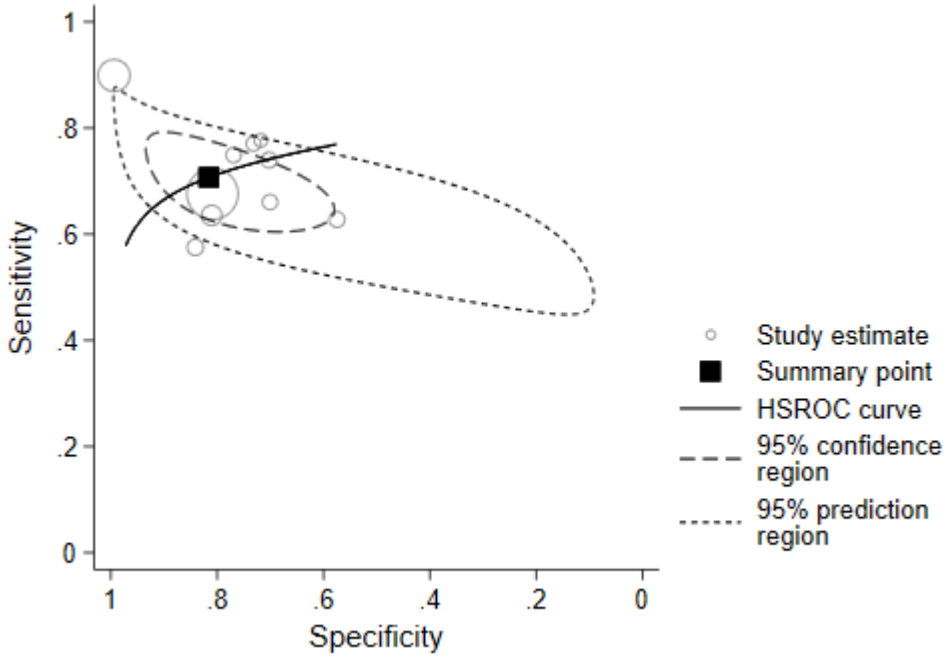


Figure 20 HSROC for all urine NGAL assays (Abbott and BioPorto) for detection of AKI in adults- critical care setting

Urine NGAL assays (Abbott and BioPorto) across all settings

Figure 21 shows the forest plots of sensitivity and specificity estimates for all 14 uNGAL (BioPorto) studies (5319 patients in total) across all clinical settings. Sensitivity values ranged from 0.46 to 0.90 and specificity values from 0.48 to 1.00. Summary estimates for sensitivity and specificity were 0.71 (95% CI 0.64 to 0.76)

and 0.78 (95% CI 0.67 to 0.87), respectively. Figure 22 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. The prediction region is large indicating heterogeneity across studies.

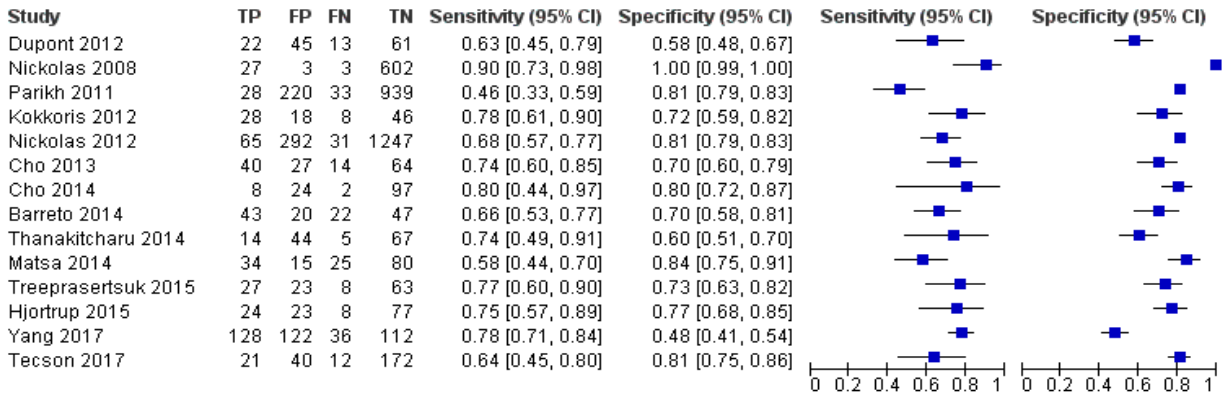


Figure 21 Forest plots of sensitivity and specificity for all urine NGAL assays (Abbott and BioPorto) for detection of AKI in adults across all clinical settings

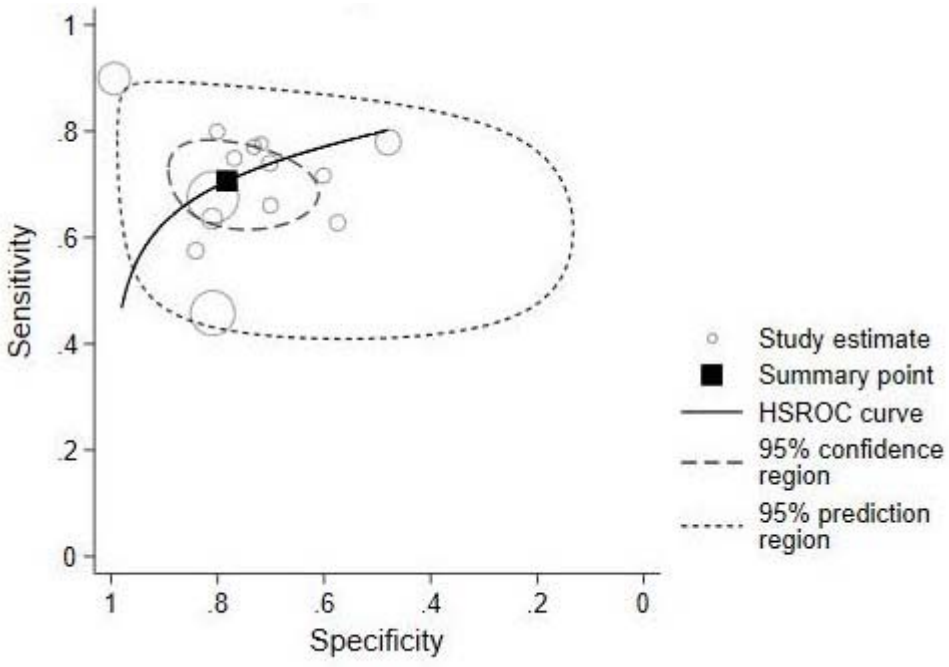


Figure 22 HSROC for all urine NGAL assays (Abbott and BioPorto) for detection of AKI in adults- all clinical settings

Plasma NGAL assay (BioPorto) – adult population

No suitable data in any post-surgical setting (cardiac surgery or major non-cardiac surgery) were available from the included studies.

Critical care - mixed population

Four studies (771 patients in total) assessed the use of plasma NGAL (BioPorto) for detection of AKI in patients admitted to ICU or critical care for various clinical reasons. Cut off varied across studies (see Table 9). Prevalence of AKI ranged from 13% to 38% across studies. Table 9 shows a summary of the diagnostic data for the four studies and Figure 23 the forest plots of sensitivity and specificity. Sensitivity values ranged from 0.58 to 0.93 and specificity values from 0.23 to 0.85. The summary estimate of sensitivity was 0.76 (95% CI 0.56 to 0.89) and that of specificity 0.67 (95% CI 0.40 to 0.86). Figure 24 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. Confidence and prediction regions are large and greater for sensitivity than specificity. While this indicates the presence of heterogeneity across studies, it is worth noting that all studies and the confidence and prediction regions are positioned in the left side of the graph, above the diagonal of no effect. It is worth paying attention to the Itenov et al.'s study, which shows a high sensistivity estimate and a very low specificity estimate.

Table 9 Summary of diagnostic accuracy data for plasma NGAL (BioPorto) for AKI in the critical care setting (adult population)

STUDY ID	Target Population (setting)	Assay	Timing of Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Matsa 2014[75]	Critical care - mixed population (ICU/ITU)	pNGAL, BioPorto	ICU admission	400 ng/mL	0.60 (0.47, 0.73)	0.85 (0.77, 0.92)	0.77	0.38
Hjortrup 2015[74]	Critical care - mixed population (sepsis)	pNGAL, BioPorto	ICU admission	558 ng/mL	0.58	0.76	0.66 (0.54, 0.77)	0.24
Tecson 2017[80]	Critical care - mixed population (ICU/ITU)	pNGAL, BioPorto	Within 48 hours of ICU admission	142 ng/mL	0.79 (0.61, 0.91)	0.73 (0.67, 0.79)	0.76 (0.64, 0.87)	0.13
Itenov 2017[83]	Critical care - mixed population (ICU/ITU)	pNGAL, BioPorto	ICU admission	185 ng/mL	0.93	0.23	NR	0.36

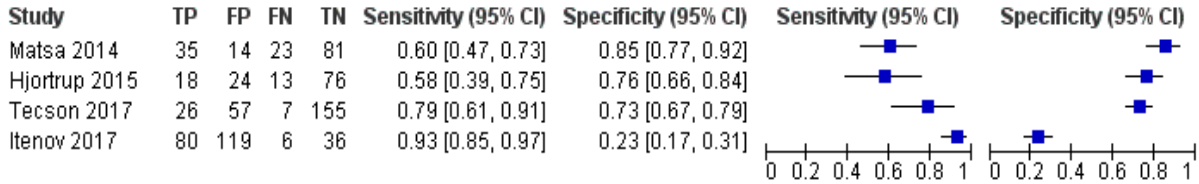


Figure 23 Forest plots of sensitivity and specificity for plasma NGAL (BioPorto) for detection of AKI in adults - the critical care setting

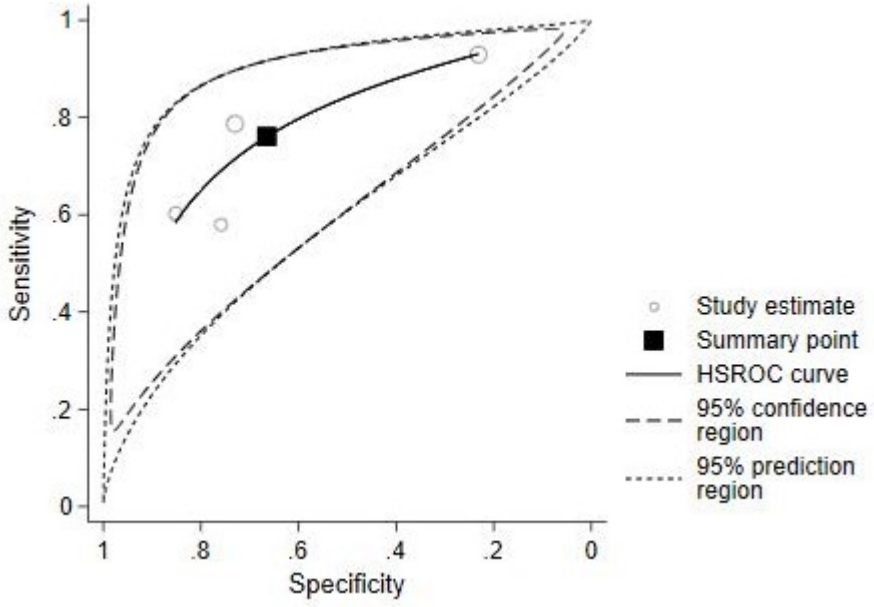


Figure 24 HSROC for plasma NGAL (BioPorto) studies for detection of AKI in adults - critical care setting

Table 10 presents a summary of the diagnostic data for the seven uNGAL studies that assessed AKI in children. All but one study assessed children who underwent cardiac surgery. Across studies, the age of the peadiatric population ranged from 1 day to 8 years.

Table 10 Summary of diagnostic accuracy data for uNGAL assays (Abbott and BioPorto) for detection of AKI - child population

STUDY ID	Population (setting)	Assay	Timing of Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI or SE)	Prevalence of AKI
Parikh 2011[86]	Cardiac Surgery	uNGAL, ARCHITECT, Abbott	ICU admission	>72 ng/mL	0.42	0.85	0.71	0.17
Cantinotti 2012[90]	Cardiac Surgery	uNGAL, ARCHITECT, Abbott	2 h after surgery	49.9 ng/mL	0.784	0.815	0.85 (0.03)	0.27
Bennett 2013[89]	Cardiac Surgery	uNGAL, ARCHITECT, Abbott	2 h after surgery	>150 ng/mL	0.79 (0.69, 0.86)	0.92 (0.84, 0.96)	0.93	0.50
Seitz 2013[92]	Cardiac Surgery	uNGAL, ARCHITECT, Abbott	2h after end of surgery	27.6 ng/mL	0.55	0.43	0.56	0.55
Alcaraz 2014[91]	Cardiac Surgery	uNGAL, ARCHITECT, Abbott	ICU admission	100 ng/mL	0.82	0.76	0.84 (0.76, 0.92)	0.34
Yang 2017[67]	Cardiac Surgery	uNGAL, BioPorto	6 h after surgery	186µg/g Cr	0.77	0.47	0.72 (0.64, 0.80)	0.39
Zwiers 2015[93]	Critical care - mixed population (ICU/ITU)	uNGAL, ARCHITECT, Abbott	ICU admission	126 ng/mL	0.76	0.84	0.81 (0.68, 0.94)	0.35

Urine NGAL ARCHITECT assay (Abbott) - child population

Cardiac surgery

Five studies (887 children in total) assessed the use of uNGAL ARCHITECT for detection of AKI in children who underwent cardiac surgery. Cut off used to define a positive test and timing of biomarkers measurements varied across studies (see Table 10). Prevalence of AKI ranged from 17% to 55% across studies. Table 10 shows a summary of the diagnostic data for the five studies and Figure 25 the forest plots of sensitivity and specificity. Sensitivity values ranged from 0.42 to 0.83 and specificity values from 0.43 to 0.92. The summary estimate of sensitivity was 0.68 (95% CI 0.53 to 0.80) and that of specificity 0.79 (95% CI 0.63 to 0.89). Figure 26 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are very large indicating considerable heterogeneity between studies.

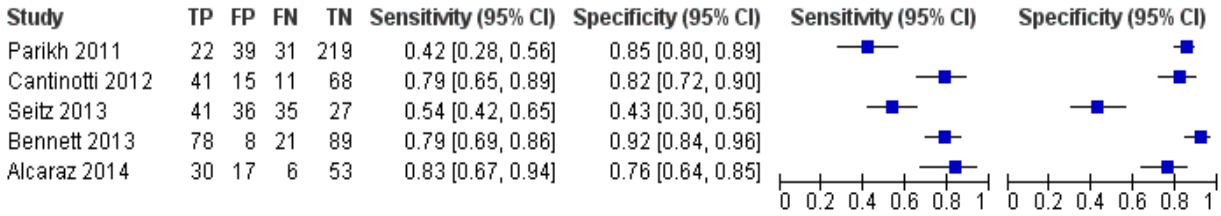


Figure 25 Forest plots of sensitivity and specificity for urine NGAL ARCHITECT (Abbott) for detection of AKI in children - cardiac surgery setting

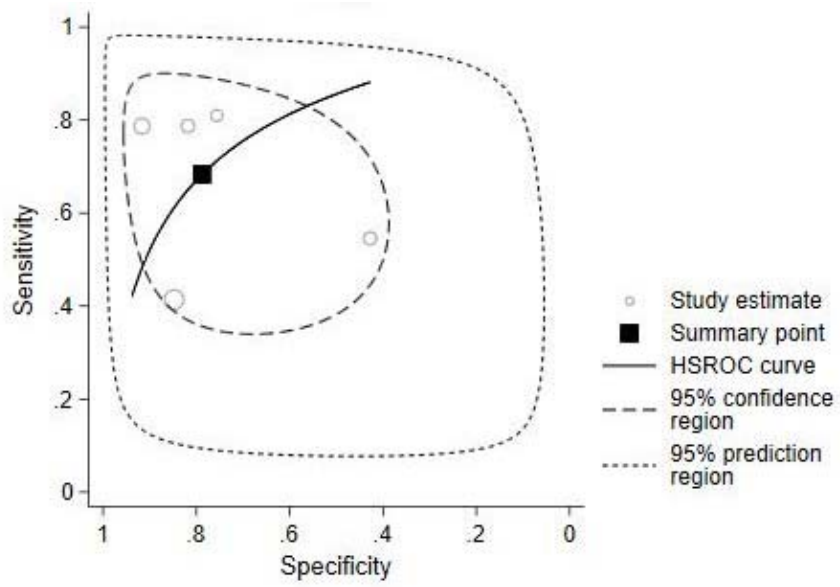


Figure 26 HSROC for urine NGAL ARCHITECT (Abbott) studies for detection of AKI in chidlren - cardiac surgery setting

Critical care - mixed population

One study, Zwiers 2015,[93] assessed the use of uNGAL ARCHITECT for detection of AKI in 324 children admitted to ICU or critical care for various clinical reasons. The cut off was 126 ng/mL. The prevalence of AKI was 35%. The sensitivity and specificity values for the urine sample collected at ICU admission were 0.77 (95% CI 0.60 to 0.90) and 0.85 (95% CI 0.74 to 0.92), respectively. The prevalence of AKI in the study was 35%.

Urine NGAL assay (BioPorto) - child population

Cardiac surgery

One study, Yang 2017,[67] assessed the use of uNGAL (BioPorto) for detection of AKI in 323 children who underwent cardiac surgery. uNGAL was measured using a concentration normalised by units of creatinine (see Table 4). The sensitivity and specificity values for the urine sample collected 6 hours after surgery were 0.77 (95% CI 0.69 to 0.84) and 0.47 (95% CI 0.40 to 0.54), respectively. The prevalence of AKI in the study was 39%.

Urine NGAL assays (Abbott and BioPorto) in the cardiac surgery setting – child population

Figure 27 shows the forest plots of sensitivity and specificity estimates for the six studies (1210 children in total) that assessed uNGAL assays (ARCHITECT by Abbott and uNGAL by BioPorto) for detection of AKI in children who underwent cardiac surgery. Sensitivity values ranged from 0.42 to 0.83; specificity values from 0.43 to 0.92. Summary estimates for sensitivity and specificity were 0.70 (95% CI 0.57 to 0.80) and 0.74 (95% CI 0.57 to 0.86), respectively. Figure 28 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. Both the confidence and prediction regions are very large indicating considerable heterogeneity between studies.

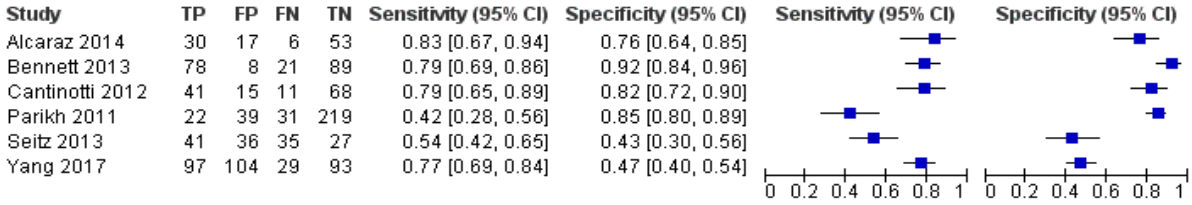


Figure 27 Forest plots of sensitivity and specificity for all urine NGAL assays (Abbott and BioPorto) for detection of AKI in children who underwent cardiac surgery

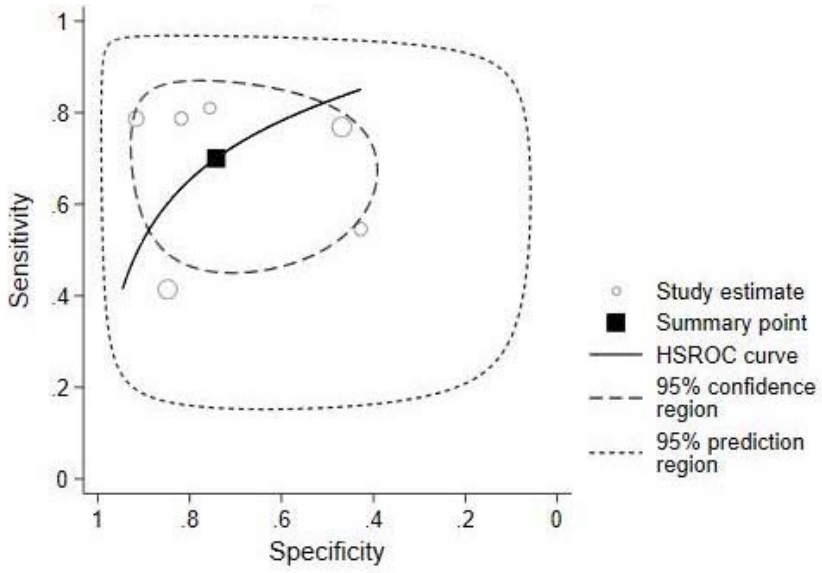


Figure 28 HSROC for all urine NGAL (Abbott and BioPorto) studies for detectionof AKI in children - cardiac surgery setting

Urine NGAL assays (Abbott and BioPorto) all clinical settings - child population

Figure 29 shows the forest plots of sensitivity and specificity estimates for the seven studies (1310 children in total) assessing uNGAL assays (ARCHITECT by Abbott and uNGAL by BioPorto) for detection of AKI in children across all clinical settings. Sensitivity values ranged from 0.42 to 0.83; specificity values from 0.43 to 0.92. Summary estimates for sensitivity and specificity were 0.71 (95% CI 0.60 to 0.80) and 0.76 (95% CI 0.61 to 0.86), respectively. Figure 30 shows the HSROC with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are very large indicating considerable heterogeneity between studies.

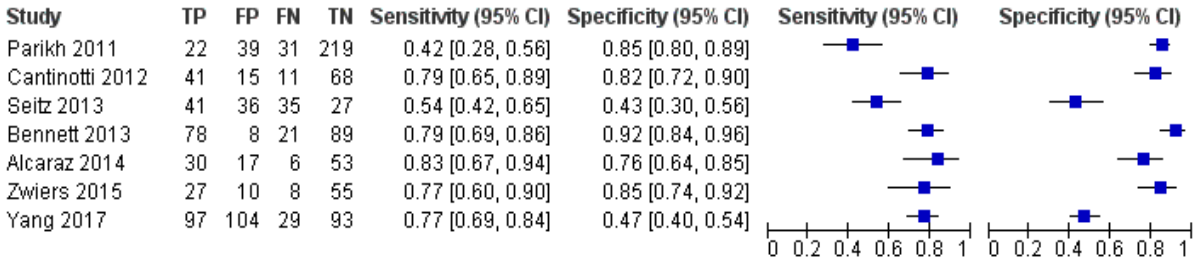


Figure 29 Forest plots of sensitivity and specificity for all urine NGAL assays (Abbott and BioPorto) for detection of AKI in children across all clinical settings

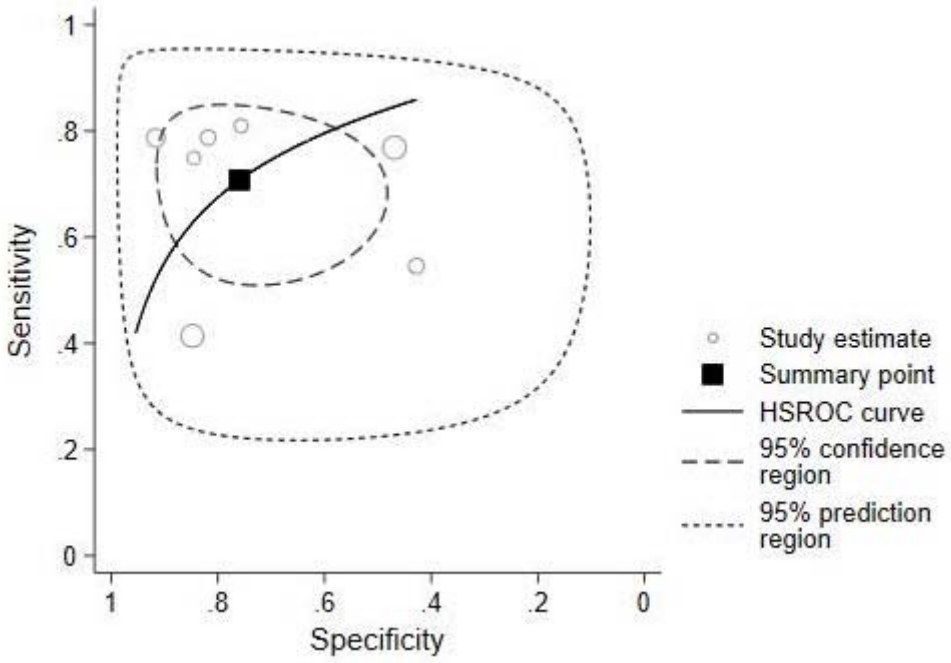


Figure 30 HSROC for all urine NGAL studies (Abbott and BioPorto assays) for detection of AKI in children - all clinical settings

Accuracy of NephroCheck, ARCHITECT NGAL and BioPorto NGAL assays for detection of AKI in critically ill patients

The accuracy of NephroCheck, urine ARCHITECT NGAL, and urine and plasma BioPorto NGAL studies for detection of AKI in each clinical setting for both adults and children is shown in Table 11 below. The table displays either the AUC estimates as reported by individual studie or the AUC summary estimates together with the corresponding prediction intervals when pooling of AUC was feasible. Associated forest plots of the AUC meta-analyses are presented in Appendix 9. For the adult population the AUC summary estimates ranged from 0.62 for uNGAL BioPorto to 0.74 for pNGAL BioPorto in the cardiac surgery setting; and from 0.72 for urine and plasma NGAL BioPorto to 0.76 for uNGAL ARCHITECT in the critical care setting. For the children population in the cardiac surgery setting, the AUC summary estimates ranged from 0.80 for uNGAL ARCHITECT to 0.88 for uNGAL BioPorto. All AUC summary estimates had relatively large 95% prediction intervals indicating heterogeneity between studies. The forest plots in Appendix 9 show that variation is both between and within studies.

For each biomarker, Table 11 shows the AUC for detection of AKI compared with that of sCR or conventional clinical assessment as reported by the individual studies that provided this information. AUC values varied across studies. In the majority of cases, the reported AUC indicated a slightly better performance of the biomarkers compared with that of sCr or conventional clinical assessment for detection of AKI. However, in a number of cases sCr or conventional clinical assessment appeared to perform better than the biomarkers under assessment.

Table 11 AUC and pooled AUC for NephroCheck and NGAL studies for detection of AKI

Population, biomarker and setting	**No of studies**	**AUC estimate (95% CI)**	**AUC summary estimate (95% CI)**	**(95% prediction interval)**
Adults NephroCheck across all settings	7	-	0.76 (0.50, 0.91)	(0.47, 0.90)
Adults NephroCheck cardiac surgery	1	0.68 (0.54, 0.81)	-	-
Adults NephroCheck major non-cardiac surgery	-	-	-	-
Adults NephroCheck critical care	6	-	0.74 (0.67, 0.81)	(0.44, 0.91)
Adults uNGAL ARCHITECT (Abbott) all settings	14	-	0.73 (0.68, 0.78)	(0.53, 0.87)
Adults uNGAL ARCHITECT (Abbott) cardiac surgery	6	-	0.70 (0.65, 0.74)	(0.58, 0.79)
Adults uNGAL ARCHITECT (Abbott) major non-cardiac surgery	1	0.50 (034, 0.66)	-	-
Adults uNGAL ARCHITECT (Abbott) critical care	7	-	0.76 (0.69, 0.82)	(0.50, 0.91)
Adults uNGAL (BioPorto) across settings	15	-	0.70 (0.65, 0.74)	(0.53, 0.82)
Adults uNGAL (BioPorto) cardiac surgery	4	-	0.62 (0.55, 0.69)	(0.33, 0.84)

Adults uNGAL (BioPorto) major non-cardiac surgery	1	0.78 (0.66, 0.90)	-	-
Adults uNGAL (BioPorto) critical care	10	-	0.72 (0.67, 0.77)	(0.54, 0.85)
Adult uNGAL (Abbott and BioPorto) cardiac surgery	10	-	0.67 (0.62, 0.78)	(0.53, 0.78)
Adult uNGAL (Abbott and BioPorto) major non-cardiac surgery	2	-	0.65 (0.35, 0.86)	-
Adult uNGAL (Abbott and BioPorto) critical care	17	-	0.74 (0.70, 0.78)	(0.56, 0.86)
Adult uNGAL (Abbott and BioPorto) all settings	29	-	0.71 (0.68, 0.74)	(0.55, 0.84)
Adults pNGAL (BioPorto) across all settings	10	-	0.72 (0.66, 0.77)	(0.52, 0.86)
Adults pNGAL (BioPorto) cardiac surgery	3	-	0.74 (0.65, 0.82)	(0.06, 0.99)
Adults pNGAL (BioPorto) major non-cardiac surgery	1	0.78 (0.66, 0.90)	-	-
Adults pNGAL (BioPorto) critical care	7	-	0.72 (0.65, 0.78)	(0.47, 0.88)
Child uNGAL (Abbott and	9	-	0.81 (0.71, 0.88)	(0.37, 0.97)

BioPorto) across settings				
Child uNGAL ARCHITECT (Abbott) cardiac surgery	5	-	0.80 (0.65, 0.90)	(0.17, 0.99)
Child uNGAL (BioPorto) cardiac surgery	2	-	0.88 (0.47, 0.98)	-
Child uNGAL (Abbott and BioPorto) all cardiac surgery	7	-	0.82 (0.71, 0.90)	(0.31, 0.98)
Child uNGAL ARCHITECT (Abbott) critical care	1	0.81 (0.69, 0.94)	-	-
Child uNGAL (BioPorto) critical care	1	0.68 (0.55, 0.81)	-	-
Child uNGAL (Abbott and BioPorto) critical care	2	-	0.73 (0.58, 0.84)	-

Table 12 AUC forNephroCheck, urine NGAL ARCHITECT, and urine and plasma BioPorto NGAL for detection of AKI compared with the AUC for creatinine or conventional clinical assessment

			AUC (95% CI or SEM)	
Study ID, geographical location, patient popualtion	**Clinical setting**	**Biomarker and setting**	**Creatinine or clinical model**	**Biomarker**
Bihorac 2014[31], USA, Adult population	Critical care (mixed population)	Nephrocheck	Serum creatinine 0.63 (0.56-0.70)	0.82 (0.76-0.88)
Kashani 2013[36], North America and Europe, Adult population	Critical care (mixed population)	Nephrocheck	Serum creatinine 0.75 (0.70-0.80)	0.80 (0.75-0.84)
Kimmel 2016[38], Germany, Adult population	Critical care (mixed population)	Nephrocheck	Serum creatinine 0.60 (0.53-0.66)	0.74 (0.66-0.81)
		pNGAL, BioPorto	Serum creatinine 0.60 (0.53-0.66)	0.55 (0.5-0.66)
		uNGAL, BioPorto	Serum creatinine 0.60 (0.53-0.66)	0.66 (0.58-0.73)
Haase 2014[62], Germany, Adult population	Cardiac surgery	uNGAL, ARCHITECT	Serum creatinine 0.66 (0.51-0.76)	0.71 (0.6- 0.83)
		pNGAL BioPorto	Serum creatinine 0.66 (0.51-0.76)	0.71 (0.58-0.83)
Kokkoris 2012[56], Greece, Adult population	Critical care (mixed population)	uNGAL, ARCHITECT	Serum creatinine 0.77 (0.67–0.84)	0.74 (0.64–0.82)
		pNGAL	Serum creatinine 0.77 (0.67–0.84)	0.78 (0.68-0.85)
Liebetrau 2013[49], Germany, Adult population	Cardiac surgery	uNGAL, ARCHITECT	Serum creatinine 0.74 (0.58-0.91)	0.90 (0.811-0.99)
Parikh 2011[39], North America, Adult population	Cardiac surgery	uNGAL, ARCHITECT	Clinical model 0.69 (0.04)	0.67 (0.04)
Parikh 2011[97], North America, Adult population	Cardiac surgery	uNGAL, ARCHITECT	Serum creatinine 0.46 (0.04)	0.71 (0.04)

Nickolas 2012[58], USA and Germany, Adult population	Critical care (mixed population)	uNGAL, ARCHITECT, Abbot	Serum creatinine 0.91 (0.87-0.94)	0.81 (NR)
Treeprasertsuk 2015[61], Thailand, Adult population	Critical care (mixed population)	uNGAL, ARCHITECT, Abbot	Serum creatinine 0.58 (NR)	0.83 (0.76–0.91)
De Loor 2017[65], Belgium, Adult population	Cardiac surgery	uNGAL, BioPorto	Serum creatinine 0.78 (0.72-0.83)	0.65 (0.58-0.72)
Hjortrup 2015[74], Denmark, Adult population	Critical care (mixed population)	uNGAL, BioPorto	Plasma creatinine 0.66 (0.56–0.77)	0.71 (0.59–0.82)
		pNGAL, BioPorto	Plasma creatinine 0.66 (0.56-0.77)	0.66 (0.54-0.77)
Nickolas 2008[76], USA, Adult population	Critical care (mixed population)	uNGAL, BioPorto	Serum creatinine 1.4 mg/dL 0.92 (0.87-0.98)	0.95 (0.88-1.00)
Verna 2014[81], USA, Adult population	Critical care (mixed population)	uNGAL, BioPorto	Serum creatinine 0.89	0.86 (NR)
Alcaraz 2014[91], Spain, Child population	Cardiac surgery	uNGAL, ARCHITECT	Clinical model 0.85 (0.78-0.93)	0.84 (0.76-0.92)

Role of NephroCheck, ARCHITECT urine NGAL and BioPorto NGAL assays in predicting worsening of AKI in critically ill people with AKI and of mortality and RRT in critically ill patients at risk of AKI

Table 13 below displays the AUC and the pooled AUC estimates with corresponding 95% CI for NephroCheck, urine ARCHITECT NGAL and urine and plasma BioPorto NGAL studies for the prediction of worsening of AKI, mortality and RRT in each clinical setting for both adults and children. Only limited studies were available for AUC meta-analyses. Associated forest plots are presented in Appendix 9. In the critical care setting (adult population) the AUC values reported in individual studies ranged from 0.66 for pNGAL BioPorto to 0.71 for uNGAL BioPorto for worsening of AKI, and from 0.55 for pNGAL BioPorto for prediction of 90-day mortality to 0.75 for uNGAL ARCHITECT for prediction of 30-day mortaliy. One study reported a AUC of 0.70 for pNGAL BioPorot for prediction of RRT. The AUC summary estimate (pooling of 2 studies) for worseningof AKI in the critical care setting was 0.65 (0.43, 0.82) for uNGAL ARCHITECT. AUC summary estimates ranged from 0.62 for uNGAL BioPorto for 90-day mortality to 0.68 for pNGAL BioPorto for in-hospital mortality with 95% CI spanning from 0.58 to 0.73. The AUC summary estimate (2 studies) for prediction of RRT in critical care for uNGAL BioPorto was 0.74 (0.49-0.89). In the cardiac surgery setting (adult population) AUC values from individual studies ranged from 0.68 for uNGAL ARCHITECT to 0.78 for NephroCheck for prediction of RRT with 95% CI ranging from 0.57 to 0.84.

Table 13 AUC estimates for prediction of worsening of AKI, mortality and RRT

Population, biomarker and setting	Follow-up	No of studies	AUC estimate (95% CI)	AUC summary estimate (95% CI)
AKI				
Adults uNGAL ARCHITECT (Abbott) Critical care	During hospital stay	1	-	0.65 (0.43, 0.82)
Adults uNGAL BioPorto Critical care	During ICU stay	1	0.71 (0.59, 0.82)	-
Adults pNGAL BioPorto Critical care	During ICU stay	1	0.66 (0.54, 0.77)	-
Mortality				
Adults uNGAL ARCHITECT (Abbott) cardiac surgery	During hospital stay 11/288 died	1	0.70 (0.56, 0.84)	-
Adults uNGAL ARCHITECT (Abbott) major non-cardiac surgery	30 days 10/109 died	1	0.65 (0.45, 0.85)	-
Adults uNGAL ARCHITECT (Abbott) critical care	30 days 17/121 died	1	0.75 (0.66, 0.85)	-
Adults uNGAL (BioPorto) critical care	90 days	2	-	0.62 (0.58, 0.66)
Adults pNGAL (BioPorto) critical care	In hospital	2	-	0.68 (0.63, 0.73)
Adults pNGAL (BioPorto) critical care	30 days 7/105 died	1	0.72 (0.49, 0.87)	-
Adults pNGAL (BioPorto) critical care	90 days	1	0.55 (0.47, 0.63)	-
Adults NGAL (Abbott and BioPorto) critical care	In hospital	2	-	0.76 (0.64, 0.85)
Children uNGAL ARCHITECT (Abbott) cardiac surgery	In hospital 3/196 died	1	0.91 (0.55, 0.99)	-

Need of RRT				
Adults NephroCheck (Medical Astute) cardiac surgery	NR	1	0.78 (0.71, 0.84)	-
Adults uNGAL ARCHITECT (Abbott) cardiac surgery	Up to 12 months 22/288 received RRT	1	0.68 (0.57, 0.79)	-
Adults uNGAL (BioPorto) critical care	-	2	-	0.74 (0.49, 0.89)
Adults pNGAL (BioPorto) critical care	During ICU stay 40/222 received RRT	1	0.70 (0.61, 0.78)	-
Child uNGAL ARCHITECT (Abbott) cardiac surgery	During hospital stay 4/196	1	0.86 (0.57, 0.97)	-

Table 14 below presents the AUC with 95% CI or the OR with 95% CI for the addition of the biomarkers to existing clinical models for the predicition of AKI, mortality and RRT. It is worth noting, that the statistical models differed between studies and often were not sufficiently detailed. In particular, although most of the adjusting predictors were specified, information on the potential candidate variables was missing. In general, the number of events was low given the number of prediciting variables, even for AKI outcomes. Overall, the addition of biomarkers to the clinical models improved risk prediction of newly developed AKI or worsening of AKI, and mortality. However, only a limited amount of data were available for each biomarker in each clinical setting restricting any generalisable interpretation.

Table 14 Addition of biomarkers to existing clinical models for prediction of development or worsening of AKI, mortality and RRT

Study ID, geographical location, biomarker, setting		AUC (95% CI or SEM)			OR (95% CI)		Adjustment of the model	
	Diagnosis or Prediction	Clinical Model	Biomarker	Biomarker + Clinical Model	Clinical Model	Biomarker	Biomarker + Clinical Model	
	AKI							
Kashani 2013[36], North America and Europe, NephroCheck (Astute Medical) Critical care - mixed population	Diagnosis of AKI within 12h. Events=101	0.81 (0.76-0.85)*	0.80 (0.75-0.84) *	0.87 (0.84-0.90)*	NR	NR	NR	Age, sCR, APACHE III score, HT, nephrotoxic diagnosis, liver disease, DM and CKD.
Bihorac 2014[31], USA, NephroCheck (Astute Medical) Critical care - mixed population	Diagnosis of AKI within 12h. Events=71	0.70 (0.63-0.76) p<0.001	NR	0.86 (0.80-0.90) p<0.001	NR	NR	NR	Included clinical variables for which a univariate association with AKI at p<0.1 was found. Also included sCR and the KDIGO criteria. They also then used univariate sig of p<.1. Final model seems to include enrolment serum creatinine, APAHE III score (non renal), BMI.
Parikh 2011[39], North America, uNGAL ARCHITECT, Cardiac surgery	Diagnosis of AKI within 72h Events=60	0.69 (0.04)	0.67 (0.04)	0.73 (0.04) (p=0.12)	NR	NR	NR	Variables included in the clinical model were: age, gender, white race, CPB time > 120 minutes, non-elective surgery, pre-operative eGFR, diabetes, and hypertension. The improvement of risk prediction with the addition of biomarkers to the clinical model,was determined using NRI and IDI indices.
Schley 2015[63], Germany urine and plasma NGAL BioPorto, Cardiac surgery	Diagnosis of AKI within 72h from surgery. Events=37	0.76 (p<0.001)	pNGAL 0.81 (0.73-0.90) (p<0.001) uNGAL 0.63 (0.51-0.74)	pNGAL 0.80 (p<0.001) uNGAL 0.76 (p<0.001)	NR	NR	NR	The clinical model was based on the European System for Cardiac Operative Risk Evaluation (EuroSCORE). A multivariable analysis was conducted to analyse

			(p<0.001)					the combination of biomarkers and clinical scores.
Kokkoris 2012[56], Greece, uNGAL, ARCHITECT, Abbott, Critical care - mixed population	AKI detection within 7days Events=36	0.76 (0.66–0.83)	0.78 (0.68-0.85)	0.85 (NR) p=0.03	NR	NR	NR	The most efficient reference clinical model for AKI prediction included SAP III and INR. Addition of pNGAL to the clinical model improved the AUC. However, the combination of pNGAL + sCR showed the best AUC (0.86 p=0.04).
Isshiki 2017[55], Japan, uNGAL, ARCHITECT, Critical care – mixed population	Worsening kidney function within 7 days Events=58	0.85 (0.77-0.92)	0.74 (0.65-0.84)	0.85 (0.77-0.92)	NR	NR	NR	Variables included in the clinical model for the prediction of newly developed AKI were: age, sex, APACHE II score, sepsis, baseline eGFR, sCR level at ICU admission.
Lee 2018[84], South Korea, pNGAL BioPorto, Critical care - mixed population	Development of AKI Events=111	NR	NR	NR	5.31 (0.67– 11)	0.6 (0.2–1.7) p= 0.314	1.004 (1.002–1.006) p= 0.001	Adjusting for potential confounders as determined by the univariate analyses. The Adjusted model includes age, CHF, DM, adrenaline dosage, time to ROSC, Glasgow coma score, lactate, PaO2.PaCO2, initial creatinine, SOFA (cardiac, pulmonary, renal, hepatic, hematologic), CVI and NGAL. Of these only SOFA renal, NGAL and CVI were significant but a final model was not selected.
Alcaraz 2014[91], Spain, Child population, uNGAL, ARCHITECT, Cardiac surgery	Prediction of AKI Events=36	0.85 (0.78-0.93)	0.84 (0.76-0.92)	0.91 (0.84-0.97) p=0.057	NR	NR	NR	A multivariable logistic regression analysis was used to assess the predictors of AKI and the performance of the model. The clinical model (age, CPB time, total circulatory arrest use, and RACHS-1

								score) was determined using backward elimination.
	Mortality							
Isshiki 2017[55], Japan, uNGAL, ARCHITECT, Critical care – mixed population	In hospital mortality (38 died)	0.79 (0.71-0.86)	0.72 (0.65-0.78)	0.79 (0.71-0.86)	NR	NR	NR	Variables included in the clinical model for the prediction of mortality were: age, sex, APACHE II score, sepsis. Variables were derived from univariate logistic regression analysis.
Verna 2012[81], USA, uNGAL, BioPorto, Critical care - mixed population (cirrhosis)	In hospital mortality (15 died)	NR	NR	NR	2.95 (1.68-5.61)	2.00 (1.36-2.94)	6.05 (1.35-27.2)	Adjusted for age, sCr, MELD>17, HRS

* C-Statistics

AKI = acute kidney injury; APACHE = acute physiology and chronic health evaluation; AUC = area under the (receiver operating characteristic) curve; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; CPB = cardiopulmonary bypass; CVI = cumulative vasopressor index; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HRS = hepatorenal syndrome; HT = hypertension; ICU = intensive care unit; IDI = integrated discrimination index; INR = international normalised ratio; KDIGO = Kidney Disease Improving Global Outcomes; MELD = model for end stage liver disease; NR = not reported; NRI = net classification index; PaCO2 = partial pressures of carbon dioxide; PaO2 = partial pressures of oxygen; pNGAL = plasma neutrophil gelatinase-associated lipocalin; RACHS = risk adjustment for congenital heart surgery; ROSC = return of spontaneous circulation; SAP = simplified acute physiology score; sCR = serum creatinine; SEM = standard error of the mean; SOFA = sequential organ failure assessment; uNGAL = urine neutrophil gelatinase-associated lipocalin

Interpretation of clinical effectiveness evidence

The results of the meta-analyses of sensitivity and specificity estimates suggest that the biomarkers under investigation (NephroCheck, urine NGAL ARCHITECT and urine and plsma NGAL BioPorto assays) may potentially have a role in the detection of AKI in critically ill patients. However, due to the considerable clinical and statiatical heterogeneity observed across studies and the limited number of studies available for certain clinical settings or/and type of biomarker, these results should be interpreted with caution and require further evidence to substantiate them. Further, the threshold level for NGAL varied considerably across strudies. However, as a common threshold for NGAL has yet to be defined acoordingly to different sample media and clinical setting, we took the decision to pool results across studies with similar characteristics despite this obvious limitation. For the adult population we were able to conduct meta-analyses for studies that assessed patients in the critical care (mixed population) setting and for studies across all clinical settings. There were too few studies assessing patients after cardiac surgery or major non-cardiac surgery. The urine Nephrocheck test had the higher pooled sensitivity (0.83) but the worst pooled specificity (0.51) while the uNGAL ARCHITECT and the BioPorto uNGAL tests had slightly lower pooled sensitivity estimates (0.70 and 0.72, respectively) but better pooled specificity estimates (0.72 and 0.87 respectively). The urine NGAL BioPorto pooled sensitivity was similar to that of plasma NGAL BioPorto (0.72 versus 0.76) whilst the pooled specificity was better for urine NGAL BioPorto (0.87 versus 0.67). The biomarkers had a similar performance across all clinical settings (NephroCheck pooled sensitivity and specificity were 0.75 and 0.61, respectively; uNGAL ARCHITECT pooled sensitivity and specificity were 0.67 and 0.72, respectively; uNGAL BioPorto pooled sensitivity and specificity were 0.73 and 0.83, respectively; pNGAL BioPorto pooled sensitivity and specificity were 0.76 and 0.67, respectively) with pNGAL BioPorto showing the higher sensitivity (0.76) and uNGAL BioPorto the higher specificity (0.83).

With regard to the observed low specificy of the NephroCheck test, we do not know with certainty whether this is due to the relative poor performamce of the biomarker or to the fact that serum creatinine is an imperfect reference standard for assessing kidney injury.

We also noted that when the studies had lower number of AKI events (low prevalence) the relationship observed between sensitivity and specificity estimates became quite different compared to that of studies for which prevalence was higher.

For the child population we were able to conduct meta-anlyses for the five urine NGAL ARCHITECT studies that assessed children who underwent cardiac surgery. The pooled sensitivity was 0.68 and the pooled specificity 0.79. Too few studies were available fort other assays or clinical settings. When we combined all urine NGAL studies (Abbott and BioPorto) across all settings (seven studies), we obtained similar estimates of accuracy (sensitivity 0.71, specificity 0.76).

For prediction of relevant clinical outcomes, only a limited number of studies were available for each biomarker in each clinical setting and this hampered the possibility to perform pooled analyses. Furthermore, the details of the methodology used for the stastical analyses were insufficient especially for older studies. The more recent studies appeared to use some of the PROBAST[22] recommendations and terminology but they were still far from satisfactory as demonstrated by the results of the PROBAST assessment (see Figures 3 and 4 above). Moreover, while information on the adjustment strategies and on the process of variables selection was provided in individual studies, the original cohort of potential predictors, prior to the multivariable analysis, was never clearly specified leading to potential risk of data mining and, hence, methodological bias.

Similarly, while there was an indication that addition of biomarkers to existing clinical models might improve the prediction of relevant clinical outcomes, studies varied substantially in terms of study characteristics and statistical methods used to assess prediction limiting any reliable conclusion.

On the whole, we observed considerable clinical and statistical heterogeneity in all analyses, especially with regard to clinical setting, NGAL threshold levels, time of sample collection, definition of AKI, time of AKI diagnosis, number of AKI events, assay platforms. Therefore, we have limited confidence in the validity and reliability of the observed results.

Chapter 4 Assessment of cost-effectiveness

This chapter assesses the cost-effectiveness of alternative biomarkers (NephroCheck, ARCHITECT urine NGAL, BioPorto urine and plasma NGAL assays) used in combination with standard clinical assessment (i.e., serum creatinine and urine output) compared with standard clinical assessment alone for evaluating critically ill people who are at risk of developing AKI and who are being considered for possible critical care admission in a UK NHS hospital setting. The specific objectives are to review the existing cost-effectiveness evidence base for these tests and to develop a de novo economic model to assess cost-effectiveness from a UK NHS and personal social services perspective.

Systematic review of existing cost-effectiveness evidence

Objective

The aim of the review of economic evaluations was to identify, report and critically appraise existing economic evaluations of NephroCheck, ARCHITECT urine NGAL, urine and plasma NGAL BioPorto assays for evaluating critically ill people (adults and children) at risk of developing AKI.

Search strategies

Comprehensive electronic searches were conducted to identify economic evaluations of the candidate tests. Highly sensitive search strategies were developed, to include index terms, free-text words, abbreviations, and synonyms. The electronic databases Ovid MEDLINE, Ovid EMBASE, NHS Economic Evaluations Database, HTA Database, Research Papers in Economics, and ISPOR Scientific Presentations were searched, with no restriction on date, language, or publication type. The searches were undertaken 27 May 2019, with additional searches on 11 September 2019.

Inclusion and exclusion criteria

Studies were deemed appropriate for inclusion in the review of economic evaluations if they were A) full economic evaluations, defined as a comparative assessment of costs and outcomes in the framework of cost-utility, cost-effectiveness, cost-benefit or cost-minimisation analyses and B) assessed the cost-effectiveness of the candidate

tests within the population defined in the NICE scope (i.e. critically ill people, adults and children, at risk of AKI who are being considered for admission to ICU) and C) provided sufficient information to judge the quality of the study and obtain any relevant data (i.e. conference abstracts alone were unlikely to meet this criteria). Economic evaluations conducted alongside single effectiveness studies (e.g. RCTs) and decision analysis models were all deemed relevant for inclusion. Studies were excluded if they were methodological studies, systematic reviews of cost-effectiveness studies (though these were retained for reference), or cost-of-illness studies. Studies were also excluded if they only assessed tests / biomarkers outside of the NICE scope (e.g. Cystatin C) or used the candidate tests for a purpose other than determining risk of AKI.

Quality assessment of included studies

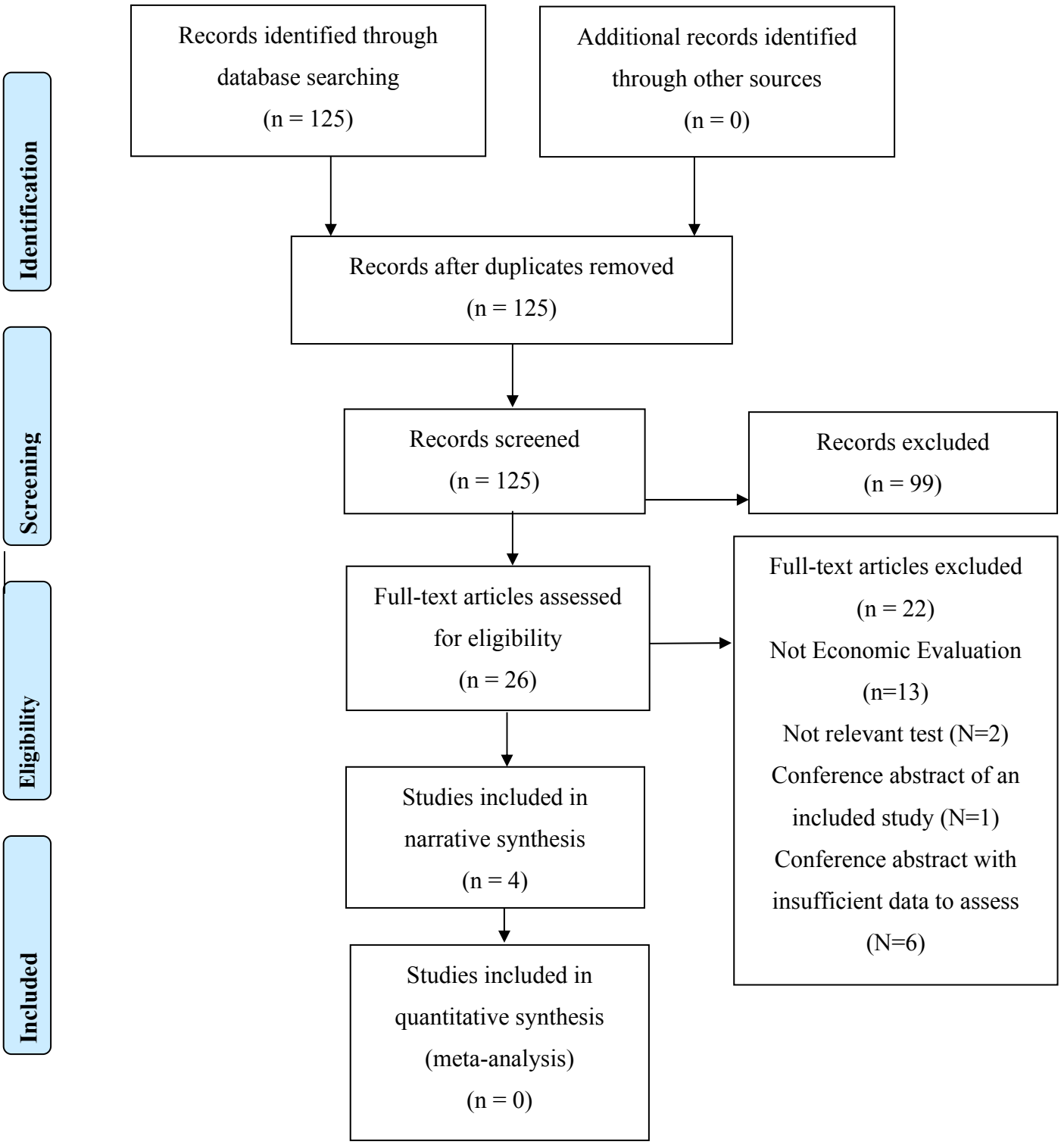
Included studies are appraised against the NICE reference case for the assessment of cost-effectiveness of diagnostic tests.[98]

Evidence synthesis of cost-effectiveness studies

The main findings are summarised in a narrative review, with key study characteristics and findings tabulated for ease of comparison.

Results

Figure 31 illustrates the PRISMA flow chart for the review of economic evaluations. The searches identified 125 potentially relevant abstracts. After abstract screening, 99 (79.2%) studies were excluded because they did not meet the inclusion criteria. Full text articles were sought for the remaining 26 (20.8%) studies for further assessment against the inclusion / exclusion criteria. Of those 26 studies, four studies were ultimately included in the review[97, 99-101]. A tabulated summary of the study characteristics and results is provided in Table 15 and a quality assessment against the NICE reference case provided in Table 16.



CA: Conference Abstract; EE: Economic Evaluation

Figure 31 PRISMA flow chart for review of cost-effectiveness studies

Table 15 Summary of study characteristics and results from the review of economic evaluations

Author, Year	**Hall, 2018[99]**	**Parikh, 2017[97]**	**Petrovic, 2015[100]**	**Shaw, 2011[101]**
Population	Adults, aged 18+	Adults, aged 18+, without ESRD or need for RRT	Paediatric, age 18 and under	Base case: 67 year old male
Setting	Hospital critical care (all-comers) and post cardiac surgery subgroup	hospital (ED) setting, data from 2 sites	Post-cardiac surgery, country unclear (assume Serbia)	Post-cardiac surgery
Objective	- To assess the potential cost-effectiveness of AKI biomarkers - To determine the value of future research	- To determine if NGAL can reduce hospital costs	- To determine cost-effectiveness of the candidate tests	To determine cost-effectiveness uNGAL for AKI diagnosis
Country	UK	USA	Unclear (assume USA)	UK
Intervention (s)	AKI biomarkers + standard care: - NephroCheck - Cystatin C (plasma) - Cystatin C (urine) - Cystatin C (serum) - NGAL (plasma) - NGAL (urine) - NGAL (serum)	Serum Creatinine + NGAL (urine)	- CysC (serum) - NGAL (urine) - uL-FABP	NGAL (urine) + current practice (monitoring of creatinine, blood urea nitrogen, urine output)
Comparator (s)	Standard care alone (serum creatinine and urine output testing)	Serum Creatinine alone	Serum Creatinine alone	Current practice alone
Source of effectiveness / diagnostic accuracy data	- No direct effectiveness data - Linked evidence approach - Diagnostic accuracy data obtained from a meta-analysis of diagnostic accuracy studies	N/A (cost only)	- Linked evidence approach - Selected literature	- Linked evidence approach - Selected literature
Evaluation type (DAM / RCT)	Decision tree (diagnostic pathway) + Markov cohort model (long term outcomes including CKD, ESRD [with or without dialysis], Transplant)	Cost-simulation	Decision tree (diagnostic pathway) + Markov cohort model (long term outcomes including CKD, ESRD, Transplant and death)	- Decision tree
Measure of benefit	QALYs	N/A	QALYs	QALYs

<table>
<tr><td>Author, Year</td><td>Hall, 2018[99]</td><td>Parikh, 2017[97]</td><td>Petrovic, 2015[100]</td><td>Shaw, 2011[101]</td></tr>
<tr><td>Perspective</td><td>NHS and PSS</td><td>Payer</td><td>3rd party payer</td><td>NHS perspective (though societal perspective stated)</td></tr>
<tr><td>Cost year</td><td>2015 prices</td><td>Unclear</td><td>Unclear</td><td>2008</td></tr>
<tr><td>Time horizon</td><td>Decision tree: 90 Days
Markov model: Lifetime</td><td>Unclear, assume hospital admission duration</td><td>Lifetime (max age 100)</td><td>Life time</td></tr>
<tr><td>Discount rate</td><td>Costs: 3.5% p.a
QALYs: 3.5% p.a</td><td>NR</td><td>Costs: 3% p.a
QALYs: 3% p.a</td><td>NR</td></tr>
<tr><td>Sensitivity analyses conducted?</td><td>Deterministic sensitivity analyses conducted around time horizon, test costs, AKI incidence, impact of early treatment, costs of AKI intervention, ICU utility, diagnostic accuracy, additional mortality risk for FP tests results, impact of negative test results

PSA conducted: Yes</td><td>Deterministic sensitivity analysis: varying hospital cost, LOS, proportion with baseline CKD, proportion developing UTI, costs of further testing.

PSA conducted: cost simulation</td><td>Deterministic sensitivity analysis: Incidence of AKI and associated mortality, sensitivity and specificity

PSA conducted: Yes</td><td>Deterministic sensitivity analysis: mainly different treatment effects, also: baseline AKI probability, probability of CKD, effect of early intervention on AKI, change in hospital costs, change in diagnostic accuracy, cost per NGAL test

PSA conducted: Yes</td></tr>
<tr><td>Base case results (including summary of incremental analyses)</td><td>
<table>
<tr><th>Test (ascending order of cost)</th><th>Inc. cost</th><th>Inc. QALY</th><th>ICER (vs. std care)</th><th>ICER (incr.)</th></tr>
<tr><td>Standard care</td><td>--</td><td>--</td><td>--</td><td></td></tr>
<tr><td>Cystatin C (serum)</td><td>+£149</td><td>+0.013</td><td>£11,476</td><td>£11,476</td></tr>
<tr><td>Cystatin C (urine)</td><td>+£155</td><td>+0.012</td><td>£13,449</td><td>Dominated</td></tr>
<tr><td>NGAL (urine)</td><td>+£164</td><td>+0.012</td><td>£13,742</td><td>Dominated</td></tr>
<tr><td>NGAL (plasma)</td><td>+£164</td><td>+0.012</td><td>£13,372</td><td>Dominated</td></tr>
<tr><td>Cystatin C (plasma)</td><td>+£166</td><td>+0.012</td><td>£13,504</td><td>Dominated</td></tr>
<tr><td>NGAL (serum)</td><td>+£215</td><td>+0.016</td><td>£13,828</td><td>£25,492</td></tr>
</table>
</td><td>
<table>
<tr><th>Test</th><th>Inc. cost (site 1)</th><th>Inc. cost (site 2)</th></tr>
<tr><td>Standard care</td><td>--</td><td>--</td></tr>
<tr><td>NGAL (urine)</td><td>-$408</td><td>-$522</td></tr>
</table>
</td><td>
<table>
<tr><th>Test (ascending order of cost)</th><th>Inc. cost</th><th>Inc. QALY</th><th>ICER (vs. std care)</th></tr>
<tr><td>Standard care</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>uL-FABP</td><td>+$8,522</td><td>+1.43</td><td>$5,959</td></tr>
<tr><td>sCysC</td><td>+$9,696</td><td>+1.37</td><td>$7,077</td></tr>
<tr><td>uNGAL</td><td>+$12,855</td><td>+1.38</td><td>$9,315</td></tr>
</table>
</td><td>
<table>
<tr><th>Test (ascending order of cost)</th><th>Inc. cost[A]</th><th>Inc. QALY[A]</th><th>ICER (vs. std care)</th></tr>
<tr><td>Standard care</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>uNGAL (tx: 12.5% improvement)</td><td>-£173</td><td>+0.03</td><td>Dominant</td></tr>
<tr><td>uNGAL (tx: 25% improvement)</td><td>-£428</td><td>+0.07</td><td>Dominant</td></tr>
<tr><td>uNGAL (tx: 50% improvement)</td><td>-£937</td><td>+0.14</td><td>Dominant</td></tr>
</table>
[A] Calculated from study
</td></tr>
</table>

Author, Year	Hall, 2018[99]	Parikh, 2017[97]	Petrovic, 2015[100]	Shaw, 2011[101]
	<table><tr><td>Nephro-Check</td><td>+£301</td><td>+0.016</td><td>£19,324</td><td>£12.86m</td></tr></table> *note some ICERs may not represent reported inc cost / inc. QALY due to rounding errors			
Sensitivity analysis results	All test results were sensitive to changes in assumptions around test guided changes in patient management and associated outcomes resulting from tests driven by diagnostic accuracy. Page 150 of Hall discusses the full range of sensitivity analysis results. High degree of uncertainty and feasible assumptions could change conclusions	Results were most sensitive to the costs in hospital and the assumptions about length of stay, additional test requirements and the baseline proportion of the population with CKD. Urine NGAL remained cost saving for all analyses undertaken	Significant variation in price was not found to impact on overall conclusions.	Under all conditions, NGAL in addition to current practice was the most cost-effective strategy when compared with current practice alone, even when the treatment effect was minimal. Results were driven by the impact of early intervention on hospital length of stay.

Table 16 Appraisal of included studies against the NICE reference case[98] and scope[102]

Attribute	Reference case and TA Methods guidance	Hall, 2018[99]	Parikh, 2017[97]	Petrovic, 2015[100]	Shaw, 2011[101]
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	Yes	Yes	Yes
Patient group	As per NICE scope (i.e. critically ill pre-icu)	No: ICU group of patients out-with the NICE scope which is pre-icu.	Partially, NICE scope includes adults as well as children	Partially, however NICE scope is broader than post cardiac surgery only.	Partially, however NICE scope is broader than post cardiac surgery only.
Perspective costs	UK NHS & Personal Social Services	Yes	No	No	Partially
Perspective benefits	All health effects on individuals	Yes	No	Yes	Yes
Form of economic evaluation	Cost-effectiveness analysis (QALYs)	Yes	No	Yes	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	No	Yes	Unclear
Synthesis of evidence on outcomes	Systematic review	Yes	No	No	No
Outcome measure	Quality adjusted life years	Yes	N/A	Yes	Yes
Health states for QALY	Described using a standardised and validated instrument (i.e. EQ-5D)	Yes, where possible	N/A	Unclear	Unclear
Benefit valuation	Time-trade off or standard gamble	Yes, where possible	N/A	Unclear	Unclear
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes, where possible	N/A	Unclear	Unclear
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	No	No	No
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	N/A	Yes	Yes
Probabilistic modelling	Probabilistic modelling	Yes	Yes	Yes	Yes
Sensitivity analysis	Deterministic sensitivity analyses conducted	Yes	Yes	Yes	Yes

Relevance of the included studies for the current decision problem

Of the four studies identified in the review, three conduct cost-effectiveness analyses based on decision analysis modelling. Two of the studies include decision trees to capture the diagnostic phase of the model and include Markov cohort modelling to capture the long-run sequelae of diagnosis and possible prevention of AKI. Both modelling strategies were similar and appropriate for the current decision problem, in that they both modelled the progression of AKI to CKD, End Stage Renal Disease (ESRD), transplantation and death. However, only one study (Hall et al.)[99] was conducted in the UK setting and provided results that might be informative for UK decision making. Hall et al. was also the only study to assess all the candidate tests specified within the NICE scope. Whilst Hall et al provide a comprehensive and high-quality assessment of the cost-effectiveness of the relevant tests, their setting relates to AKI occurring in the context of people already admitted to intensive care units and is therefore outside the scope for this assessment. Therefore, substantial revision of the Hall et al model is required, particularly for the early acute phase to generate results that are appropriate for decision making in critically ill patients who are at risk of AKI and are being considered for possible admission to ICU, but are not yet in the ICU setting.

Additional literature searches

Further searches were conducted to help develop the economic model. Broader searches were carried out to identify existing economic models in the area of AKI, in addition to those identified for the candidate biomarker tests. A separate search was also developed for health state utility data relevant to the health states included in the economic model. As searches for models and parameters were conducted by Hall et al up to 2016, our searches aimed to identify any relevant studies published after this date. Supplementary searches were carried out in Medline, Embase, NHS EED, HTA database, Research Papers in Economics, and ISPOR Scientific Presentations. The searches were undertaken on 11 September 2019 without any language restrictions. The relevant data are discussed in the subsections to follow.

Independent assessment of cost-effectiveness

A two-phase model was developed using TreeAge Pro, 2018 (TreeAge Software, Williamstown, MA, 2018)[103] to assess the cost-effectiveness of using biomarker tests to help detect the risk of AKI development and to help initiate early preventative care.

As described in Chapter 3, there was no direct evidence regarding the clinical effectiveness of biomarker guided preventative care versus standard monitoring guided preventative care on final health outcomes (e.g. AKI status, mortality, need for RRT). Therefore, a linked evidence approach was required to determine the potential value of the tests. The model structure was therefore built to reflect hypothesised associative benefits of averting AKI or reducing its severity through biomarker guided early intervention. The structure was informed by the review of cost-effectiveness studies and was based largely on Hall et al. who kindly provided access to their model (built in R) under a creative commons licence. The appropriateness of the model structure was validated with the External Assessment Group's (EAG) clinical experts. Data sources to populate the model are described in the sections that follow. The model was built and analysed following the guidelines stipulated in the NICE reference case for diagnostic test evaluation.[104]

Methods

Relevant population(s)

The baseline population and prevalence of CKD in hospital for the model was obtained from a Grampian population cohort (described below). The model base case analysis is therefore based on a mixed cohort of CKD and non-CKD patients, average age 63, 54.3% female.

Diagnostic biomarkers evaluated

The model aims to assess the cost-effectiveness of the NephroCheck test, NGAL urine (i.e. the ARCHITECT Urine NGAL assay and the BioPorto NGAL urine test), and the BioPorto NGAL plasma test in combination with standard clinical assessment, compared with standard clinical assessment alone (including serum creatinine and urine output) for evaluating critically ill people at risk of developing AKI and who are being assessed for possible critical care admission.

Model structure: Initial decision tree phase

The systematic review did not identify any randomised trials providing causal evidence for the effect of biomarker guided care versus standard monitoring (serum creatinine) guided care on patient relevant outcomes such as peak AKI severity, admission to ICU, need for renal replacement therapy, CKD or mortality.

In the absence of such data, the initial decision tree phase of the model used a linked evidence approach to first capture the potential impact of diagnostic test accuracy (sensitivity and specificity) on the probability of averting AKI or reducing its severity through earlier adoption of a KDIGO care bundle triggered by a positive biomarker test result. Second, the model then captures possible effects on changes in health outcomes through associative links between AKI severity and the relevant outcomes (need for ICU care, length of stay, 90 Day mortality, and development of CKD).

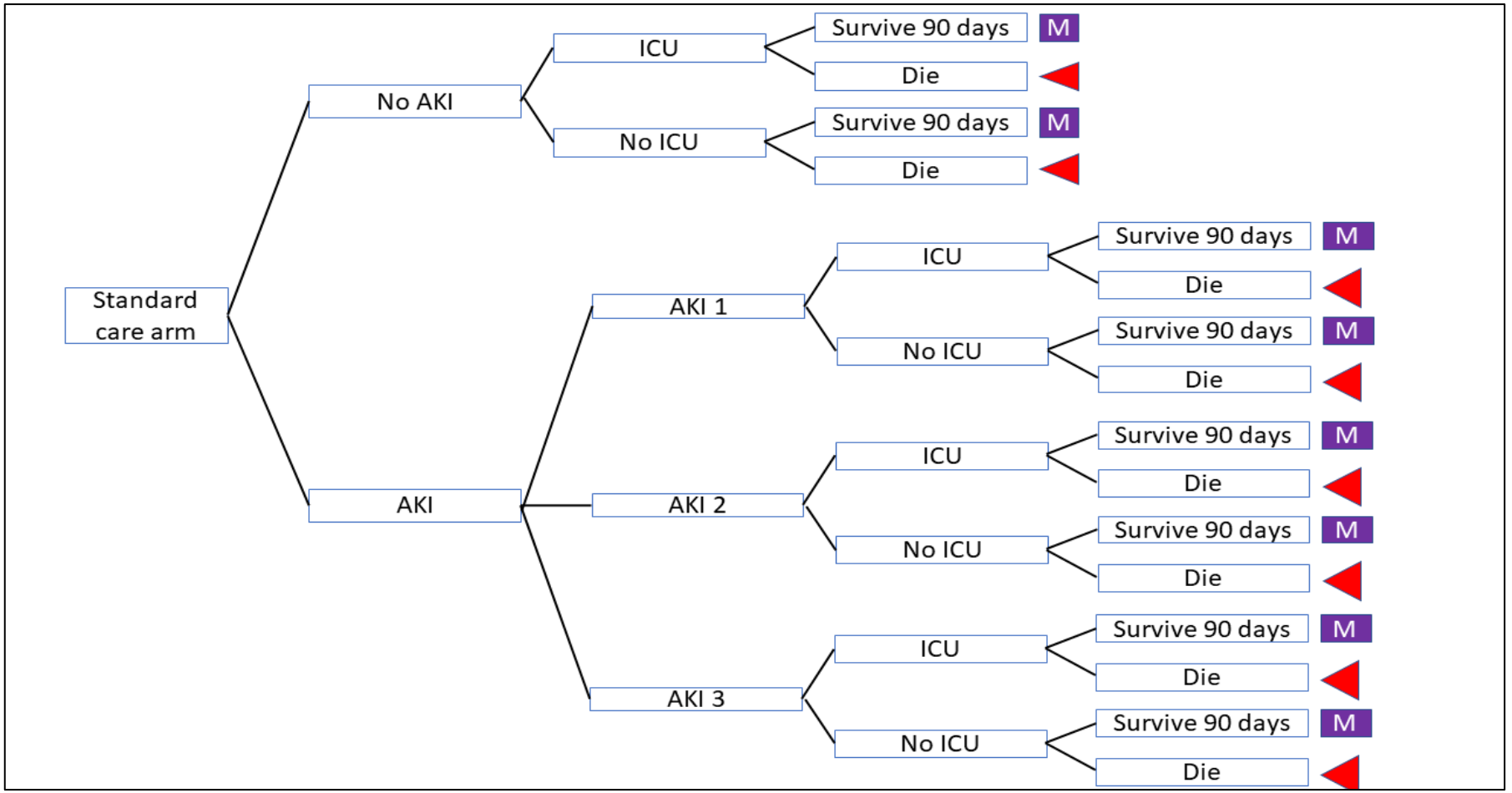
These associative links have been built up in the decision tree by re-analysis of observational data from Grampian.[105] The dataset includes 17,630 adult patients admitted to hospital in Grampian in 2003 and is the complete population of all patients who had an abnormal kidney function blood test on hospital admission, including all patients who developed AKI. The study methodology is described in detail by Sawhney et al,[106] but the data derived from the dataset used to populate the model are unpublished. These observational, population level data were used to define the starting age, sex, and underlying proportion of prevalent CKD cases in the modelled cohort. The data were also used to populate the model with respect to the distribution of peak AKI severity, as well as length of stay in hospital, probability of admission to ICU, and 90-day mortality parameters (by KDIGO AKI stage) for the decision tree phase of the model.

In the decision tree, patients who were critically ill in hospital, at risk of developing AKI, and who are having their kidney function monitored, are divided into two cohorts, those with AKI and those without AKI, depending on the underlying prevalence.[105, 106] The underlying prevalence of AKI was calculated directly from a more recent version of the Grampian dataset, describing all hospital admissions with at least one overnight stay in 2012 (for patients having their kidney function monitored). The base case prevalence of AKI generated from these data was 9.2%,

sampled probabilistically from a beta distribution in the model based on count data. Sensitivity analysis uses prevalence data directly from the systematic review studies used to generate the diagnostic test accuracy parameters.

AKI is defined in the model as patients who have or are destined to develop AKI during their hospital admission and is classified based on the peak severity of AKI. There is an assumption in the model that it is possible to avert AKI with early biomarker guided treatment in people who would otherwise develop it under standard care. However, it should be noted that in some circumstances it may not be possible to avoid AKI by earlier detection as AKI may not always be modifiable.[3] The probability of averting AKI is 0 in the standard care arm. AKI is split into 4 KDIGO defined stages (stage 1-3), with stage 3 split by the proportion of patients receiving renal replacement therapy or not. The initial phase of the model describes the associations between peak AKI classification and probability of admission to ICU, length of stay in ICU, length of hospital stay, and 90-day mortality. These associative effects are all derived from the Grampian population cohort described above. At the end of the 90 days, costs and QALY payoffs are assigned based on the decision tree pathway followed, before surviving patients enter the Markov cohort model.

The standard care cohort are assumed to be perfectly identified as having AKI or no AKI, based on a combination of serum creatinine levels, other diagnostic workup, and clinical expert opinion, which represents clinical practice. The hypothesised advantage of the biomarkers is that they may help to detect AKI earlier, but will not detect additional cases of AKI compared to current practice. Figure 32 provides an illustration of the initial decision tree pathways for the standard care arm of the model.



*Note that the AKI 3 pathway in the model is replicated for the proportion of the cohort receiving acute RRT and those not receiving acute RRT

Figure 32 Simplified decision tree structure up to 90 days for the standard care (Scr) arm of the model

The intervention (test) arms of the model are similarly split into AKI and no AKI, according to the same prevalence data, but all receive additional testing. It is assumed that the background diagnostic work-up is similar for all arms of the model (i.e. all patients will continue to have their serum creatinine and urine output monitored). As the diagnostic accuracy test data are primarily based on single use of the test, it is assumed in the base case model that each test will be administered once only. It is assumed that the test is administered as soon as possible after the patient has been determined to be at risk of AKI to enable early detection and preventative measures to be implemented. Sensitivity analysis explores the impact of more frequent multiple use tests on the results.

The diagnostic accuracy of the candidate tests in addition to serum creatinine, compared to serum creatinine alone was obtained from the results of the systematic review and meta-analysis described in Chapter 3. Table 17 describes the diagnostic accuracy parameters, namely sensitivity and specificity, used in the modelling. All diagnostic data are incorporated probabilistically in the model, accounting for the joint uncertainty in sensitivity and specificity for each biomarker test. The logit of the sensitivity / specificity for each of the biomarker tests was derived from the meta-analysis of diagnostic accuracy studies. The model specified the correlation between sensitivity and specificity parameters (on the logit scale). These parameters were converted to Cholesky decomposition matrices, with the decomposed data referenced by multi-normal distributions, sampling from the mean and standard error (on the logit scale). The probabilistic draws were back-transformed from the logit scale for application in the model. It should be noted that diagnostic accuracy data obtained from the meta-analyses are based on heterogeneous studies with different thresholds. This is particularly true for the NGAL assays, and therefore the results of the economic model, particularly for comparisons between different NGAL assays should be interpreted cautiously. Further details have been provided in Chapter 3.

Table 17 Sensitivity and specificity data used in the model.

Test	Parameter	Mean value (95% CI)	Mean (logit scale)	Standard error (logit scale)	Correlation for MVN distribution (logit scale)	Source
Nephro-check	Sensitivity	0.75 (0.58 to 0.87)	1.1178	0.3967	-0.824	Meta-analysis (Chapter 3)
	Specificity	0.61 (0.49 to 0.72)	0.4573	0.2567		
NGAL plasma (BioPorto)	Sensitivity	0.76 (0.56 to 0.89)	1.1563	0.4615	-1.000	Meta-analysis (Chapter 3)
	Specificity	0.67 (0.40 to 0.86)	0.6863	0.5659		
NGAL urine Abbot ARCHITECT	Sensitivity	0.67 (0.58 to 0.76)	0.7273	0.2047	-0.5168	Meta-analysis (Chapter 3)
	Specificity	0.72 (0.64 to 0.79)	0.9553	0.1909		
NGAL urine BioPorto	Sensitivity	0.73 (0.65 to 0.80)	1.017	0.195	+0.526	Meta-analysis (Chapter 3)
	Specificity	0.83 (0.64 to 0.93)	1.562	0.511		

For the respective biomarker test groups, the proportion of true AKI cases that are true positive (TP), and false negative (FN) is determined by test sensitivity, whilst the proportion of AKI negative cases that are true negative (TN) or false positive (FP) is determined by the test specificity.

Based on the External Assessment Group's (EAG) own clinical expert opinion, it is assumed in the base case that patients testing negative would not have any adaptions made to their care pathway. That is because it would be unlikely that care would be de-escalated based solely on a negative NephroCheck or NGAL result, as the conservative practitioner would wait to ensure no rise in serum creatinine before concluding no AKI was present and stepping down care.

The model assumes that all patients will receive the KDIGO care bundle once they are defined as AKI positive using current standard practice methods (i.e. monitoring

serum creatinine and urine output), regardless of their NephroCheck or NGAL test result. The potential to benefit from use of the biomarkers therefore lies in early adoption of a preventative care bundle. For patients testing positive, the model includes the functionality to reflect uncertainty in clinical decision making, that is the probability that a positive test would be acted upon. This parameter is assumed to take a value of 100%, in accordance with best practice guidance where positive biomarker tests should have a preventative KDIGO care bundle implemented with the associated costs. Whilst all positive test results will trigger the KDIGO bundle, only those who are TP will accrue any potential benefits of having their AKI averted, or having reduced severity (i.e. peak KDIGO stage) AKI. For exploratory scenarios where a test might not be acted upon in practice, the cohort would follow standard care pathways according to whether they had AKI or not as measured using current clinical practice.

There is no direct evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, risk of 90-day mortality or development of new / progression of existing chronic kidney disease). Therefore, a linked-evidence approach was required, where we have relied on observational associations to infer how prevention or mitigation of AKI may affect changes in health outcomes. The associative effects are benefits of averting or mitigating AKI that lead to better health outcomes (need for ICU care, CKD and mortality).

These associations necessitate causal assumptions, but while a causal link between AKI and poor outcomes is plausible, the extent of this causal relationship is uncertain and controversial. It cannot necessarily be assumed that by averting or changing the severity of AKI, a patient would have the exact same risks (associative effects from the Grampain observational data described above) of ICU and mortality as a patient who was never going to develop AKI in the first place.

As the true causal relationship between AKI and health outcomes is unknown, the model includes the functionality to apply none, all or a proportion of the relative risk of health outcomes such as ICU, mortality and CKD (AKI vs. none) to the AKI

averted proportion of the cohort. This is achieved whilst maintaining the observational associations in the standard care arm of the model.

The base case analysis assumes that there are no adverse health consequences of a false positive test on either NephroCheck or NGAL. Clinical expert opinion indicates that there may be a risk to a patient's health of inappropriate fluid resuscitation, delay of access to appropriate imaging due to concerns regarding contrast exposure, or removal of the most effective but potentially nephrotoxic treatments for a critically ill patient. However, the magnitude of this negative effect is difficult to quantify. Sensitivity analysis therefore explores scenarios where an additional mortality risk is added for FP tests.

In summary, the early stage, up to 90 days, costs and outcomes depend on a) the diagnostic accuracy of the test, b) clinical decision making in the presence of positive or negative test results, c) the initiation of a KDIGO care bundle to avert AKI and amend the distribution of peak AKI severity and d) the degree to which the hypothesised associative effects between AKI and final health outcomes, such as length of hospital stay, admission to ICU, need for RRT, 90 day mortality and risk of CKD is modifiable simply by amending the AKI distribution.

Model structure: follow up Markov model

One potential route to patient benefit is that avoiding AKI or reducing its severity may reduce the risk of later developing CKD. As CKD is defined as a minimum of 3 months of persistent reduced renal function[107, 108], progression from AKI to CKD is incorporated in the Markov phase of the model.

Figure 33 illustrates the long term follow up model structure.

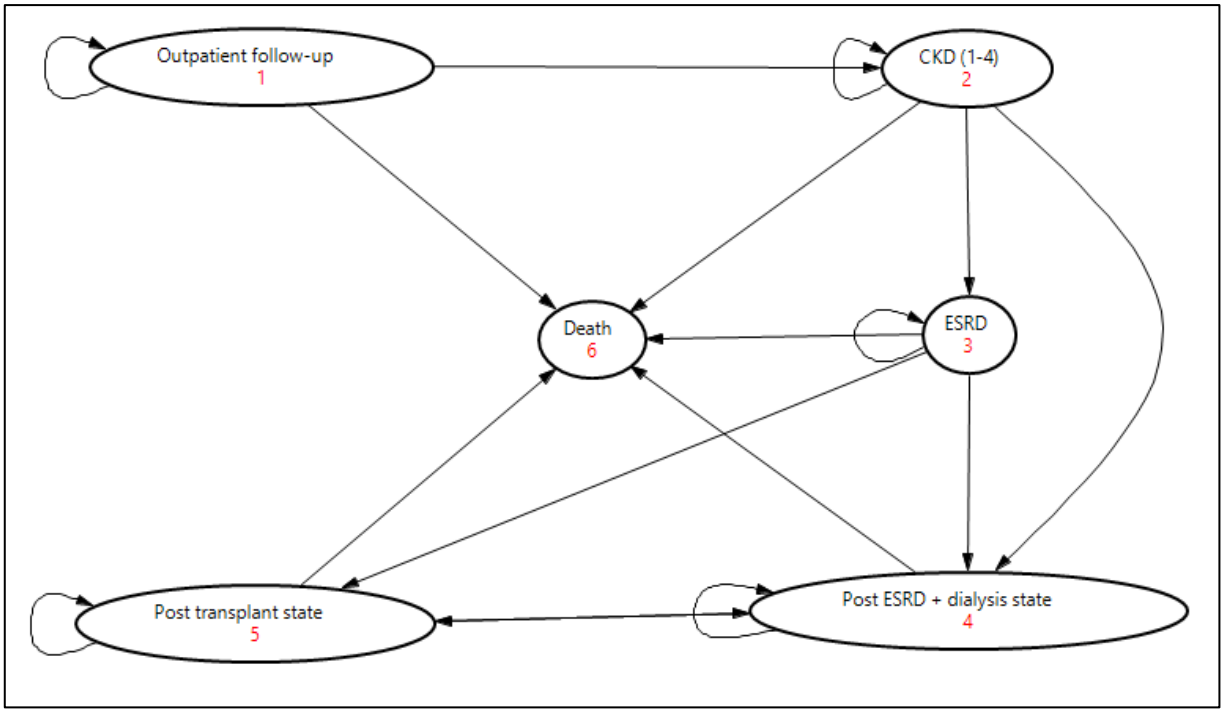


Figure33 Markov chronic model phase structure

After 90 days, the surviving cohort from each of the decision tree pathways enters a life-time Markov model. The model follows a similar structure to Hall et al[99] and Parikh et al[97] with six mutually exclusive health states: outpatient follow up, chronic kidney disease (stages 1-4), ESRD not requiring dialysis, ESRD requiring dialysis, post-transplant and death. The cohort either enter the model in the outpatient follow up state, where they experience an annual baseline risk of developing CKD, or they can directly enter in the CKD state, with the starting proportion in the CKD state determined by the underlying CKD prevalence, and the severity of AKI from the acute (decision tree) phase of the model. The base case model assumes the outpatient cohort have an increased risk of CKD in the first cycle that is dependent on their AKI experience, but thereafter the transition between the outpatient follow up and CKD states is independent of whether a patient had AKI in the hospital period. Sensitivity analysis explores the impact of an increased CKD risk applied for the full life-time horizon as per Hall et al.[99]

The cohort are then modelled to transition through the disease pathway, starting with CKD stages 1-4 (defined as a single Markov state), to ESRD, with or without the requirement for dialysis, the need for transplant, the success or failure of that

transplant, and ultimately progression to death with state specific mortality probabilities. The proportion of the cohort having a transplant failure are assumed to return to the dialysis health state where they have the same probabilities of a second transplant as a first. The cohort are exposed to a probability of all-cause mortality from each model state and are assigned mortality probabilities based on the higher value of age and sex adjusted all-cause mortality (ACM) or the disease state specific mortality obtained from the literature.

Model parameters – probabilities and duration of length of stay

Early phase probabilities and length of stay (LOS):

The potential associative links between AKI and ICU admission, ICU LOS, hospital LOS and 90-day mortality are all sourced from the Grampian dataset. For chance nodes in the decision tree with only two possible branches, probabilities are sampled from beta distributions. Where there are three or more branches, probabilities are incorporated using Dirichlet distributions.

The model assumes, based on expert opinion and consistent with Hall et al[99] that RRT is provided only in AKI stage 3 and this is deemed reflective of most current clinical practice. Assuming no RRT in patients who have a peak AKI of stage 1 or 2 might be considered a favourable scenario for biomarker tests that can reduce AKI severity, thereby generating reductions in cost. In the absence of published UK data, the proportion of AKI 3 patients requiring RRT is taken from a retrospective analysis of N=5242 ICU survivors with AKI, across 23 French intensive care units.[109] N=1603 had KDIGO AKI stage 3, of which 55.2% received RRT. It is assumed that the French ICU setting is broadly transferrable to a UK pre-ICU setting for critically ill patients and is therefore appropriate for populating the model. Data reported from Hall et al are not used because they relate only to a single UK ICU setting with a small sample of AKI 3 (N=18). The EAG's clinical experts validated these data as relevant to the UK setting and noted that the probability was lower than that applied in Hall et al, which was consistent with clinical experience outside the ICE setting. Further, more detailed data on need for RRT in England is currently being collected by the UK renal registry but is not yet publicly available. Table 18 describes the early phase probability parameters applied in the model.

Table 18 Model parameters for acute, decision tree, phase of the model

	n	N	%	RR	Standard error	Distribution	Source
Incidence of AKI[A]							
No AKI	42,570	46,884	0.908	--		Remainder	Grampian data[110]
Any AKI	4314	46884	0.092	--	--	Beta	Grampian data[110]
AKI1 (given AKI)	2,965	4,314	0.687	--	--	Dirichlet	Grampian data[110]
AKI2 (given AKI)	836	4,314	0.194	--	--	Dirichlet	Grampian data[110]
AKI3 (given AKI)	513	4,314	0.119	--	--	Dirichlet	Grampian data[110]
Probability of admission to ICU							
No AKI	197	14,204	0.014	--	0.0038	Beta	Grampian data[105]
AKI 1	208	2072	0.100	--	0.0254	Beta	Grampian data[105]
AKI 2	116	812	0.143	1.423	0.1082	LN vs. AKI 1	Grampian data[105]
AKI 3	105	542	0.194	1.930	0.1096	LN vs. AKI 1	Grampian data[105]
Probability of 90 Day mortality							
No AKI	692	14,204	0.049	--	0.0069	Beta	Grampian data[105]
AKI 1	446	2,072	0.215	--	0.0347	Beta	Grampian data[105]
AKI 2	280	812	0.345	1.602	0.0640	LN vs. AKI 1	Grampian data[105]
AKI 3	251	542	0.463	2.151	0.0624	LN vs. AKI 1	Grampian data[105]
Probability of requiring renal replacement therapy							
No AKI, AKI 1 & 2	0	--	--	--	--	--	Assumption
AKI 3	885	1603	0.550		--	Beta	Truche et al. 2018[111]

[A] Note that incidence of AKI data are obtained from 2012 Grampian cohort, whereas probabilities of ICU admission and 90 day mortality are obtained from an earlier (2003) dataset.

The data described show potentially strong associations between AKI status or severity of AKI, and the probability of needing ICU care, and of dying within 90-days following hospital admission. However, these data should not be interpreted as definitive causative effects and sensitivity analysis explores the application of different assumptions around these highly uncertain associations.

Table 19 reports the average LOS in hospital and in ICU. Data for length of stay in hospital are obtained from the Grampian dataset but ICU LOS was unavailable by peak AKI status. ICU LOS data were therefore obtained from an alternative source, Bastin et al. 2013,[112] a large cohort study of N=1881 adults who had cardiac surgery

(and therefore deemed critically ill, and sufficiently matching the scope for this assessment). Bastin et al reported median los in ICU by AKI stage (according to AKIN and KDIGO criteria). Given the likely skewed distribution of LOS data, a log-normal distribution, fitted to mean and median days duration is used to generate the simulated draws for the probabilistic analysis. As mean LOS in ICU was not available to parameterise the LN distribution, it was assumed that the mean was twice the median, reflecting the ratio of mean : median days stay reported in the Leeds Teaching Hospitals NHS Trust, AKI registry data, for ICU patients, as reported in Hall et al.[99]

As the variable 'hospital length of stay' also includes the time spent in ICU, the time on hospital ward is obtained by subtracting ICU LOS from total hospital LOS for the application of costs and utilities in the model. As the probabilistic analysis samples independently from these distributions, an additional correction is added to the model to ensure LOS in ICU cannot exceed LOS overall in hospital in any of the sampled draws. The average LOS in hospital / ICU for those with a peak AKI 3 is applied to both those requiring / not requiring RRT. The assumption that requirement for RRT would not usually extend the hospital admission for this patient cohort has been validated by the EAG's clinical experts.

Table 19 Duration parameters used for the acute phase of the model

	Mean	SD	Median	IQR	N	Distribution	Source
Hospital LOS							
No AKI	8.1	22.8	3	1 to 8	14204	LN	Grampian data
AKI 1	26.3	38.1	14	7 to 31	2072	LN	Grampian data
AKI 2	32.4	56.5	18	8 to 36	812	LN	Grampian data
AKI 3	28.4	32.5	17	9 to 35	542	LN	Grampian data
ICU LOS [A]							
No AKI	2	--	1	1 to 2		LN	Bastin et al. 2013[112]
AKI 1	4	--	2	1 to 3		LN	Bastin et al. 2013[112]
AKI 2	8	--	4	1 to 8		LN	Bastin et al. 2013[112]
AKI 3	26	--	13	6 to 27		LN	Bastin et al. 2013[112]

AKI: Acute Kidney Injury; ICU: Intensive Care Unit; IQR: Inter-quartile range; LOS: Length of Stay

[A] For LOS in ICU, only median LOS information was available. For the purposes of parameterising the LN distribution and to account for the likely skewed nature of the data, it was assumed that the mean was twice the median. This ratio was obtained by dividing the mean LOS reported in Hall et al by the median LOS for all AKI patients in the ICU setting.

The relative effects of diagnostic biomarkers on AKI and clinical outcomes: the impact of early adoption of a KDIGO care bundle

The impact of an early KDIGO care bundle on AKI

National level guidelines[16] indicate that a patient defined as being at risk of developing AKI, through a positive biomarker result, should have all appropriate efforts to ensure that AKI does not develop, and if it does, should be minimised in terms of severity (i.e. providing maximum support possible for the kidneys). The model therefore assumes that all AKI patients will receive a KDIGO care bundle, and the only difference between the testing strategies is the duration for which that bundle is implemented, with earlier implementation assumed to incur additional resource use in terms of fluid management, nephrologist review and pharmacist review of medications as well as the removal of any potentially nephrotoxic agents where necessary.[15]

There are two potential mechanisms by which early adoption of a KDIGO care bundle might lead to patient benefit. These are a) to avert AKI in people in whom it would

otherwise develop, and b) to shift the distribution of AKI severity (between KDIGO AKI stages 1-3) given that it occurs.

Hall et al. conducted a review of the literature to identify studies testing the impact of early preventative intervention for AKI.[99] Their searches identified 8 studies relevant to early intervention in the UK setting (excluding early RRT which was deemed contentious). Four studies explored the impact of early nephrologist involvement which was deemed to be most reflective proxy for the non-specific care bundles that a patient may access as part of the KDIGO care bundle recommendations.[15] The largest of these 4 studies, with a sample of 1,096 was used in the Hall et al. economic model, reporting that early nephrologist consultation reduced AKI incidence, adjusted odds ratio (early involvement vs. not): 0.71 (95% CI 0.53 to 0.95).

The EAG have conducted a further supplementary targeted search of trials for the post-Hall period to identify any further potentially relevant studies exploring the impact of early preventative intervention or application of AKI care bundles on the probability of developing AKI and / or the severity of peak AKI. In brief, 39 additional titles and abstracts were identified from the targeted searches, of which 17 (44%) were full text assessed. Based on the NICE scope,[102] KDIGO care guidelines,[15] and clinical expert opinion, it was decided that studies testing the impact of a KDIGO care provided the most appropriate source of data to populate the economic model. Three trials (18%) assessed the effect of NephroCheck guided application of a KDIGO bundle compared to standard care treatment where information about the NephroCheck test result was not available to the patient's hospital care team. No studies assessed the impact of NGAL guided treatment.

All three studies reported results in terms of the probability of developing AKI.[113-115] However, only 1 study (Meersch et al)[113] described the impact on both the incidence and severity of AKI. Meersch et al reported the results of a single centre trial, with sample N=276, in a German setting. The population all had positive NephroCheck test results, using a 0.3 threshold, consistent with the sources of diagnostic accuracy data obtained from the systematic review of diagnostic accuracy studies (see Chapter 3). Patients were then randomised to receive a strict implementation of the KDIGO guidelines or standard care. The intervention group included avoidance of

nephrotoxic agents, discontinuation of ACEi and ARBs, close monitoring of urine output, serum creatinine, avoidance of hyperglycemia (for 72 hours), consideration of alternatives to radiocontrast agents, and fluid optimisation. The control (standard care) group followed the recommendations of the American College of Cardiology Foundation 2011 and included specification to keep mean arterial pressure (MAP) >65 mmHg and central venous pressure (CVP) between 8 and 10 mmHg. ACEi and ARBs were used only when the hemodynamic situation stabilised and hypertension occurred. Knowledge of the NephroCheck test result was not revealed to the treating hospital team for patients in the standard care arm of the study. The primary outcome from Meersch et al was 72-hour AKI, and the study showed an absolute risk reduction of 16.6% (95% CI: 5.5% to 27.99%). The Meersch et al study was supported by the German Research Foundation, the European Society of Intensive Care Medicine, the Innovative Medizinische Forschung, and an unrestricted research grant from Astute Medical.

A second (Gӧcze et al),[114] smaller study (N=121), also in a German setting, showed that NephroCheck guided care demonstrated a trend towards a lower probability of AKI , though results were not statistically significant with OR (95% CI) for standard care vs. NephroCheck of 1.96 (0.93 to 4.10). The study did however show a significantly greater odds of AKI (defined as stage 2 and 3 combined), in the standard care group compared to NephroCheck: OR (95% CI) for standard care vs. NephroCheck: 3.43 (1.04 to 11.32). A third study (Schanz et al),[115] with only N=100 participants, compared the effect of a NephroCheck triggered consultation with the patient implementing KDIGO recommendations for AKI to standard care alone in an emergency department in Germany. AKI outcomes were similar in both groups. The probability of AKI 2 or 3 at day 1 and day 3 post admission was intervention: 32.1%; control: 33.3% and intervention: 38.9% and control: 39.1% respectively. Neither the Gocze et al study nor the Schanz et al study report any funding involvement from the test manufacturers.

As the Meersch et al study has a larger sample, and reports data for both the probability of AKI and the distribution of AKI severity given that it occurs these data were used for the model base case analysis. While the clinical context of the immediate post-operative period after cardiac surgery from Meersch et al. is likely to

be generalisable between the UK and other countries, the nature of the AKI insult (ischaemia/reperfusion, post-operative haemodynamic, oxidative stress, haemolysis, in people with cardiac comorbidity) is specific to this context, as is acknowledged by the authors. Accordingly, this study may not be generalisable to AKI in the context of other acute or critical illness circumstances where biomarker performance and the potential for AKI prevention / mitigation may be different.

Table 20 describes the potential impacts of a biomarker guided care bundle on 1) the chance that patients may get AKI, and 2) the severity of AKI given that it occurs. The assumption is that early biomarker guided implementation of the KDIGO care bundle may reduce the proportion who get AKI and help ensure that if they do get AKI, it will be of reduced severity. These effects are applied probabilistically as relative risks in the model for those with a true positive test results only, using Log Normal distributions.

Table 20 The effects of early adoption of A KDIGO care bundle

Parameter	Mean RR[B]	SE, Log RR[B]	Dist.	Source
NephroCheck (and NGAL)[A]				
Any AKI	0.768	0.094	LN	Meersch et al[113]
AKI 1 (given AKI)	1.232	0.180	LN	Meersch et al[113]
AKI 2 (given AKI)	0.868	0.180	LN	Meersch et al[113]
AKI 3 (given AKI)	0.843	0.356	LN	Meersch et al[113]

[A] Base case assumes that the impact of NGAL guided care on AKI is the same as NephroCheck guided care. Sensitivity analysis explores a scenario where NGAL cannot avert AKI.
[B] Mean RR and SE log RR calculated by the EAG using data from Meersch et al[113].

In the absence of any data on the impact of NGAL guided KDIGO care bundles on the probability of developing AKI, or the severity of AKI, the base case model assumes that the potential to avert AKI is similar for both biomarkers. However, based on clinical expert opinion and the manufacturer described role of the tests, NGAL measures injury and can be used to define AKI, whereas NephroCheck can identify stress enabling intervention before AKI develops. Therefore, sensitivity

analysis explores a scenario where the RR of AKI for NGAL guided care is equal to 1, whilst retaining the same effect on the AKI distribution given that AKI occurs as for NephroCheck. It is acknowledged that these assumptions are uncertain, and the sensitivity analysis may present a bias against NGAL if data were to become available to suggest an effect on AKI prevention.

It was assumed that there are no negative health effects of early intervention for the proportion of the respective test groups with FP results, but the additional costs of the bundle were still incurred. The model also includes the functionality to explore the impact of an additional mortality risk; for example, due to excessive resuscitation as a result of fluid administration or removal of effective but nephrotoxic treatments in patients with a false positive test result.

Whilst the model describes the impact of biomarker guided early intervention on the distribution of AKI, it is unclear whether these effects translate into final clinical and patient relevant health outcomes like requirement for ICU care, need for RRT, mortality or the development of CKD. The limited evidence that exists from Meersch et al. suggests that whilst there is a significant reduction in the primary study outcome of AKI within 72 hours for NephroCheck guided implementation of a care bundle compared to standard critical care, OR (95% CI): 0.483 (0.293, 0.796), this ability to avert AKI was not demonstrated to translate into improvements in a range of clinical and patient relevant outcomes, including: requirement for RRT therapy in hospital, OR (95% CI): 1.618 (0.676, 3.874), 90 day all-cause mortality, OR (95% CI): 1.213 (0.486, 3.028), ICU LOS, median difference (95% CI): 0(-1,0) or hospital LOS, median difference (95% CI): 0(-1,1). While the study was not powered to detect differences in these outcomes, there are no trends in the data that are suggestive of an effect size. Furthermore, the uncertainty regarding the link between increased resource use and clinical outcomes is emphasised by Wilson et al.[116] who show in their RCT of an electronic alert system for AKI that an early warning system increase resource utilisation (e.g. renal consultation), but with no evidence that this translates into measurable clinical or patient benefit in terms of mortality, or length of stay. Indeed, for a subgroup on a surgical ward, the mortality rate was significantly higher in the electronic alert group. As these causal links between AKI and changes in health outcomes are all highly uncertain and are hypothesised based on observational data in

the model, extensive sensitivity analyses are conducted to test the impact of a range of plausible assumptions on cost-effectiveness.

Follow-up phase probabilities

Starting proportions applied in Markov cohorts

One plausible route to patient benefit from averting or reducing the severity of AKI is through the prevention of new CKD and the indirectly associated longer-term progression to ESRD and transplant. It should be noted that the model does not assume a direct effect of peak AKI on ESRD at 90 days, therefore patients can only enter the Markov model in either the outpatient follow-up, or CKD (stage 1-4) health state. A re-analysis of 2012 data from the Grampian cohort indicate that only a very small proportion 13/4314 (~0.03%) of patients with AKI, almost all of whom had underlying CKD, progressed directly to ESRD at 90 days. Therefore, we assumed no direct transition from the decision tree to the ESRD state in the Markov model. The starting proportions (after 90 days) for each health state are dependent on the decision tree pathway through which the cohort have come, and what peak AKI severity they had. The baseline prevalence of CKD in the UK general population has been estimated from Kerr 2017 at 6.1%.[117] However, in a group of critically ill, hospitalised patients, this prevalence may be substantially higher. For the base case analysis, we use the underlying prevalence of CKD in the Grampian dataset, calculated as the prevalence of CKD in all hospitalised patients having their kidney function monitored. Multiplying through by the sampling fraction for no CKD (20%) and taking the proportion of CKD / full sample gives the baseline prevalence in this group, calculated as 5,935 / 53,691 (11.05%).

Health state transition probabilities

The baseline incidence of new onset CKD for the Markov model uses the same source as Hall et al. with an annual probability of progressing from the outpatient to CKD state of 0.0044 95% CI: (0.0039 to 0.0049) for patients in the no AKI cohort.[118] The data are obtained from a large cohort study of 97,782 ICU patients enrolled on the Swedish intensive care register. The parameter value 0.0044 reflects the CKD incidence at 1-year post ICU admission for the proportion of patients with no AKI. The same baseline proportion of CKD was applied for those without AKI, and for

those modelled to have AKI averted due to early preventative treatment. The proportion of the 'no AKI' cohorts starting in the CKD state at day 90 was calculated as the underlying prevalence + the new annual incidence adjusted to the 90-day time horizon of the decision tree component of the model.

Hazard ratios for AKI1, AKI2 and AKI3 on the development of CKD (defined as CKD stage 3 or above) were obtained from a systematic review by See et al.[119] The review included a total of 82 studies quantifying the association between AKI and longer-term renal outcomes (including CKD) and mortality. However, only 3 studies reported the impact of each KDIGO stage of AKI on CKD development. One study (N=104,764) in a UK setting generated slightly counter intuitive results with point estimates of the HR reducing as AKI stage increases. However, two other Asian studies (N=77 and N=1363) illustrated an increasing HR for more severe AKI stages. The systematic review has meta-analysed these three studies and the summary effects by AKI stage on CKD, defined as CKD stage 3, are used in the base case analysis. The advantage of these studies is that they allow a demonstration of the impact of adapting the distribution of AKI severity on longer-term development of CKD. However, they are not conducted in a UK setting and may lack relevance. Therefore, as a sensitivity analysis we apply a HR for the association between AKI and CKD that is constant across all AKI stages, as reported by Sawhney, 2017 for N=9004 hospitalised patients with AKI in Grampian. The HR for development of stage 4 CKD (AKI vs. no AKI) was 2.55 (1.41 to 4.64). This study has the advantage of relevance to the setting but does not include risks by AKI severity. However, it should be noted that the definition of CKD is stage 4 in Sawhney et al compared to Stage 3 in the meta-analysed studies which may limit comparability of the reported HRs.

The HRs of CKD by AKI stage are applied to the new incidence over the first 90 days and to the first annual transition in the model. Thereafter, the transition probabilities from outpatient follow up to CKD follow the baseline 0.0044 per year. This approach is based on expert opinion that any longer-term effect of AKI on CKD development will become attenuated over time, particularly if it has not occurred in the first year following hospital discharge. Sensitivity analysis explores a scenario where the HR of CKD is applied for the full duration of the model, reflecting the assumption applied in Hall et al.[99]

Prevalence of CKD and incidence of new onset CKD are parameterised in the model using beta distributions and the hazard ratios for the effect of peak AKI severity on CKD incidence (i.e. transition probabilities to CKD state) are parameterised using log normal distributions. Table 21 describes the relevant parameters.

Table 21 Parameters to link AKI and CKD

Parameter	n	N		%	HR	Standard error	Distribution	Source
Prevalence of CKD (starting proportion)	5,935	53,691		0.1105	--	--	Beta	Grampian data
Baseline incidence of CKD	--	--		0.0044	--	0.0003	Beta	Rimes-Stigare et al[118].
Hazard Ratio of CKD given AKI1					2.32	Ln SE: 0.0363	LN	See et al[119]
Hazard Ratio of CKD given AKI2					4.00	LN SE: 0.5656	LN	See et al[119]
Hazard Ratio of CKD given AKI3					7.98	LN SE: 0.9675	LN	See et al[119]

Progression from CKD

The transition probability from outpatient follow-up to CKD is 0.0044 as described above. The model cohort can then subsequently progress from CKD to ESRD, with or without dialysis and from ESRD to transplant according to the modelled transition probabilities. It is assumed that AKI can only influence the number of people who get CKD, and then has no further direct effect on how fast they progress through the CKD stages to ESRD, dialysis or transplant. The cohort are also exposed to an increasing mortality risk as they progress through more severe disease states from CKD (1-4) to ESRD without dialysis, and ESRD with dialysis. Transitions from CKD (1-4) to ESRD, from ESRD (no dialysis) to ESRD (with dialysis) and from CKD (1-4) / ESRD to death are obtained from Kent et al. who reported data on progression of kidney disease from the large (N=7246), international (Europe, North America and Australasia) Study of Heart and Renal Protection (SHARP) RCT.[120] The median study follow-up was 4.9 years, with a mean age of 63 and 64% male.

For those with ESRD on dialysis, the proportion transiting to kidney transplant and mortality were obtained from 5-year data published in the 2018 UK Renal Registry report (Table 1.17) which provided information on transition from incident RRT in 2012, to transplant and mortality 1, 3 and 5 years later.[1.21] The 3- and 5-year probabilities were annualised; the year 3 probability was applied to year 2 and 3, while the 5-year probability was applied to years 4 onwards. These probabilities were converted to the relevant annual cycle specific probabilities and applied in the model using tunnel states to track time from entering a given health state. The UK renal registry also provided data on the probability of transition back to dialysis for failed transplants and the probability of death over 5 years following transplant. After 5 years post-transplant, mortality is assumed to revert to the general population all-cause mortality probability and the annual probability of transplant failure remains at that reported from years 3-5 in the UK renal registry. It is further assumed that the proportion of the cohort with a transplant failure return to dialysis where their probability of progressing from ESRD on dialysis to a second transplant is the same as progression to the first transplant.

In the first 5 years of the follow-up phase of the model, mortality in all Markov states is modelled as the average mortality risk for patients discharged from hospital and ICU, unless health-state specific (ESRD, dialysis or transplant) mortality was higher, in which case the latter is applied. If at any point mortality falls below all-cause mortality, all-cause mortality is applied in the model. The 5-year post-discharge mortality data were based on Lone et al., a matched UK cohort study (mean age of 60) using national registries; the Scottish Intensive Care Society Audit Group (SIGSAG), the Scottish Morbidity Record of acute hospital admissions (SMR01) and the Scottish death records. The model base case used an average of the ICU and non-ICU cohorts. Beyond 5 years, patients in the outpatient follow-up health state were applied the age and sex adjusted all-cause mortality probability[122], and those with CKD, ESRD, chronic dialysis or a transplant would be assigned the health state specific mortality probability, unless age and sex adjusted all-cause mortality was higher than the health state specific mortality. Sensitivity analysis explores the impact of assigning long-term mortality risks that are dependent on whether the cohort had been admitted to ICU or not during their index hospitalisation (as described in Table 22).

Transition probabilities are incorporated into the model probabilistically using beta distributions. As the cycle lengths for the model in Hall et al are the same as the current assessment (annual), it was not necessary to provide any further adjustment of the published transition probabilities.

Table 22 Transition probabilities used in the Markov model

Parameter	Value	SD	Alpha	Beta	Dist.	Source
From outpatient state						
Outpatient to CKD	0.0044	0.0003	--	--	Beta	Rimes-Stigare et al[118]
Outpatient to death [B]	No ICU: Yr 1: 0.075 Yr 2-5[A]: 0.164 ICU: Yr 1: 0.108 Yr 2-5[A]: 0.225		No ICU: Year 1: 391 Years 2-5[A]: 748 ICU: Year 1: 564 Year 2-5: 964	No ICU: Year 1: 4,824 Years 2-5[A]: 3,810 ICU: Year 1: 4,651 Year 2-5: 3,322	Beta	Lone et al[123].
Remain outpatient				--	Remainder	
From CKD						
CKD to death	0.03	0.002	--	--	Beta	Kent et al[120]
CKD (survivors) to ESRD	0.01	0.001	--	--	Beta	Kent et al[120]
CKD (survivors) to ESRD + dialysis	0.04	0.002	--	--	Beta	Kent et al[120]
Remain with CKD					Remainder	
From ESRD (no dialysis)						
ESRD to death	0.12	0.005	--	--	Beta	Kent et al[120]
ESRD (survivors) to ESRD + dialysis	0.18	0.006	--	--	Beta	Kent et al[120]
ESRD (survivors) to transplant	0.09	0.004	--	--	Beta	Kent et al[120]
Remain ESRD, no dialysis					Remainder	
From ESRD (on dialysis)						
ESRD + dialysis to Death	--	--	Year 1: 951 Year 3: 2116 Year 5: 2990	Year 1: 5178 Year 3: 3988 Year 5: 3254	Beta	UK Renal Registry report (Table 1.17)[121]
ESRD + dialysis to Transplant	--	--	Year 1: 417 Year 3: 1056 Year 5: 1305	Year 1: 5712 Year 3: 5048 Year 5: 4939	Beta	
Remain in ESRD + dialysis					Remainder	
From Transplant						
Transplant to ESRD + dialysis	--	--	Year 1: 4 Year 3: 16 Year 5: 26	Year 1: 487 Year 3: 475 Year 5: 431	Beta	UK Renal Registry report (Table 1.17)[121]
Transplant to Death	--	--	Year 1: 8 Year 3: 16 Year 5: 31	Year 1: 483 Year 3: 475 Year 5: 426	Beta	
Transplant successful					Remainder	

[A] Converted to annual cycle specific probabilities for application in the model.

[B] Average of ICU and hospitalised (non-icu) mortality applied in the model base case analysis.

Model parameters – costs

The health care costs included are: 1) the costs of conducting the tests, including equipment and staff resource use; 2) acute care within the first 90 days post hospital admission, including the additional cost of early application of a KDIGO care bundle, the cost of hospital/ICU length of stay, and acute renal replacement therapy; and 3) the annual, cycle-specific costs associated with Markov health states (CKD, ESRD, dialysis and transplant) over the longer term follow-up phase. All costs are included from a UK NHS perspective and are reported in 2017/18-GBP values. Where possible, resource use has been costed directly using 2017/18 UK national unit cost sources (PSSRU for staff time, NHS reference costs for secondary care procedures and the BNF for drugs). Where this has not been possible, for example if total costs are reported in the literature without enough data regarding the underlying resource use to enable re-costing, these costs are inflated from their base year to 2017-18 values using the Cochrane and Campbell economic methods group online inflation calculation tool[124].

Diagnostic test costs

NephroCheck testing is usually conducted on an Astute 140 Meter, costing £3000 and an additional meter would need to be purchased. This cost was converted to an annuity, assuming the platform's lifetime is 5 years, and an annual depreciation rate of 3.5%. The test could also be conducted on a VITROS 3600 Immunodiagnostic System; however, UK hospitals rarely have this system in laboratories (Hall et al. 2016), confirmed at NICE scoping workshop by clinical expert opinion. The NGAL tests would not require a new platform for NGAL only, because it would be performed on platforms already available at the hospital labs. The capital costs of the lab analyser apportioned to each NGAL test are assumed to be negligible. Sensitivity analysis excludes capital and training costs to explore the impact on cost-effectiveness of scenarios where a hospital might already have the required analyser in place and all staff are fully trained in their use.

The process of taking the sample for analysis, sending samples to the lab, processing at the lab and interpretation of test results would require the involvement of several members of the hospital team. Firstly, a urine sample is collected by a nurse, which is thereafter picked up by a porter who takes it to the laboratory. It is assumed that

because the tests are classified as urgent samples, a porter would generally prioritise single test collection for the lab. A biomedical scientist conducts the diagnostic test in the laboratory. After completion of the test, the results from the lab would be authorised by a biochemist and released for review on the hospital information management system where it can be interpreted by either a nephrologist, intensive care specialist or a junior doctor. The base case analysis assumes an average of the three healthcare professional costs for interpretation. Under some criteria (such as very abnormal results) a laboratory team might directly contact the care provider, but we assume this would not be the approach used routinely. For the purposes of test cost calculation, it is assumed that, on average, the role of interpreting the tests is equally split across the three specialist team members. The unit costs for each of the staff resources involved in the testing process are obtained from PSSRU and are provided in Table 23 below and the resource use assumptions are described in Table 24.

Table 23 Staff unit cost

Staff	**Unit cost (per hour)**	**Source**
Prepare urine sample: nurse band 5	£37.00	PSSRU 2018[125]
Porter brings urine sample to laboratory: health care assistant	£27.26	PSSRU 2018[125]
Conduct test: Scientific and professional staff, Band 6 (biomedical scientist)	£44.00	PSSRU 2018 [125]
Interpret test[A]		
Intensive care specialist: Hospital-based doctor, medical consultant	£108.00	PSSRU 2018[125]
Nephrologist: Hospital-based doctor, medical consultant	£108.00	PSSRU 2018[125]
Junior doctor: Foundation doctor FY2	£32.00	PSSRU 2018[125]

[A] Base case assumes an average of hospital doctor, Nephrologist and junior doctor to interpret results.

The duration of resource use for each member of the team is based on a combination of information provided by manufacturer and clinical expert opinion regarding the flow from obtaining the test sample to result interpretation. The staff time to process the test in the lab was based on the NICE request for information documents to the different test manufacturers and the Final scope. Estimates of the time taken to

prepare the urine sample and interpret the test was based on the EAGs clinical expert opinion.

Four test strategies were compared in the economic model and costed according to Table 24 below (NephroCheck, NGAL urine (BioPorto), NGAL ARCHITECT (Abbott) and NGAL plasma (BioPorto). The NGAL test manufacturer (BioPorto) have not identified costs separately by sample type (plasma or urine). It is therefore assumed that these tests incur equal costs. The cost of the Alinity NGAL urine test (Abbott) was not considered in the base case economic evaluation because the review identified no diagnostic accuracy data for the test. However, the Alinity test costs are also provided in Table 24 for information. Further details regarding the calculation of maintenance and consumables costs is provided in Appendix 12, Table 45 .

Table 24 Test costs

	Astute medical NephroCheck	BioPorto (urine and plasma)	Abbott ARCHITECT	Abbott (Alinity)[F]
Platform (Astute 140 Meter), NephroCheck only				
Cost	£3000	--	--	--
Expected service life	5	--	--	--
Equivalent annual cost (EAC)	£664.44[G]	--	--	--
Subtotal: Platform (cost per test)	**£0.53[A]**	**--**	**--**	**--**
Subtotal: Equipment (cost per test)	**£49.80[B]**	**£20.00[C]**	**£25.71[D]**	**£28.29[E]**
Subtotal: Maintenance/consumables (cost per test)[H]	**£4.23**	**£1.90**	**£3.51**	**£3.51**
Staff resource use				
Time to conduct test (sample preparation + time to get result) (minutes)	20	20	20	20
Time to interpret test (minutes)	5	5	5	5
Prepare urine sample: nurse band 5 (minutes)	15	15	15	15
Bring urine sample to laboratory: porter (minutes)	15	15	15	15
Staff time for testing (per test)	£14.67	£14.67	£14.67	£14.67
Staff for interpreting (per test)	£6.89	£6.89	£6.89	£6.89
Staff to prepare urine sample (per test)	£9.25	£9.25	£9.25	£9.25
Delivery to lab (per test)	£6.82	£6.82	£6.82	£6.82
Subtotal: staff costs (per test)	**£37.62**	**£37.62**	**£37.62**	**£37.62**
Staff training [I]				
Assumed average turnover (years)	5	5	5	5
Time for training (minutes)	90	30	30	30
Total training costs	£438.00	£146.00	£146.00	£146.00
EAC of total training	£97.01	£32.34	£32.34	£32.34
EAC of total training per test	**£0.08**	**£0.03**	**£0.03**	**£0.03**
TOTAL COST	**£92.26**	**£59.55**	**£66.87**	**£69.44**

[A] Assuming the number of tests performed annually is 1253 (Hall et al. 2018[99]), based on throughput at the ICU department of St James teaching hospital, Leeds. This is likely a conservative estimate of throughput that might be observed outside the ICU department and likely reflect the maximum bound of the allocated platform cost per test.
[B] NephroCheck single use test cartridge;
[C] BioPorto NGAL test,
[D] ARCHITECT Urine NGAL Test Reagent 100-test kit (produces 80 tests) (Source: Company submitted request for information to NICE)
[E] Alinity Urine NGAL Test Reagent 100-test kit (produces 80 tests) (Source: Company submitted request for information to NICE)
[F] The cost of Alinity is not included in the model because none of the studies in the clinical effectiveness review evaluated Alinity Urine NGAL.
[G] £644.44=£3000/((1-(1.035)^-5)/0.035), where 3.5% is the discount rate applied to the platform cost.
[H] The detailed calculations on the maintenance and consumables costs are provided in Appendix 12.
[I] Staff training time for all tests was based on information provided by the manufacturers where possible. For NephroCheck, training takes 1-2 hours, therefore, we assumed that on average training would take 1.5 hours (NICE's request for information document). Training was assumed 30 minutes for all NGAL tests because the manufactures stated that only "limited training" (BioPorto) or time "to read the instructions for use" (Abbott) would be required. The total training cost was based on the total cost of training staff that would be conducting and interpreting the test results.

Cost of early treatment

The additional cost of early treatment with the KDIGO care bundle was calculated as £106.36 per patient treated, assuming an additional three days application of the care bundle in test positive patients. An additional three days of treatment was assumed in line with the primary outcome from Meersch et al[113] (i.e. AKI at 72 hours) and based on clinical expert opinion that a care bundle could potentially be implemented for up to an extra three days. The care bundle cost is based on the NICE guidelines for preventing AKI,[16] which state that measures to prevent AKI are: avoidance of nephrotoxic agents, discontinuation of medication (angiotensin-converting-enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs)), close monitoring of serum creatinine and urine output, avoidance of hyperglycaemia, alternatives to radio contrast and close hemodynamic monitoring. The NICE recommendations for preventing AKI include seeking advice from nephrology team and pharmacist with regards to giving "iodinated contrast agent to adults with contraindications to intravenous fluids" and medications (ACE inhibitors, ARBs), respectively. Therefore, both a nephrologist and pharmacist time are included in the cost of the care bundle. The costs are listed in Table 25. The additional cost of early adoption of the care bundle was applied to the proportion of the cohort with a positive biomarker test result, reflecting an assumption that care would be delivered for an additional three days over and above the cohort monitored using serum creatinine alone. The cost was applied using a gamma distribution with a standard deviation of 10% of the mean.

Table 25 Care bundle costs

Resource use	Assumptions	Care bundle cost	Source
Intravenous fluids			
Intravenous sodium chloride 0.9% infusion 2litre bags (Terumo BCT Ltd)	1L per hour for 3 hours, thereafter 2L per day for 3 days (5 2 litre bags)	£22.14	Clinical expert opinion, BNF 2019[126]
Band 6 nurse	Initial fluid: 10 minutes	£5.33	Clinical expert opinion, PSSRU 2018[125]
Band 6 nurse	Fluid replacement: 5 minutes	£10.67	Clinical expert opinion, PSSRU 2018[125]
Nephrologist review			
Hospital-based doctor, medical consultant	30 minutes	£54.00	Clinical expert opinion, PSSRU 2018[125]
Pharmacist review			
Pharmacist, band 6 AfC	20 minutes	£15	Clinical expert opinion, PSSRU 2018[125]
Stop blood pressure medication			
	Stop blood pressure medication for 3 days	-£0.78	Clinical expert opinion, BNF 2019[126]. Based on the annual cost of blood pressure medication (See Appendix 12, Table 47), and calculated over 3 days.
Total cost for 3 additional days of the KDIGO care bundle		**£106.36**	

Acute phase costs

The base case total cost in the acute phase (90 days) of the model depends on the number of days spent in hospital and ICU (See Table 26). It also depends on the duration of acute RRT delivered to the proportion of AKI stage 3 patients receiving RRT. For the base case analysis, data from the Adding Insult to Injury report show that 52 % of RRT patients receive continuous RRT (daily) and 48% receive intermittent dialysis (an average of 3 sessions per week)[3]. The duration of RRT delivery is obtained from a randomised trial conducted in a US critical care setting[127]

comparing intensive, six days per week (N=563) vs. less intensive three days per week (N=561) RRT strategies. The mean (SD) N duration, in days, of RRT per patient was similar in both groups: intensive: 13.4 (9.6) 563; less intensive: 12.8 (9.3) 561. The base case model conservatively assumes the less intensive duration for the application of costs in the economic model. To incorporate the uncertainty and to reflect the likely skewed nature of the distribution, duration of RRT is incorporated probabilistically into the model using a log normal distribution. Data available from an alternative source (Bagshaw, 2009),[128] as used in NICE guidance for the comparison of early vs. late renal replacement therapy was not considered because median rather than mean durations were reported, and the data were assessed as low quality in the NICE guidance.[16] An additional daily excess cost of AKI was applied in a sensitivity analysis to capture the potential excess cost per day in hospital or ICU of an AKI patient. This excess cost was not applied in the base case scenarios because it was assumed that the cost of having AKI is captured in the cost of being in hospital or ICU. All other acute costs and follow-up costs are applied a gamma distribution.

Table 26 Acute phase costs applied in the model

	Daily cost	Lower quartile	Upper quartile	SE	Source
Hospital ward setting – daily cost	£313	£207	£357	£38.27	NHS reference costs 2017/18[129]
ICU setting – daily cost	£1,395	£1,223	£1,562	£251.38	NHS reference costs 2017/18[129]. Quartiles are sourced from 2015/16 and inflated to 2018 costs. [A]
Excess daily cost of AKI (applied in sensitivity analysis only) [C]	£298	£232.36	£319.28	£65.65	NHS reference costs 2017/18[129]. Quartiles are sourced from 2016/17 and inflated to 2018 costs. [A]
Additional cost of acute, in hospital RRT					
Cost of HD per session	£271	£137	£339	£149	NHS reference costs 2017/18[129].
% on intermittent HD	48%				Adding insult to injury report 2009[3]. Applied deterministically in the model
Estimated daily cost [B]	£197				Assumed 3 sessions per week for intermittent HD and 1 session per day for continuous HD.

[A] Note that it has been necessary to obtain standard errors from older data as variability in costs are not reported in the 17/18 NHS reference costs; Standard errors calculated as SD / sqrt (N); [B] Per day cost calculated as (cost per session x proportion on intermittent HD x 3 days per week) + (cost per session x proportion on continuous HD x daily) = (£271 x 0.48 x 3/7) + (£271 x 0.52 x 1) = £196.67 per day on average. [C] Applied in sensitivity analysis as an additional cost over and above the ward / ICU daily cost

Long term follow-up costs

There are four ways in which long term follow up costs may be driven by the proportion of the cohort that progress through different pathways from the initial decision tree. These are: 1) whether or not long-term follow up costs depend on whether the patient received ICU care in the initial decision tree; 2) whether there are additional follow up costs beyond 5 years post index hospitalisation discharge; 3) whether an excess long term cost is applied for the proportion of the cohort coming through AKI arms of the decision tree; and 4) health state specific costs incurred as the cohort progress through CKD stages to dialysis or transplant.

The out-patient follow-up costs in the Markov model post index hospitalisation discharge were obtained from Lone et al,[123] who reported 5 years of follow-up costs post index ICU and hospital discharge, using a matched cohort obtained from registries in Scotland (Scottish Intensive Care Society Audit Group (SICSAG), Scottish Morbidity Record of acute hospital admissions (SMR01), and Scottish mortality data). The base case analysis assumes that the average of post-ICU and post-non-ICU admissions are applied in the Markov model. This is because the cohort for this assessment are already deemed to be critically ill and at risk of needing ICU care, so might all be expected to have significant resource use post discharge. Sensitivity analysis allows the application of differential long-term costs that depend on the whether the patient had received ICU care in the first 90 days or not.

The annual costs beyond 5 years are unknown. Therefore, the base case analysis assumes no additional costs beyond year five. Sensitivity analysis explores the impact of these assumptions by applying further costs between years 6 to 11 that reduce annually following a logarithmic function (see Table 27 below) with year 11 costs applied for the remaining duration of the model.

Table 27 Long term follow-up costs stratified by admission to ICU or not during index hospitalisation

	Mean (£)	95% CI (£)		SE (£)	Source
For those not admitted to ICU during their initial hospitalisation					
Year 1	3,954	3,644	4,264	158	Lone et al[123]
Year 2	2,864	2,592	3,138	139	
Year 3	2,547	2,272	2,822	140	
Year 4	2,277	2,023	2,530	129	
Year 5	2,090	1,846	2,334	125	
Year 6 (Sensitivity analysis)	1,794			Assumed: £125	Calculation based on Lone et al[123]
Year 7 (Sensitivity analysis)	1,618				
Year 8 (Sensitivity analysis)	1,465				
Year 9 (Sensitivity analysis)	1,331				
Year 10 (Sensitivity analysis)	1,210				
Year 11+ (Sensitivity analysis)	1,102				
For those admitted to ICU during their initial hospitalization					
Year 1	6,500	6,110	6,888	198	Lone et al[123]
Year 2	4,183	3,864	4,501	163	
Year 3	3,975	3,629	4,321	176	
Year 4	3,774	3,402	4,145	190	
Year 5	3,315	2,978	3,654	172	
Year 6 (Sensitivity analysis)	2,806			Assumed £125	Calculation based on Lone et al[123]
Year 7 (Sensitivity analysis)	2,521				
Year 8 (Sensitivity analysis)	2,274				
Year 9 (Sensitivity analysis)	2,056				
Year 10 (Sensitivity analysis)	1,861				
Year 11+ (Sensitivity analysis)	1,685				

*All data incorporated probabilistically in the model using gamma distributions; Note that the base case analysis applies the average of ICU and hospital, with differential costs applied as a sensitivity analysis to the proportion who require ICU care and hospital care in the initial 90-day phase

The base case analysis assumes that there are no long-term excess follow-up costs as a result of having had AKI in the initial 90-days post hospitalisation. However, sensitivity analysis explores a scenario where patients entering the Markov model having had AKI in hospital incur an additional 15% of the non-AKI cohort costs for

the first 5 years. The additional AKI cost factor was based on a proxy using the RR reported in Lone et al. on the number of admissions patients on RRT had over five years compared to those who were not on RRT. These additional costs are applied in the model as sensitivity analysis, with a mean ratio of 1.15, log SE: 0.074 sampling from a log normal distribution.

Annual cycle-specific health-state costs were applied to the proportion of the cohort transiting through the CKD, ESRD, ESRD on dialysis and transplant health states. Costs were obtained from Kent et al., using data from the SHARP trial reporting outpatient, day case and inpatient admissions. The CKD (stage 1-4) health state cost applied in the model was calculated as the weighted average of CKD stage 1-3 and CKD stage 4 as reported in Kent et al. [120] The average weighted cost applied was therefore £445.98 per cycle. The cost of medications (immunosuppressant for transplant patient, ESA for dialysis patients and blood pressure medications for dialysis patients) were not captured in the study, therefore, these costs were added to the costs observed in Kent et al.[120] The added transplant costs (immunosuppressants) were based on the approach applied in Scotland et al. 2018[130] for calculating the annual cost of immunosuppressants, using 2018 prices. The added costs to dialysis patients due to medications for blood pressure and ESA are also based on the approach applied in Scotland et al. 2018, with 2018 prices.

Table 28 CKD, dialysis and transplant costs

Health state [B]	Mean (£)	95% CI (£)		Standard error (£)	Additional medication costs	Total	Sources
CKD 1-3	453	388	519	33.53		453	Kent et al. 2015[120]
CKD 4	441	441	499	14.61		441	Kent et al. 2015[120]
Weighted average (CKD 1-4)	446						
ESRD (no dialysis) [A]	590	504	676	43.84		590	Kent et al. 2015[120]
ESRD year 1 (with dialysis)	21,328	20,917	21,739	209.77	2,601[C]	23,929	Kent et al. 2015[120]
ESRD year 2 onwards (with dialysis)	26,203	26,096	26,310	54.45	2,601[C]	28,804	Kent et al. 2015[120]
Functioning transplant year 1	27,636	26,991	28,284	329.84	10,623	38,260	Kent et al. 2015[120], NICE Guidance 2015[131] and BNF 2019[126]
Transplant follow up	1,290	1,099	1,481	97.43	9,063	10,352	Kent et al. 2015[120], NICE Guidance 2015[131] and BNF 2019[126]

[A] ESRD reported as CKD stage 5 in Kent et al.

[B] All costs incorporated probabilistically using gamma distributions.

[C] This cost is based on the total annual cost of both ESA medication and BP medication. See calculation in Table 46 and 47 in the Appendix 12.

Health measurement and valuation

Acute (decision tree) phase of the model

We have updated the searches from Hall et al. to identify studies that report utilities for the initial decision tree phase of the model. Our post-Hall et al. review identified four further potentially relevant studies. However, the only utilities that meet the NICE reference case are those proposed by Hall et al. All other studies identified from the literature review use non-UK value sets and so are not appropriate for UK decision making. Given that there are no appropriate utility studies for AKI stage, the analysis uses the utilities identified in Hall et al. applied to the model based on length of stay in hospital, length of stay in ICU and duration discharged prior to 90 days following hospital admission. Due to a lack of appropriate data, and to avoid double counting the utility impact of time in hospital / ICU, we have not attempted to apply any additional utility decrements by AKI stage (other than to those on acute RRT). The application of utilities is consistent with that used by Hall et al[99] The utilities used in the model, together with age and sex adjustment are described in Table 30 alongside the parameters of the normal and beta distributions used to incorporate the data probabilistically within the model. It is difficult to find utility values for patients in ICU. Two systematic reviews were consulted, one by Dritsaki et al. 2017[132] and one by Gerth et al. 2019.[133] Both reviews focused on a population admitted to ICU, however, no studies identified in the reviews were deemed suitable. Therefore, the utility value of an unconscious patient, has been applied for the duration of ICU stay, using data sourced from Kind et al[134] and following the same approach as Hall et al.[99] As a sensitivity analysis we consider an alternative approach to calculate ICU utility to explore the substantial uncertainty in this parameter. The alternative value takes the average of the unconscious state (-0.402 from Kind et al) and the average post ICU discharge from Hernández et al[135] from the PRACTICAL study (0.44) that followed up a cohort of ICU survivors reporting their quality of life using the EQ-5D instrument. The calculated utility value applied in sensitivity analysis was (-0.402 + 0.44)/2) = +0.019.

Table 29 Utility studies for acute kidney injury (AKI) that were considered for economic modelling

Author	Year	Population	Country	Utility measure	Value set	N	Age	Male (%)	Utility values reported	Mean	Median	SD	IQR low	IQR high
Ethgen[136]	2015	AKI, intensive care	USA	DAM: Unclear (sourced from lit)	Unclear	NR	NR	NR	CCRT (ICU) CCRT (DI) CCRT (DD) IRRT (ICU) IRRT(DI) IRRT (DD)	0.13 0.84 0.62 0.13 0.84 0.62		NR		
Hall[99]	2018	AKI, intensive care	UK	Mix	various	Mix			ICU Ward (post ICU) Discharged (post ICU) DD decrement	-0.402 0.44 0.62 0.11		0.20 0.31 0.32 0.02		
Kaier[137]	2016	Surgical aortic value replacement	Germany	EQ-5D-3L	German	Baseline: 169 Follow up: 2294	82.15 (5.16)	NR	Baseline Follow up AKIN 1 AKIN 2 AKIN 3	0.78 0.77 +.0659 -0.158 -0.177		0.23 0.25 NR NR NR		
Oeyen[138]	2015	Critically ill after AKI, need RRT	Belgium	EQ-5D-3L	None	141	57	66%	None	NR		NR		
Solimann[139]	2016	AKI patients mixed ICU	Netherlands	EQ-5D-3L	Dutch	All: 2420 No AKI: 1588 Risk: 456 Injury: 253 Failure: 123	Median (IQR) 59; (47-69) 59; (47-69) 59; (47-69) 59; (47-69) 59; (47-69)	58.7% 58.3% 57.0% 61.7% 63.4%	All: No AKI: Risk: Injury: Failure:		0.806 0.810 0.778 0.772 0.666		0.590 0.640 0.570 0.470 0.370	0.940 1.000 0.890 0.870 0.850

DI: Dialysis Independence; DD: dialysis dependence

Table 30 Health state utilities applied for the acute phase of the model

Decision tree branch	Mean utility	SE	SD	Age	Male (%)	Age related pop. norm	Age adjusted multiplier applied to model	Utility value applied in model	Dist.	Source
ICU [A]	-0.402	0.02		--	--	--	--	-0.402	Normal	Kind et al. (Appendix B)[134]
Ward	0.44	0.0259	0.31	60	60	0.8285	0.5311	0.432	Beta	Hernández et al[135].
Discharge	0.62	0.0268	0.32	60	60	0.8285	0.7483	0.608	Beta	Hernández et al[135]..
Acute dialysis decrement [B]	0.11	0.02		--	--	--	--	(0.11)	Beta	Wyld et al[140]
Death	0	--	--	--	--	--	--	0	--	

[A] assumed standard error equal to 5% of the mean utility for an unconscious patient.

[B] decrement applied to utility in ward only.

Utility values for the chronic phase of the model

First, the Hall et al. HTA assessment and economic model for long-term follow-up post AKI and the Scotland et al. assessment of Multiple frequency bioimpedance devices to guide fluid management in people with chronic kidney disease having dialysis (DG29) for NICE[130] were consulted to obtain appropriate health state utility values for application in the model. The Hall report conducted a thorough review of the literature prior to 2016 for utility parameters. They identified two systematic reviews of utility data that provided data that could be used in the economic model. The first, a systematic review and meta-regression published by Wyld et al[140] predicted utility according to treatment (transplant, dialysis, pre-treatment, conservative management). This model predicted an EQ-5D utility value for patients on dialysis of 0.64, and an EQ-5D utility for transplant patients of 0.75. The utilities from Wyld et al. were used in the Hall et al. model.

However, a limitation of Wyld et al. was that some of the EQ-5D scores were calculated from mapping algorithms, and the age to which the mean utility estimates applied was not reported. The earlier systematic review by Liem et al restricted a meta-analysis to those studies using the EQ-5D index directly for each modality of chronic RRT, and reported the pooled mean age and sex distribution for the corresponding pooled EQ-5D values.[141]

In addition to the two reviews identified by Hall et al, a further structured literature search was conducted to obtain any more recent utility studies that match the NICE DAP reference case (i.e. studies that included EQ-5D-3L data for UK patients, valued using UK general population tariffs). A range of databases were searched for English language, full text publications, published between 2016 (end data of Hall et al. searches) and 2019. N=7 were identified that were deemed appropriate to meet the NICE reference case for the DAP, specifically, they reported EQ-5D based utilities valued according to the UK general population preference-based value sets. Studies where EQ-5D was administered to non-uk population but valued according to the UK tariff were also included. These relevant studies are summarised in Table 31.

The age and sex matched EQ-5D UK population norms were calculated using an equation published by Ara and Brazier[142] and used to derive age/sex adjusted utility multipliers from the raw pooled estimates, based on the age and sex distribution of the source studies.[143] The final set of utility data used to populate the base case economic model are summarised in Table 32. The utility of the proportion of the cohort having a successful transplant is assumed to revert to that of the outpatient follow up state. All utility data were incorporated into the model probabilistically using beta distributions.

Table 31 Summary of post-Hall utility studies considered for the economic modelling

Author	Yr	Population	Country	Utility measure	Valuation set	N	Age	Proportion male	Utility values reported	Mean	Median	SE	SD	CI low	CI high	IQR low	IQR high
						Total: 1687	Total: NR										
		ESRD with				HD: 1403	HD: 57.1 (13.6)	HD: 49.9%	HD	0.83			0.19				
Chang[144]	2016	PD and HD	Taiwan	EQ-5D-3L	UK	PD: 284	PD: 46.7 (13.2)	PD: 51.1%	PD	0.90			0.16				
							Median (IQR)	All CKD:									
						All CKD: 745	All CKD 64; (50-76)	60.80%	All CKD		0.74					0.66	0.88
		pre-dialysis CKD (as per NICE guidance,				G1/2: 29	G1/2 41; (34.5-55.5)	G1/2: 65.52%	G1/2		0.85					0.70	1
						G3a: 45	G3a 55; (45-66.5)	G3a: 71.11%	G3a		0.80					0.69	1
						G3b: 173	G3b 61.5; (48.3-73.8)	G3b: 66.86%	G3b		0.80					0.68	1
						G4: 423	G4: 69; (54-75.5)	G4: 59.00%	G4		0.74					0.62	0.85
Jesky[145]	2016	CKD, 2008)	UK	EQ-5D-3L	UK	G5: 75	G5: 64; (53.5-75.5)	G5: 49.35%	G5		0.73					0.62	1
						Early Stage: 254			Early:	0.588			0.30				
						Stage 4: 614			Stage 4:	0.566			0.42				
						Stage 5: 151			Stage 5:	0.467			0.42				
Kularatna[146]	2019	CKD	Sri Lanka	EQ-5D-3L	UK	Dialysis: 38	Median approx age 41	56.10%	Dialysis:	0.126			0.39				
		Kidney transplant recipients and				Transplant recipients: 512			waiting list	0.773		0.005					
						Waiting list:	Median ~ 50	60%	transplant								
Li[147]	2017	waiting list	UK	EQ-5D-5L	UK	1704	Median ~ 50	58%	(inc)	+0.054		0.011					
										base				base			
						CKD1: 56	44.6 (18.2)	33.9%	S1	NR				NR	base NR		
						CKD2: 106	60 (17.4)	50.0%	S2	-0.112				-0.189	-0.034		
						CKD3a: 155	65.3 (14.8)	46.5%	S3a	-0.062				-0.128	+0.005		
		CKD and				CKD3b: 35	74.1 (13.4)	60.0%	S3b	-0.185				-0.299	-0.071		
Nguyen[148]	2018	ESRD	UK	EQ-5D-3L	UK	CKD 4/5: 5	72.2 (10.3)	40.0%	S4/5	-0.284				-0.408	-0.160		
									Regression Mean								
									(intercept)	0.86				0.84	0.88		
									Male	+0.06				+0.05	+0.07		
		Moderate to							Age +10y	-0.05				-0.05	-0.04		
		advanced							PFKT	-0.07				-0.11	-0.03		
Schlackow[149]	2017	CKD	UK	EQ-5D-3L	UK	6356	62 (12)	63%	dialysis	-0.06				-0.07	-0.04		

Author	Yr	Population	Country	Utility measure	Valuation set	N	Age	Proportion male	Utility values reported	Mean	Median	SE	SD	CI low	CI high	IQR low	IQR high
Snowsill[150]	2017	Kidney transplant recipients	UK	EQ-5D-3L	UK	N/A	N/A	N/A	<u>Regression</u> Mean (intercept) Age Age sq Male FG HD PD PTDM	 0.968 -0.002 -0.000 +0.023 -0.053 -0.277 -0.264 -0.060		NR					

PFKT: Previous Failed Kidney Transplant; CM: Conservative Management

Table 32 Health state utilities for chronic phase of the model

Health state	Study mean utility	SE	SD	Mean Age	Male (%)	Age related pop. norm	Age adjusted multiplier applied to model	Adjusted SE	HSUV applied in model	Dist.	Source
Post discharge (year 1)	0.666	0.016	0.280	60.5	0.590	0.8262	0.806	--	0.655	Beta	Cuthbertson et al. 2010[151]
Post discharge (years 2-4)	0.701	0.016	0.281	60.5	0.590	0.8262	0.849	--	0.689	Beta	Cuthbertson et al. 2010[151]
Post discharge (year 5 onwards)	0.677	0.017	0.301	60.5	0.590	0.8262	0.819	--	0.665	Beta	Cuthbertson et al. 2010[151]
CKD (1-4) [A, C]	--	--	--	CKD 2: 60.0 CKD 3A: 65.3 CKD 3B: 74.1 CKD 4: 72.2	CKD 2: 0.50 CKD 3A: 0.465 CKD 3B: 0.600 CKD 4: 0.400	CKD 2: 0.826 CKD 3A: 0.802 CKD 3B: 0.762 CKD 4: 0.768	0.708	0.031	0.575	Beta	Nguyen et al. 2018[148]
ESRD [C]	--	--	--	72.2	0.400	0.768	0.488	0.053	0.396	Beta	Nguyen et al. 2018[148]
ESRD: HD[B]	0.560	0.033	-	60.4	0.580	0.826	0.678	0.040	0.551	Beta	Liem et al. 2008[141];

											Ara and Brazier, 2010[143]
ESRD: PD[B]	0.580	0.043	-	57.9	0.550	0.836	0.694	0.052	0.564	Beta	Liem et al. 2008[141]; Ara and Brazier, 2010[143]

[A] A weighted average utility value (with proportions based on Nguyen et al. 2018[148]) across the CKD stages 1-4. [B] For application in the model, the ESRD (dialysis) utility is applied as the weighted average utility based on the proportion of long-term dialysis delivered as HD and PD, obtained from the UK renal registry report, 2018 [C] The study reports utility decrements only and the mean utilty applied in the model is back calculated using the utility decrement from Nguyen et al. applied to age and sex-adjusted UK general population norms.

Time horizon and discounting

The model was run over a life time horizon, up to age 100 (for a cohort with a starting age of 63 in the model). The life-time horizon was chosen to ensure that all the long-term costs and consequences of AKI induced CKD were captured, including the long-term health effects of ultimate progression to ESRD, transplant and death. The cycle length for the model was annual and half cycle corrections have been applied to costs and utilities. All costs and outcomes accruing beyond the first yearly cycle of the model were discounted at a rate of 3.5% per annum in line with the NICE reference case. The discount rate was varied between 0% and 6% in deterministic sensitivity analyses.

Analyses

The model calculated the expected costs and expected QALYs over the lifetime of the respective cohorts. This includes the costs and QALYs incurred in the first 90-day acute phase of the model, based on diagnostic test accuracy, preventative action to avert AKI, resultant peak AKI status and requirement for admission to ICU. It also includes the longer-term extrapolations from the Markov cohort model, simulating the long-term transitions between progressive stages of CKD for those that develop it.

The model is fully probabilistic to simultaneously describe the impact of all parameter uncertainty on the model results. All model parameter estimates are sampled from their assigned distributions as described in the preceding sections, using 1000 simulations. Where it was not possible to derive a distribution, for example when insufficient information existed to determine the SD of the distribution, it was assumed that the SD of a parameter was equal to 10% of its mean unless otherwise stated.

Results are reported as cost-utility analyses, in terms of incremental cost per QALY expressed as the incremental cost-effectiveness ratio (ICER). Test strategies are plotted on the cost-effectiveness frontier. Tests are ranked in ascending order of benefit (QALYs), with results reported for all tests incrementally against each other to enable the exclusion of strictly dominated (less beneficial and more costly) alternatives from the ICER calculations. ICERs vs. standard care are also reported. Results from the probabilistic analysis simulations are plotted using cost-effectiveness

acceptability curves based on the net benefit calculation to identify the optimal diagnostic testing strategy at different threshold values of willingness to pay (WTP) for a QALY.

Model validation

The economic model was checked for errors using the approach suggested by Tappenden and Chilcott[152] that specified verification tests. Components of the model tested were the estimation of the costs and QALYs, distributions of model parameters and other general tests for accuracy of the implementation of input parameters. No specific issues were identified through the verification tests.

Results

The model was developed and configured to assess the cost-effectiveness of the NephroCheck test, Urine NGAL (i.e. the ARCHITECT Urine NGAL assay and the BioPorto NGAL urine test), and BioPorto plasma NGAL in combination with standard clinical assessment, compared with standard clinical assessment alone.

There is no direct evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, risk of 90-day mortality or development of new / progression of existing chronic kidney disease). Accordingly, the cost-effectiveness results are based on a linked-evidence approach where we have relied on observational associations to infer how prevention or mitigation of AKI may affect changes in health outcomes. These associations necessitate causal assumptions, but while a causal link between AKI and poor outcomes is plausible, the extent of this causal relationship is uncertain and controversial. The cost-effectiveness results are therefore presented for a range of alternative, but potentially plausible, scenario analyses ranging from a set of optimistic assumptions where biomarker-guided care bundles may lead to substantial improvements in health outcomes (need for ICU, CKD, mortality) to a set of more conservative assumptions where changing of AKI status has no effects on health outcomes. It is likely that the true estimate of cost-effectiveness lies somewhere between these two extremes.

Furthermore, the model includes the following key assumptions:

- The model base case analysis is run for a mixed cohort of CKD and non-CKD patients, average age 63, 54.3% female, based on the characteristics of hospitalised patients in Grampian, Scotland who have at least one night hospital stay and are having their kidney function monitored and so are deemed to be at risk of AKI.
- It is assumed that NephroCheck and NGAL can rise at similar time-points and in the absence of any evidence to suggest otherwise, it is assumed that the time gain, relative to serum creatinine, in terms of early implementation of a care KDIGO bundle is equal for both.
- The base case analyses assume that there are no adverse consequences in terms of health effects of false positive or false negative test results compared to standard care. False positive results would incur the additional futile application of the care bundle costs, whilst clinical expert opinion indicates that false negatives will be monitored until the negative test result is confirmed and would represent current practice without biomarkers. However, there is some concern that a false positive test may lead to unnecessary fluid resuscitation, especially if encountered by inexperienced clinicians, which could lead to an increased mortality risk, though the magnitude of that risk is unknown. Sensitivity analysis explores this.
- For the Markov models, it is assumed that a patient can only develop CKD linked to the index AKI event for the first cycle of the model, reflecting a total time exposure to increased CKD risk of 1 year + 90 days. Thereafter, the background risk of developing CKD in the population is applied.
- It is assumed that the proportion of the cohort who have graft failure post-transplant return to the 'ESRD on dialysis' health state, where they are exposed to the same risks of transition to transplant / death as when they first entered the dialysis state.
- For the proportion of the cohort who don't develop long-term CKD, the base case models assume that the longer-term follow up costs and mortality risks are not dependent on events in the acute phase of the model (i.e. AKI severity and associated ICU admission). Sensitivity analysis explores the impact of

applying additional costs and mortality risks for those admitted to ICU in the acute phase of the model.

- The model is run for a lifetime horizon, or 100 years whichever comes first, with costs and QALYs discounted at an annual rate of 3.5% per annum.

Evidence from Meersch et al. shows that NephroCheck guided early implementation of a KDIGO care bundle can avert AKI. However, the impact of NGAL guided implementation of a care bundle is unknown. Therefore, two alternative base case assumptions are considered. The first assumes that NGAL and NephroCheck have the same potential to avert AKI (based on Meersch et al).[113] The second assumes that NGAL can only reduce the severity of AKI (also from Meersch et al[113] but cannot prevent it from occurring. The rationale for the latter analysis is that NGAL detects injury to the kidneys, whereas NephroCheck can potentially detect stresses on the kidneys and may offer an earlier warning of impending AKI. The two base case models and a range of scenario analyses conducted around important model assumptions are described in Table 33. A total of 15 scenario analyses are reported on each of these two plausible base case configurations to illustrate the significant uncertainty in the cost-effectiveness findings. Table 34 reports the results for scenarios where NGAL can avert AKI and Table 35 reports results of scenarios where NGAL cannot avert AKI.

Table 33 Base case model configuration and scenario analyses

Parameter / assumptions	Value	Base case justification / source	Sensitivity / scenario analyses	Scenario analysis reference
Alternative base case assumptions				
Potential for biomarker tests to avert AKI (vs. standard care)	RR AKI = 0.77	Based on Meersch et al.[113]	Base case 1: Applied to all tests Base case 2: Applied to NephroCheck only	Base case 1: NGAL and NephroCheck can both avert AKI Base case 2: Only NephroCheck can avert AKI.
Scenario analyses applied to base case 1 and base case 2				
Proportion of the RR of ICU admission (AKI vs. none) that can be achieved by averting AKI	0.5	Based on clinical expert opinion	Varied between 0 and 1	Scenario B: **Averting** AKI leads to **no** improvement in health outcomes **Reducing** AKI severity leads to **full** associative effects on health outcomes Scenario C: **Averting or reducing** severity of AKI leads to **no** improvement in health outcomes Scenario D: **Averting or reducing** severity of AKI leads to **full** improvement in health outcomes
Proportion of the HR of CKD (AKI vs. none) that can be achieved by averting AKI	1	Based on clinical expert opinion / See et al[119]	Varied between 0 and 1	
Proportion of the RR of 90-day mortality (Aki vs. none) that can be achieved by averting AKI	0	Based on Meersch et al[113], who show effects on AKI, but not on mortality. Similar data from Wilson et al[116]	Varied between 0 and 1	
Proportion of the difference in hospital and ICU length of stay (AKI vs. none) that can be achieved by averting AKI	0.5	Based on clinical expert opinion	Varied between 0 and 1	
Impact of AKI stage on hospital and ICU length of stay	Duration applied by AKI stage	Based on observational data from Grampian[105]	Duration assumed not to vary by stage, with same durations applied to all AKI stages based on average from Grampian observational data[105]	

Parameter / assumptions	Value	Base case justification / source	Sensitivity / scenario analyses	Scenario analysis reference
Impact of AKI stage on the probability of ICU admission	Probability applied by AKI stage	Based on observational data from Grampian[105]	Probability assumed not to vary by stage, with same probability applied to all AKI stages based on average from Grampian observational data[105]	
Impact of AKI stage on the probability of developing CKD.	HR applied by AKI stage	Based on systematic review and meta-analysis from See et al[119]	HR assumed not to vary by stage, with same HR applied to all AKI stages based on Sawhney 2017[105]	
Impact of AKI stage on the probability of 90-day mortality	Average probability applied for all AKI stages	Based on a lack of evidence that changing AKI severity can impact directly on mortality, as per Meersch et al[113]	Probabilities applied by AKI stage to explore uncertainty in this assumption	
AKI excess cost per day in hospital / ICU	No excess cost applied	Conservative approach to ensure avoidance of double counting	Additional hospital excess bed day cost applied as per Hall et al[99] to all patients (ICU / ward)	Scenario E: as per Scenario D with additional AKI costs.
The following analyses are applied to the base case configuration (Scenario A above)				
Additional costs associated per day on RRT	Yes	Based on HRG costs	No additional costs of RRT	Scenario F
Impact of AKI on long term follow up costs beyond 90 days	None (ratio =1)	Conservative assumption	All long-term Markov model costs multiplied by 1.15 as per Hall et al[105]	Scenario G Differential long term outpatient cost and mortality applied according to whether patient entered ICU or not.
Long term outpatient follow-up costs, up to 5 years	Average of hospitalised and ICU patients	Based on average of two cohorts from Lone et al[123]	Differential cost streams applied for 5 years according to whether cohort admitted to ICU in first 90 days, based on Lone et al[123]	

Parameter / assumptions	Value	Base case justification / source	Sensitivity / scenario analyses	Scenario analysis reference
Long term outpatient follow-up costs, after 5 years	No additional costs applied	Assumption that patients surviving post icu to 5 years will incur no further excess costs	Additional annual costs applied for full life-time based on extrapolation of Lone et al[123] data, applied separately to those who had ICU / no ICU admission at index hospitalisation.	
Impact of ICU admission on Long term mortality	Average of hospitalised and ICU patients	Lone et al[123]	Differential mortality applied according to whether cohort admitted to ICU	
Duration by which AKI event can impact on excess CKD risk	90 days + 1 year	Assumption	Assume additional risk of CKD development over full life-time horizon	Scenario H
Discount rate (Cost)	3.5%	NICE guidelines	Varied 0% - 6%	Scenario I (0%) Scenario J (6%)
Discount rate (QALY)	3.5%	NICE guidelines	Varied 0% - 6%	
Source of AKI prevalence data	9.2%	Grampian data for hospitalised patients at risk of AKI	Alternative source: obtained directly from systematic review studies	Scenario K
Number of times test is used	1	Based on NICE scope	All tests conducted twice	Scenario L
RR of 90-day mortality for FP test results	1	Assumes no additional risk of unnecessary fluid resuscitation	Apply an additional RR=1.5 to explore impact on results.	Scenario M
Test capital and training costs in test cost	Included	As per company advice	Exclude in sensitivity analysis, assuming all capital equipment required is available for all tests (including NephroCheck)	Scenario N

Parameter / assumptions	Value	Base case justification / source	Sensitivity / scenario analyses	Scenario analysis reference
Source of ICU utility data	-0.402	Kind et al (unconscious patient)	Average of unconscious (-0.402) and utility at discharge from ICU reported in the Practical trial (Hernandez et al[135])	Scenario O
Long term outpatient utility	Varies by year	Long term utility implication of hospitalisation / ICU, based on Hall et al. [105]	General population norms, assuming quicker recovery.	Scenario P
Source of diagnostic accuracy data	All comers	All	Exploratory analysis applying available test accuracy data for children to the adult model.	Scenario Q

Table 34 Scenario analyses assuming that the NGAL tests can avert AKI

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Scenario 1A: Preferred base case assuming an associative effect of averting and mitigating AKI								
Test 3 (NGAL urine - BioPorto)	£22,887	--	6.07332	--	--	Dominant	43.5%	54.6%
Test 2 (NGAL plasma - BioPorto)	£22,900	£14	6.07332	0.00001	£2,694,918	Dominant	11.1%	47.6%
Standard care (Scr)	£22,901	Dominated	6.07296	Dominated	Dominated	--	45.1%	--
Test 4 (NGAL urine - ARCHITECT)	£22,912	Dominated	6.07328	Dominated	Dominated	£32,131	0.1%	41.4%
Test 1 (Nephrocheck)	£22,938	Dominated	6.07332	Dominated	Dominated	£101,456	0.2%	31.9%
Scenario 1B: Apply the full associative effect on the redistributed cohort only and assuming that the test impacts on the probability of dying at 90 days.								
Standard care (Scr)	£22,829	--	6.08377	--	--	--	57.5%	--
Test 3 (NGAL urine - BioPorto)	£22,937	£108	6.08602	0.00226	£47,877	£47,877	30.4%	42.5%
Test 4 (NGAL urine - ARCHITECT)	£22,951	Dominated	6.08584	Dominated	Dominated	£58,813	0.0%	37.3%
Test 2 (NGAL plasma - BioPorto)	£22,951	£14	6.08608	0.00006	£228,616	£52,816	11.9%	39.5%
Test 1 (Nephrocheck)	£22,988	Dominated	6.08604	Dominated	Dominated	£70,141	0.2%	31.0%
Scenario 1C: No associative effect								
Standard care (Scr)	£23,340	--	6.07257	--	--	--	100.0%	--
Test 3 (NGAL urine - BioPorto)	£23,420	Dominated	6.07257	Dominated	Dominated	Dominated	0.0%	0.0%
Test 2 (NGAL plasma - BioPorto)	£23,436	Dominated	6.07257	Dominated	Dominated	Dominated	0.0%	0.0%
Test 4 (NGAL urine - ARCHITECT)	£23,437	Dominated	6.07257	Dominated	Dominated	Dominated	0.0%	0.0%

Test 1 (Nephrocheck)	£23,473	Dominated	6.07257	Dominated	Dominated	Dominated	0.0%	0.0%
Scenario 1D: Full associative effect								
Standard care (Scr)	£22,959	--	6.08383	--	--	--	0.7%	--
Test 3 (NGAL urine - BioPorto)	£23,013	£54	6.11006	0.02623	£2,052	£2,052	40.7%	99.3%
Test 2 (NGAL plasma - BioPorto)	£23,028	£15	6.11091	0.00084	£17,702	£2,538	47.5%	99.1%
Test 4 (NGAL urine - ARCHITECT)	£23,031	Dominated	6.10799	Dominated	Dominated	£2,981	1.1%	98.8%
Test 1 (Nephrocheck)	£23,065	Dominated	6.11064	Dominated	Dominated	£3,955	10.0%	97.7%
Scenario 1E: As per Scenario 1D but apply a daily excess AKI costs to patients in hospital/ICU								
Test 3 (NGAL urine - BioPorto)	£23,638	--	6.11049	--	--	Dominant	38.6%	99.2%
Test 2 (NGAL plasma - BioPorto)	£23,650	£12	6.11104	0.00055	£21,968	Dominant	43.8%	98.9%
Test 4 (NGAL urine - ARCHITECT)	£23,664	Dominated	6.10823	Dominated	Dominated	Dominant	2.0%	98.9%
Standard care (Scr)	£23,681	Dominated	6.08377	Dominated	Dominated	--	0.8%	--
Test 1 (Nephrocheck)	£23,687	Dominated	6.11102	Dominated	Dominated	£210	14.8%	98.7%
Scenario 1F: Exclude RRT cost								
Test 3 (NGAL urine - BioPorto)	£23,258	--	6.07092	--	--	Dominant	39.5%	49.9%
Standard care (Scr)	£23,266	Dominated	6.07060	Dominated	Dominated	--	49.8%	--
Test 2 (NGAL plasma - BioPorto)	£23,271	£14	6.07093	0.00001	£1,403,330	£17,694	10.0%	44.9%
Test 4 (NGAL urine - ARCHITECT)	£23,282	Dominated	6.07089	Dominated	Dominated	£54,497	0.3%	39.0%
Test 1 (Nephrocheck)	£23,309	Dominated	6.07092	Dominated	Dominated	£132,748	0.4%	29.5%
Scenario 1G: [A] Apply the differential long-term follow-up costs and mortality according to whether patient entered ICU or not								
Test 3 (NGAL urine - BioPorto)	£30,290	--	6.56602	--	--	Dominant	50.2%	99.5%
Test 2 (NGAL plasma - BioPorto)	£30,296	£7	6.56605	0.00003	£227,069	Dominant	39.7%	99.1%
Test 1 (Nephrocheck)	£30,335	Dominated	6.56605	Dominated	Dominated	Dominant	8.1%	97.2%

Test 4 (NGAL urine - ARCHITECT)	£30,337	Dominated	6.56591	Dominated	Dominated	Dominant	1.4%	98.6%
Standard care (Scr)	£30,606	Dominated	6.56457	Dominated	Dominated	--	0.5%	--
Scenario 1H: Apply an excess CKD risk for those who experienced an AKI event over the full lifetime horizon								
Test 3 (NGAL urine - BioPorto)	£23,201	--	6.07247	--	--	Dominant	54.8%	76.5%
Test 2 (NGAL plasma - BioPorto)	£23,212	£12	6.07251	0.00005	£254,012	Dominant	20.3%	73.0%
Test 4 (NGAL urine - ARCHITECT)	£23,228	Dominated	6.07234	Dominated	Dominated	Dominant	0.6%	68.4%
Test 1 (Nephrocheck)	£23,251	Dominated	6.07250	Dominated	Dominated	Dominant	1.0%	58.2%
Standard care (Scr)	£23,254	Dominated	6.07186	Dominated	Dominated	--	23.3%	--
Scenario 1I [A] 0% discount rate applied to both costs and QALYs								
Test 3 (NGAL urine - BioPorto)	£27,644	--	8.20147	--	--	Dominant	44.3%	57.9%
Test 2 (NGAL plasma - BioPorto)	£27,657	£13	8.20149	0.00001	£996,593	Dominant	13.5%	51.4%
Standard care (Scr)	£27,664	Dominated	8.20095	Dominated	Dominated	--	41.6%	--
Test 4 (NGAL urine - ARCHITECT)	£27,668	Dominated	8.20143	Dominated	Dominated	£9,262	0.2%	47.4%
Test 1 (Nephrocheck)	£27,694	£37	8.20149	0.00000	£4,020,759	£56,151	0.3%	37.4%
Scenario 1J [A] 6% discount rate applied to both costs and QALYs								
Test 3 (NGAL urine - BioPorto)	£20,961	--	5.11682	--	--	Dominant	39.7%	49.9%
Standard care (Scr)	£20,969	Dominated	5.11654	Dominated	Dominated	--	49.4%	--
Test 2 (NGAL plasma - BioPorto)	£20,974	£13	5.11683	0.00001	£1,295,058	£16,259	10.4%	44.2%
Test 4 (NGAL urine - ARCHITECT)	£20,984	Dominated	5.11680	Dominated	Dominated	£55,509	0.3%	39.5%
Test 1 (Nephrocheck)	£21,011	Dominated	5.11683	Dominated	Dominated	£145,369	0.1%	30.6%
Scenario 1K [A] Apply alternative source for AKI prevalence (average prevalence of 0.2332 across systematic review studies)								
Test 3 (NGAL urine - BioPorto)	£23,050	--	5.85835	--	--	£1,073	42.3%	79.0%
Test 2 (NGAL plasma - BioPorto)	£23,055	£5	5.85837	0.00002	£256,153	£1,050	30.7%	77.3%

Test 4 (NGAL urine - ARCHITECT)	£23,084	Dominated	5.85827	Dominated	Dominated	£1,164	1.2%	75.2%
Test 1 (Nephrocheck)	£23,093	£39	5.85837	0.00000	£20,956,862	£1,049	5.0%	69.3%
Standard care (Scr)	£23,225	Dominated	5.85742	Dominated	Dominated	--	20.7%	--
Scenario 1L Increase the number of times test is conducted to 2								
Standard care (Scr)	£22,811	--	6.07532	--	--	--	70.3%	--
Test 3 (NGAL urine - BioPorto)	£22,853	£41	6.07567	0.00035	£118,796	£118,796	19.9%	28.9%
Test 2 (NGAL plasma - BioPorto)	£22,865	£13	6.07567	0.00001	£2,201,973	£152,384	9.7%	25.4%
Test 4 (NGAL urine - ARCHITECT)	£22,8[illegible]	Dominated	6.0754[illegible]	Dominated	Dominated	£227,155	0.1%	19.2%
Test 1 (Nephrocheck)	£22,9[illegible]	£7[illegible]	6.0757[illegible]	0.0000[illegible]	£69,48[illegible],954	£350,812	0.0%	12.4%
Scenario 1M Apply an additional risk of mortality to those with a false positive test (RR=1.5)								
Test 3 (NGAL urine - BioPorto)	£23,039	--	6.07593	--	--	Dominant	36.5%	48.8%
Standard care (Scr)	£23,044	Dominated	6.07560	Dominated	Dominated	--	50.8%	--
Test 2 (NGAL plasma - BioPorto)	£23,052	£13	6.07594	0.00001	£2,250,040	£22[illegible]6	11.9%	42.2%
Test 4 (NGAL urine - ARCHITECT)	£23,062	Dominated	6.07591	Dominated	Dominated	£56,5[illegible]4	0.2%	37.7%
Test 1 (Nephrocheck)	£23,089	£37	6.07594	0.00000	£19,767,388	£128,239	0.6%	28.9%
Scenario 1N Exclude capital and training costs in test costs								
Test 3 (NGAL urine - BioPorto)	£22,952	--	6.07161	--	--	Dominant	39.6%	51.7%
Standard care (Scr)	£22,964	Dominated	6.07126	Dominated	Dominated	--	47.9%	--
Test 2 (NGAL plasma - BioPorto)	£22,965	£13	6.07163	0.00001	£999,957	£2,229	12.2%	45.6%
Test 4 (NGAL urine - ARCHITECT)	£22,975	Dominated	6.07159	Dominated	Dominated	£35,302	0.0%	40.5%
Test 1 (Nephrocheck)	£23,002	Dominated	6.07162	Dominated	Dominated	£105,799	0.3%	31.4%
Scenario 1O Apply alternative ICU utility value (average of -0.402 and 0.44)								
Test 3 (NGAL urine - BioPorto)	£23,020	--	6.07328	--	--	Dominant	42.4%	53.9%

Standard care (Scr)	£23,032	Dominated	6.07296	Dominated	Dominated	--	45.9%	--
Test 2 (NGAL plasma - BioPorto)	£23,033	£13	6.07329	0.00001	£1,565,836	£1,487	11.0%	47.4%
Test 4 (NGAL urine - ARCHITECT)	£23,044	Dominated	6.07326	Dominated	Dominated	£39,666	0.2%	41.3%
Test 1 (Nephrocheck)	£23,071	Dominated	6.07329	Dominated	Dominated	£118,201	0.5%	30.2%
Scenario 1P [A] Alternative outpatient utility source in the long term (apply general population norms)								
Test 3 (NGAL urine - BioPorto)	£23,149	--	7.05770	--	--	Dominant	41.8%	53.5%
Standard care (Scr)	£23,161	Dominated	7.05712	Dominated	Dominated	--	45.8%	--
Test 2 (NGAL plasma - BioPorto)	£23,161	£12	7.05771	0.00002	£779,444	£1,133	11.3%	47.1%
Test 4 (NGAL urine - ARCHITECT)	£23,172	Dominated	7.05765	Dominated	Dominated	£22,019	0.4%	41.1%
Test 1 (Nephrocheck)	£23,199	Dominated	7.05771	Dominated	Dominated	£65,271	0.5%	33.6%
Scenario 1Q Applying diagnostic test accuracy data for children to the adult AKI model (exploratory only)								
Standard care (Scr)	£22,952		6.07678				55.1%	
Test 4 (NGAL urine - ARCHITECT)	£22,957	£5	6.07709	0.00031	£15,835	£15,835	24.2%	43.3%
Test 3 (NGAL urine - BioPorto)	£22,968	£11	6.07713	0.00004	£260,525	£45,510	20.6%	40.4%

[A] *Probability of indifference < 0.002 at a threshold of cost indifference < £0.01*

Table 35 Scenario analyses assuming that the NGAL tests cannot avert AKI

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Scenario 2A: Alternative base case assuming NephroCheck is the only test that can lead to averted AKI								
Standard care (Scr)	£22,978	--	6.07277	--	--	--	64.5%	--
Test 1 (Nephrocheck)	£23,016	£38	6.07313	0.00036	£105,965	£105,965	29.7%	32.0%
Test 3 (NGAL urine - BioPorto)	£23,049	Dominated	6.07290	Dominated	Dominated	£539,041	5.3%	11.0%
Test 2 (NGAL plasma - BioPorto)	£23,064	Dominated	6.07290	Dominated	Dominated	£633,846	0.3%	7.3%
Test 4 (NGAL urine - ARCHITECT)	£23,065	Dominated	6.07289	Dominated	Dominated	£725,061	0.0%	6.3%
Scenario 2B: Apply the full associative effect on the redistributed cohort only and assuming that the test impacts on the probability of dying at 90 days								
Standard care (Scr)	£22,947	--	6.08411	--	--	--	36.8%	--
Test 3 (NGAL urine - BioPorto)	£23,033	£87	6.08912	0.00502	£17,290	£17,290	34.4%	53.7%
Test 4 (NGAL urine - ARCHITECT)	£23,049	Dominated	6.08875	Dominated	Dominated	£22,071	0.4%	43.7%
Test 2 (NGAL plasma - BioPorto)	£23,050	£17	6.08934	0.00022	£75,026	£19,717	11.1%	48.9%
Test 1 (Nephrocheck)	£23,101	Dominated	6.08615	Dominated	Dominated	£75,634	17.3%	31.4%
Scenario 2C: No associative effect								

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Standard care (Scr)	£23,012	--	6.07534	--	--	--	100.0%	--
Test 3 (NGAL urine - BioPorto)	£23,094	£82	6.07534	Dominated	Dominated	Dominated	0.0%	0.0%
Test 2 (NGAL plasma - BioPorto)	£23,110	£16	6.07534	Dominated	Dominated	Dominated	0.0%	0.0%
Test 4 (NGAL urine - ARCHITECT)	£23,110	Dominated	6.07534	Dominated	Dominated	Dominated	0.0%	0.0%
Test 1 (Nephrocheck)	£23,145	Dominated	6.07534	Dominated	Dominated	Dominated	0.0%	0.0%
Scenario 2D: Full associative effect								
Standard care (Scr)	£23,114	--	6.08592	--	--	--	0.7%	--
Test 3 (NGAL urine - BioPorto)	£23,199	Ext Dom	6.09125	Ext Dom	Ext Dom	£15,974	0.5%	55.8%
Test 2 (NGAL plasma - BioPorto)	£23,214	Ext Dom	6.09137	Ext Dom	Ext Dom	£18,364	0.3%	50.3%
Test 4 (NGAL urine - ARCHITECT)	£23,215	Dominated	6.09080	Dominated	Dominated	£20,721	0.0%	46.0%
Test 1 (Nephrocheck)	£23,223	£109	6.11360	0.02768	£3,941	£3,941	98.5%	99.1%
Scenario 2E: As per Scenario 2D but apply a daily excess AKI costs to patients in hospital/ICU								
Standard care (Scr)	£23,729	--	6.08549	--	--	--	0.7%	--
Test 1 (Nephrocheck)	£23,730	£1	6.11261	0.02712	£29	£29	98.8%	99.1%
Test 3 (NGAL urine - BioPorto)	£23,815	Dominated	6.09063	Dominated	Dominated	£16,615	0.5%	54.0%

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Test 4 (NGAL urine - ARCHITECT)	£23,830	Dominated	6.09020	Dominated	Dominated	£21,436	0.0%	45.1%
Test 2 (NGAL plasma - BioPorto)	£23,831	Dominated	6.09079	Dominated	Dominated	£19,153	0.0%	49.9%
Scenario 2F: Exclude RRT cost								
Standard care (Scr)	£22,779	--	6.07846	--	--	--	68.1%	--
Test 1 (Nephrocheck)	£22,823	£43	6.07882	0.00036	£119,317	£119,317	27.7%	29.6%
Test 3 (NGAL urine - BioPorto)	£22,850	Dominated	6.07859	Dominated	Dominated	£533,230	3.8%	9.0%
Test 2 (NGAL plasma - BioPorto)	£22,865	Dominated	6.07859	Dominated	Dominated	£633,002	0.4%	6.8%
Test 4 (NGAL urine - ARCHITECT)	£22,867	Dominated	6.07858	Dominated	Dominated	£730,093	0.0%	5.6%
Scenario 2G: Apply the differential long-term follow-up costs and mortality according to whether patient entered ICU or not								
Test 1 (Nephrocheck)	£30,438	--	6.55843	--	--	Dominant	97.2%	97.2%
Standard care (Scr)	£30,712	Dominated	6.55697	Dominated	Dominated	--	2.8%	--
Test 3 (NGAL urine - BioPorto)	£30,776	Dominated	6.55733	Dominated	Dominated	£181,324	0.0%	15.4%

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Test 2 (NGAL plasma - BioPorto)	£30,790	Dominated	6.55733	Dominated	Dominated	£217,350	0.0%	11.8%
Test 4 (NGAL urine - ARCHITECT)	£30,793	Dominated	6.55730	Dominated	Dominated	£249,264	0.0%	9.3%
Scenario 2H: Apply an excess CKD risk for those who experienced an AKI event over the full lifetime horizon								
Test 1 (Nephrocheck)	£23,172	--	6.07060	--	--	Dominant	55.5%	57.7%
Standard care (Scr)	£23,174	Dominated	6.06893	Dominated	Dominated	--	39.9%	--
Test 3 (NGAL urine - BioPorto)	£23,231	Dominated	6.06947	Dominated	Dominated	£106,920	3.6%	21.2%
Test 2 (NGAL plasma - BioPorto)	£23,246	Dominated	6.06948	Dominated	Dominated	£132,282	1.0%	16.6%
Test 4 (NGAL urine - ARCHITECT)	£23,250	Dominated	6.06942	Dominated	Dominated	£154,900	0.0%	12.7%
Scenario 2I: 0% discount rate applied to both costs and QALYs								
Standard care (Scr)	£27,689	--	8.20138	--	--	--	60.5%	--
Test 1 (Nephrocheck)	£27,717	£28	8.20191	0.00053	£52,565	£52,565	34.1%	36.6%
Test 3 (NGAL urine - BioPorto)	£27,757	Dominated	8.20157	Dominated	Dominated	£371,108	4.9%	12.7%

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Test 2 (NGAL plasma - BioPorto)	£27,771	Dominated	8.20157	Dominated	Dominated	£439,959	0.4%	9.5%
Test 4 (NGAL urine - ARCHITECT)	£27,774	Dominated	8.20155	Dominated	Dominated	£500,966	0.1%	7.0%
Scenario 2J: 6% discount rate applied to both costs and QALYs								
Standard care (Scr)	£21,153	--	5.11027	--	--	--	67.1%	--
Test 1 (Nephrocheck)	£21,192	£40	5.11055	0.00028	£140,771	£140,771	27.4%	30.7%
Test 3 (NGAL urine - BioPorto)	£21,221	Dominated	5.11037	Dominated	Dominated	£686,941	4.7%	10.8%
Test 2 (NGAL plasma - BioPorto)	£21,235	Dominated	5.11038	Dominated	Dominated	£808,828	0.8%	8.0%
Test 4 (NGAL urine - ARCHITECT)	£21,238	Dominated	5.11036	Dominated	Dominated	£937,507	0.0%	6.3%
Scenario 2K: Apply alternative source for AKI prevalence (average prevalence 0.2332 across systematic review studies)								
Test 1 (Nephrocheck)	£23,014	--	5.85682	--	--	Dominant	63.1%	67.0%
Standard care (Scr)	£23,122	Dominated	5.85589	Dominated	Dominated	--	28.4%	--
Test 3 (NGAL urine - BioPorto)	£23,171	Dominated	5.85623	Dominated	Dominated	£142,617	6.7%	33.2%

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Test 2 (NGAL plasma - BioPorto)	£23,183	Dominated	5.85624	Dominated	Dominated	£174,191	1.8%	30.1%
Test 4 (NGAL urine - ARCHITECT)	£23,188	Dominated	5.85620	Dominated	Dominated	£211,691	0.0%	26.1%
Scenario 2L: Increase the number of times test is conducted to 2								
Standard care (Scr)	£22,246	--	6.07904	--	--	--	88.8%	--
Test 3 (NGAL urine - BioPorto)	£22,873	Ext Dom	6.07916	Ext Dom	Ext Dom	£1,053,861	1.9%	2.6%
Test 1 (Nephrocheck)	£22,875	£129	6.07939	0.00035	£369,737	£369,737	9.0%	9.4%
Test 2 (NGAL plasma - BioPorto)	£22,888	Dominated	6.07916	Dominated	Dominated	£1,167,690	0.3%	1.5%
Test 4 (NGAL urine - ARCHITECT)	£22,898	Dominated	6.07915	Dominated	Dominated	£1,330,281	0.0%	0.7%
Scenario 2M: Apply an additional risk of mortality to those with a false positive test (RR=1.5)								
Standard care (Scr)	£23,246	--	6.06815	--	--	--	66.8%	--
Test 1 (Nephrocheck)	£23,286	£40	6.06849	0.00034	£115,982	£115,982	28.0%	30.3%
Test 3 (NGAL urine - BioPorto)	£23,315	Dominated	6.06827	Dominated	Dominated	£565,245	4.9%	11.2%
Test 2 (NGAL plasma - BioPorto)	£23,330	Dominated	6.06827	Dominated	Dominated	£679,219	0.3%	8.2%

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Test 4 (NGAL urine - ARCHITECT)	£23,332	Dominated	6.06826	Dominated	Dominated	£776,790	0.0%	6.5%
Scenario 2N: Exclude capital and training costs in test costs								
Standard care (Scr)	£22,987	--	6.08128	--	--	--	65.1%	--
Test 1 (Nephrocheck)	£23,025	£39	6.08162	0.00035	£111,620	£111,620	29.4%	32.2%
Test 3 (NGAL urine - BioPorto)	£23,051	Dominated	6.08139	Dominated	Dominated	£546,618	4.5%	12.6%
Test 2 (NGAL plasma - BioPorto)	£23,066	Dominated	6.08140	Dominated	Dominated	£663,328	1.0%	9.3%
Test 4 (NGAL urine - ARCHITECT)	£23,069	Dominated	6.08138	Dominated	Dominated	£766,927	0.0%	6.1%
Scenario 2O: Apply alternative ICU utility value (average of -0.402 and 0.44)								
Standard care (Scr)	£23,234	--	6.07749	--	--	--	67.2%	--
Test 1 (Nephrocheck)	£23,274	£41	6.07783	0.00034	£120,580	£120,580	28.0%	29.9%
Test 3 (NGAL urine - BioPorto)	£23,302	Dominated	6.07761	Dominated	Dominated	£586,840	4.4%	11.0%
Test 2 (NGAL plasma - BioPorto)	£23,317	Dominated	6.07761	Dominated	Dominated	£696,184	0.4%	8.1%
Test 4 (NGAL urine - ARCHITECT)	£23,319	Dominated	6.07760	Dominated	Dominated	£796,431	0.0%	6.2%

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Scenario 2P: Alternative outpatient utility source in the long term (apply general population norms)								
Standard care (Scr)	£22,867	--	7.05869	--	--	--	63.5%	--
Test 1 (Nephrocheck)	£22,904	£36	7.05928	0.00059	£61,809	£61,809	32.0%	34.1%
Test 3 (NGAL urine - BioPorto)	£22,938	Dominated	7.05889	Dominated	Dominated	£360,613	4.3%	9.9%
Test 2 (NGAL plasma - BioPorto)	£22,954	Dominated	7.05889	Dominated	Dominated	£431,098	0.2%	7.8%
Test 4 (NGAL urine - ARCHITECT)	£22,955	Dominated	7.05887	Dominated	Dominated	£483,707	0.0%	5.7%
Scenario 2Q Applying diagnostic test accuracy data for children to the adult AKI model (exploratory only)								
Standard care (Scr)	£23,012		6.07121				91.0%	
Test 4 (NGAL urine - ARCHITECT)	£23,093	£80	6.07132	0.00011	£713,879	£713,879	6.5%	8.8%
Test 3 (NGAL urine - BioPorto)	£23,114	£21	6.07134	0.00001	£1,477,906	£801,274	2.5%	7.0%

[A] Probability of indifference < 0.002 at a threshold of cost indifference < £0.01

Scenarios 1A and 2A describe two potential base-case analyses on which all the sensitivity analyses are conducted. These scenarios assume that there is a potential benefit of averting or having less severe AKI, in terms of improved outcomes (need for ICU care, risk of CKD and length of stay), but the magnitude of that benefit may be less than that observed in observational data. Given the lack of direct evidence demonstrating the impact of biomarker tests on mortality, the base case assumes there is no impact of averting AKI on 90-day mortality.

Scenarios B to E illustrate the impact of assumptions around the magnitude of the associative benefits of averting/having less severe AKI on health outcomes. Scenarios F to P explore the impact of applying alternative follow-up costs and mortality, CKD projection, discount rate, alternative source data for AKI prevalence, test costs, excess mortality risk due to a false positive result, and alternative utility sources.

The results are highly uncertain, with no clear optimal biomarker strategy. The findings are highly sensitive to each of the associative links applied between AKI and health outcomes; i.e. probability of ICU admission, LOS in hospital, probability of dying at 90 days, and the risk of developing CKD.

In scenarios where NGAL tests are assumed to be equally effective as NephroCheck at averting AKI, the BioPorto urine test generally has the greatest probability of cost-effectiveness. That is because the main drivers of the relative cost-effectiveness of each of the biomarker tests against each other are the cost of the test and the diagnostic accuracy. The BioPorto urine NGAL test is slightly cheaper and comes out of the meta-analysis as having slightly better diagnostic accuracy in the all-comers cohort. However, these findings should be interpreted cautiously due to the heterogeneity in the diagnostic test accuracy studies, which lead to further uncertainty in the cost-effectiveness results.

Conversely, NephroCheck and Abbott ARCHITECT NGAL urine are never the most cost-effective strategy when assuming all tests are equally efficacious in averting AKI, because they are more costly tests, with comparatively poorer diagnostic accuracy. NephroCheck is estimated to have poorer specificity compared to the NGAL urine tests, thereby generating additional costs of treating false positive test

cases unnecessarily with a KDIGO care bundle. However, under the alternative base case assumptions, where the NGAL tests are assumed to have no effect on averting AKI, the probability of NephroCheck being the most cost-effective test rises considerably. In the most optimistic scenario, NephroCheck is 100% cost-effective. In the most pessimistic scenario, standard care is the most cost-effective strategy.

Applying a daily excess cost of AKI in hospital or ICU, i.e. if the cost incurred by patients with AKI is not fully captured in the hospital/ICU daily cost, results in the tests being even more favorable compared to base case because more costs are offset by averting AKI or having less severe AKI in the test arms. This results in the NGAL tests being dominant and NephroCheck cost-effective (ICER <£20,000) compared to standard care.

ARCHITECT is generally less likely to be cost-effective in all scenarios because of the test accuracy and test cost. ARCHITECT is estimated to have lower sensitivity and specificity compared to the other tests, and costs more than the other NGAL tests.

In general, the results are also sensitive to the assumption on having hospital/ICU specific follow-up costs and mortality (instead of an average of the two), increased long term cost of AKI, including the linked effect between AKI and probability of CKD for the whole duration of the model (instead of for one cycle as in the base-case) and using an alternative source of AKI prevalence data (with higher prevalence), with all scenarios favouring the test strategies, making them increasingly more cost-effective compared with standard care. In most of these cases, NGAL urine (BioPorto) is the most cost-effective test strategy, however, in the most optimistic scenario, NGAL plasma is the most cost-effective choice of test. On the other hand, assuming that a false positive test result can lead to an increased risk of mortality at 90 days (i.e. RR = 1.5), favours standard care, which becomes the strategy with the highest probability of cost-effectiveness.

We have included an exploratory analysis where the limited available diagnostic accuracy data for children are applied in the adult model. Diagnostic accuracy data were only available for two biomarkers (NGAL urine ARCHITECT and NGAL urine BioPorto). The following diagnostic accuracy estimates were included in this run of

the model: NGAL urine BioPorto: Sensitivity 0.77 (0.70 to 0.84); Specificity: 0.47 (0.40 to 0.54) and for the NGAL urine ARCHITECT test: Sensitivity 0.68 (0.53 to 0.80) and Specificity: 0.79 (0.63 to 0.89)

This analysis should be considered as speculative only as to ensure a robust assessment of cost-effectiveness in children would require the reconfiguration of the model for a pediatric cohort, with appropriate care pathways and age specific risks of transition between health states.

In summary, the results are highly uncertain, and it is impossible to ascertain the most likely ICER given the available evidence. The range of ICERs across different plausible sets of assumptions is substantial and the probabilistic analyses indicate substantial uncertainties regarding the optimal test strategy. Any of the scenarios explored might be feasible and so it is important to consider these findings in light of the substantial uncertainty underlying the impact of the tests on AKI and the causative links between AKI and changes in health outcomes. The substantial heterogeneity in the study populations for the diagnostic accuracy data for the candidate tests raises further concerns about the relative cost-effectiveness of the comparators in the absence of head to head trial comparisons across multiple candidate tests.

Cohort traces from the base case Markov models

Figure 34 shows the Markov traces for the standard care arm of the model under base-case 1 assumptions. In the standard care arm, at 10 years, the mortality for the 63-year old cohort was 45% for the no AKI cohort and 59% for the average of AKI 1,2 and 3cohorts. The mortality for the no AKI group is consistent with the observed 10-year mortality in the Grampian data[1.05] However, the mortality observed for the AKI cohorts at 10 years is lower than in the observational data from Grampian. This is because we did not apply an additional AKI specific excess mortality risk beyond the first year of follow-up in the model as to assume such an additional risk is directly caused by AKI is questionable, based on existing evidence (e.g. Meersch et al).[113]

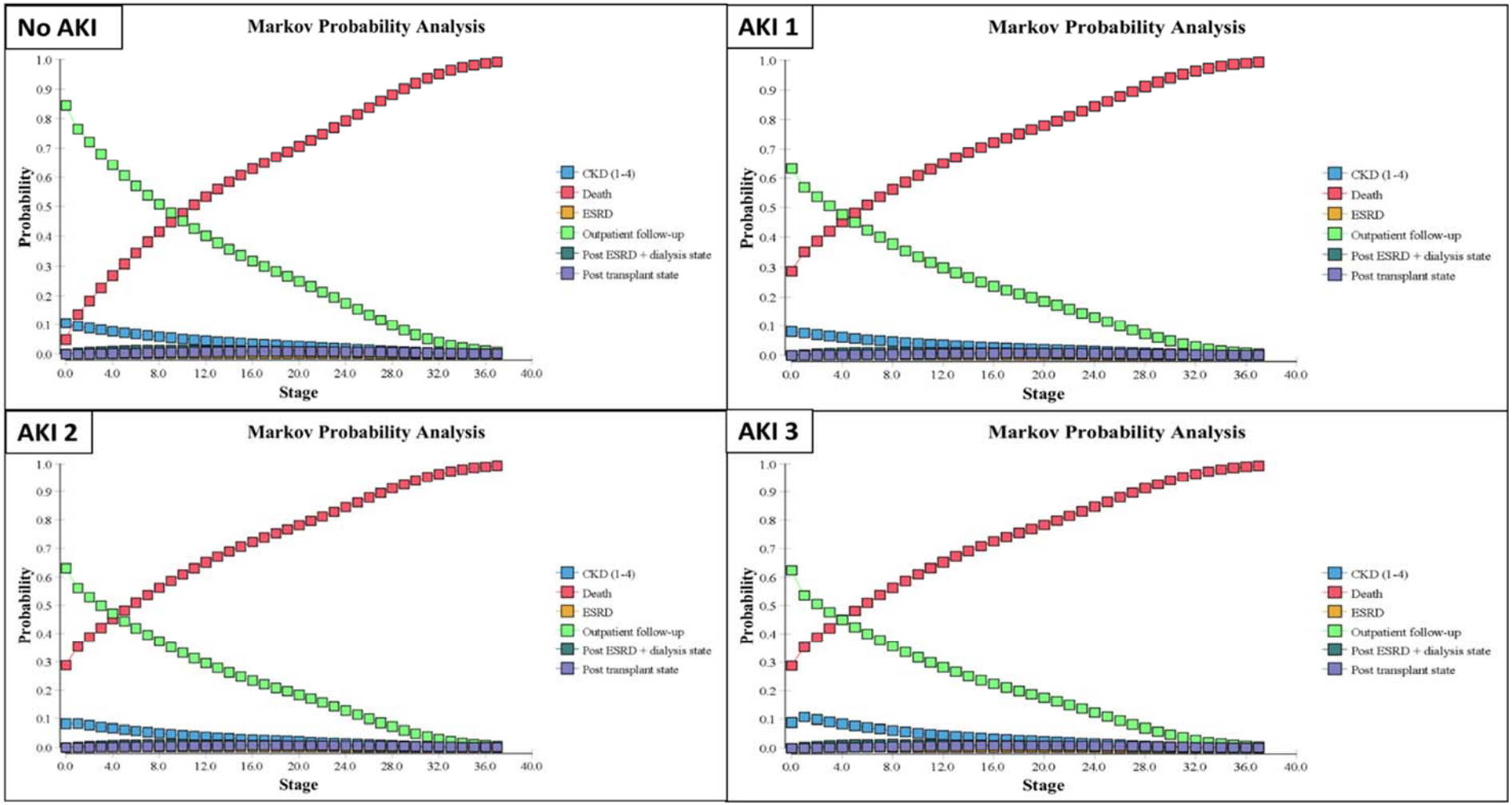


Figure 34 Markov cohort traces for base case model configuration

Cost-effectiveness acceptability curves

Figure 35 and Figure 36 report cost-effectiveness acceptability curves for the two potential base case scenarios.

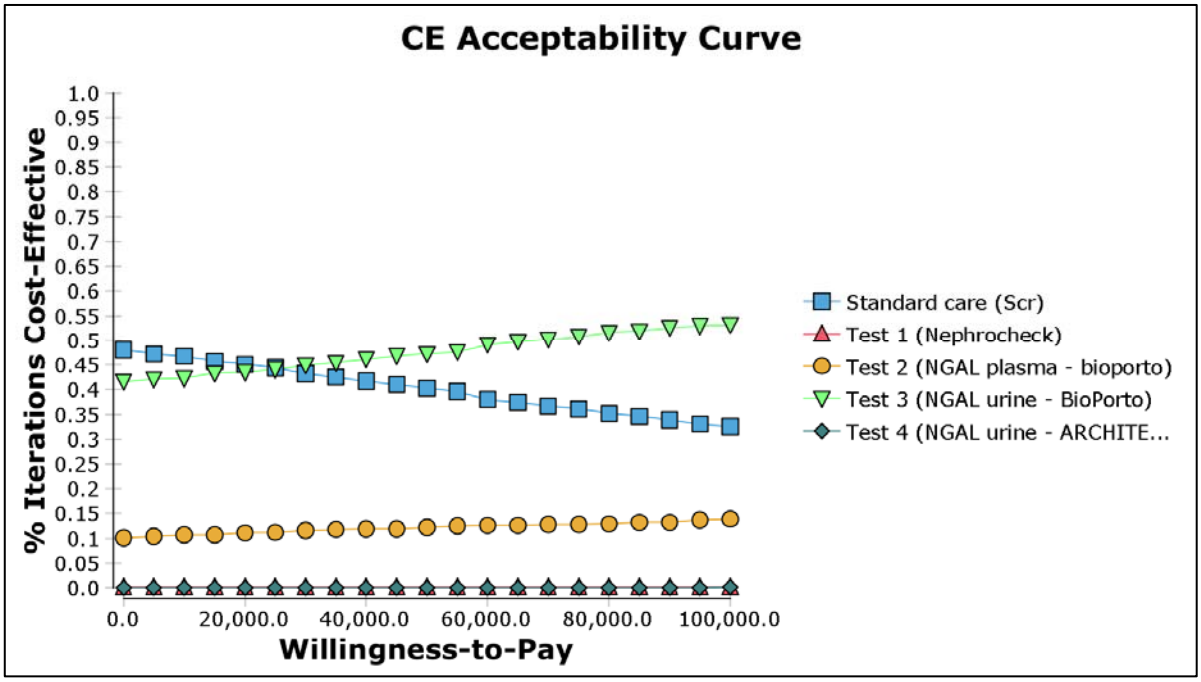


Figure 35 Cost-effectiveness acceptability curves: Base case 1

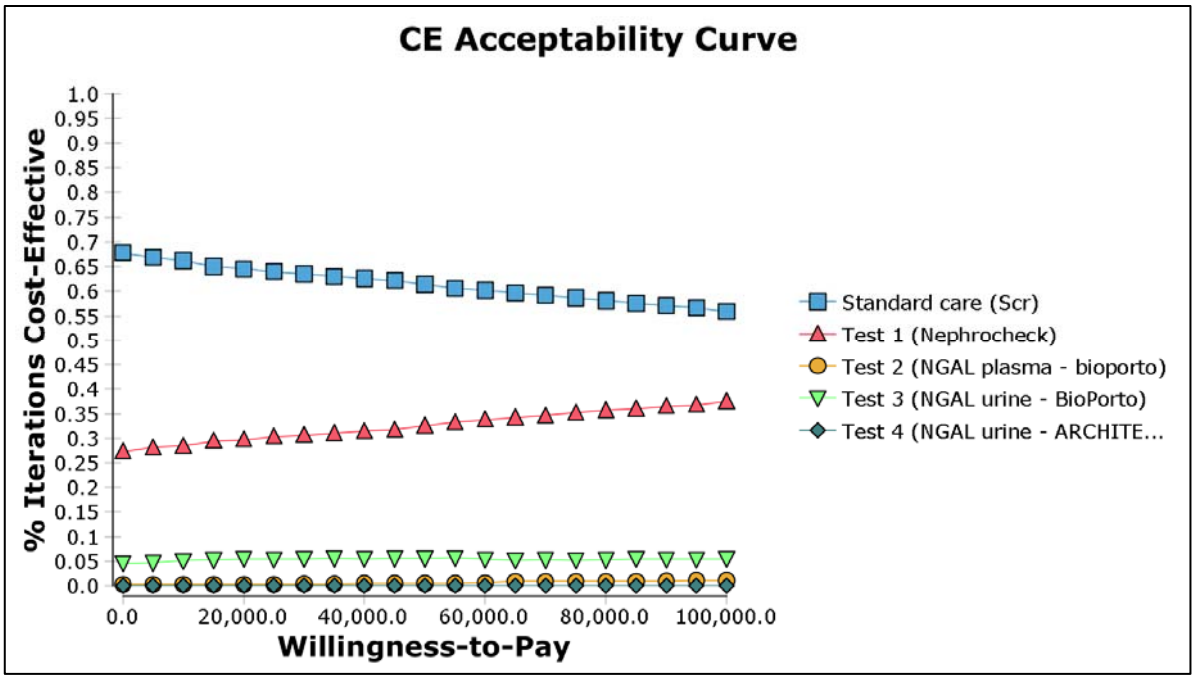


Figure 36 Cost-effectiveness acceptability curves: Base case 2

Subgroup analyses

Three subgroup analyses have been carried out on the two EAG suggested base case strategies (based on whether NGAL is assumed to be capable of averting AKI or not). The subgroups considered are adult critical care and adult post cardiac surgery. As there was not sufficient data to populate a robust model for a children subgroup, this was only considered as an exploratory analysis (as per Tables 34 and 35 above.

Critical care subgroup

For the critical care subgroup, the same parameter values as the all-comers are used for the downstream model probabilities, costs and utilities. This subgroup may be useful for decision making as it could be considered as an alternative, potentially more seriously ill, definition of the population in the NICE scope. Whilst the group are defined as "critical care", the populations described in the source diagnostic accuracy studies are often more reflective of a seriously ill patient group who would not yet be in ICU in the UK setting. The diagnostic accuracy data used for this subgroup are described in Table 36 below.

Table 36 Diagnostic accuracy data used for Critical Care subgroup analysis

Test	measure	Mean (95 % CI)	Mean logit	SE logit	Correlation for MVN analysis	Source
NephroCheck	Sensitivity	0.83 (0.72 to 0.91)	1.615	0.336	-1.000	Meta analysis (Chapter 3)
	Specificity	0.51 (0.48 to 0.54)	0.040	0.064		
NGAL urine (BioPorto)	Sensitivity	0.72 (0.61 to 0.80)	0.926	0.247	+0.905	Meta analysis (Chapter 3)
	Specificity	0.87 (0.66 to 0.96)	1.876	0.617		
NGAL urine (ARCHITECT)	Sensitivity	0.70 (0.63 to 0.76)	0.855	0.165	+1.000	Meta analysis (Chapter 3)
	Specificity	0.72 (0.63 to 0.80)	0.958	0.226		
NGAL plasma (BioPorto)	Sensitivity	0.76 (0.56 to 0.89)	1.156	0.462	-1.000	Meta analysis (Chapter 3)
	Specificity	0.67 (0.40 to 0.86)	0.686	0.566		

The results of the critical care subgroup analysis are provided in Table 37

Table 37 Results of the critical care subgroup analysis

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Critical care subgroup, applied to base case 1								
Test 3 (NGAL urine - BioPorto)	£23,008	--	6.07439	--	--	Dominant	37.0%	51.5%
Test 2 (NGAL plasma - BioPorto)	£23,022	£14	6.07440	0.00002	£900,179	Dominant	12.1%	45.7%
Standard care (Scr)	£23,024	Dominated	6.07406	Dominated	Dominated	--	47.9%	--
Test 4 (NGAL urine - ARCHITECT)	£23,029	Dominated	6.07438	Dominated	Dominated	£15,046	1.8%	42.3%
Test 1 (Nephrocheck)	£23,057	£36	6.07444	0.00004	£905,334	£87,368	1.2%	34.2%
Critical care subgroup, applied to base case 2								
Standard care (Scr)	£22,904		6.07716				65.0%	--
Test 1 (Nephrocheck)	£22,937	£32	6.07755	0.00039	£82,079	£82,079	31.4%	32.8%
Test 3 (NGAL urine - BioPorto)	£22,971	Dominated	6.07728	Dominated	Dominated	£555,173	3.0%	11.1%
Test 2 (NGAL plasma - BioPorto)	£22,991	Dominated	6.07729	Dominated	Dominated	£676,218	0.5%	8.3%
Test 4 (NGAL urine - ARCHITECT)	£22,991	Dominated	6.07728	Dominated	Dominated	£732,572	0.1%	7.9%

Cardiac Surgery subgroup

Diagnostic accuracy data were not available from the systematic review for all biomarker strategies for this group and were only available from single studies for some tests. Where data were not available from the review, we have taken pooled estimates from Hall et al., but note that this analysis should be considered with caution as it includes test manufacturers out with the scope of the NICE assessment. The diagnostic accuracy data for the cardiac surgery subgroup are provided in Table 38 and are included probabilistically in the model where possible.

We caution again that these results should be interpreted cautiously because of the lack of / limitations with the diagnostic accuracy data, and the questionable relevance of the downstream parameters / model structure for a cohort of post-cardiac patients only.

Table 38 Diagnostic accuracy data used for cardiac surgery subgroup

Test	measure	Mean (95 % CI)	Mean logit	SE logit	Correlation for MVN analysis [A]	Source
Nephro-Check	Sensitivity	0.31 (0.09 to 0.61)	-0.800	0.704	-0.824	Cummings, 2019[28]
	Specificity	0.78 (0.74 to 0.82)	1.266	0.120		
NGAL urine (BioPorto)	Sensitivity	0.78 (0.72 to 0.84)	1.266	0.182	+0.526	Yang, 2017[67]
	Specificity	0.48 (0.42 to 0.54)	-0.080	0.123		
NGAL urine (ARCHITECT)	Sensitivity	0.46 (0.33 to 0.59)	-0.160	0.274	-0.517	Parikh, 2017[97]
	Specificity	0.81 (0.79 to 0.83)	1.450	0.067		
NGAL plasma (BioPorto)	Sensitivity	0.62 (0.49 to 0.74)	0.490	0.277	-1.000	Hall, 2018[99]
	Specificity	0.78 (0.75 to 0.81)	1.266	0.090		

[A] Note that in the absence of meta-analysed studies for this subgroup, all correlations are assumed equal to the all-comers, base case analysis.

The results of the post cardiac surgery subgroup analysis are provided in Table 39

Table 39 Results of the post cardiac surgery subgroup analysis

Scenario	Cost	Inc. Cost	QALY	Inc. QALY	ICER (inc)	ICER vs. SC	p (C/E) @ 20k	p (C/E) @ 20k vs. SC
Post cardiac surgery subgroup (applied to scenario 1)								
Standard care (Scr)	£22,912		6.07358				54.2%	
Test 2 (NGAL plasma - BioPorto)	£22,914	£2	6.07387	0.00029	£7,822	£7,822	17.8%	45.5%
Test 3 (NGAL urine - BioPorto)	£22,922	£8	6.07394	0.00007	£112,645	£29,127	28.0%	41.9%
Test 4 (NGAL urine - ARCHITECT)	£22,938	Dominated	6.07380	Dominated	Dominated	£120,552	0.0%	30.1%
Test 1 (Nephrocheck)	£22,984	Dominated	6.07373	Dominated	Dominated	£484,944	0.0%	9.6%
Post cardiac surgery subgroup (applied to scenario 6)								
Standard care (Scr)	£22,983		6.07043				85.6%	
Test 2 (NGAL plasma - BioPorto)	£23,055	Ext Dom	6.07054	Ext Dom	Ext Dom	£679,042	3.8%	8.4%
Test 1 (Nephrocheck)	£23,057	£74	6.07059	0.00016	£465,544	£465,544	6.5%	8.1%
Test 4 (NGAL urine - ARCHITECT)	£23,062	Dominated	6.07051	Dominated	Dominated	£996,121	0.1%	4.0%
Test 3 (NGAL urine - BioPorto)	£23,082	Dominated	6.07056	Dominated	Dominated	£737,663	4.0%	7.5%

Interpretation of the results

Published data show that NephroCheck-guided implementation of a KDIGO care bundle has potential to avert AKI. However, no such data exist for the NGAL tests. Therefore, two base case analyses are considered. Base case 1 can be considered an optimistic scenario for the NGAL assays and assumes that all NGAL tests are equally effective as NephroCheck in terms of the potential to avert AKI. Base case 2 can be considered a more conservative approach, in the absence of evidence and assumes that only NephroCheck can avert AKI, but that all tests have the potential to reduce AKI severity if it occurs.

Fifteen scenario analyses are provided for each potential base case, ranging from a set of optimistic assumptions where biomarker-guided care bundles may lead to substantial improvements in health outcomes (need for ICU, hospital length of stay, CKD, mortality) to a set of more conservative assumptions where changing of AKI status has no effects on health outcomes.

ICERs are highly uncertain, and subject to wide variation depending on the set of scenarios chosen. The probability of cost-effectiveness at an ICER < £20,000 per QALY gained for scenarios where NGAL is assumed equally effective as NephroCheck in preventing AKI ranged from 0% to 15% (NephroCheck); 0-55% (NGAL Urine BioPorto); 0-2% (NGAL ARCHITECT Abbott) and 0-48% (NGAL BioPorto Plasma). NGAL urine (BioPorto) was generally the test associated with the greatest probability of cost-effectiveness, albeit highly uncertain, when compared to standard care only. This is because NGAL urine (BioPorto) had slightly better diagnostic test accuracy data and slightly lower test costs compared to the comparator tests. However, there is substantial uncertainty in the diagnostic test accuracy, driven by study heterogeneity, therefore results should be interpreted cautiously.

When it is assumed NGAL cannot avert AKI, but can only reduce its severity, the cost-effectiveness case for NephroCheck improves substantially, but remains highly uncertain with a probability of cost-effectiveness ranging from 0% to 99% across the explored scenarios.

Given the significant uncertainties across the range of scenario analyses undertaken, it is not possible to draw robust conclusions on the cost-effectiveness of the respective biomarkers.

5 Discussion

Statement of principal findings

In current clinical practice, identification of patients at risk of developing AKI poses a significant challenge to clinicians. Markers of kidney stress and/or injury are hoped to be a useful adjunct to current clinical care as they may facilitate patient management and informed decisions about treatment. Nevertheless, pathways of presentation and care in AKI are complex and the potential for modifiability and clinical benefit is uncertain. This assessment looked at the performance of NephroCheck, ARCHITECT and Alinity urine NGAL and BioPorto urine and plasma NGAL to assess the risk of AKI in critically ill patients considered for admission to critical care. We included 56 studies with a total of 17,967 patients.

Clinical effectiveness

The main clinical effectiveness findings suggest that these biomarkers may have a potential role in the AKI risk assessment in patients admitted to critical care. Evidence for other clinical settings (cardiac surgery, major non-cardiac surgery) was limited.

Meta-analyses results indicate that the use of biomarkers may be useful for identifying AKI. However, because of substantial clinical and statistical heterogeneity between studies and large 95% confidence and prediction regions there is considerable uncertainty surrounding the validity and reliability of these findings. Moreover, the overall performance of the biomarkers for detection of AKI as seen by the meta-analyses of AUC estimates appear to be modest with large boundaries of uncertainty rather than excellent. For example, for the adult population the highest AUC value for detection of AKI was 0.76 but prediction intervals ranged from 0.33 up to 0.99.

For prediction of relevant clinical outcomes, only a small number of studies were available for each biomarker in each clinical setting and this limited the possibility to perform pooled analyses.

Similarly, while there was an indication that addition of biomarkers to existing clinical models might improve the prediction of relevant clinical outcomes, studies

varied considerably in terms of study characteristics and statistical methods used to assess prediction limiting any reliable conclusion.

Overall, as studies varied considerably in terms of clinical setting, timing of sample collection, optimal threshold level, assay platforms, definition of AKI, number of AKI events, time of AKI diagnosis, inclusion /exclusion criteria the reliability and generalizability of the observed findings is highly uncertain.

We did not find any study that used the Alinity test (Abbott) or assessed the performance of the biomarkers for prediction of CKD. Similarly, we did not identify any study that assessed the impact of the routine use of the biomarkers on specific clinical outcomes in critically ill patients over current standard care.

Cost-effectiveness

A probabilistic decision tree and Markov model were developed (adapted from the model used by Hall et al.)[99] to describe the care pathway for a mixed prevalence cohort of CKD / no CKD patients in a hospital setting for patients at risk of developing AKI. The decision tree part of the model captured the acute phase, up to the first 90 days and modelled the risk of AKI, the potential for the use of biomarkers to prevent AKI or reduce its severity. We used a linked evidence approach to derive hypothesised links between the presence / absence of AKI and AKI severity on changes in health outcomes (need for ICU care, length of stay in hospital, need for acute RRT, 90-day mortality and development of CKD). In the absence of robust trial data, we derived these associations from an existing large observational dataset.[105] The Markov model describes the progression of 4 cohorts (no AKI, AKI1, AKI2 and AKI3) through a set of mutually exclusive health states capturing CKD, ESRD, long term dialysis, kidney transplant and mortality. Progression through these states depends on an individual's AKI status in hospital, which influences the starting proportions in the Markov model CKD state.

The model includes health service perspective costs of biomarkers, early application of a KDIGO care bundle, hospitalisation (including ICU and ward costs), acute and long-term dialysis costs, long-term outpatient follow up costs, and transplant and immunosuppressant costs. Health state utility values and modelled mortality risk were

combined to generate estimates of QALYs gained for each test. The model included the functionality to apply additional follow up costs and mortality risk over the longer term for patients admitted into ICU in their index admission.

The cumulative expected value of costs and QALYs were simulated over a lifetime horizon for each cohort under the standard care and each of the biomarker strategies and all results were reported as probabilistic ICERs. We found no trial data that could provide effect estimates for the extent to which biomarkers could both mitigate AKI and improve outcomes. Therefore, the model was built around a series of plausible proportional effects of averting / reducing the severity of AKI on changes in health outcomes. These ranged from optimistic scenarios where patients who had AKI averted as result of a biomarker-guided early implementation of a care bundle, experienced the same risk of ICU, mortality and CKD as if they were in the no AKI cohort; to more pessimistic scenarios where the prevention of AKI or reduction of its severity had no impact on health outcomes.

The costs and QALYs for standard care and each biomarker test strategy were ranked in ascending order of costs, where strategies that were more costly and less effective than an alternative were dominated and excluded from the calculation of the ICERs. In this scenario, the highest ICER value under the threshold represents the best value for money strategy. All scenarios were also compared directly with standard care. In all cases, the probability of cost-effectiveness from the probabilistic simulation was reported.

Cost-effectiveness results were highly uncertain, and ICERs were subject to wide variation depending on the set of scenarios chosen. The probability of cost-effectiveness at an ICER < £20,000 per QALY gained for scenarios where NGAL is assumed equally effective as NephroCheck in preventing AKI ranged from 0% to 15% (NephroCheck); 0-55% (NGAL Urine BioPorto); 0-2% (NGAL ARCHITECT Abbott) and 0-48% (NGAL BioPorto Plasma). NGAL urine (BioPorto) was generally the test associated with the greatest probability of cost-effectiveness, albeit highly uncertain, when compared to standard care only. This is because NGAL urine (BioPorto) had slightly better diagnostic test accuracy data and slightly lower test costs compared to the comparator tests. However, there is substantial uncertainty in

the diagnostic test accuracy, driven by study heterogeneity, therefore results should be interpreted cautiously.

When it is assumed NGAL cannot avert AKI, but can only reduce its severity, the cost-effectiveness case for NephroCheck improves substantially, but remains highly uncertain with a probability of cost-effectiveness ranging from 0% to 99% across the explored scenarios.

In general, our model results generate a less favourable assessment of cost-effectiveness for the biomarker tests compared to that of Hall et al[99]. There are five reasons why this is the case. First, the prevalence of AKI in the Hall et al. study was much higher (31.7%) compared to our prevalent AKI population (9.2%). The higher prevalence might be explained by AKI being more common in the ICU setting (starting cohort in Hall et al.) than in a hospital ward (the starting cohort in our economic model).

Secondly, the settings are different. Hall et al. evaluated the cost-effectiveness of biomarkers for detecting AKI in a critical care setting while our assessment evaluated the cost-effectiveness of AKI biomarkers in a critically ill, hospitalised, cohort considered for admission to critical care. The data sources used to populate the acute phase of the model are different. Hall et al. relied on daily transitions between ICU, hospital and discharge up to 90 days, whereas we have relied on a large observational dataset to populate the potential link between changes in AKI status and health outcomes. Therefore, the costs and utilities applied in the acute phase of the base case models differ between the two analyses.

Thirdly, both models produce estimates of cost-effectiveness that are sensitive to the data used for the diagnostic accuracy of the tests. The diagnostic accuracy data applied in Hall et al. are different from those obtained from our meta-analyses, likely due to new studies becoming available since the Hall et al. publication and the wider setting for our model. For example, the sensitivity of NephroCheck was 0.90 in Hall et al. and 0.75 in our meta-analysis. Consequently, NephroCheck identified more true positive cases, which generated greater QALY gains in Hall et al, compared to our model.

Fourthly, we take a more conservative approach to the estimation of long term follow up costs for the base case analysis and have not applied excess lifetime costs beyond the 5-year data reported in Lone et al[123].

Fifthly, we further assume that there is no impact of AKI on follow up costs beyond the 90 days, while Hall et al. assume excess costs applied for the full life-time horizon. We also assume that the causal impact of AKI on CKD development ceases beyond the first cycle of the Markov model (i.e. 1.25 years after the AKI event), whereas Hall et al. assume additional risk of CKD for the full lifetime horizon of the model.

Overall, both models conclude that there is substantial uncertainty in the results, albeit predicting different base case ICERs. The results are highly sensitive to key parameters in the model, and any combination of the presented scenarios may be plausible.

Strength and limitations of the assessment

The methods used to conduct this assessment were detailed and thorough. We conducted comprehensive literature searches of major electronic databases and relevant websites and assessed more than 1000 full text studies for eligibility. The large number of screened and extracted articles was necessary because key information (e.g., information on biomarker assays) was not available from the abstract. This resulted in a need for significant literature screening resources and for considering strict inclusion criteria in order to ensure the assessment remained feasible and timely. We restricted inclusion to studies that enrolled at least 100 participants and excluded studies on low-weight and pre-term babies. It is possible that inclusion of all existing studies, irrespective of the sample size, might produce relevant findings. However, we reached a consensus that small and niche studies would not provide clinically generalisable evidence for pooling and would be underpowered to provide reliable evidence in isolation. Low-weight and pre-term babies were considered a category of patients with specific care needs, not generalisable to the population included in this assessment.

The primary weakness of the systematic review of clinical effectiveness evidence was the substantial clinical heterogeneity observed between studies. There was considerable heterogeneity especially with regard to NGAL threshold levels, time of sample collection, definition of AKI and prevalence of AKI, time of AKI diagnosis, assays platforms. Consequently, the diagnostic accuracy of individual tests varied considerably and the confidence and prediction regions in the pooled analyses were notably large. Moreover, when the studies had lower number of AKI events (low prevalence) the relationship observed between sensitivity and specificity estimates became quite different compared to that of studies for which prevalence was higher. Indeed, the shape and size of the prediction regions in the HSROC plots was influenced by studies that showed a different relationship between sensitivity and specificity compared with other studies. Hence, we do not have much confidence in the pooled estimates.

In particular, the intrinsic complexity of this assessment (multiple research questions, multiple biomarkers and sample media, multiple clinical settings, broad patient population, differences in assay platforms, definition of AKI) means that the findings reported here are also complex, particularly given the absence of robust trial evidence to support economic model development. While the original scope of this assessment was the assessment of hospitalised patients considered to be at risk of admission to critical care, no studies focused on this specific group of patients (pre-admission to critical care). Most studies were conducted outside the UK and assessed patients already admitted to intensive or critical care after different surgical procedures or with different (or multiple) clinical conditions. Furthermore, the provision of Intensive Care resources across the world are heterogeneous, so many studies will not be representative of how intensive care is utilised in the UK. This means that it is unclear how well findings of studies that are predominantly based in intensive care, non-UK and heterogenous, can be applied to a UK clinical scenario of people not currently receiving critical care but at risk of it.

Criteria used for the definition of AKI were consistent with current KDIGO recommendations but differ slightly across studies with respect to operationalisation. This means that the extent of bidirectional misclassification of AKI and CKD may vary between studies and setting, which may affect biomarker performance[153]. In

some studies, it was unclear whether the reported associations between biomarkers and AKI were indeed attributed to kidney injury. The current definition of AKI is based on elevations in serum creatinine concentration, which poses the conundrum of using an imperfect standard to assess the biomarkers' performance. Serum creatinine is not always measured at the same frequency as the biomarkers and to ascertain the exact time of creatinine rise it is problematic. As a result, the "ground truth" of AKI existence could not be established with a gold standard reference in any of the studies. In addition, no studies considered alternative methods for early or incipient AKI detection, such as the use of machine learning algorithms[154].

In some studies, we observed a very small number of AKI events compared with other included studies. Interestingly, two studies both conducted in the cardiac surgery setting [a medium size single centre study (Cummings et al[28]., 400 participants) and a large multicenter study (Parikh et al[40]., the TRIBE trial, 1219 participants)] showed similar prevalence rates (4% and 5%, respectively) and a similar pattern of accuracy (poor sensitivity estimates and good specificity estimates). The number of AKI events are known to vary depending on both AKI definition and clinical setting, which underlies the heterogeneity of existing studies.

An unavoidable limitation of this evaluation is the variation in use of NGAL tests. Threshold cut points to classify patients with and without AKI in each clinical setting were not consistent across studies. This means that differences between studies could relate to chosen threshold rather than NGAL performance. We selected one threshold per study according to our inclusion criteria and estimated the underlying summary ROC curve using a hierarchical model, which takes into account the within and between studies variability. NGAL studies also varied with respect to analytic methods of measurement Some studies used absolute urine concentrations, while others used NGAL concentrations normalised for urine creatinine concentrations. There was insufficient data available per type of biomarker and clinical setting to further investigate this source of variability and determine the extent to which analytic methods influence estimates of diagnostic accuracy and whether it was sensible to pool results across studies. Nevertheless, we note that in the multicentre TRIBE (Translational Research Involving Biomarkers and Endpoints) prospective study assessing 1219 adults undergoing cardiac surgery, the authors repeated the analyses

using NGAL urine-creatinine corrected values and did not observe improvements in the AUCs compared with uncorrected results.[40]

Several studies did not provide sensitivity, specificity and AUC for the biomarkers for the diagnostic or prognostic accuracy of AKI. In future studies, accuracy measures such as sensitivity and specificity must be considered and defined rigorously at transparent cut points for predictive biomarkers as they may need to vary according to clinical setting.[155]

Notwithstanding analytic and threshold heterogeneity, the number of available studies for each type of assay in each clinical setting limited our ability to assess the role of the biomarkers for the prediction of relevant clinical outcomes. Furthermore, the number of events was small in many studies and the duration of follow up was not consistent across studies so mortality and RRT could not be assessed, reliably, at the same time points. Furthermore, details of the methods used for prediction analyses were insufficient in many studies. While information on adjustment strategies and on the process of variables selection were usually provided, the original cohort of potential predictors, prior to the multivariable analysis, was never clearly specified leading to potential risk of bias.

Finally, introduction of a biomarker would require evidence not just that it performs well as a predictor of modifiable and intervenable AKI, but also that there is incremental improvement of existing or alternative approaches to clinical care. There was insufficient information to determine with certainty whether the biomarkers had an incremental advantage over the traditional marker of serum creatinine and urine output or available information for clinical assessment. Only a limited number of studies compared the AUC of the biomarkers under investigation with that of serum creatinine for the detection of AKI and fewer studies compared the performance of the biomarkers with that of clinical models for prediction of AKI or of relevant patient outcomes.

Uncertainties

Clinical effectiveness evidence

There is considerable uncertainty surrounding the generalisability of the studies to the UK population. Most of the studies were conducted outside the UK and assessed patients already admitted to critical care. Because no studies were identified for inclusion, we were not able to assess the impact that the routine use of these biomarkers may have on clinical outcomes of critically ill people considered for admission to critical care compared to standard clinical assessment.

At present, in the literature there is limited information on the benefits of incorporating biomarkers results with that of current clinical criteria (serum creatinine and urine output) to improve the clinical management of patients with AKI. Recently, Zarbock et al.,[156] in the ELAIN RCT of critically ill surgical patients with AKI assessed the use of early versus delayed RRT. Plasma NGAL >150 ng/mL was one of the inclusion criteria together with the KDIGO criteria. The trial results showed that early RRT compared with delayed RRT reduced mortality, duration of RRT and hospital stay and that the combination of the KDIGO classification system in combination with plasma NGAL was effective in identifying patients with deteriorating AKI. Subsequent negative results from the AKIKI RCT for critically medical patients suggests that these findings may only apply to targeted circumstances (and if reproduced in other studies).[157] More recently, the Zarbock group conducted a biomarker guided RCT of patients who underwent cardiac surgery.[113] They used a biomarker-based approach (NephroCheck test) to identify high-risk patients and implement a bundle of supportive measures recommended by the KDIGO guidelines to reduce the occurrence of AKI as well as that of mortality and RRT. Their results showed that implementation of the KDIGO guidelines compared to standard care reduced the frequency of AKI within 72 hours after cardiac surgery. However, the trial did not show a reduction in the need of RRT nor an improvement in mortality, or a positive effect measure on any hard clinical outcome. The authors concluded that future, adequately powered, multicentre trials are required. Similarly, Gocze et al.[114] in a study of major non-cardiac surgery patients showed that the early adoption of a bundle of supportive measures according to the KDIGO guidelines in patients with NephroCheck concentrations higher than 0.3 $(ng/mL)^2/1000$ resulted in a reduced

occurrence of AKI, decreased hospital and ICU stay, and reduced costs, but again there was no evidence of improvement of hard outcomes (RRT, mortality, or major kidney events).

Overall, despite some evidence suggesting possible improvement of care processes and health care utilisation when biomarker guided care bundles are used alongside KDIGO criteria, there is still considerable uncertainty and confusion about how and when to use them in clinical practice, and no evidence of benefit to hard outcomes. In addition, the optimal threshold for NGAL, and how this changes according to different clinical settings, has yet to be established. Future studies should evaluate the targeted use of the biomarkers within specific clinical populations and circumstances were there is potential for benefit with a plausible and feasible intervention. In particular, they should focus on the assessment of the impact of routine biomarker use on a reduction in mortality, major clinical adverse events, modification of clinical care, and resource utilization. In other words, future research should evaluate the use of these biomarkers to improve patients' clinical outcomes and management.

Discrete urine and plasma NGAL cut offs for differentiating between AKI and non-AKI patients in each clinical setting need to be identified and the timing of collection of biomarker concentrations should be set out more clearly according to each setting. In line with the recommendations from the 10th Acute Dialysis Quality Initiative Consensus Conference,[158] there is also a need to harmonise the methods and platforms for collection, handling and storage of urine and plasma samples. Furthermore, it would be useful to harmonise the reporting of biomarkers concentrations (e.g., absolute concentrations, ratio to urine creatinine) and corroborate techniques for normalising urine biomarker concentrations to urine creatinine concentrations.

Finally, it is well recognised that AKI encompasses a range of clinical aetiologies, phenotypes and patterns of renal recovery. In addition, current measures of AKI may be insufficient to disentangle AKI that is predominantly functional without kidney damage, from people with incipient subclinical damage, to people with both AKI and kidney damage. Within this context, it remains unclear how phenotypic information on people with AKI should most usefully be combined to help target those most likely

to benefit from earlier recognition and timely intervention, nor how such intervention may differ between clinical phenotypes.[158]

Cost-effectiveness evidence

There are three key areas of uncertainty in the economic evaluation modelling that limit the robustness of the cost-effectiveness results: i) the lack of evidence on the impact of the biomarkers on health outcomes; ii) the heterogeneity in the diagnostic accuracy data (including uncertainty in the prevalence of AKI in a broad, poorly defined population); iii) the uncertainty around the impact of a NGAL-guided implementation of a KDIGO care bundle on the frequency and severity of AKI. Given these uncertainties, the choice of a preferred base case scenario is challenging, and the observed results should be considered cautiously. These are speculative analyses ranging from a set of pessimistic to a set of optimistic scenarios for the use of the biomarkers under assessment.

Specifically, there is no evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, risk of 90-day mortality or development of new / progression of existing chronic kidney disease). Accordingly, the cost-effectiveness results are based on a linked-evidence approach where we have relied on observational associations to infer how prevention or mitigation of AKI may affect changes in health outcomes. These associations necessitate causal assumptions, but while a causal link between AKI and poor outcomes is plausible, the extent of this causal relationship is uncertain and controversial.[159, 160] The cost-effectiveness results are therefore presented for a range of alternative, but potentially plausible, scenario analyses ranging from a set of optimistic assumptions where biomarker-guided care bundles may lead to substantial improvements in health outcomes (need for ICU, CKD, mortality) to a set of more conservative assumptions where changing of AKI status has no effects on health outcomes. It is likely that the true estimate of cost-effectiveness lies somewhere between these two extremes.

Furthermore, the diagnostic accuracy data used in the economic model are obtained from studies that are considerably heterogeneous in terms of baseline AKI prevalence, timing of sample collection, threshold values, and definition of AKI. Given the

difficulty in defining the population that fits within the scope of this assessment, it is unclear how generalisable the diagnostic accuracy data are to the UK population in which the biomarkers could be used.

Also of note are additional uncertainties in the model that make conclusions about the relative cost-effectiveness of each biomarkers difficult. For example, whilst there is some evidence in the literature from Meersch et al. that early NephroCheck guided implementation of a KDIGO care bundle may improve AKI status at 72 hours,[113] the potential for similar improvements using NGAL is unknown. Therefore, we have considered two scenarios for the cost-effectiveness analyses. The first assumes, optimistically, that all NGAL tests are equally as effective at preventing AKI or reducing its severity as NephroCheck; the second based on the available data from Meersch et al assumes that NGAL can only reduce the severity of AKI once occurs but cannot prevent its occurrence.

Because of these uncertainties, the results of the cost-effectiveness modelling are largely speculative and should be interpreted with caution. Whilst extensive probabilistic analyses are carried out for scenario analyses, these may still not fully capture the uncertainty faced in the implementation of these biomarkers in clinical practice.

6 Conclusions

Overall clinical message and future research requirements

In summary, the current evidence base is insufficient to make a full appraisal of the economic value of the biomarkers under investigation to provide cost effective improvements in clinical outcomes of AKI. As such, we have provided a range of scenarios that cannot answer the full remit of this evaluation. We believe the scenarios illustrate what might be required for the biomarkers to be cost effective, highlighting through the assumptions involved the current gaps where further research is required:

We found that novel biomarkers have the ability to predict the presence or onset of AKI, but additional research is required to understand whether such biomarkers can do so incrementally above existing standard care. In addition, research that considers the utility of biomarkers on top of other novel approaches such as machine learning approaches to recognise incipient AKI in different clinical environments would be valuable.

There was limited trial evidence that the course of AKI in critical care circumstances may be potentially modifiable, or avoidable with early biomarker-guided care bundle approaches. Future research is needed to understand whether this is dependent on a well-performing timely biomarker, a care bundle appropriate for clinical context, or both. Research is also required to further evaluate such approaches outside of a critical care setting.

Current literature is inadequate to determine whether biomarker-guided intervention can lead to hard clinical and economic outcomes in addition to amelioration of AKI severity. The specific clinical circumstances where benefit exists, and whether such benefit is dependent on reduction of AKI severity or is mediated through other means would also be informative for future evaluations.

Uncertainty remains around the process of renal recovery and non-recovery after AKI. Mechanistic work exploring the nature, timing and extent of the recovery process could inform the nature and circumstance where a biomarker-guided intervention

might be effective. Similarly, clinical research on the timing and extent of renal recovery with different AKI phenotypes would enhance the ability to model cost effectiveness of biomarker-guided therapies within different subsets of AKI.

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159. Rifkin DE, Coca SG, Kalantar-Zadeh K. Does AKI truly lead to CKD? *J Am Soc Nephrol* 2012; 23(6), 979-84.

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8 Appendices

Appendix 1 Literature search strategies

NephroCheck/NGAL clinical effectiveness search strategies

Ovid **Embase** <1974 to 2019 May 14>, Ovid **MEDLINE**(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 14, 2019>
Date of search: 27 May 2019

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1 Acute Disease/ and exp Kidney Diseases/ use ppezv (8605)
2 exp acute disease/ and exp *kidney disease/ use oemezd (2443)
3 exp *acute kidney failure/ use oemezd (31083)
4 acute kidney injury/ use ppezv (41584)
5 exp *kidney injury/ use oemezd (12360)
6 kidney tubular necrosis, acute/ use ppezv (2352)
7 exp *kidney tubule necrosis/ use oemezd (1519)
8 (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (50969)
9 (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (58624)
10 ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or "nephrotoxic injur*").tw. (9425)
11 aki.tw. (27925)
12 exp *contrast induced nephropathy/ use oemezd (2540)
13 "contrast induced nephropathy".tw. (5028)
14 or/1-13 (159431)
15 *reperfusion injury/ (47279)
16 reperfusion/ use ppezv (4705)
17 (reperfusion adj5 (injur* or isch?emi*)).tw. (129126)
18 exp *Delayed Graft Function/ (1612)
19 "delayed graft function*".tw. (9243)
20 or/15-19 (144655)
21 (renal or kidney* or nephr* or "tubular necrosis" or aki).tw. (2045747)
22 (or/1-7) or 21 (2056977)
23 20 and 22 (25897)
24 14 or 23 [All AKI] (177838)
25 lipocalins/ or lipocalin-2/ use ppezv (6282)
26 neutrophil gelatinase associated lipocalin/ or lipocalin/ use oemezd (12442)
27 (NGAL or uNGAL or sNGAL).tw,kw. (7409)
28 ("Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin).tw,kw,nm. use ppezv (4262)
29 ("Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin).tw,kw,tn. use oemezd (5997)
30 or/25-29 [NGAL] (16697)

31 "Tissue Inhibitor of Metalloproteinase-2"/ use ppezv (3445)
32 "tissue inhibitor of metalloproteinase 2"/ use oemezd (6871)
33 Metalloproteinase inhibitor 2.tw,nm,kw. use ppezv (15)
34 Metalloproteinase inhibitor 2.tw,kw. use oemezd (28)
35 tissue inhibitor of metalloproteinase-2.tw,nm,kw. use ppezv (3699)
36 tissue inhibitor of metalloproteinase-2.tw,kw. use oemezd (883)
37 TIMP metallopeptidase inhibitor 2.tw,nm,kw. use ppezv (10)
38 TIMP metallopeptidase inhibitor 2.tw,kw. use oemezd (11)
39 (TIMP 2 or TIMP2 or DDC8 or CSC-21K).tw,nm,kw. use ppezv (4818)
40 (TIMP 2 or TIMP2 or DDC8 or CSC-21K).tw,kw. use oemezd (6114)
41 or/31-40 [TIMP2] (14536)
42 (IGFBP7 or IBP-7 or IGFBP-rP1).tw,nm,kw. use ppezv (410)
43 (IGFBP7 or IBP-7 or IGFBP-rP1).tw,kw. use oemezd (614)
44 IGF-binding protein 7.tw,nm,kw. use ppezv (16)
45 IGF-binding protein 7.tw,kw. use oemezd (23)
46 Insulin-like growth factor-binding protein 7.tw,nm,kw. use ppezv (220)
47 Insulin-like growth factor-binding protein 7.tw,kw. use oemezd (326)
48 MAC25 protein.tw,nm,kw. use ppezv (5)
49 MAC25 protein.tw,kw. use oemezd (5)
50 PGI2-stimulating factor.tw,nm,kw. use ppezv (6)
51 PGI2-stimulating factor.tw,kw. use oemezd (9)
52 “Prostacyclin-stimulating factor”.tw,nm,kw. use ppezv (29)
53 Prostacyclin-stimulating factor.tw,kw. use oemezd (31)
54 #32 or #33 or #34 or #35 or #36 or #37.tw,nm,kw. use ppezv (15)
55 Tumor-derived adhesion factor.tw,kw. use oemezd (7)
56 or/42-55 [IGFBP7] (1273)
57 41 and 56 [TIMP2 AND IGFBP7] (278)
58 nephrocheck.tw,kw. use ppezv (24)
59 nephrocheck.tw,dv,kw. use oemezd (55)
60 58 or 59 (79)
61 30 or 57 or 60 (16915)
62 24 and 61 (5763)
63 remove duplicates from 62 (4053)

CINAHL (via EBSCOHost)
Date of search: 17 May 2019

S1 (MH "Kidney Diseases") AND (MH "Acute Disease") 257
S2 (MM "Kidney Failure, Acute") 5,995
S3 (MH "Kidney Tubular Necrosis, Acute") 190
S4 TX Acute N3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction) 10,442
S5 TX Acute N3 (renal disease* or renal injury or renal failure or renal dysfunction) 3,651
S6 TX (Acute N3 (Tubular Necrosis or nephrotoxic*)) OR TX "nephrotoxic injur*" 447
S7 TX aki 3,496
S8 TX "contrast induced nephropathy". 677
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 13,805
S10 (MM "Reperfusion Injury") 1,816

S11 (MH "Reperfusion") 947
S12 TX "delayed graft function*".213
S13 TX reperfusion N5 (injur* or isch?emi*) 4,919
S14 S10 OR S11 OR S12 OR S13 5,890
S15 TX renal or kidney* or nephr* or "tubular necrosis" or aki 157,197
S16 S1 OR S2 OR S3 OR S15 157,197
S17 S14 AND S16 1,057
S18 S9 OR S17 14,436
S19 TX (NGAL or uNGAL or sNGAL). 558
S20 TX "Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin 762
S21 TX "Metalloproteinase inhibitor 2" OR TX "tissue inhibitor of metalloproteinase-2" OR TX "TIMP metallopeptidase inhibitor 2" OR TX ("TIMP 2 or TIMP2 or DDC8 or CSC-21K")
S22 TX ((IGFBP7 or IBP-7 or IGFBP-rP1)) OR TX "IGF-binding protein 7" OR TX "Insulin-like growth factor-binding protein 7" 63
S23 TX "MAC25 protein" OR TX "PGI2-stimulating factor" OR TX "Prostacyclin-stimulating factor" 0
S24 S22 OR S23 63
S25 S21 AND S24 12
S26 S19 OR S20 OR S25 853
S27 S18 AND S26 473

Cochrane Central Register of Controlled Trials (via Wiley Online Library)
Date of search: 17 May 2019

#1 MeSH descriptor: [Acute Kidney Injury] explode all trees 1214
#2 MeSH descriptor: [Kidney Tubular Necrosis, Acute] explode all trees 37
#3 (Acute NEAR/3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)):ti,ab,kw 23064
#4 (Acute NEAR/3 (renal disease* or renal injury or renal failure or renal dysfunction)):ti,ab,kw 23415
#5 (Acute NEAR/3 (Tubular Necrosis or nephrotoxic*)):ti,ab,kw 312
#6 ("nephrotoxic injur*"):ti,ab,kw 0
#7 (aki):ti,ab,kw 1209
#8 ("contrast induced nephropathy"):ti,ab,kw 822
#9 MeSH descriptor: [Acute Disease] explode all trees 9276
#10 MeSH descriptor: [Kidney Diseases] explode all trees 14389
#11 #9 and #10 193
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #11 24407
#13 MeSH descriptor: [Reperfusion Injury] explode all trees 1006
#14 (reperfusion NEAR/5 (injur* or ischemi* or ischaemi*)):ti,ab,kw 2932
#15 MeSH descriptor: [Delayed Graft Function] explode all trees 89
#16 ("delayed graft function*"):ti,ab,kw 597
#17 #13 or #14 or #15 or #16 3470
#18 (renal or kidney* or nephr* or "tubular necrosis" or aki):ti,ab,kw 79148
#19 #1 or #2 or #11 or #18 79196
#20 #17 and #19 997
#21 MeSH descriptor: [Lipocalins] explode all trees 199
#22 MeSH descriptor: [Lipocalin-2] explode all trees 93

#23 (NGAL or uNGAL or sNGAL):ti,ab,kw 550
#24 ("Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin):ti,ab,kw 533
#25 #21 or #22 or #23 or #24 816
#26 ("Metalloproteinase inhibitor 2"):ti,ab,kw 0
#27 ("tissue inhibitor of metalloproteinase-2"):ti,ab,kw 70
#28 ("TIMP metallopeptidase inhibitor 2"):ti,ab,kw 0
#29 (TIMP 2 or TIMP2 or DDC8 or CSC-21K):ti,ab,kw 303
#30 MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-2] explode all trees 42
#31 #26 or #27 or #28 or #29 or #30 315
#32 (IGFBP7 or IBP-7 or IGFBP-rP1):ti,ab,kw 26
#33 ("IGF-binding protein 7"):ti,ab,kw 1
#34 ("Insulin-like growth factor-binding protein 7"):ti,ab,kw 22
#35 (MAC25 protein):ti,ab,kw 0
#36 ("PGI2-stimulating factor"):ti,ab,kw 0
#37 ("Prostacyclin-stimulating factor"):ti,ab,kw 1
#38 ("Tumor-derived adhesion factor"):ti,ab,kw 0
#39 #32 or #33 or #34 or #35 or #36 or #37 33
#40 #31 and #39 21
#41 (nephrocheck):ti,ab,kw 4
#42 #25 or #40 or #41 832
#43 #12 or #20 25125
#44 #42 and #43 292

Clarivate Analytics **Web of Science**
Indexes=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=All years
Date of search: 22 May 2019

1 24,763 TOPIC: ("acute kidney injury" OR "acute kidney failure")
2 715 TOPIC: (kidney NEAR/2 necrosis)
3 25,532 TOPIC: (Acute NEAR/3 ("kidney disease*" or "kidney injury" or "kidney failure" or "kidney dysfunction"))
4 32,865 TOPIC: (Acute NEAR/3 ("renal disease*" or "renal injury" or "renal failure" or "renal dysfunction"))
5 3,029 TOPIC: ("contrast induced nephropathy")
6 54,254 #5 OR #4 OR #3 OR #2 OR #1
7 3,258 TOPIC: (NGAL or sNGAL or uNGAL)
8 3,078 TOPIC: (neutrophil NEAR/2 lipocalin)
9 4,099 #8 OR #7
10 10,021 TOPIC: (Inhibitor NEAR/2 Metalloproteinase)
11 12,633 TOPIC: (TIMP)
12 18,219 #11 OR #10
13 470 TOPIC: (IGFBP7 or IBP-7 or IGFBP-rP1)
14 242 TOPIC: ("Insulin-like growth factor-binding protein 7")
15 539 #14 OR #13
16 108 #15 AND #12
17 29 TOPIC: (nephrocheck)
18 4,192 #17 OR #16 OR #9
19 1,943 #18 AND #6

20 3,841,039 TOPIC: (rat or rats or mouse or mice or murine or dog or dogs or canine or pig or pigs or porcine)
21 428 #20 AND #19
22 1,543 #19 not #21

The following resources were searched using appropriate text terms, in combination where allowed by the search interface.

HTA database (http://www.crd.york.ac.uk/PanHTA/)

WHO Global Index Medicus
(http://www.globalhealthlibrary.net/php/index.php?lang=en)

EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)

International Clinical Trials Registry Platform (http://www.isrctn.com/)

ClinicalTrials.gov (via the US National Institutes of Health; Advanced Search Interface)

Search terms used:
Acute kidney/renal injury
Acute kidney/renal failure
Kidney Tubular Necrosis
contrast induced nephropathy
Nephrocheck
TIMP-2
Metalloproteinase
IGFBP7
Insulin-like growth factor-binding protein 7
NGAL or uNGAL or sNGAL
Neutrophil gelatinase-associated lipocalin

Results retrieved: 86

Appendix 2 Screening tool

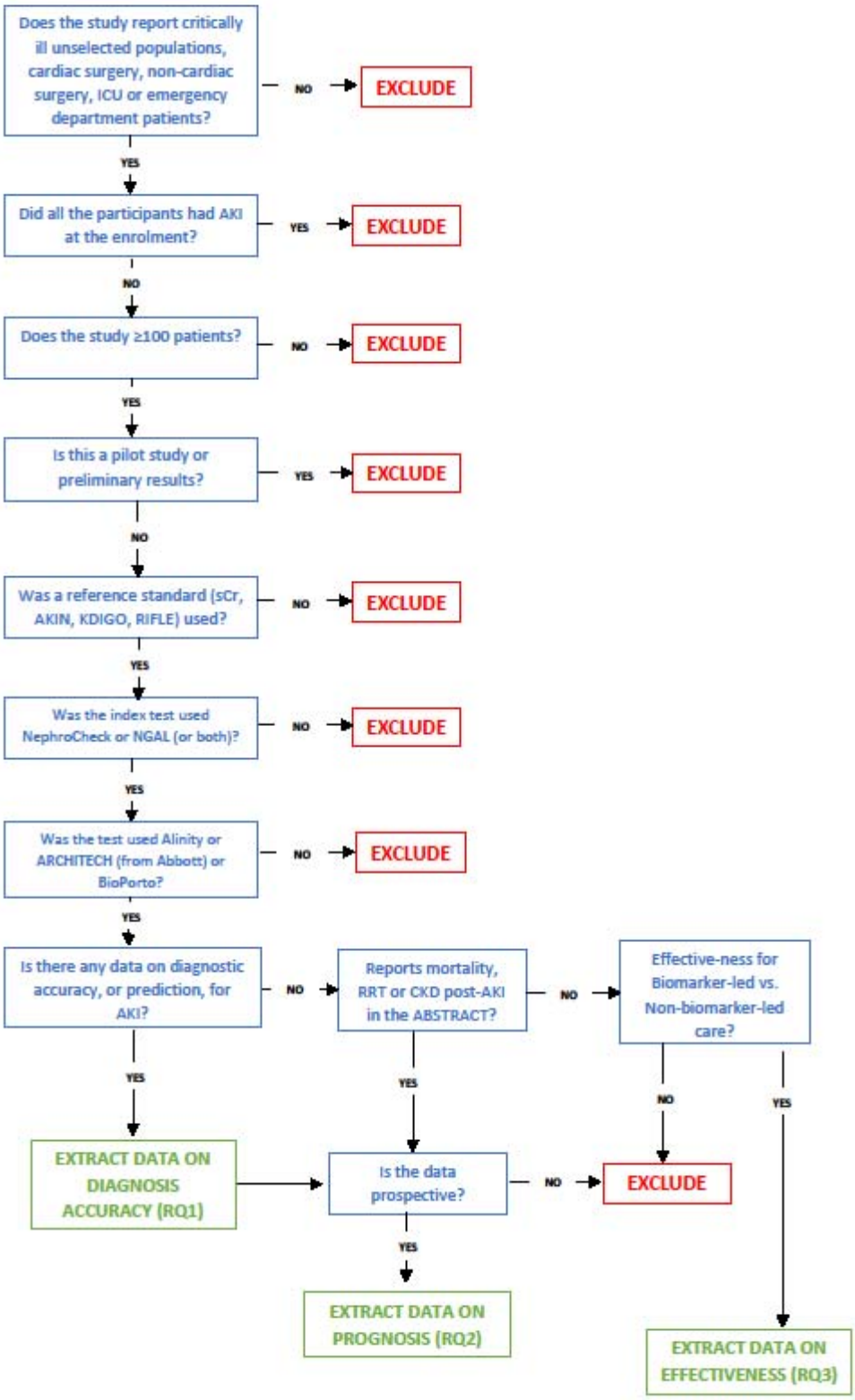

Figure 37 Screening tool

Appendix 3 Data extraction form

- REF ID
    - Study 1st Author
    - Year
    - Project study name
- Reviewer

BASELINE CHARACTERISTICS

- Population (adults/child/both)
- Taret population (surgery – cardiac/surgery – other/ICU/ITU mixed pop/other mixed pop (A&E, general hosp)/Sepsis/CKD/Liver disease/Organ transplant (except kidney)/Hip replacement/Trauma/Cardiac non-surgical)
- Recruitment period
- Study Centre(number of centres and names)
- Country
- Funding
- Index Test1 (uNGAL, pNGAL or Nephrocheck) and Index Test kit 1 (e.g. ARCHITECT or ALINITY from ABBOTT, or ELISA BIOPORTO)
- Age for all the sample
- Sex
- sCr
- eGFR
- SOFA Score
- CKD
- Time point of measurement (Non-surgical: Closest to admission, Surgical: Immediate after surgery, truly prognosis record different time points)
- Threshold reported
- Report cut-off for NephroCheck or NGAL
- TP, FN, FP, TN
- N with AKI present (TP + FN) confirmed by RefStd
- N with AKI absent (FP+ TN) confirmed by RefStd
- N with AKI present (TP + FP) confirmed by TEST
- N with AKI absent (FN +TP) confirmed by TEST

FOR EACH OUTCOME (AKI DIAGNOSIS, MORTALITY PROGNOSIS, RRT PROGNOSIS and AKI PROGNOSIS)

- SENSITIVITY (Lower-Upper 95% CI)
- SPECIFICITY (Lower-Upper 95% CI)
- Area Under the Curve (Lower -Upper 95% CI)
- PPV (Lower -Upper 95% CI)
- NPV (Lower -Upper 95% CI)
- PLR (Lower-Upper 95% CI)
- NLR (Lower-Upper 95% CI)
- Comment

Appendix 4 QUADAS 2 form

- Selection of participants (e.g. prospective, consecutive, recruited ALL patients, random sample)
- **1A Could the selection of patients have introduced bias? (Low/ Unclear/High)**
    - 1A(a) Was a consecutive or random sample of patients enrolled? (Low/ Unclear/High)
    - 1A(b) Was a case-control design avoided? (Yes/ Unclear/No)
    - 1A(c) Did the study avoid inappropriate exclusions? (Yes/ Unclear/No)
- Inclusion criteria
- Exclusion criteria
- Included patients: Describe any concerns/specifics regarding included patients (prior testing, presentation, intended use of index test and setting)
- **1B Is there concern that the included patients do not match the review question? (Low/ Unclear/High)**
- Test method
- Test timing
- Test How Work: Describe the index test and how it was conducted and interpreted
- **2A Could the conduct or interpretation of the index test have introduced bias? (Low/ Unclear/High)**
    - 2A(a) Were the index test results interpreted without knowledge of the results of the reference standard? (Yes/ Unclear/No)
    - 2A(b) If a threshold was used, was it pre-specified? (Yes/ Unclear/No)
- **2B Is there concern that the index test, its conduct, or interpretation differ from the review question? (Low/ Unclear/High)**
- Reference standard (e.g. AKIN, KDIGO, RIFLE, sCr)
- **3A Could the reference standard, its conduct, or its interpretation have introduced bias? (Low/ Unclear/High)**
    - 3A (a) Is the reference standard likely to correctly classify the target condition? (Yes/ Unclear/No)
    - 3 (b) Were the reference standard results interpreted without knowledge of the results of the index test? (Yes/ Unclear/No)
- **3B Is there concern that the target condition as defined by the reference standard does not match the review question? (Low/ Unclear/High)**
- Number enrolled
- Number analysed: Sample size
- Attrition: Number excluded with reason
- Time Interval: Describe the time interval and any interventions between index test(s) and reference standard (Low/ Unclear/High)
- **4A Could the patient flow have introduced bias? (Low/ Unclear/High)**
    - 4A (a) Was there an appropriate interval between index test(s) and reference standard? (Yes/ Unclear/No)
    - 4A(b) Did all patients receive a reference standard? (Yes/ Unclear/No)
    - 4A(c) Did patients receive the same reference standard? (Yes/ Unclear/No)
    - 4A(d) Were all patients included in the analysis? (Yes/ Unclear/No)

Appendix 5 PROBAST form

- ID Study
- Year
- Participants
  - 1.1Were appropriate data sources used, e.g., cohort, RCT, or nested case–control study dat
  - 1.2Were all inclusions and exclusions of participants appropriate?
  - Risk of bias introduced by selection of participants (low/high/unclear)
  - Concern that the included participants do not match the review question (low/high/unclear)
- Predictors
  - 2.1. Were predictors defined and assessed in a similar way for all participants?
  - 2.2. Were predictor assessments made without knowledge of outcome data?
  - 2.3. Are all predictors available at the time the model is intended to be used?
  - Risk of bias introduced by predictors or their assessment (low/high/unclear)
  - Concern that the definition, assessment or timing of predictors in the model do not match the review question (low/high/unclear)
- 3 Outcomes
  - 3.1. Was the outcome determined appropriately?
  - 3.2. Was a prespecified or standard outcome definition used?
  - 3.3. Were predictors excluded from the outcome definition?
  - 3.4. Was the outcome defined and determined in a similar way for all participants?
  - 3.5. Was the outcome determined without knowledge of predictor information?
  - 3.6. Was the time interval between predictor assessment and outcome determination appropriate
  - Risk of bias introduced by the outcome or its determination
  - Concern that the outcome, its definition, timing or determination do not match the review question (low/high/unclear)
- Analysis
  - 4.1. Were there a reasonable number of participants with the outcome?
  - 4.2. Were continuous and categorical predictors handled appropriately?
  - 4.3. Were all enrolled participants included in the analysis?
  - 4.4. Were participants with missing data handled appropriately?
  - 4.5. Was selection of predictors based on univariable analysis avoided?†
  - 4.6. Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately?
  - 4.7. Were relevant model performance measures evaluated appropriately?

    - 4.8. Were model overfitting, underfitting, and optimism in model performance accounted for?†
    - 4.9. Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?†

- Risk of bias introduced by the analysis (low/high/unclear)

- Risk of bias (low/high/unclear)

- Applicability (low/high/unclear

Appendix 6 List of included studies

* denotes primary reference

Albert 2018

Albert, C., Albert, A., Bellomo, R., Kropf, S., Devarajan, P., Westphal, S., Baraki, H., Kutschka, I., Butter, C., Haase, M. and Haase-Fielitz, A. Urinary neutrophil gelatinase-associated lipocalin-guided risk assessment for major adverse kidney events after open-heart surgery. *Biomarkers in Medicine*, 12(9), 975-985, 2018. [14954]

Alcaraz 2014

Alcaraz, A. J., Gil-Ruiz, M. A., Castillo, A., Lopez, J., Romero, C., Fernandez, S. N. and Carrillo, A. Postoperative neutrophil gelatinase-associated lipocalin predicts acute kidney injury after pediatric cardiac surgery. *Pediatric Critical Care Medicine*, 15(2), 121-130, 2014. [14959]

Ariza 2016

* Ariza, X., Graupera, I., Coll, M., Sola, E., Barreto, R., Garcia, E., Moreira, R., Elia, C., Morales-Ruiz, M., Llopis, M., Huelin, P., Sole, C., Fabrellas, N., Weiss, E., Nevens, F., Gerbes, A., Trebicka, J., Saliba, F., Fondevila, C., Hernandez-Gea, V., Fernandez, J., Bernardi, M., Arroyo, V., Jimenez, W., Deulofeu, C., Pavesi, M., Angeli, P., Jalan, R., Moreau, R., Sancho-Bru, P., Gines, P. and Canonic Investigators, E. C. C. Neutrophil gelatinase-associated lipocalin is a biomarker of acute-on-chronic liver failure and prognosis in cirrhosis. *Journal of Hepatology*, 65(1), 57-65, 2016. [15012]

Markwardt, D., Holdt, L., Steib, C., Benesic, A., Bendtsen, F., Bernardi, M., Moreau, R., Teupser, D., Wendon, J., Nevens, F., Trebicka, J., Garcia, E., Pavesi, M., Arroyo, V. and Gerbes, A. L. Plasma cystatin C is a predictor of renal dysfunction, acute-on-chronic liver failure, and mortality in patients with acutely decompensated liver cirrhosis. *Hepatology*, 66(4), 1232-1241, 2017. [16084]

Asada 2016

Asada, T., Isshiki, R., Hayase, N., Sumida, M., Inokuchi, R., Noiri, E., Nangaku, M., Yahagi, N. and Doi, K. Impact of clinical context on acute kidney injury biomarker performances: Differences between neutrophil gelatinase-associated lipocalin and l-type fatty acid-binding protein. *Scientific reports*, 6(33077, 2016. [15021]

Barreto 2014

Barreto, R., Elia, C., Sola, E., Moreira, R., Ariza, X., Rodriguez, E., Graupera, I., Alfaro, I., Morales-Ruiz, M., Poch, E., Guevara, M., Fernandez, J., Jimenez, W., Arroyo, V. and Gines, P. Urinary neutrophil gelatinase-associated lipocalin predicts kidney outcome and death in patients with cirrhosis and bacterial infections. *Journal of Hepatology*, 61(1), 35-42, 2014. [15075]

Beitland 2016

Beitland, S., Waldum-Grevbo, B. E., Nakstad, E. R., Berg, J. P., Troseid, A. S., Brusletto, B. S., Brunborg, C., Andersen, G. O. and Sunde, K. Urine biomarkers give early prediction of acute kidney injury and outcome after out-of-hospital cardiac arrest. *Critical Care*, 20(1), 314, 2016. [15098]

Bennett 2013

Bennett, M., Dent, C. L., Ma, Q., Dastrala, S., Grenier, F., Workman, R., Syed, H., Ali, S., Barasch, J. and Devarajan, P. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: A prospective study. *Clinical Journal of The American Society of Nephrology: CJASN*, 3(3), 665-673, 2008. [3985]

Bihorac 2014

Bihorac, A., Chawla, L. S., Shaw, A. D., Al-Khafaji, A., Davison, D. L., Demuth, G. E., Fitzgerald, R., Gong, M. N., Graham, D. D., Gunnerson, K., Heung, M., Jortani, S., Kleerup, E., Koyner, J. L., Krell, K., Letourneau, J., Lissauer, M., Miner, J., Nguyen, H. B., Ortega, L. M., Self, W. H., Sellman, R., Shi, J., Straseski, J., Szalados, J. E., Wilber, S. T., Walker, M. G., Wilson, J., Wunderink, R., Zimmerman, J. and Kellum, J. A. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. *American Journal of Respiratory and Critical Care Medicine*, 189(8), 932-939, 2014. [15129]

Bojan 2014

Bojan, M., Vicca, S., Lopez-Lopez, V., Mogenet, A., Pouard, P., Falissard, B. and Journois, D. Predictive performance of urine neutrophil gelatinase- associated lipocalin for dialysis requirement and death following cardiac surgery in neonates and infants. *Clinical Journal of the American Society of Nephrology*, 9(2), 285-294, 2014. [15136]

Cantinotti 2012

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Cho 2013

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Zwiers, A. J. M., De Wildt, S. N., Van Rosmalen, J., De Rijke, Y. B., Buijs, E. a. B., Tibboel, D. and Cransberg, K. Urinary neutrophil gelatinase-associated lipocalin identifies critically ill young children with acute kidney injury following intensive care admission: A prospective cohort study. *Critical Care*, 19(1), 181, 2015. [17018]

Appendix 7 Excluded studies

Table 40 List of excluded studies

First aut+A1:J918hor	Year	Reason for exclusion	Reference
Abassi	2013	<100 participants	Z. Abassi, A. Shalabi, R. Sohotnik, O. Natev, H. Awad, B. Bishara, V. Frajewicki, I. Sukhotnik, A. Abbasi and O. Nativ. Urinary NGAL and KIM-1: Biomarkers for assessment of acute ischemic kidney injury following nephron sparing surgery. Journal of Urology, 189(4), 1559-1566. [14922]
Abdelsalam	2018	Not relevant type of population	M. Abdelsalam, E. Elmorsy, H. Abdelwahab, O. Algohary, M. Naguib, A. A. El Wahab, A. Eldeeb, E. Eltoraby, A. Abdelsalam, A. Sabry, M. El-Metwally, M. Akl, N. Anber, M. El Sayed Zaki, F. Almutairi and T. Mansour. Urinary biomarkers for early detection of platinum based drugs induced nephrotoxicity. BMC Nephrology, 19(1), 1022. [14926]
Aberg	2014	Not relevant biomarker assay or test	F. Aberg, M. Lempinen, M. Hollmen, A. Nordin, H. Makisalo and H. Isoniemi. Neutrophil gelatinase-associated lipocalin associated with irreversibility of pre-liver transplant kidney dysfunction. Clinical Transplantation, 28(8), 869-876. [14927]
Adams	2019	<100 participants	P. S. Adams, D. Vargas, T. Baust, L. Saenz, W. Koh, B. Blasiole, P. M. Callahan, A. S. Phadke, K. N. Nguyen, Y. Domnina, M. Sharma, J. A. Kellum and J. Sanchez-de-Toledo. Associations of Perioperative Renal Oximetry Via Near-Infrared Spectroscopy, Urinary Biomarkers, and Postoperative Acute Kidney Injury in Infants After Congenital Heart Surgery: Should Creatinine Continue to Be the Gold Standard?. Pediatric critical care medicine, 20(1), 27-37. [14930]
Adler	2018	<100 participants	C. Adler, T. Heller, F. Schregel, H. Hagmann, M. Hellmich, J. Adler and H. Reuter. TIMP-2/IGFBP7 predicts acute kidney injury in out-of-hospital cardiac arrest survivors. Critical Care, 22(1), 126. [14932]
Afify	2016	<100 participants	M. F. M. Afify, S. E. Maher, N. M. Ibrahim and W. M. A. El-Hamied. Serum Neutrophil Gelatinase-Associated Lipocalin in Infants and Children with Sepsis-Related Conditions with or without Acute Renal Dysfunction. Clinical medicine insights. Pediatrics, 10(85-9. [14933]
Afzal	2018	Not a primary study	A. Afzal, R. C. Vallabhan and P. A. McCullough. Acute kidney injury in cardiogenic shock: in search of early detection and clinical certainty. European Journal of Heart Failure, 20(3), 582-584. [14934]
Aghel	2010	<100 participants	A. Aghel, K. Shrestha, W. Mullens, A. Borowski and W. H. W. Tang. Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Predicting Worsening Renal Function in Acute Decompensated Heart Failure. Journal of Cardiac Failure, 16(1), 49-54. [14935]
Ahmad	2015	No focus on DTA for AKI	T. Ahmad, T. Wang, E. C. O'Brien, M. D. Samsky, J. A. Pura, Y. Lokhnygina, J. G. Rogers, A. F. Hernandez, D. Craig, D. E. Bowles, C. A. Milano, S. H. Shah, J. L. Januzzi, G. M. Felker and C. B. Patel. Effects of left ventricular assist device support on biomarkers of cardiovascular stress, fibrosis, fluid homeostasis, inflammation, and renal injury. JACC: Heart Failure, 3(1), 30-39. [14937]

Ahmad	2018	Not relevant biomarker assay or test	T. Ahmad, K. Jackson, V. S. Rao, W. H. W. Tang, M. A. Brisco-Bacik, H. H. Chen, G. M. Felker, A. F. Hernandez, C. M. O'Connor, V. S. Sabbisetti, J. V. Bonventre, F. P. Wilson, S. G. Coca and J. M. Testani. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. Circulation, 137(19), 2016-2028. [14936]
Ahmed	2012	No focus on DTA for AKI	M. S. Ahmed, R. Lim, V. Selvaratnam, A. James, P. O. Kelly, K. A. Abraham and C. F. Wong. Survival akin to injury, hospitalized patients with acute kidney injury based on the AKIN classification. Clinical nephrology, 78(5), 370-375. [18365]
Ahmed	2014	Retracted study	Q. A. Ahmed, F. S. El Sayed, H. Emad, E. Mohamed, B. Ahmed and P. Heba. Urinary biomarkers of acute kidney injury in patients with liver cirrhosis. Medical archives (Sarajevo, Bosnia and Herzegovina), 68(2), 132-136. [14939]
Ahn	2016	Not relevant type of population	J. Y. Ahn, M. J. Lee, J. S. Seo, D. Choi and J. B. Park. Plasma neutrophil gelatinase-associated lipocalin as a predictive biomarker for the detection of acute kidney injury in adult poisoning. Clinical Toxicology, 54(2), 127-133. [14940]
Ahsan Ejaz	2012	Not relevant biomarker assay or test	A. Ahsan Ejaz, G. Kambhampati, N. I. Ejaz, B. Dass, V. Lapsia, A. A. Arif, A. Asmar, M. Shimada, M. M. Alsabbagh, R. Aiyer and R. J. Johnson. Post-operative serum uric acid and acute kidney injury. Journal of Nephrology, 25(4), 497-505. [14941]
Akcay	2012	Not relevant type of population	A. B. Akcay, M. F. Ozlu, N. Sen, S. Cay, O. H. Ozturk, F. YalNcn, P. Bilen, S. Kanat, M. F. Karakas, A. Isleyen, A. D. Demir, S. Sogut, A. Covic and M. Kanbay. Prognostic significance of neutrophil gelatinase-associated lipocalin in St-segment elevation myocardial infarction. Journal of Investigative Medicine, 60(2), 508-513. [14946]
Akrawinthawong	2013	<100 participants	K. Akrawinthawong, M. K. Shaw, J. Kachner, E. O. Apostolov, A. G. Basnakian, S. Shah, J. Tilak and P. A. McCullough. Urine catalytic iron and neutrophil gelatinase-associated lipocalin as companion early markers of acute kidney injury after cardiac surgery: A prospective pilot study. CardioRenal Medicine, 3(1), 7-16. [14948]
Akrawinthawong	2015	<100 participants	K. Akrawinthawong, J. Ricci, L. Cannon, S. Dixon, K. Kupfer, D. Stivers, P. Alexander, S. David and P. A. McCullough. Subclinical and clinical contrast-induced acute kidney injury: Data from a novel blood marker for determining the risk of developing contrast-induced nephropathy (ENCINO), a prospective study. Renal Failure, 37(2), 187-191. [14947]
Al-Afify	2013	<100 participants	A. A. Al-Afify. Prognostic value of neutrophil gelatinase-associated lipocalin in predicting in-hospital complications in patients with ST-segment elevation myocardial infarction. Research Journal of Cardiology, 6(1), 10-18. [14949]
Albeladi	2017	<100 participants	F. I. Albeladi and H. M. Algethamy. Urinary Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Acute Kidney Injury, Severe Kidney Injury, and the Need for Renal Replacement Therapy in the Intensive Care Unit. Nephron Extra, 7(2), 62-77. [14953]

Albert	2014	No focus on DTA for AKI	C. Albert, J. Kube, A. Haase-Fielitz, A. Dittrich, D. Schanze, M. Zenker, H. Kuppe, R. Hetzer, R. Bellomo, P. R. Mertens and M. Haase. Pilot study of association of catechol-O-methyl transferase rs4680 genotypes with acute kidney injury and tubular stress after open heart surgery. Biomarkers in Medicine, 8(10), 1227-1238. [14956]
Albuquerque	2019	<100 participants	P. L. M. M. Albuquerque, G. B. D. S. Junior, G. C. Meneses, A. M. C. Martins, D. B. Lima, J. Raubenheimer, S. Fathima, N. Buckley and E. D. F. Daher. Acute kidney injury induced by bothrops venom: Insights into the pathogenic mechanisms. Toxins, 11(3), 148. [14957]
Algethamy	2017	<100 participants	H. M. Algethamy and F. I. Albeladi. Urinary neutrophil gelatinase-associated lipocalin is an excellent predictor of mortality in intensive care unit patients. Saudi Medical Journal, 38(7), 706-714. [14962]
Alharazy	2014	Not relevant type of population	S. M. Alharazy, N. Kong, R. Saidin, A. H. A. Gafor, O. Maskon, M. Mohd and S. Z. S. Zakaria. Serum neutrophil gelatinase-associated lipocalin and cystatin C are early biomarkers of contrast-induced nephropathy after coronary angiography in patients with chronic kidney disease. Angiology, 65(5), 436-442. [14963]
Alharazy	2014	Not relevant type of population	S. M. Alharazy, N. Kong, R. Saidin, A. H. A. Gafor, O. Maskon, M. Mohd and S. Z. S. Zakaria. Neutrophil gelatinase-associated lipocalin as an early marker of contrast-induced nephropathy after coronary angiography. Angiology, 65(3), 216-223. [14964]
Aljumah	2018	<100 participants	A. A. Aljumah, H. Tamim, M. Saeed, W. Tamimi, H. Alfawaz, S. Al Qurashi, A. Al Dawood and A. Al Sayyari. The Role of Urinary Neutrophil Gelatinase-Associated Lipocalin in Predicting Acute Kidney Dysfunction in Patients With Liver Cirrhosis. Journal of clinical medicine research, 10(5), 419-428. [14966]
Allavena	2013	<100 participants	C. Allavena, K. Bach-Ngohou, E. Billaud, S. Secher, T. Dejoie, V. Reliquet, F. Fakhouri and F. Raffi. Neutrophil gelatinase-associated lipocalin, a marker of tubular dysfunction, is not increased in long-term virologically controlled patients receiving a tenofovir/emtricitabine1nevirapine regimen. Journal of Antimicrobial Chemotherapy, 68(12), 2866-2870. [14968]
Almalky	2015	<100 participants	M. A. Almalky, S. A. Hasan, T. H. Hassan, D. A. Shahbah, M. A. Arafa, N. A. Khalifa and R. E. Ibrahim. Detection of early renal injury in children with solid tumors undergoing chemotherapy by urinary neutrophil gelatinase-associated lipocalin. Molecular and Clinical Oncology, 3(6), 1341-1346. [14970]
Al-Shamma	2017	<100 participants	Z. A. A. Al-Shamma, N. G. Alklyali and I. Y. Alani. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a predictive biomarker of kidney injury in renal transplanted patients and chronic kidney disease. International Journal of Pharmacy and Pharmaceutical Sciences, 9(6), 59-63. [14951]
Alvelos	2011	Not relevant biomarker assay or test	M. Alvelos, R. Pimentel, E. Pinho, A. Gomes, P. Lourenco, M. J. Teles, P. Almeida, J. T. Guimaraes and P. Bettencourt. Neutrophil gelatinase-associated lipocalin in the diagnosis of type 1 cardio-renal syndrome in the general ward. Clinical journal of the American Society of Nephrology : CJASN, 6(3), 476-81. [14973]

Alvelos	2013	Not relevant biomarker assay or test	M. Alvelos, P. Lourenco, C. Dias, M. Amorim, J. Rema, A. B. Leite, J. T. Guimaraes, P. Almeida and P. Bettencourt. Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure. International Journal of Cardiology, 165(1), 51-55. [14974]
Anagnostopoulos	2016	Not a primary study	P. V. Anagnostopoulos. Prediction of severe acute kidney injury after pediatric cardiac surgery with the use of novel biomarkers: A new trend in clinical research and risk stratification. The Journal of thoracic and cardiovascular surgery, 152(1), 187-8. [14979]
Angeletti	2016	<100 participants	S. Angeletti, M. Fogolari, D. Morolla, F. Capone, S. Costantino, S. Spoto, M. De Cesaris, A. Lo Presti, M. Ciccozzi and G. Dicuonzo. Role of neutrophil gelatinase-associated lipocalin in the diagnosis and early treatment of acute kidney injury in a case series of patients with acute decompensated heart failure: A case series. Cardiology Research and Practice, 2016(3708210. [14984]
Anonymous	2008	Not a primary study	Anonymous. A single measurement of urinary NGAL can identify acute kidney injury. Nature Clinical Practice Nephrology, 4(9), . [2109]
Anonymous	2010	Non-English publication	Anonymous. Early biomarker for AKI. Japanese Journal of Nephrology, 52(5), 566-571. [14998]
Antonelli	2018	Systematic review - retained as background material	A. Antonelli, M. Allinovi, A. Cocci, G. I. Russo, R. Schiavina, B. Rocco, G. A. Pini, A. Celia, A. Galfano, V. Varca, G. Bozzini, C. Ceruti, F. Greco, P. Verze, A. L. Pastore, A. Porreca and A. Minervini. The Predictive Role of Biomarkers for the Detection of Acute Kidney Injury After Partial or Radical Nephrectomy: A Systematic Review of the Literature. European Urology Focus, . [15001]
Antonopoulos	2011	<100 participants	C. N. Antonopoulos, A. Kalkanis, G. Georgakopoulos, T. N. Sergentanis and D. N. Rigopoulos. Neutrophil gelatinase-associated lipocalin in dehydrated patients: a preliminary report. BMC research notes, 4(435. [15002]
Anusha	2015	<100 participants	R. Anusha, S. Silambanan and M. Veerasamy. Plasma neutrophil gelatinase associated lipocalin in the early detection of acute kidney injury in patients undergoing cardiac surgery. International Journal of Pharma and Bio Sciences, 6(4), B64-B71. [15004]
Arambašić	2016	Not relevant type of population	J. Arambasic, S. Mandic, Z. Debeljak, D. Mandic, V. Horvat and V. Seric. Differentiation of acute pyelonephritis from other febrile states in children using urinary neutrophil gelatinase-associated lipocalin (uNGAL). Clinical chemistry and laboratory medicine, 54(1), 55-61. [15006]
Arampatzis	2017	Not relevant biomarker assay or test	S. Arampatzis, G. Chalikias, V. Devetzis, S. Konstantinides, U. Huynh-Do and D. Tziakas. C-terminal fragment of agrin (CAF) levels predict acute kidney injury after acute myocardial infarction. BMC Nephrology, 18(1), 202. [15007]
Aregger	2014	<100 participants	F. Aregger, D. E. Uehlinger, J. Witowski, R. A. Brunisholz, P. Hunziker, F. J. Frey and A. Jorres. Identification of IGFBP-7 by urinary proteomics as a novel prognostic marker in early acute kidney injury. Kidney international, 85(4), 909-919. [15008]

Arena	2010	<100 participants	A. Arena, G. Stassi, D. Iannello, D. Gazzara, M. Calapai, C. Bisignano, D. Bolignano, A. Lacquaniti and M. Buemi. Both IL-1 beta and TNF-alpha Regulate NGAL Expression in Polymorphonuclear Granulocytes of Chronic Hemodialysis Patients. Mediators of inflammation, 613937-613937. [18367]
Ariza	2015	<100 participants	X. Ariza, E. Sola, C. Elia, R. Barreto, R. Moreira, M. Morales-Ruiz, I. Graupera, E. Rodriguez, P. Huelin, C. Sole, J. Fernandez, W. Jimenez, V. Arroyo and P. Gines. Analysis of a urinary biomarker panel for clinical outcomes assessment in cirrhosis. PLoS ONE, 10(6), e0128145. [15013]
Arora	2016	Not a primary study	R. C. Arora, C. Rigatto and R. K. Singal. Neutrophil gelatinase-associated lipocalin to predict cardiac surgery-associated acute kidney injury: A holy grail or just another fancy cup?. Journal of Thoracic and Cardiovascular Surgery, 151(6), 1482-1483. [15016]
Arora	2017	Not a primary study	R. C. Arora and R. K. Singal. Is routine use of renal injury biomarkers in cardiac surgery patients putting the cart before the horse?. Journal of Thoracic and Cardiovascular Surgery, 154(3), 938-939. [15015]
Arsalan	2018	<100 participants	M. Arsalan, E. Ungchusri, R. Farkas, M. Johnson, R. J. Kim, G. Filardo, B. D. Pollock, M. Szerlip, M. J. Mack and E. M. Holper. Novel renal biomarker evaluation for early detection of acute kidney injury after transcatheter aortic valve implantation. Proceedings (Baylor University. Medical Center), 31(2), 171-176. [15017]
Arthur	2014	<100 participants	J. M. Arthur, E. G. Hill, J. L. Alge, E. C. Lewis, B. A. Neely, M. G. Janech, J. A. Tumlin, L. S. Chawla and A. D. Shaw. Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery. Kidney International, 85(2), 431-438. [15019]
Arun	2015	<100 participants	O. Arun, G. Celik, B. Oc, A. Unlu, J. B. Celik, M. Oc and A. Duman. Renal effects of coronary artery bypass graft surgery in diabetic and non-diabetic patients: A study with urinary neutrophil gelatinase-associated lipocalin and serum Cystatin C. Kidney and Blood Pressure Research, 40(2), 141-152. [15020]
Ascher	2018	Not relevant type of population	S. B. Ascher, R. Scherzer, M. M. Estrella, W. R. Zhang, A. N. Muiru, V. Jotwani, C. Grunfeld, C. R. Parikh, D. Gustafson, M. Young, A. Sharma, M. H. Cohen, D. K. Ng, F. J. Palella, M. D. Witt, K. Ho and M. G. Shlipak. Association of urinary biomarkers of kidney injury with estimated GFR decline in HIV-infected individuals following tenofovir disoproxil fumarate initiation. Clinical Journal of the American Society of Nephrology, 13(9), 1321-1329. [15022]
Ashalatha	2017	No relevant outcome	V. L. Ashalatha, A. R. Bitla, V. S. Kumar, D. Rajasekhar, M. M. Suchitra, A. Y. Lakshmi and P. V. L. N. S. Rao. Biomarker response to contrast administration in diabetic and nondiabetic patients following coronary angiography. Indian Journal of Nephrology, 27(1), 20-27. [15024]
Askenazi	2011	Not relevant type of population	D. J. Askenazi, A. Montesanti, H. Hunley, R. Koralkar, P. Pawar, F. Shuaib, A. Liwo, P. Devarajan and N. Ambalavanan. Urine biomarkers predict acute kidney injury and mortality in very low birth weight infants. Journal of Pediatrics, 159(6), 907. [15030]

Askenazi	2011	Not relevant type of population	D. J. Askenazi, R. Koralkar, E. B. Levitan, S. L. Goldstein, P. Devarajan, S. Khandrika, R. L. Mehta and N. Ambalavanan. Baseline values of candidate urine acute kidney injury biomarkers vary by gestational age in premature infants. Pediatric Research, 70(3), 302-306. [15031]
Askenazi	2012	<100 participants	D. J. Askenazi, R. Koralkar, H. E. Hundley, A. Montesanti, P. Parwar, S. Sonjara and N. Ambalavanan. Urine biomarkers predict acute kidney injury in newborns. Journal of Pediatrics, 161(2), 270. [15029]
Askenazi	2016	Not relevant type of population	D. J. Askenazi, R. Koralkar, N. Patil, B. Halloran, N. Ambalavanan and R. Griffin. Acute kidney injury urine biomarkers in very low-birth-weight infants. Clinical Journal of the American Society of Nephrology, 11(9), 1527-1535. [15028]
Assadi	2019	<100 participants	F. Assadi and F. G. Sharbaf. Urine KIM-1 as a Potential Biomarker of Acute Renal Injury after Circulatory Collapse in Children. Pediatric Emergency Care, 35(2), 104-107. [15033]
Ataei	2015	<100 participants	S. Ataei, M. Hadjibabaie, A. Moslehi, M. Taghizadeh-Ghehi, A. Ashouri, E. Amini, K. Gholami, A. Hayatshahi, M. Vaezi and A. Ghavamzadeh. A double-blind, randomized, controlled trial on N-acetylcysteine for the prevention of acute kidney injury in patients undergoing allogeneic hematopoietic stem cell transplantation. Hematological Oncology, 33(2), 67-74. [15037]
Ataei	2018	<100 participants	N. Ataei, S. Ameli, M. Yousefifard, A. Oraei, F. Ataei, B. Bazargani, A. Abbasi and M. Hosseini. Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Cystatin C in Early Detection of Pediatric Acute Kidney Injury; a Diagnostic Accuracy Study. Emergency (Tehran, Iran), 6(1), e2. [15035]
Au	2016	Not relevant biomarker assay or test	V. Au, J. Feit, J. Barasch, R. N. Sladen and G. Wagener. Urinary neutrophil gelatinase-associated lipocalin (NGAL) distinguishes sustained from transient acute kidney injury after general surgery. Kidney international reports, 1(1), 3-9. [15038]
Audard	2014	<100 participants	V. Audard, S. Moutereau, G. Vandemelebrouck, A. Habibi, M. Khellaf, P. Grimbert, Y. Levy, S. Loric, B. Renaud, P. Lang, B. Godeau, F. Galacteros and P. Bartolucci. First evidence of subclinical renal tubular injury during sickle-cell crisis. Orphanet Journal of Rare Diseases, 9(1), 67. [15039]
Axelrod	2016	No focus on DTA for AKI	D. M. Axelrod, S. M. Sutherland, A. Anglemyer, P. C. Grimm and S. J. Roth. A Double-Blinded, Randomized, Placebo-Controlled Clinical Trial of Aminophylline to Prevent Acute Kidney Injury in Children Following Congenital Heart Surgery with Cardiopulmonary Bypass. Pediatric Critical Care Medicine, 17(2), 135-143. [15041]
Aydin	2014	<100 participants	S. A. Aydin, S. Pozam, F. Ozdemir, M. L. Ozkan and O. Koksal. The role of Neutrophil Gelatinase-Associated Lipocalin in identifying contrast induced nephropathy development in the emergency department. Journal of the Pakistan Medical Association, 64(10), 1109-1113. [15042]

Aydogdu	2013	Not relevant biomarker assay or test	M. Aydogdu, G. Gursel, B. Sancak, S. Yeni, G. Sari, S. Tasyurek, M. Turk, S. Yuksel, M. Senes and T. N. Ozis. The use of plasma and urine neutrophil gelatinase associated lipocalin (NGAL) and Cystatin C in early diagnosis of septic acute kidney injury in critically ill patients. Disease Markers, 34(4), 237-246. [15043]
Azzalini	2017	Not a primary study	L. Azzalini and X. Garcia-Moll. On Contrast-Induced Acute Kidney Injury, Risk Prediction, and the Future of Predictive Model Development. Canadian Journal of Cardiology, 33(6), 711-713. [15044]
Bachorzewska-Gajewska	2006	<100 participants	H. Bachorzewska-Gajewska, J. Malyszko, E. Sitniewska, J. S. Malyszko and S. Dobrzycki. Neutrophil-gelatinase-associated lipocalin and renal function after percutaneous coronary interventions. American Journal of Nephrology, 26(3), 287-92. [4025]
Bachorzewska-Gajewska	2007	Not relevant type of population	H. Bachorzewska-Gajewska, J. Malyszko, E. Sitniewska, J. S. Malyszko, K. Pawlak, M. Mysliwiec, S. Lawnicki, M. Szmitkowski and S. Dobrzycki. Could neutrophil-gelatinase-associated lipocalin and cystatin C predict the development of contrast-induced nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine values?. Kidney & Blood Pressure Research, 30(6), 408-15. [4007]
Bachorzewska-Gajewska	2009	<100 participants	H. Bachorzewska-Gajewska, B. Poniatowski and S. Dobrzycki. NGAL (neutrophil gelatinase-associated lipocalin) and L-FABP after percutaneous coronary interventions due to unstable angina in patients with normal serum creatinine. Advances in Medical Sciences, 54(2), 221-4. [3926]
Bachorzewska-Gajewska	2009	Not relevant type of population	H. Bachorzewska-Gajewska, B. Poniatowski and S. Dobrzycki. NGAL (neutrophil gelatinase-associated lipocalin) and L-FABP after percutaneous coronary interventions due to unstable angina in patients with normal serum creatinine. Advances in Medical Sciences, 54(2), 221-224. [15047]
Bachorzewska-Gajewska	2013	Not relevant type of population	H. Bachorzewska-Gajewska, J. Malyszko, E. Sitniewska, J. S. Malyszko, B. Poniatowski, K. Pawlak and S. Dobrzycki. NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C: are they good predictors of contrast nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine?. International Journal of Cardiology, 127(2), 290-1. [4000]
Bachorzewska-Gajewska	2013	Not relevant type of population	H. Bachorzewska-Gajewska, A. Tomaszuk-Kazberuk, I. Jarocka, E. Mlodawska, P. Lopatowska, M. Zalewska-Adamiec, S. Dobrzycki, W. J. Musial and J. Malyszko. Does neutrophil gelatinase-asociated lipocalin have prognostic value in patients with stable angina undergoing elective PCI? A 3-year follow-up study. Kidney and Blood Pressure Research, 37(4-5), 280-285. [15046]
Baek	2019	Not relevant type of population	S. D. Baek, J.-Y. Kang, S. Shin, H.-S. Park, M.-S. Kim, S. M. Kim, E. K. Lee and J. W. Chang. Predictive Factors of Duration of Continuous Renal Replacement Therapy in Acute Kidney Injury Survivors. Shock (Augusta, Ga.), . [15051]

Bagheri	2018	<100 participants	S. Bagheri, N. Einollahi, M. T. Goodarzi, H. Tatari, H. Moradi-Sardareh and N. Sheikh. Neutrophil gelatinase-associated lipocalin, cystatin C and matrix metalloproteinase-9 as possible biomarkers in early detection of acute kidney injury after cardiac surgery. Journal of Clinical and Diagnostic Research, 12(4), BC05-BC09. [15053]
Bagshaw	2011	Not a primary study	S. M. Bagshaw. Subclinical acute kidney injury: a novel biomarker-defined syndrome. Critical Care and Resuscitation, 13(3), 201-203. [18373]
Bagshaw	2013	<100 participants	S. M. Bagshaw, M. Bennett, P. Devarajan and R. Bellomo. Urine biochemistry in septic and non-septic acute kidney injury: A prospective observational study. Journal of Critical Care, 28(4), 371-378. [15055]
Balkanay	2015	<100 participants	O. O. Balkanay, D. Goksedef, S. N. Omeroglu and G. Ipek. The dose-related effects of Dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: A randomized, triple-blind, placebo-controlled study. Interactive Cardiovascular and Thoracic Surgery, 20(2), 209-214. [15066]
Balkanay	2018	<100 participants	O. O. Balkanay, D. Goksedef, S. N. Omeroglu and G. Ipek. The reliability of the use of serum neutrophil gelatinase-associated lipocalin levels in the assessment of renal functions after coronary artery bypass grafting. Cardiology Research and Practice, 2018(7291254. [15065]
Barbarash	2017	No focus on DTA for AKI	O. L. Barbarash, I. S. Bykova, V. V. Kashtalap, M. V. Zykov, O. N. Hryachkova, V. V. Kalaeva, K. S. Shafranskaya, V. N. Karetnikova and A. G. Kutikhin. Serum neutrophil gelatinase-associated lipocalin has an advantage over serum cystatin C and glomerular filtration rate in prediction of adverse cardiovascular outcome in patients with ST-segment elevation myocardial infarction. Bmc Cardiovascular Disorders, 17(81-81. [18375]
Baron-Stefaniak	2017	<100 participants	J. Baron-Stefaniak, J. Schiefer, E. J. Miller, G. A. Berlakovich, D. M. Baron and P. Faybik. Comparison of macrophage migration inhibitory factor and neutrophil gelatinase-associated lipocalin-2 to predict acute kidney injury after liver transplantation: An observational pilot study. PLoS ONE, 12(8), e0183162. [15072]
Bassareo	2013	Not relevant type of population	P. P. Bassareo, V. Fanos, M. Mussap, G. Flore, A. Noto, M. Puddu, L. Saba and G. Mercuro. Urinary NGAL and hematic ADMA levels: an early sign of cardio-renal syndrome in young adults born preterm?. Journal of Maternal-Fetal & Neonatal Medicine, 26(80-83. [18377]
Basturk	2017	<100 participants	T. Basturk, O. Sari, Y. Koc, N. Eren, M. Isleem, E. Kara, M. Sevinc, T. Sakaci, E. Ahbap, N. B. Hasbal, F. Bayrakdarcaglayan and A. Unsal. Prognostic significance of NGAL in early stage chronic kidney disease. Minerva Urologica e Nefrologica, 69(3), 307-312. [15079]
Basu	2014	Not relevant biomarker assay or test	R. K. Basu, Y. Wang, H. R. Wong, L. S. Chawla, D. S. Wheeler and S. L. Goldstein. Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clinical Journal of the American Society of Nephrology, 9(4), 654-662. [15082]

Basu	2014	Not relevant biomarker assay or test	R. K. Basu, H. R. Wong, C. D. Krawczeski, D. S. Wheeler, P. B. Manning, L. S. Chawla, P. Devarajan and S. L. Goldstein. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. Journal of the American College of Cardiology, 64(25), 2753-2762. [15081]
Bataille	2017	No relevant outcome	A. Bataille, A. Tiepolo, T. Robert, A. Boutten, D. Longrois, M. Dehoux and S. Provenchere. Reference change values of plasma and urine NGAL in cardiac surgery with cardiopulmonary bypass. Clinical Biochemistry, 50(18), 1098-1103. [15088]
Baumert	2017	<100 participants	M. Baumert, P. Surmiak, A. Wiecek and Z. Walencka. Serum NGAL and copeptin levels as predictors of acute kidney injury in asphyxiated neonates. Clinical and Experimental Nephrology, 21(4), 658-664. [15092]
Bayram	2014	<100 participants	A. Bayram, A. Ulgey, A. Baykan, N. Narin, F. Narin, A. Esmaoglu and A. Boyaci. The effects of dexmedetomidine on early stage renal functions in pediatric patients undergoing cardiac angiography using non-ionic contrast media: A double-blind, randomized clinical trial. Paediatric Anaesthesia, 24(4), 426-432. [15093]
Bayram	2014	<100 participants	M. Bayram, M. Ezelsoy, E. Usta, K. Oral, A. Saracoglu, Z. Bayramoglu and O. Yildirim. Rapid Detection of Acute Kidney Injury by Urinary Neutrophil Gelatinase-Associated Lipocalin in Patients Undergoing Cardiopulmonary Bypass. Turkish journal of anaesthesiology and reanimation, 42(5), 239-44. [15094]
Bedford	2016	<100 participants	M. Bedford, P. Stevens, S. Coulton, J. Billings, M. Farr, T. Wheeler, M. Kalli, T. Mottishaw and C. Farmer. Development of risk models for the prediction of new or worsening acute kidney injury on or during hospital admission: a cohort and nested study. Health Services and Delivery Research 4(6). [6148]
Beitland	2018	Not a primary study	S. Beitland and M. Joannidis. Biomarkers of acute kidney injury - a mission impossible?. Acta anaesthesiologica Scandinavica, 62(1), 2-5. [15096]
Belcher	2014	<100 participants	J. M. Belcher, A. J. Sanyal, A. J. Peixoto, M. A. Perazella, J. Lim, H. Thiessen-Philbrook, N. Ansari, S. G. Coca, G. Garcia-Tsao and C. R. Parikh. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. Hepatology, 60(2), 622-632. [15102]
Belcher	2015	Not relevant type of population	J. M. Belcher, G. Garcia-Tsao, A. J. Sanyal, H. Thiessen-Philbrook, A. J. Peixoto, M. A. Perazella, N. Ansari, J. Lim, S. G. Coca and C. R. Parikh. Urinary biomarkers and progression of AKI in patients with cirrhosis. Clinical Journal of the American Society of Nephrology, 9(11), 1857-1867. [15100]
Bell	2015	<100 participants	M. Bell, A. Larsson, P. Venge, R. Bellomo and J. Martensson. Assessment of cell-cycle arrest biomarkers to predict early and delayed acute kidney injury. Disease Markers, 2015(158658. [15105]
Bellos	2018	Meta-analysis - retained as background material	I. Bellos, G. Fitrou, G. Daskalakis, D. N. Perrea and V. Pergialiotis. Neutrophil gelatinase-associated lipocalin as predictor of acute kidney injury in neonates with perinatal asphyxia: a systematic review and meta-analysis. European Journal of Pediatrics, 177(10), 1425-1434. [15110]

Benli	2017	<100 participants	E. Benli, S. N. Ayyildiz, S. Cirrik, T. Noyan, A. Ayyildiz and A. Cirakoglu. Early term effect of ureterorenoscopy (URS) on the Kidney: research measuring NGAL, KIM-1, FABP and CYS C levels in urine. International Braz J Urol, 43(5), 887-895. [18378]
Benoit	2019	<100 participants	S. W. Benoit, B. P. Dixon, S. L. Goldstein, M. R. Bennett, A. Lane, D. T. Lounder, S. J. Rotz, N. J. Gloude, K. E. Lake, B. Litts and S. M. Davies. A novel strategy for identifying early acute kidney injury in pediatric hematopoietic stem cell transplantation. Bone Marrow Transplantation, . [15115]
Benzer	2016	<100 participants	M. Benzer, H. Alpay, O. Baykan, A. Erdem and I. H. Demir. Serum NGAL, cystatin C and urinary NAG measurements for early diagnosis of contrast-induced nephropathy in children. Renal Failure, 38(1), 27-34. [15117]
Berghaus	2012	Not a primary study	T. M. Berghaus, M. Schwaiblmair and W. von Scheidt. Renal biomarkers and prognosis in acute pulmonary embolism. Heart (British Cardiac Society), 98(16), 1185-6. [15119]
Bhavsar	2012	Not relevant type of population	N. A. Bhavsar, A. Kottgen, J. Coresh and B. C. Astor. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) as predictors of incident CKD stage 3: The atherosclerosis risk in communities (ARIC) study. American Journal of Kidney Diseases, 60(2), 233-240. [15121]
Biernawska	2017	<100 participants	J. Biernawska, J. Bober, K. Kotfis, A. Bogacka, E. Barnik and M. Zukowski. Cardiac surgery related cardio-renal syndrome assessed by conventional and novel biomarkers - Under or overestimated diagnosis?. Archives of Medical Science, 13(5), 1111-1120. [15126]
Biernawska	2018	<100 participants	J. Biernawska, J. Bober, K. Kotfis, I. Nocen, A. Bogacka, E. Barnik, D. Chlubek and M. Zukowski. Iron excretion in urine in patients with acute kidney injury after cardiac surgery. Advances in Clinical and Experimental Medicine, 27(12), 1671-1676. [15125]
Bignami	2015	<100 participants	E. Bignami, E. Frati, R. Meroni, M. Simonini, A. Di Prima, P. Manunta and A. Zangrillo. Urinary neutrophil gelatinase-associated lipocalin time course during cardiac surgery. Annals of Cardiac Anaesthesia, 18(1), 39-44. [15127]
Bojan	2016	<100 participants	M. Bojan, M. C. Basto Duarte, N. Ermak, V. Lopez-Lopez, A. Mogenet and M. Froissart. Structural equation modelling exploration of the key pathophysiological processes involved in cardiac surgery-related acute kidney injury in infants. Critical Care, 20(1), 171. [15135]
Bojan	2018	<100 participants	M. Bojan, M. C. Basto Duarte, V. Lopez, L. Tourneur, S. Vicca and M. Froissart. Low perfusion pressure is associated with renal tubular injury in infants undergoing cardiac surgery with cardiopulmonary bypass: A secondary analysis of an observational study. European journal of anaesthesiology, 35(8), 581-587. [15134]
Bojic	2015	Not relevant biomarker assay or test	S. Bojic, J. Kotur-Stevuljevic, N. Kalezic, P. Stevanovic, Z. Jelic-Ivanovic, D. Bilanovic, L. Memon, M. Damnjanovic, Z. Kalaba and S. Simic-Ogrizovic. Diagnostic value of matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 in sepsis-associated acute kidney injury. Tohoku Journal of Experimental Medicine, 237(2), 103-109. [15137]

Bolignano	2008	<100 participants	D. Bolignano, A. Lacquaniti, G. Coppolino, S. Campo, A. Arena and M. Buemi. Neutrophil gelatinase-associated lipocalin reflects the severity of renal impairment in subjects affected by chronic kidney disease. Kidney & Blood Pressure Research, 31(4), 255-8. [3974]
Bolignano	2009	<100 participants	D. Bolignano, A. Lacquaniti, G. Coppolino, V. Donato, S. Campo, M. R. Fazio, G. Nicocia and M. Buemi. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clinical Journal of the American Society of Nephrology, 4(2), 337-344. [15143]
Bolignano	2009	Not a primary study	D. Bolignano, G. Coppolino, L. Lombardi and M. Buemi. NGAL: A new missing link between inflammation and uremic anemia. Renal Failure, 31(7), 622-623. [2036]
Bolignano	2009	Not a primary study	D. Bolignano, G. Coppolino, A. Lacquaniti and M. Buemi. Neutrophil gelatinase-associated lipocalin in the intensive care unit: time to look beyond a single, threshold-based measurement?. Critical Care Medicine, 37(10), 2864; author reply 2864-5. [3927]
Bolignano	2012	Not a primary study	D. Bolignano. Serum creatinine and the search for new biomarkers of acute kidney injury (AKI): The story continues. Clinical Chemistry and Laboratory Medicine, 50(9), 1495-1499. [15141]
Bolignano	2013	<100 participants	D. Bolignano, A. Lacquaniti, G. Coppolino, V. Donato, S. Campo, M. R. Fazio, G. Nicocia and M. Buemi. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clinical Journal of The American Society of Nephrology: CJASN, 4(2), 337-44. [3955]
Bolliger	2018	Not a primary study	D. Bolliger and M. Siegemund. The More, the Merrier? - Urinary Biomarkers for Prediction of Acute Kidney Injury After Cardiac Surgery. Journal of Cardiothoracic and Vascular Anesthesia, 32(5), 2201-2202. [15150]
Bonventre	2008	No focus on DTA for AKI	J. V. Bonventre. Urine neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in critically ill children. Nature Clinical Practice Nephrology, 4(2), 78-9. [3999]
Bouchard	2015	No focus on DTA for AKI	J. Bouchard, R. Malhotra, S. Shah, Y. T. Kao, F. Vaida, A. Gupta, D. T. Berg, B. W. Grinnell, B. Stofan, A. J. Tolwani and R. L. Mehta. Levels of protein C and soluble thrombomodulin in critically ill patients with acute kidney injury: A multicenter prospective observational study. PLoS ONE, 10(3), e0120770. [15160]
Bramham	2016	No relevant outcome	K. Bramham, P. T. Seed, L. Lightstone, C. Nelson-Piercy, C. Gill, P. Webster, L. Poston and L. C. Chappell. Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. Kidney international, 89(4), 874-85. [15166]
Breidthardt	2012	Not relevant biomarker assay or test	T. Breidthardt, T. Socrates, B. Drexler, M. Noveanu, C. Heinisch, N. Arenja, T. Klima, C. Zusli, T. Reichlin, M. Potocki, R. Twerenbold, J. Steiger and C. Mueller. Plasma neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury in acute heart failure. Critical Care, R2. [15168]

Breidthardt	2012	Not relevant type of population	T. Breidthardt, M. Christ-Crain, D. Stolz, R. Bingisser, B. Drexler, T. Klima, C. Balmelli, P. Schuetz, P. Haaf, M. Schrer, M. Tamm, B. Mller and C. Mller. A combined cardiorenal assessment for the prediction of acute kidney injury in lower respiratory tract infections. American Journal of Medicine, 125(2), 168-175. [15169]
Brinkman	2015	<100 participants	R. Brinkman, K. T. HayGlass, W. A. C. Mutch and D. J. Funk. Acute Kidney Injury in Patients Undergoing Open Abdominal Aortic Aneurysm Repair: A Pilot Observational Trial. Journal of Cardiothoracic and Vascular Anesthesia, 29(5), 1212-1219. [15175]
Brulotte	2013	Not relevant type of population	V. Brulotte, F. A. Leblond, S. Elkouri, E. Therasse, V. Pichette and P. Beaulieu. Bicarbonates for the prevention of postoperative renal failure in endovascular aortic aneurysm repair: A randomized pilot trial. Anesthesiology Research and Practice, 2013(467326. [15178]
Brunner	2006	<100 participants	H. I. Brunner, M. Mueller, C. Rutherford, M. H. Passo, D. Witte, A. Grom, J. Mishra and P. Devarajan. Urinary neutrophil gelatinase-associated lipocalin as a biomarker of nephritis in childhood-onset systemic lupus erythematosus. Arthritis & Rheumatism, 54(8), 2577-84. [4021]
Bruno	2016	<100 participants	N. Bruno, J. M. ter Maaten, E. S. Ovchinnikova, E. L. Vegter, M. A. E. Valente, P. van der Meer, R. A. de Boer, P. van der Harst, D. Schmitter, M. Metra, C. M. O'Connor, P. Ponikowski, J. R. Teerlink, G. Cotter, B. Davison, J. G. Cleland, M. M. Givertz, D. M. Bloomfield, H. C. Dittrich, Y. M. Pinto, D. J. van Veldhuisen, H. L. Hillege, E. Berezikov and A. A. Voors. MicroRNAs relate to early worsening of renal function in patients with acute heart failure. International journal of cardiology, 203(564-9. [15180]
Buelow	2012	<100 participants	M. W. Buelow, A. Dall, K. Regner, C. Weinberg, P. J. Bartz, J. Sowinski, N. Rudd, L. Katzmark, J. S. Tweddell and M. G. Earing. Urinary Interleukin-18 and Urinary Neutrophil Gelatinase-associated Lipocalin Predict Acute Kidney Injury Following Pulmonary Valve Replacement Prior to Serum Creatinine. Congenital Heart Disease, 7(5), 441-447. [15184]
Bugra	2014	Not relevant type of population	O. Bugra, A. Baysal, A. Fedakar, K. Erdem, H. Sunar and B. Daglar. Does serum neutrophil gelatinase-associated lipocalin biomarker detect the early deterioration in renal functions in patients with insulin-dependent diabetes mellitus undergoing coronary artery bypass graft surgery?. Turk Gogus Kalp Damar Cerrahisi Dergisi-Turkish Journal of Thoracic and Cardiovascular Surgery, 22(1), 63-70. [18386]
Bulluck	2016	Not relevant biomarker assay or test	H. Bulluck, R. Maiti, B. Chakraborty, L. Candilio, T. Clayton, R. Evans, D. P. Jenkins, S. Kolvekar, G. Kunst, C. Laing, J. Nicholas, J. Pepper, D. M. Yellon and D. J. Hausenloy. Neutrophil gelatinase-associated lipocalin prior to cardiac surgery predicts acute kidney injury and mortality. Heart (British Cardiac Society), . [15186]
Bunchman	2012	Not a primary study	T. E. Bunchman. Biomarkers for acute kidney injury: Is the serum creatinine worthless?. Pediatric Critical Care Medicine, 13(1), 119-120. [15188]

Bunel	2017	<100 participants	V. Bunel, Y. Tournay, T. Baudoux, E. De Prez, M. Marchand, Z. Mekinda, R. Marechal, T. Roumeguere, M. H. Antoine and J. L. Nortier. Early detection of acute cisplatin nephrotoxicity: Interest of urinary monitoring of proximal tubular biomarkers. Clinical Kidney Journal, 10(5), 639-647. [15190]
Bunz	2015	<100 participants	H. Bunz, P. Weyrich, A. Peter, D. Baumann, O. Tschritter, M. Guthoff, R. Beck, G. Jahn, F. Artunc, H. U. Haring, N. Heyne and R. Wagner. Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) and proteinuria predict severity of acute kidney injury in Puumala virus infection. BMC Infectious Diseases, 15(1), 464. [15191]
Burke-Gaffney	2014	<100 participants	A. Burke-Gaffney, T. Svermova, S. Mumby, S. J. Finney and T. W. Evans. Raised plasma Robo4 and cardiac surgery-associated acute kidney injury. PLoS ONE, 9(10), e111459. [15193]
Cai	2009	<100 participants	L. Cai, J. Borowiec, S. Xu, W. Han and P. Venge. Assays of urine levels of HNL/NGAL in patients undergoing cardiac surgery and the impact of antibody configuration on their clinical performances. Clinica Chimica Acta, 403(1-2), 121-5. [3948]
Cai	2009	<100 participants	L. Cai, J. Borowiec, S. Xu, W. Han and P. Venge. Assays of urine levels of HNL/NGAL in patients undergoing cardiac surgery and the impact of antibody configuration on their clinical performances. Clinica Chimica Acta, 403(1-2), 121-125. [15196]
Camou	2013	<100 participants	F. Camou, S. Oger, C. Paroissin, E. Guilhon, O. Guisset, G. Mourissoux, H. Pouyes, T. Lalanne and C. Gabinski. Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) predicts acute kidney injury in septic shock at ICU admission. Annales Francaises d'Anesthesie et de Reanimation, 32(3), 157-164. [15198]
Canakci	2018	<100 participants	E. Canakci, A. Karatas, T. Noyan and B. Sertacayhan. Can acute kidney injury be diagnosed using biomarkers in intensive care patients?. Acta Medica Mediterranea, 34(6), 2023-2029. [15199]
Cangemi	2013	Not relevant type of population	G. Cangemi, S. Storti, M. Cantinotti, A. Fortunato, M. Emdin, M. Bruschettini, D. Bugnone, G. Melioli and A. Clerico. Reference values for urinary neutrophil gelatinase-associated lipocalin (NGAL) in pediatric age measured with a fully automated chemiluminescent platform. Clinical Chemistry and Laboratory Medicine, 51(5), 1101-1105. [15200]
Capuano	2009	<100 participants	F. Capuano, M. Goracci, R. Luciani, G. Gentile, A. Roscitano, U. Benedetto and R. Sinatra. Neutrophil gelatinase-associated lipocalin levels after use of mini-cardiopulmonary bypass system. Interactive Cardiovascular and Thoracic Surgery, 9(5), 797-801. [15207]
Carey	2018	No focus on DTA for AKI	I. Carey, R. Byrne, K. Childs, M. Horner, M. Bruce, B. Wang, G. Dusheiko and K. Agarwal. Serum NGAL can act as an early renal safety biomarker during long-term nucleos(t)ide analogue antiviral therapy in chronic hepatitis B. Journal of viral hepatitis, 25(10), 1139-1150. [18388]

Carrillo-Esper	2014	<100 participants	R. Carrillo-Esper, A. A. Perez-Calatayud, C. A. Pena-Perez, M. A. Diaz-Carrillo, J. A. Nava-Lopez, I. E. De Los Monteros-Estrada and A. D. Zepeda-Mendoza. Urinary sediment microscopic score as diagnostic marker of acute kidney lesion in sepsis. Medicina Interna de Mexico, 30(5), 602-606. [15210]
Carter	2014	No focus on DTA for AKI	J. L. Carter and E. J. Lamb. Evaluating new biomarkers for acute kidney injury: Putting the horse before the cart. American Journal of Kidney Diseases, 63(4), 543-546. [15214]
Carter	2016	<100 participants	J. L. Carter, C. T. Parker, P. E. Stevens, G. Eaglestone, S. Knight, C. K. T. Farmer and E. J. Lamb. Biological variation of plasma and urinary markers of acute kidney injury in patients with chronic kidney disease. Clinical Chemistry, 62(6), 876-883. [15213]
Carter	2016	<100 participants	J. L. Carter, C. T. Parker, P. E. Stevens, G. Eaglestone, S. Knight, C. K. T. Farmer and E. J. Lamb. Biological Variation of Plasma and Urinary Markers of Acute Kidney Injury in Patients with Chronic Kidney Disease. Clinical chemistry, 62(6), 876-885. [18389]
Cecchi	2017	<100 participants	E. Cecchi, G. Avveduto, M. G. D'Alfonso, A. Terreni, E. Gelera, A. Caldini and C. Giglioli. Cystatin C, but not urinary or serum NGAL, may be associated with contrast induced nephropathy after percutaneous coronary invasive procedures: A single center experience on a limited number of patients. Acta medica academica, 46(1), 34-43. [15217]
Celik	2013	<100 participants	T. Celik, E. Altekin, R. Isguder, Y. Kenesari, M. Duman and N. Arslan. Evaluation of neutrophil gelatinase-associated lipocalin in pediatric patients with acute rotavirus gastroenteritis and dehydration. Italian Journal of Pediatrics, 39(1), 52. [15218]
Cemil	2014	<100 participants	K. Cemil, C. Elif, Y. M. Serkan, Y. Fevzi, A. E. Deniz, D. Tamer and D. Polat. The value of serum NGAL in determination of dialysis indication. JPMA. The Journal of the Pakistan Medical Association, 64(7), 739-42. [15219]
Cervellin	2012	Not a primary study	G. Cervellin and S. Di Somma. Neutrophil gelatinase-associated lipocalin (NGAL): The clinician's perspective. Clinical Chemistry and Laboratory Medicine, 50(9), 1489-1493. [15220]
Chae	2015	Not relevant type of population	H. Chae, H. Ryu, K. Cha, M. Kim, Y. Kim and C. K. Min. Neutrophil gelatinase-associated lipocalin as a biomarker of renal impairment in patients with multiple myeloma. Clinical Lymphoma, Myeloma and Leukemia, 15(1), 35-40. [15222]
Chagan-Yasutan	2016	No focus on DTA for AKI	H. Chagan-Yasutan, Y. Chen, T. L. Lacuesta, P. S. A. Leano, H. Iwasaki, F. Hanan, D. Taurustiati, Y. Ohmoto, Y. Ashino, H. Saitoh, H. Kiyomoto, Y. Suzuki, F. O. E. Telan and T. Hattori. Urine levels of defensin alpha1 reflect kidney injury in leptospirosis patients. International Journal of Molecular Sciences, 17(10), 1637. [15223]
Chang	2009	<100 participants	C. K. Chang, T. A. M. Chuter, C. U. Niemann, M. G. Shlipak, M. J. Cohen, L. M. Reilly and J. S. Hiramoto. Systemic inflammation, coagulopathy, and acute renal insufficiency following endovascular thoracoabdominal aortic aneurysm repair. Journal of vascular surgery, 49(5), 1140-6. [15228]

Chang	2013	<100 participants	C. K. Chang, T. A. Chuter, C. U. Niemann, M. G. Shlipak, M. J. Cohen, L. M. Reilly and J. S. Hiramoto. Systemic inflammation, coagulopathy, and acute renal insufficiency following endovascular thoracoabdominal aortic aneurysm repair. Journal of Vascular Surgery, 49(5), 1140-6. [3946]
Chang	2015	Not relevant biomarker assay or test	C. H. Chang, C. H. Yang, H. Y. Yang, T. H. Chen, C. Y. Lin, S. W. Chang, Y. T. Chen, C. C. Hung, J. T. Fang, C. W. Yang and Y. C. Chen. Urinary biomarkers improve the diagnosis of intrinsic acute kidney injury in coronary care units. Medicine (United States), 94(40), e1703. [15227]
Chang	2017	No focus on DTA for AKI	C. Chang, Y. Hu, S. L. Hogan, N. Mercke, M. Gomez, C. O'Bryant, D. W. Bowles, B. George, X. Wen, L. M. Aleksunes and M. S. Joy. Pharmacogenomic variants may influence the urinary excretion of novel kidney injury biomarkers in patients receiving cisplatin. International Journal of Molecular Sciences, 18(7), 1333. [15226]
Chang	2018	Not relevant biomarker assay or test	W. Chang, S. Zhu, C. Pan, J.-F. Xie, S.-Q. Liu, H.-B. Qiu and Y. Yang. Predictive utilities of neutrophil gelatinase-associated lipocalin (NGAL) in severe sepsis. Clinica Chimica Acta, 481(200-206. [18397]
Channanayaka	2016	<100 participants	C. Channanayaka and A. Venkatkrishnan. Clinical utility of serum neutrophil gelatinase associated lipocalin (NGAL) as an early marker of acute kidney injury in asphyxiated neonates. Journal of Nepal Paediatric Society, 36(2), 121-125. [15231]
Che	2010	<100 participants	M. Che, B. Xie, S. Xue, H. Dai, J. Qian, Z. Ni, J. Axelsson and Y. Yan. Clinical usefulness of novel biomarkers for the detection of acute kidney injury following elective cardiac surgery. Nephron - Clinical Practice, 115(1), c66-c72. [15235]
Chen	2014	<100 participants	T. Chen, Y. H. Lu, W. J. Wang, C. Y. Bian, X. Y. Cheng, Y. Su and P. M. Zhou. Elevated urinary levels of cystatin C and neutrophil gelatinase-associated lipocalin in Henoch-Schonlein purpura patients with renal involvement. PLoS ONE, 9(6), e101026. [15241]
Chen	2019	Not relevant type of population	X. Chen, Z. Chen, T. Wei, P. Li, L. Zhang and P. Fu. The Effect of Serum Neutrophil Gelatinase-Associated Lipocalin on the Discontinuation of Continuous Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury. Blood Purification, . [15244]
Chen	2012	Not relevant biomarker assay or test	T. H. Chen, C. H. Chang, C. Y. Lin, C. C. Jenq, M. Y. Chang, Y. C. Tian, C. C. Hung, J. T. Fang, C. W. Yang, M. S. Wen, F. C. Lin and Y. C. Chen. Acute kidney injury biomarkers for patients in a coronary care unit: A prospective cohort study. PLoS ONE, 7(2), e32328. [15242]
Chen	2016	Not relevant type of population	C. Chen, X. Yang, Y. Lei, Y. Zha, H. Liu, C. Ma, J. Tian, P. Chen, T. Yang and F. F. Hou. Urinary biomarkers at the time of AKI diagnosis as predictors of progression of AKI among patients with acute cardiorenal syndrome. Clinical Journal of the American Society of Nephrology, 11(9), 1536-1544. [15236]
Chen	2016	Not a primary study	C. F. Chen and C. C. Lin. Neutrophil gelatinase-associated lipocalin: Still a good predictive marker of acute kidney injury in severe septic patients?. Journal of the Chinese Medical Association, 79(8), 411-412. [15237]

Cheng	2012	<100 participants	C. W. Cheng, Y. C. Chen, C. H. Chang, H. P. Yu, C. C. Lin, M. W. Yang, W. C. Lee and C. J. Chang. The ratio of plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury in patients undergoing liver transplantation. Transplantation Proceedings, 44(3), 776-779. [15245]
Chiara Vermi	2014	<100 participants	A. Chiara Vermi, C. Costopoulos, A. Latib, D. Piraino, F. Maisano, C. Naim, T. Naganuma, F. Figini, A. Chieffo, F. Ceriotti, M. Montorfano and A. Colombo. Urinary neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury after transcatheter aortic valve implantation. Hellenic Journal of Cardiology, 55(1), 77-79. [15247]
Chindarkar	2015	No relevant outcome	N. S. Chindarkar, L. S. Chawla, J. A. Straseski, S. A. Jortani, D. Uettwiller-Geiger, R. R. Orr, J. A. Kellum and R. L. Fitzgerald. Demographic data for urinary Acute Kidney Injury (AKI) marker [IGFBP7].[TIMP2] reference range determinations. Data in brief, 5(888-92. [15249]
Chindarkar	2016	Not relevant type of population	N. S. Chindarkar, L. S. Chawla, J. A. Straseski, S. A. Jortani, D. Uettwiller-Geiger, R. R. Orr, J. A. Kellum and R. L. Fitzgerald. Reference intervals of urinary acute kidney injury (AKI) markers [IGFBP7] . [TIMP2] in apparently healthy subjects and chronic comorbid subjects without AKI. Clinica Chimica Acta, 452(32-37. [15248]
Cho	2014	<100 participants	E. Cho, J. H. Lee, H. J. Lim, S. W. Oh, S. K. Jo, W. Y. Cho, H. K. Kim and S. Y. Lee. Soluble CD25 is increased in patients with sepsis-induced acute kidney injury. Nephrology, 19(6), 318-324. [15252]
Cho	2018	Not a primary study	S. Y. Cho and M. Hur. Neutrophil Gelatinase-Associated Lipocalin as a Promising Novel Biomarker for Early Detection of Kidney Injury. Annals of laboratory medicine, 38(5), 393-394. [15254]
Choi	2013	Not relevant type of population	H. M. Choi, K. T. Park, J. W. Lee, E. Cho, S. K. Jo, W. Y. Cho and H. K. Kim. Urine neutrophil gelatinase-associated lipocalin predicts graft outcome up to 1 year after kidney transplantation. Transplantation Proceedings, 45(1), 122-128. [15256]
Choi	2015	Not relevant type of population	J. W. Choi, T. Fujii and N. Fujii. Corrected Neutrophil Gelatinase-Associated Lipocalin (NGAL) Level Adjusted by the Scoring System of an Inflammation Index for Screening Renal Dysfunction in Patients with Systemic Inflammation. Annals of Clinical and Laboratory Science, 45(3), 248-255. [18405]
Choi	2017	Not relevant type of population	J. W. Choi, T. Fujii and N. Fujii. Diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin (NGAL) as an inflammatory biomarker for low-grade inflammation. Biomedical Research-India, 28(14), 6406-6411. [18404]
Chou	2013	Not relevant type of population	K. M. Chou, C. C. Lee, C. H. Chen and C. Y. Sun. Clinical Value of NGAL, L-FABP and Albuminuria in Predicting GFR Decline in Type 2 Diabetes Mellitus Patients. PLoS ONE, 8(1), e54863. [15259]
Choudhry	2018	Not relevant type of population	N. Choudhry, A. Ihsan, S. Mahmood, F. U. Haq and A. J. Gondal. Neutrophil gelatinase associated lipocalin, an early biomarker for diagnosis of acute kidney injury after percutaneous coronary intervention. Turkish Journal of Biochemistry, 43(1), 15-21. [15260]

Chun	2018	<100 participants	W. Chun, Y. Kim, J. Yoon, S. Lee, H. Yim, Y. S. Cho, D. Kym, J. Hur and H. T. Yang. Assessment of Plasma Neutrophil Gelatinase-Associated Lipocalin for Early Detection of Acute Kidney Injury and Prediction of Mortality in Severely Burned Patients. Journal of Burn Care and Research, 39(3), 387-393. [15267]
Civiletti	2019	<100 participants	F. Civiletti, B. Assenzio, A. T. Mazzeo, D. Medica, F. Giaretta, I. Deambrosis, V. Fanelli, V. M. Ranieri, V. Cantaluppi and L. Mascia. Acute Tubular Injury is Associated With Severe Traumatic Brain Injury: in Vitro Study on Human Tubular Epithelial Cells. Scientific reports, 9(1), 6090. [15272]
Coca	2013	Retained as background material	S. G. Coca, A. X. Garg, M. Swaminathan, S. Garwood, K. Hong, H. Thiessen-Philbrook, C. Passik, J. L. Koyner and C. R. Parikh. Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrology Dialysis Transplantation, 28(11), 2787-2799. [15276]
Coca	2013	Systematic review - retained as background material	S. G. Coca, R. Yalavarthy, J. Concato and C. R. Parikh. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney International, 73(9), 1008-16. [3998]
Codorniu	2018	Meta-analysis - retained as background material	A. Codorniu, L. Lemasle, M. Legrand, A. Blet, A. Mebazaa and E. Gayat. Methods used to assess the performance of biomarkers for the diagnosis of acute kidney injury: a systematic review and meta-analysis. Biomarkers, 23(8), 766-772. [15278]
Codsi	2017	Not relevant type of population	E. Codsi, V. D. Garovic, M. L. Gonzalez-Suarez, N. Milic, K. S. Borowski, C. H. Rose, N. P. Davies, K. B. Kashani, J. C. Lieske and W. M. White. Longitudinal characterization of renal proximal tubular markers in normotensive and preeclamptic pregnancies. American Journal of Physiology-Regulatory Integrative and Comparative Physiology, 312(5), R773-R778. [18410]
Connolly	2018	Not relevant type of population	M. Connolly, M. Kinnin, D. McEneaney, I. Menown, M. Kurth, J. Lamont, N. Morgan and M. Harbinson. Prediction of contrast induced acute kidney injury using novel biomarkers following contrast coronary angiography. QJM, 111(2), 103-110. [15283]
Constantin	2010	<100 participants	J. M. Constantin, E. Futier, S. Perbet, L. Roszyk, A. Lautrette, T. Gillart, R. Guerin, M. Jabaudon, B. Souweine, J. E. Bazin and V. Sapin. Plasma neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in adult critically ill patients: A prospective study. Journal of Critical Care, 25(1), 176. [15285]
Corbacıoglu	2017	<100 participants	S. K. Corbacioglu, Y. Cevik, E. Akinci, H. Uzunosmanoglu, S. Dagar, T. Safak, V. Oncul and M. Guvendi. Value of plasma neutrophil gelatinase-associated lipocalin (NGAL) in distinguishing between acute kidney injury (AKI) and chronic kidney disease (CKD). Turkish Journal of Emergency Medicine, 17(3), 85-88. [15290]

Cordova-Sanchez	2019	<100 participants	B. M. Cordova-Sanchez, E. B. Ruiz-Garcia, A. Lopez-Yanez, M. Barragan-Dessavre, A. R. Bautista-Ocampo, A. Meneses-Garcia, A. Herrera-Gomez and S. A. Namendys-Silva. Plasma neutrophil gelatinase-associated lipocalin and factors related to acute kidney injury and mortality in critically ill cancer patients. Ecancermedicalscience, 13(903. [15291]
Coupes	2015	<100 participants	B. Coupes, D. G. de Freitas, S. A. Roberts, I. Read, H. Riad, P. E. Brenchley and M. L. Picton. rhErythropoietin-b as a tissue protective agent in kidney transplantation: a pilot randomized controlled trial. BMC research notes, 8(21. [15294]
Cruz	2009	Not a primary study	D. N. Cruz, S. Soni and C. Ronco. NGAL and Cardiac Surgery-Associated Acute Kidney Injury. American Journal of Kidney Diseases, 53(3), 565-566. [15303]
Cruz	2009	Not a primary study	D. N. Cruz, S. Soni and C. Ronco. NGAL and cardiac surgery-associated acute kidney injury. American Journal of Kidney Diseases, 53(3), 565-6; author reply 566. [3953]
Cruz	2012	Systematic review - retained as background material	D. N. Cruz, S. Gaiao, A. Maisel, C. Ronco and P. Devarajan. Neutrophil gelatinase-associated lipocalin as a biomarker of cardiovascular disease: A systematic review. Clinical Chemistry and Laboratory Medicine, 50(9), 1533-1545. [15298]
Cruz	2013	Not relevant biomarker assay or test	D. N. Cruz, M. De Cal, F. Garzotto, M. A. Perazella, P. Lentini, V. Corradi, P. Piccinni and C. Ronco. Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Medicine, 36(3), 444-451. [15300]
Cruz	2016	<100 participants	D. N. Cruz, G. M. Virzi, A. Brocca, C. Ronco and D. Giavarina. A comparison of three commercial platforms for urinary NGAL in critically ill adults. Clinical Chemistry and Laboratory Medicine, 54(2), 353-362. [15297]
Cuartero	2017	<100 participants	M. Cuartero, J. Ballus, J. Sabater, X. Perez, N. Nin, J. Ordonez-Llanos and A. J. Betbese. Cell-cycle arrest biomarkers in urine to predict acute kidney injury in septic and non-septic critically ill patients. Annals of Intensive Care, 7(1), 92. [15305]
Cullaro	2017	Not relevant biomarker assay or test	G. Cullaro, G. Kim, M. R. Pereira, R. S. Brown and E. C. Verna. Ascites Neutrophil Gelatinase-Associated Lipocalin Identifies Spontaneous Bacterial Peritonitis and Predicts Mortality in Hospitalized Patients with Cirrhosis. Digestive Diseases and Sciences, 62(12), 3487-3494. [15308]
Cullaro	2018	<100 participants	G. Cullaro, J. F. Pisa, R. S. Brown, G. Wagener and E. C. Verna. Early Postoperative Neutrophil Gelatinase-Associated Lipocalin Predicts the Development of Chronic Kidney Disease after Liver Transplantation. Transplantation, 102(5), 809-815. [15307]
da Rocha	2018	<100 participants	E. P. da Rocha, L. G. Yokota, B. M. Sampaio, K. Z. C. Eid, D. B. Dias, F. M. de Freitas, A. L. Balbi and D. Ponce. Urinary neutrophil gelatinase-associated lipocalin is excellent predictor of acute kidney injury in septic elderly patients. Aging and Disease, 9(2), 182-191. [15312]

Daggulli	2016	<100 participants	M. Daggulli, M. M. Utangac, O. Dede, M. N. Bodakci, N. K. Hatipoglu, N. Penbegul, A. A. Sancaktutar, Y. Bozkurt and H. Soylemez. Potential biomarkers for the early detection of acute kidney injury after percutaneous nephrolithotripsy. Renal Failure, 38(1), 151-156. [15314]
Dahlén	2001	<100 participants	I. Dahlén, C. Janson, E. Björnsson, G. Stålenheim, C. G. Peterson and P. Venge. Changes in inflammatory markers following treatment of acute exacerbations of obstructive pulmonary disease. Respiratory medicine, 95(11), 891â€ 897. [4656]
Dai	2015	Not relevant biomarker assay or test	X. Dai, Z. Zeng, C. Fu, S. Zhang, Y. Cai and Z. Chen. Diagnostic value of neutrophil gelatinase-associated lipocalin, cystatin C, and soluble triggering receptor expressed on myeloid cells-1 in critically ill patients with sepsis-associated acute kidney injury. Critical Care, 19(1), 223. [15317]
Dai	2016	<100 participants	X. Dai, T. Li, Z. Zeng, C. Fu, S. Wang, Y. Cai and Z. Chen. The effect of continuous venovenous hemofiltration on neutrophil gelatinase-associated lipocalin plasma levels in patients with septic acute kidney injury. BMC nephrology, 17(1), 154. [15315]
Damman	2017	Not relevant biomarker assay or test	K. Damman, M. A. E. Valente, D. J. van Veldhuisen, J. G. F. Cleland, C. M. O'Connor, M. Metra, P. Ponikowski, G. Cotter, B. Davison, M. M. Givertz, D. M. Bloomfield, H. L. Hillege and A. A. Voors. Plasma Neutrophil Gelatinase-Associated Lipocalin and Predicting Clinically Relevant Worsening Renal Function in Acute Heart Failure. International journal of molecular sciences, 18(7), . [15318]
Daniels	2012	Not relevant type of population	L. B. Daniels, E. Barrett-Connor, P. Clopton, G. A. Laughlin, J. H. Ix and A. S. Maisel. Plasma neutrophil gelatinase-associated lipocalin is independently associated with cardiovascular disease and mortality in community-dwelling older adults: The rancho bernardo study. Journal of the American College of Cardiology, 59(12), 1101-1109. [15319]
Daniels	2012	Not a primary study	R. C. Daniels and T. E. Bunchman. Is it the neutrophil gelatinase-associated lipocalin or the pediatricRIFLE?. Pediatric Critical Care Medicine, 13(6), 698. [15320]
Dankova	2016	<100 participants	M. Dankova, T. Pazmanova, V. Hricak, J. Gergel, V. Svobodova, B. Zitny, K. Danova, S. Remisova and P. Pontuch. Urinary NGAL as a predictor of acute kidney injury in patients with acute heart failure. Cardiology Letters, 25(1), 9-15. [15321]
Dardashti	2014	<100 participants	A. Dardashti, P. Ederoth, L. Algotsson, B. Bronden, E. Grins, M. Larsson, S. Nozohoor, G. Zinko and H. Bjursten. Erythropoietin and protection of renal function in cardiac surgery (the EPRICS trial). Anesthesiology, 121(3), 582-590. [15322]
Darmon	2011	Not a primary study	M. Darmon, F. Gonzalez and F. Vincent. Limits of neutrophil gelatinase-associated lipocalin at intensive care unit admission for prediction of acute kidney injury. American Journal of Respiratory and Critical Care Medicine, 184(1), 142-143. [15324]
Darmon	2017	Not a primary study	M. Darmon, M. Ostermann and M. Joannidis. Predictions are difficult...especially about AKI. Intensive Care Medicine, 43(6), 932-934. [15323]

Datzmann	2018	<100 participants	T. Datzmann, M. Hoenicka, H. Reinelt, A. Liebold and H. Gorki. Influence of 6% Hydroxyethyl Starch 130/0.4 Versus Crystalloid Solution on Structural Renal Damage Markers After Coronary Artery Bypass Grafting: A Post Hoc Subgroup Analysis of a Prospective Trial. Journal of Cardiothoracic and Vascular Anesthesia, 32(1), 205-211. [15326]
Daubin	2017	No focus on DTA for AKI	D. Daubin, J. P. Cristol, A. M. Dupuy, N. Kuster, N. Besnard, L. Platon, A. Buzancais, V. Brunot, F. Garnier, O. Jonquet and K. Klouche. Urinary biomarkers IGFBP7 and TIMP-2 for the diagnostic assessment of transient and persistent acute kidney injury in critically Ill patients. PLoS ONE, 12(1), e0169674. [15327]
De Berardinis	2015	Not relevant biomarker assay or test	B. De Berardinis, H. K. Gaggin, L. Magrini, A. Belcher, B. Zancla, A. Femia, M. Simon, S. Motiwala, A. Bhardwaj, B. A. Parry, J. T. Nagurney, C. Coudriou, M. Legrand, M. Sadoune, S. Di Somma, J. L. Januzzi, Jr. and G. Global Res Acute Conditions Team. Comparison between admission natriuretic peptides, NGAL and sST2 testing for the prediction of worsening renal function in patients with acutely decompensated heart failure. Clinical Chemistry and Laboratory Medicine, 53(4), 613-621. [18419]
de Geus	2010	Not a primary study	H. R. H. de Geus, M. G. H. Betjes and J. Bakker. Neutrophil gelatinase-associated lipocalin clearance during veno-venous continuous renal replacement therapy in critically ill patients. Intensive care medicine, 36(12), 2156-7. [15338]
De Geus	2011	Not relevant biomarker assay or test	H. R. H. De Geus, J. Bakker, E. M. E. H. Lesaffre and J. L. M. L. Le Noble. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. American Journal of Respiratory and Critical Care Medicine, 183(7), 907-914. [15336]
de Geus	2011	Not relevant biomarker assay or test	H. R. H. de Geus, J. G. Woo, Y. Wang, P. Devarajan, M. G. Betjes, J. L. M. L. le Noble and J. Bakker. Urinary Neutrophil Gelatinase-Associated Lipocalin Measured on Admission to the Intensive Care Unit Accurately Discriminates between Sustained and Transient Acute Kidney Injury in Adult Critically Ill Patients. Nephron extra, 1(1), 9-23. [15337]
De Geus	2013	Not relevant biomarker assay or test	H. R. De Geus, G. Fortrie, M. G. Betjes, R. H. Van Schaik and A. J. Groeneveld. Time of injury affects urinary biomarker predictive values for acute kidney injury in critically ill, non-septic patients. BMC Nephrology, 14(1), 273. [15332]
De Geus	2013	Not relevant biomarker assay or test	H. R. H. De Geus, M. G. Betjes, R. Van Schaick and J. A. B. J. Groeneveld. Plasma NGAL similarly predicts acute kidney injury in sepsis and nonsepsis. Biomarkers in Medicine, 7(3), 415-421. [15334]
de Geus	2017	Not a primary study	H. R. de Geus, M. Haase and L. Jacob. The cardiac surgery-associated neutrophil gelatinase-associated lipocalin score for postoperative acute kidney injury: Does subclinical acute kidney injury matter?. Journal of Thoracic and Cardiovascular Surgery, 154(3), 939-940. [15331]
de Grooth	2018	Not a primary study	H. J. de Grooth, J. J. Parienti and M. Schetz. AKI biomarkers are poor discriminants for subsequent need for renal replacement therapy, but do not disqualify them yet. Intensive Care Medicine, 44(7), 1156-1158. [15339]

De Loor	2016	Pilot study or preliminary analysis only	J. De Loor, J. Decruyenaere, K. Demeyere, L. Nuytinck, E. A. J. Hoste and E. Meyer. Urinary chitinase 3-like protein 1 for early diagnosis of acute kidney injury: A prospective cohort study in adult critically ill patients. Critical Care, 20(1), 38. [15342]
Dede	2015	<100 participants	O. Dede, M. Dagguli, M. Utangac, H. Yuksel, M. N. Bodakci, N. K. Hatipoglu, A. A. Sancaktutar and N. Penbegul. Urinary expression of acute kidney injury biomarkers in patients after RIRS: It is a prospective, controlled study. International Journal of Clinical and Experimental Medicine, 8(5), 8147-8152. [15349]
Dedeoglu	2013	<100 participants	B. Dedeoglu, H. R. H. De Geus, G. Fortrie and M. G. H. Betjes. Novel biomarkers for the prediction of acute kidney injury in patients undergoing liver transplantation. Biomarkers in Medicine, 7(6), 947-957. [15350]
Deger	2017	<100 participants	S. M. Deger, Y. Erten, E. Suyani, S. Z. Aki, G. Ulusal Okyay, O. T. Pasaoglu, H. Pasaoglu, T. Arinsoy and G. Turkoz Sucak. Early Diagnostic Markers for Detection of Acute Kidney Injury in Allogeneic Hematopoietic Stem Cell Transplant Recipients. Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation, . [15353]
Deininger	2016	No relevant outcome	S. Deininger, M. Hoenicka, K. Muller-Eising, P. Rupp, A. Liebold, W. Koenig and H. Gorki. Renal Function and Urinary Biomarkers in Cardiac Bypass Surgery: A Prospective Randomized Trial Comparing Three Surgical Techniques. Thoracic and Cardiovascular Surgeon, 64(7), 561-568. [15354]
Dekker	2019	No focus on DTA for AKI	S. E. I. Dekker, L. R. Ruhaak, F. P. H. T. M. Romijn, E. Meijer, C. M. Cobbaert, J. W. de Fijter and D. Soonawala. Urinary Tissue Inhibitor of Metalloproteinases-2 and Insulin-Like Growth Factor-Binding Protein 7 Do Not Correlate With Disease Severity in ADPKD Patients. Kidney International Reports, . [15355]
Delcroix	2013	<100 participants	G. Delcroix, N. Gillain, M. Moonen, L. Radermacher, F. Damas, J.-M. Minon and V. Fraipont. NGAL Usefulness in the Intensive Care Unit Three Hours after Cardiac Surgery. ISRN nephrology, 2013(865164. [15357]
Delfino Duarte	2015	<100 participants	P. A. Delfino Duarte, A. C. Fumagalli, V. Wandeur and D. Becker. Urinary neutrophil gelatinase-associated lipocalin in critically ill surgical cancer patients. Indian Journal of Critical Care Medicine, 19(5), 251-256. [15358]
Demirtas	2013	<100 participants	S. Demirtas, A. Caliskan, O. Karahan, C. Yavuz, O. Guclu, M. C. Cayir, F. Toktas and O. Tiryakioglu. Neutrophil gelatinase-associated lipocalin as a biomarker for acute kidney injury in patients undergoing coronary artery bypass grafting. Experimental and Clinical Cardiology, 18(2), 107-109. [15359]
Dent	2007	Not relevant biomarker assay or test	C. L. Dent, Q. Ma, S. Dastrala, M. Bennett, M. M. Mitsnefes, J. Barasch and P. Devarajan. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: A prospective uncontrolled cohort study. Critical Care, 11(6), . [2100]

Depret	2018	<100 participants	F. Depret, L. Boutin, J. Jarkovsky, M. Chaussard, S. Soussi, A. Bataille, H. Oueslati, N. Moreno, C. de Tymowski, J. Parenica, K. Benesova, T. Vauchel, A. Ferry, M. Benyamina, A. Cupaciu, M. Coutrot, J. P. Garnier, K. Serror, M. Chaouat, A. Mebazaa and M. Legrand. Prediction of major adverse kidney events in critically ill burn patients. Burns, 44(8), 1887-1894. [15363]
Derhaschnig	2014	<100 participants	U. Derhaschnig, C. Testori, E. Riedmueller, E. L. Hobl, F. B. Mayr and B. Jilma. Decreased renal function in hypertensive emergencies. Journal of Human Hypertension, 28(7), 427-431. [15364]
Devarajan	2008	Meta-analysis - retained as background material	P. Devarajan. Emerging urinary biomarkers in the diagnosis of acute kidney injury. Expert Opinion on Medical Diagnostics, 2(4), 387-398. [2191]
Devarajan	2008	Not a primary study	P. Devarajan. Neutrophil gelatinase-associated lipocalin - An emerging troponin for kidney injury. Nephrology Dialysis Transplantation, 23(12), 3737-3743. [2127]
Devarajan	2009	Not a primary study	P. Devarajan. Neutrophil Gelatinase-associated Lipocalin: An Emerging Biomarker for Angina Renalis. Yearbook of Intensive Care and Emergency Medicine, 620-626. [18422]
Devarajan	2014	Not a primary study	P. Devarajan. NGAL for the detection of acute kidney injury in the emergency room. Biomarkers in Medicine, 8(2), 217-219. [15368]
Dewey	2013	Not a primary study	M. Dewey and E. Schonenberger. Increase in creatinine for the prediction of contrast-induced nephropathy. Radiology, 269(2), 623-624. [15385]
Dewitte	2015	<100 participants	A. Dewitte, O. Joannes-Boyau, C. Sidobre, C. Fleureau, M. L. Bats, P. Derache, S. Leuillet, J. Ripoche, C. Combe and A. Ouattara. Kinetic eGFR and novel AKI biomarkers to predict renal recovery. Clinical Journal of the American Society of Nephrology, 10(11), 1900-1910. [15386]
Di Nardo	2013	<100 participants	M. Di Nardo, A. Ficarella, Z. Ricci, R. Luciano, F. Stoppa, S. Picardo, S. Picca, M. Muraca and P. Cogo. Impact of severe sepsis on serum and urinary biomarkers of acute kidney injury in critically ill children: An observational study. Blood Purification, 35(1-3), 172-176. [15391]
Diaz de Leon-Martinez	2019	<100 participants	L. Diaz de Leon-Martinez, F. Diaz-Barriga, O. Barbier, D. L. G. Ortiz, M. Ortega-Romero, F. Perez-Vazquez and R. Flores-Ramirez. Evaluation of emerging biomarkers of renal damage and exposure to aflatoxin-B1 in Mexican indigenous women: a pilot study. Environmental science and pollution research international, 26(12), 12205-12216. [15395]
Doi	2013	Not relevant biomarker assay or test	K. Doi, M. Urata, D. Katagiri, M. Inamori, S. Murata, M. Hisagi, M. Ono, T. Matsubara, T. Ishii, N. Yahagi, M. Nangaku and E. Noiri. Plasma neutrophil gelatinase-associated lipocalin in acute kidney injury superimposed on chronic kidney disease after cardiac surgery: A multicenter prospective study. Critical Care, 17(6), R270. [15408]

Donadio	2014	Not relevant biomarker assay or test	C. Donadio. Effect of glomerular filtration rate impairment on diagnostic performance of neutrophil gelatinase-associated lipocalin and B-type natriuretic peptide as markers of acute cardiac and renal failure in chronic kidney disease patients. Critical Care, 18(1), R39. [15414]
Downes	2017	<100 participants	K. J. Downes, M. Dong, T. Fukuda, J. P. Clancy, C. Haffner, M. R. Bennett, A. A. Vinks and S. L. Goldstein. Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: A population pharmacokinetic analysis. Journal of Antimicrobial Chemotherapy, 72(1), 254-260. [15418]
Du	2011	Not relevant biomarker assay or test	Y. Du, M. Zappitelli, A. Mian, M. Bennett, Q. Ma, P. Devarajan, R. Mehta and S. L. Goldstein. Urinary biomarkers to detect acute kidney injury in the pediatric emergency center. Pediatric Nephrology, 26(2), 267-274. [15422]
Du	2014	<100 participants	Y. Du, L. Hou, J. Guo, T. Sun, X. Wang and Y. Wu. Renal neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 expression in children with acute kidney injury and Henoch-Schonlein purpura nephritis. Experimental and Therapeutic Medicine, 7(5), 1130-1134. [15421]
Du	2017	<100 participants	W. Du, T. Shen, H. Li, Y. Liu, L. He, L. Tan and M. Hu. Urinary NGAL for the diagnosis of the renal injury from multiple myeloma. Cancer Biomarkers, 18(1), 41-46. [15420]
Dubin	2018	Not relevant type of population	R. F. Dubin, S. Judd, R. Scherzer, M. Shlipak, D. G. Warnock, M. Cushman, M. Sarnak, C. Parikh, M. Bennett, N. Powe and C. A. Peralta. Urinary Tubular Injury Biomarkers Are Associated With ESRD and Death in the REGARDS Study. Kidney international reports, 3(5), 1183-1192. [15423]
Dusse	2016	<100 participants	F. Dusse, M. Edayadiyil-Dudasova, M. Thielmann, D. Wendt, P. Kahlert, E. Demircioglu, H. Jakob, S. T. Schaefer and K. Pilarczyk. Early prediction of acute kidney injury after transapical and transaortic aortic valve implantation with urinary G1 cell cycle arrest biomarkers. BMC Anesthesiology, 16(1), 76. [15429]
Dwipa	2012	<100 participants	L. Dwipa, R. Soelaeman, R. M. Roesli, E. Martanto and I. G. Adhiarta. Cardiometabolic risk factors and acute kidney injury based on urinary neutrophil gelatinase associated lipocalin (NGALu) in acute coronary syndrome patients. Acta medica Indonesiana, 44(1), 3-9. [15430]
Egal	2016	Not relevant biomarker assay or test	M. Egal, H. R. H. De Geus and A. B. J. Groeneveld. Neutrophil Gelatinase-Associated Lipocalin as a Diagnostic Marker for Acute Kidney Injury in Oliguric Critically Ill Patients: A Post-Hoc Analysis. Nephron, 134(2), 81-88. [15437]
Eilenberg	2016	<100 participants	W. Eilenberg, S. Stojkovic, A. Piechota-Polanczyk, C. Kaun, S. Rauscher, M. Groger, M. Klinger, J. Wojta, C. Neumayer, I. Huk and S. Demyanets. Neutrophil Gelatinase-Associated Lipocalin (NGAL) is Associated with Symptomatic Carotid Atherosclerosis and Drives Pro-inflammatory State in Vitro. European Journal of Vascular and Endovascular Surgery, 51(5), 623-631. [15438]

Eirin	2012	<100 participants	A. Eirin, M. L. Gloviczki, H. Tang, A. D. Rule, J. R. Woollard, A. Lerman, S. C. Textor and L. O. Lerman. Chronic renovascular hypertension is associated with elevated levels of neutrophil gelatinase-associated lipocalin. Nephrology Dialysis Transplantation, 27(11), 4153-4161. [15440]
Eisenhart	2010	Not relevant type of population	E. Eisenhart, S. Benson, P. Lacombe, J. Himmelfarb, R. Zimmerman, B. Schimelman and M. G. Parker. Safety of Low Volume Iodinated Contrast Administration for Arteriovenous Fistula Intervention in Chronic Kidney Disease Stage 4 or 5 Utilizing a Bicarbonate Prophylaxis Strategy. Seminars in Dialysis, 23(6), 638-642. [15441]
Ejaz	2015	<100 participants	A. A. Ejaz, K. F. Alquadan, B. Dass, M. Shimada, M. Kanbay and R. J. Johnson. Effects of Serum Uric Acid on Estimated GFR in Cardiac Surgery Patients: A Pilot Study. American Journal of Nephrology, 42(6), 402-409. [15442]
El Raggal	2013	<100 participants	N. M. El Raggal, S. M. Khafagy, N. H. Mahmoud and S. A. El Beltagy. Serum neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in asphyxiated neonates. Indian Pediatrics, 50(5), 459-462. [15448]
El Shahawy	2018	<100 participants	M. S. El Shahawy, M. H. Hemida, H. A. Abdel-Hafez, T. Z. El-Baz, A. W. M. Lotfy and T. M. Emran. Urinary neutrophil gelatinase-associated lipocalin as a marker for disease activity in lupus nephritis. Scandinavian Journal of Clinical and Laboratory Investigation, 78(4), 264-268. [15449]
El-Akabawy	2017	<100 participants	H. El-Akabawy, M. Shafee, A. M. Roshdy and A. Abd Al Salam. Urinary neutrophil gelatinase associated lipocalin as an early marker of acute kidney injury in the recipient after liver transplantation. Egyptian Journal of Critical Care Medicine, 5(1), 49-55. [15450]
El-Farghali	2012	<100 participants	O. G. El-Farghali, N. M. El-Raggal, N. H. Mahmoud and G. A. Zaina. Serum Neutrophil Gelatinase-associated Lipocalin as a predictor of acute kidney injury in critically-ill neonates. Pakistan Journal of Biological Sciences, 15(5), 231-237. [15451]
Elia	2015	<100 participants	C. Elia, I. Graupera, R. Barreto, E. Sola, R. Moreira, P. Huelin, X. Ariza, C. Sole, E. Pose, A. Baiges, N. Fabrellas, E. Poch, J. Fernandez, V. Arroyo and P. Gines. Severe acute kidney injury associated with non-steroidal anti-inflammatory drugs in cirrhosis: A case-control study. Journal of Hepatology, 63(3), 593-600. [15453]
Elmas	2017	<100 participants	A. T. Elmas, A. Karadag, Y. Tabel, R. Ozdemir and G. Otlu. Analysis of urine biomarkers for early determination of acute kidney injury in non-septic and non-asphyxiated critically ill preterm neonates. Journal of Maternal-Fetal and Neonatal Medicine, 30(3), 302-308. [15454]
Elmedany	2017	<100 participants	S. M. Elmedany, S. S. Naga, R. Elsharkawy, R. S. Mahrous and A. I. Elnaggar. Novel urinary biomarkers and the early detection of acute kidney injury after open cardiac surgeries. Journal of Critical Care, 40(171-177. [15455]

Elmer	2016	<100 participants	J. Elmer, K. Jeong, K. Z. Abebe, F. X. Guyette, R. Murugan, C. W. Callaway and J. C. Rittenberger. Serum neutrophil gelatinase-associated lipocalin predicts survival after resuscitation from cardiac arrest. Critical Care Medicine, 44(1), 111-119. [15456]
Elsharawy	2016	<100 participants	S. Elsharawy, L. Raslan, S. Morsy, B. Hassan and N. Khalifa. Plasma neutrophil gelatinase-associated lipocalin as a marker for the prediction of worsening renal function in children hospitalized for acute heart failure. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia, 27(1), 49-54. [15457]
Emlet	2017	Not relevant type of population	D. R. Emlet, N. Pastor-Soler, A. Marciszyn, X. Wen, H. Gomez, W. H. Humphries, S. Morrisroe, J. K. Volpe and J. A. Kellum. Insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases-2: Differential expression and secretion in human kidney tubule cells. American Journal of Physiology - Renal Physiology, 312(2), F284-F296. [15459]
Endre	2011	Not relevant biomarker assay or test	Z. H. Endre, J. W. Pickering, R. J. Walker, P. Devarajan, C. L. Edelstein, J. V. Bonventre, C. M. Frampton, M. R. Bennett, Q. Ma, V. S. Sabbisetti, V. S. Vaidya, A. M. Walcher, G. M. Shaw, S. J. Henderson, M. Nejat, J. B. W. Schollum and P. M. George. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. Kidney International, 79(10), 1119-1130. [15466]
Endre	2014	No focus on DTA for AKI	Z. H. Endre. Novel biomarkers of acute kidney injury: Time for implementation?. Biomarkers in Medicine, 8(10), 1185-1188. [15460]
Endre	2014	Not a primary study	Z. H. Endre and J. W. Pickering. Acute kidney injury: Late-onset acute kidney injury-subacute or more of the same?. Nature Reviews Nephrology, 10(3), 133-134. [15461]
Endre	2014	Not a primary study	Z. H. Endre and J. W. Pickering. Acute kidney injury: Cell cycle arrest biomarkers win race for AKI diagnosis. Nature Reviews Nephrology, 10(12), 683-685. [15462]
Erturk	2015	<100 participants	A. Erturk, E. Cure, E. Parlak, M. C. Cure, S. B. Sahin and S. Yuce. Clinical Significance of Neutrophil Gelatinase-Associated Lipocalin in Crimean-Congo Hemorrhagic Fever. Biomed Research International, 374010-374010. [18429]
Espinosa-Sevilla	2013	Not a primary study	A. Espinosa-Sevilla, A. I. Amezcua-Macias, P. C. Ruiz-Palacios, F. Rodriguez-Weber and E. Diaz-Greene. New markers of acute kidney injury in critically ill patients. Medicina Interna de Mexico, 29(5), 513-517. [15476]
Essajee	2015	Not relevant biomarker assay or test	F. Essajee, F. Were and B. Admani. Urine neutrophil gelatinase-associated lipocalin in asphyxiated neonates: a prospective cohort study. Pediatric Nephrology, 30(7), 1189-1196. [15477]
Essajee	2015	Not relevant type of population	F. Essajee, F. Were and B. Admani. Urine neutrophil gelatinase-associated lipocalin in asphyxiated neonates: a prospective cohort study. Pediatric Nephrology, 30(7), 1189-1196. [18430]

Cho	2013	Duplicate of a study that had already been assessedlicate of a study that had already been assessed	E. Cho, H. N. Yang, S. K. Jo, W. Y. Cho and H. K. Kim. The Role of Urinary Liver-Type Fatty Acid-Binding Protein in Critically Ill Patients. Journal of Korean Medical Science, 28(1), 100-105. [6169]
Ezenwaka	2016	Not relevant biomarker assay or test	C. E. Ezenwaka, S. Idris, G. Davis and L. Roberts. Measurement of neutrophil gelatinase-associated lipocalin (NGAL) in patients with non-communicable diseases: any additional benefit?. Archives of Physiology and Biochemistry, 122(2), 70-74. [18432]
Fadel	2012	<100 participants	F. I. Fadel, A. M. O. Abdel Rahman, M. F. Mohamed, S. A. Habib, M. H. Ibrahim, Z. S. Sleem, H. M. Bazaraa and M. M. A. Soliman. Plasma neutrophil gelatinase-associated lipocalin as an early biomarker for prediction of acute kidney injury after cardio-pulmonary bypass in pediatric cardiac surgery. Archives of Medical Science, 8(2), 250-255. [15478]
Fagundes	2012	No focus on DTA for AKI	C. Fagundes, M. N. Pepin, M. Guevara, R. Barreto, G. Casals, E. Sola, G. Pereira, E. Rodriguez, E. Garcia, V. Prado, E. Poch, W. Jimenez, J. Fernandez, V. Arroyo and P. Gines. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. Journal of Hepatology, 57(2), 267-273. [15479]
Fan	2018	Not relevant biomarker assay or test	H. Fan, Y. Zhao, M. Sun and J. H. Zhu. Urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, N-acetyl-beta-D-glucosaminidase levels and mortality risk in septic patients with acute kidney injury. Archives of Medical Science, 14(6), 1381-1386. [15482]
Fan	2018	Not relevant biomarker assay or test	H. Fan, Y. Zhao, M. Sun and J.-H. Zhu. Urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, N-acetyl-beta-D-glucosaminidase levels and mortality risk in septic patients with acute kidney injury. Archives of Medical Science, 14(6), 1381-1386. [18433]
Fan	2014	Not relevant biomarker assay or test	H. Fan, Y. Zhao, J. H. Zhu and F. C. Song. Urine neutrophil gelatinase-associated lipocalin in septic patients with and without acute kidney injury. Renal Failure, 36(9), 1399-1403. [15484]
Fanning	2016	<100 participants	N. Fanning, S. Galvin, R. Parke, J. Gilroy, R. Bellomo and S. McGuinness. A Prospective Study of the Timing and Accuracy of Neutrophil Gelatinase-Associated Lipocalin Levels in Predicting Acute Kidney Injury in High-Risk Cardiac Surgery Patients. Journal of Cardiothoracic and Vascular Anesthesia, 30(1), 76-81. [15488]
Fathimah	2012	<100 participants	M. Fathimah, M. K. Alicezah and M. Thevarajah. Neutrophil Gelatinase-Associated Lipocalin (NGAL): an early marker for diabetic nephropathy. International Journal of Diabetes in Developing Countries, 32(1), 19-24. [18435]
Feldkamp	2011	Not a primary study	T. Feldkamp, A. Bienholz and A. Kribben. Urinary neutrophil gelatinase-associated lipocalin (NGAL) for the detection of acute kidney injury after orthotopic liver transplantation. Nephrology Dialysis Transplantation, 26(5), 1456-1458. [15495]
Feng	2016	No relevant outcome	Y. G. Feng, B. Liang, J. Liu, M. D. Jiang, H. J. Liu, Y. Q. Huang and L. Xiao. Correlation study of podocyte injury and kidney function in patients with acute kidney injury. Journal of Acute Disease, 5(6), 493-496. [15497]

Ferguson	2010	<100 participants	M. A. Ferguson, V. S. Vaidya, S. S. Waikar, F. B. Collings, K. E. Sunderland, C. J. Gioules and J. V. Bonventre. Urinary liver-type fatty acid-binding protein predicts adverse outcomes in acute kidney injury. Kidney International, 77(8), 708-714. [15500]
Fernandes	2014	<100 participants	A. Fernandes, J. Ettinger, F. Amaral, M. J. Ramalho, R. Alves and N. S. Modolo. General anesthesia type does not influence serum levels of neutrophil gelatinase-associated lipocalin during the perioperative period in video laparoscopic bariatric surgery. Clinics (Sao Paulo, Brazil), 69(10), 655-659. [15502]
Filho	2017	Systematic review - retained as background material	L. T. Filho, A. J. Grande, T. Colonetti, E. S. P. Della and M. I. da Rosa. Accuracy of neutrophil gelatinase-associated lipocalin for acute kidney injury diagnosis in children: systematic review and meta-analysis. Pediatric Nephrology, 32(10), 1979-1988. [15506]
Filiopoulos	2013	Not relevant type of population	V. Filiopoulos, D. Biblaki, D. Lazarou, D. Chrisis, M. Fatourou, S. Lafoyianni and D. Vlassopoulos. Plasma neutrophil gelatinase-associated lipocalin (NGAL) as an early predictive marker of contrast-induced nephropathy in hospitalized patients undergoing computed tomography. Clinical Kidney Journal, 6(6), 578-583. [15508]
Filiopoulos	2014	No focus on DTA for AKI	V. Filiopoulos, D. Biblaki and D. Vlassopoulos. Neutrophil gelatinase-associated lipocalin (NGAL): A promising biomarker of contrast-induced nephropathy after computed tomography. Renal Failure, 36(6), 979-986. [15507]
Finge	2017	<100 participants	T. Finge, S. Bertran, C. Roger, D. Candela, B. Pereira, C. Scott, L. Muller, B. Louart and J. Y. Lefrant. Interest of Urinary [TIMP-2] x [IGFBP-7] for Predicting the Occurrence of Acute Kidney Injury after Cardiac Surgery: A Gray Zone Approach. Anesthesia and Analgesia, 125(3), 762-769. [15510]
Fiorentino	2019	<100 participants	M. Fiorentino, F. A. Tohme, R. Murugan and J. A. Kellum. Plasma Biomarkers in Predicting Renal Recovery from Acute Kidney Injury in Critically Ill Patients. Blood purification, 1-9. [15511]
Flechet	2017	Not relevant biomarker assay or test	M. Flechet, F. Guiza, M. Schetz, P. Wouters, I. Vanhorebeek, I. Derese, J. Gunst, I. Spriet, M. Casaer, G. Van den Berghe and G. Meyfroidt. AKIpredictor, an online prognostic calculator for acute kidney injury in adult critically ill patients: development, validation and comparison to serum neutrophil gelatinase-associated lipocalin. Intensive Care Medicine, 43(6), 764-773. [15513]
Foroughi	2014	No focus on DTA for AKI	M. Foroughi, H. Argani, S. A. Hassntash, M. Hekmat, M. Majidi, M. Beheshti, B. Mehdizadeh and B. Yekani. Lack of renal protection of ultrafiltration during cardiac surgery: A randomized clinical trial. Journal of Cardiovascular Surgery, 55(3), 407-413. [15518]
Forster	2019	<100 participants	C. S. Forster, S. Goldstein, H. Pohl and E. Jackson. Association between urodynamic parameters and urine neutrophil gelatinase-associated lipocalin concentrations in children with neuropathic bladders. Journal of Pediatric Urology, 15(2), 155. [15519]
Fortova	2011	<100 participants	M. Fortova, J. Lejsek, M. Pechova and R. Prusa. Examination of urine neutrophil gelatinase-associated lipocalin following cardiac surgery in adults. Aktuality v Nefrologii, 17(4), 136-141. [15522]

Fouad	2019	<100 participants	T. R. Fouad, E. Abdelsameea, M. Elsabaawy, M. Ashraf Eljaky, S. Zaki El-shenawy and N. Omar. Urinary neutrophil gelatinase-associated lipocalin for diagnosis of spontaneous bacterial peritonitis. Tropical Doctor, . [15523]
Fouda	2013	<100 participants	M. Fouda, H. M. Sherif, M. Shehata and A. Ibrahim. Early expression of urinary neutrophil gelatinase-associated lipocalin biomarker predicts acute kidney injury complicating circulatory shock. Egyptian Journal of Critical Care Medicine, 1(2), 79-86. [15524]
Fox	2018	Not relevant type of population	E. Fox, K. Levin, Y. Zhu, B. Segers, N. Balamuth, R. Womer, R. Bagatell and F. Balis. Pantoprazole, an Inhibitor of the Organic Cation Transporter 2, Does Not Ameliorate Cisplatin-Related Ototoxicity or Nephrotoxicity in Children and Adolescents with Newly Diagnosed Osteosarcoma Treated with Methotrexate, Doxorubicin, and Cisplatin. Oncologist, 23(7), 762-e79. [15525]
Francoz	2014	Not a primary study	C. Francoz and F. Durand. Type-1 hepatorenal syndrome in patients with cirrhosis and infection vs. sepsis-induced acute kidney injury: What matters?. Journal of Hepatology, 60(5), 907-909. [15527]
Friedrich	2017	<100 participants	M. G. Friedrich, I. Bougioukas, J. Kolle, C. Bireta, F. A. Jebran, M. Placzek and T. Tirilomis. NGAL expression during cardiopulmonary bypass does not predict severity of postoperative acute kidney injury. BMC Nephrology, 18(1), 1-7. [15529]
Fuernau	2015	Not relevant biomarker assay or test	G. Fuernau, C. Poenisch, I. Eitel, D. Denks, S. de Waha, J. Poss, G. H. Heine, S. Desch, G. Schuler, V. Adams, K. Werdan, U. Zeymer and H. Thiele. Prognostic impact of established and novel renal function biomarkers in myocardial infarction with cardiogenic shock: A biomarker substudy of the IABP-SHOCK II-trial. International journal of cardiology, 191(159-66. [15531]
Gaipov	2015	<100 participants	A. Gaipov, Y. Solak, K. Turkmen, A. Toker, A. N. Baysal, H. Cicekler, Z. Biyik, F. M. Erdur, A. Kilicaslan, M. Anil, N. Gormus, H. Z. Tonbul, M. Yeksan and S. Turk. Serum uric acid may predict development of progressive acute kidney injury after open heart surgery. Renal Failure, 37(1), 96-102. [15537]
Gallagher	2015	<100 participants	S. M. Gallagher, D. A. Jones, A. Kapur, A. Wragg, S. M. Harwood, R. Mathur, R. A. Archbold, R. Uppal and M. M. Yaqoob. Remote ischemic preconditioning has a neutral effect on the incidence of kidney injury after coronary artery bypass graft surgery. Kidney International, 87(2), 473-481. [15540]
Gan	2018	Not a primary study	J. Gan and X. Zhou. Comparison of urine neutrophil gelatinase-associated lipocalin and interleukin-18 in prediction of acute kidney injury in adults. Medicine (United States), 97(39), e12570. [15541]
Garg	2017	Not a primary study	N. Garg and R. Gupta. Can Serum Neutrophil Gelatinase-Associated Lipocalin Be Precisely Used as a Diagnostic Marker of Sepsis in Pediatric Cases?. Pediatric Critical Care Medicine, 18(12), 1191-1192. [18443]

Gaspari	2010	Not relevant type of population	F. Gaspari, P. Cravedi, M. Mandala, N. Perico, F. R. De Leon, N. Stucchi, S. Ferrari, R. Labianca, G. Remuzzi and P. Ruggenenti. Predicting cisplatin-induced acute kidney injury by urinary neutrophil gelatinase-associated lipocalin excretion: A pilot prospective case-control study. Nephron - Clinical Practice, 115(2), c154-c160. [15545]
Gerbes	2011	Not a primary study	A. L. Gerbes, A. Benesic, M. Vogeser, A. Krag, F. Bendtsen and S. Moller. Serum neutrophil gelatinase-associated lipocalin - A sensitive novel marker of renal impairment in liver cirrhosis?. Digestion, 84(1), 82-83. [15551]
Ghonemy	2014	<100 participants	T. A. Ghonemy and G. M. Amro. Plasma neutrophil gelatinase-associated lipocalin (NGAL) and plasma cystatin C (CysC) as biomarker of acute kidney injury after cardiac surgery. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia, 25(3), 582-588. [15555]
Gil	2009	Not relevant type of population	H. W. Gil, J. O. Yang, E. Y. Lee and S. Y. Hong. Clinical implication of urinary neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 in patients with acute paraquat intoxication NGAL and KIM-1 in acute paraquat intoxication. Clinical Toxicology, 47(9), 870-875. [15558]
Gilquin	2017	Not relevant type of population	B. Gilquin, M. Louwagie, M. Jaquinod, A. Cez, G. Picard, L. El Kholy, B. Surin, J. Garin, M. Ferro, T. Kofman, C. Barau, E. Plaisier, P. Ronco and V. Brun. Multiplex and accurate quantification of acute kidney injury biomarker candidates in urine using Protein Standard Absolute Quantification (PSAQ) and targeted proteomics. Talanta, 164(77-84. [15560]
Gist	2017	<100 participants	K. M. Gist, S. L. Goldstein, J. Wrona, J. A. Alten, R. K. Basu, D. S. Cooper, D. E. Soranno, J. Duplantis, C. Altmann, Z. Gao and S. Faubel. Kinetics of the cell cycle arrest biomarkers (TIMP-2*IGFBP-7) for prediction of acute kidney injury in infants after cardiac surgery. Pediatric Nephrology, 32(9), 1611-1619. [15563]
Glassford	2013	Not relevant type of population	N. J. Glassford, A. G. Schneider, S. Xu, G. M. Eastwood, H. Young, L. Peck, P. Venge and R. Bellomo. The nature and discriminatory value of urinary neutrophil gelatinase-associated lipocalin in critically ill patients at risk of acute kidney injury. Intensive Care Medicine, 39(10), 1714-1724. [15566]
Gocze	2015	Not relevant type of population	I. Gocze, M. Koch, P. Renner, F. Zeman, B. M. Graf, M. H. Dahlke, M. Nerlich, H. J. Schlitt, J. A. Kellum and T. Bein. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. PLoS ONE, 10(3), e0120863. [15569]
Gocze	2017	No focus on DTA for AKI	I Göcze, D Jauch, M Götz, P Kennedy, B Jung, F Zeman, C Gnewuch, BM Graf, W Gnann, B Banas, T Bein, HJ Schlitt, T Bergler. Biomarker-guided Intervention to Prevent Acute Kidney Injury after Major Surgery. Annals of Surgery, 267(6):1013-1020. [18628]
Goknar	2014	No focus on DTA for AKI	N. Goknar, F. Oktem, I. T. Ozgen, E. Torun, M. Kucukkoc, A. D. Demir and Y. Cesur. Determination of early urinary renal injury markers in obese children. Pediatric Nephrology, 30(1), 139-144. [15570]

Goksuluk	2019	Not relevant type of population	H. Goksuluk, K. Esenboga, N. Kerimli and Y. Atmaca. The effect of renin-angiotensin system blocking agents on the risk of contrast-induced nephropathy and early detection with neutrophil gelatinase-associated lipocalin in diabetic patients undergoing coronary procedures. Acta Medica Mediterranea, 35(1), 187-192. [15571]
Goldstein	2018	<100 participants	B. H. Goldstein, S. L. Goldstein, P. Devarajan, F. Zafar, D. M. Kwiatkowski, B. S. Marino, D. L. S. Morales, C. D. Krawczeski and D. S. Cooper. First-stage palliation strategy for univentricular heart disease may impact risk for acute kidney injury. Cardiology in the Young, 28(1), 93-100. [15572]
Gomaa	2019	<100 participants	S. H. Gomaa, M. M. Shamseya and M. A. Madkour. Clinical utility of urinary neutrophil gelatinase-associated lipocalin and serum cystatin C in a cohort of liver cirrhosis patients with renal dysfunction: a challenge in the diagnosis of hepatorenal syndrome. European journal of gastroenterology & hepatology, 31(6), 692-702. [18445]
Gombert	2018	<100 participants	A. Gombert, I. Prior, L. Martin, J. Grommes, M. E. Barbati, A. C. Foldenauer, G. Schalte, G. Marx, T. Schurholz, A. Greiner, M. J. Jacobs and J. Kalder. Urine neutrophil gelatinase-associated lipocalin predicts outcome and renal failure in open and endovascular thoracic abdominal aortic aneurysm surgery. Scientific reports, 8(1), 12676. [15578]
Gombert	2019	<100 participants	A. Gombert, L. Martin, A. C. Foldenauer, C. Krajewski, A. Greiner, D. Kotelis, C. Stoppe, G. Marx, J. Grommes, T. Schuerholz, M. J. Jacobs and J. Kalder. Comparison of urine and serum neutrophil gelatinase-associated lipocalin after open and endovascular thoraco-abdominal aortic surgery and their meaning as indicators of acute kidney injury. Vasa - European Journal of Vascular Medicine, 48(1), 79-87. [15579]
Gong	2015	Non-English publication	M. Gong, Y. Yang and S. Zhang. Value of acute renal injury associated biomarkers for patients in intensive care unit. Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical sciences, 40(10), 1083-1088. [15580]
Gordillo	2016	<100 participants	R. Gordillo, T. Ahluwalia and R. Woroniecki. Hyperglycemia and acute kidney injury in critically ill children. International Journal of Nephrology and Renovascular Disease, 9(201-204. [15583]
Greenberg	2018	No relevant outcome	J. H. Greenberg, M. Zappitelli, Y. Jia, H. R. Thiessen-Philbrook, C. A. De Fontnouvelle, F. P. Wilson, S. Coca, P. Devarajan and C. R. Parikh. Biomarkers of AKI progression after pediatric cardiac surgery. Journal of the American Society of Nephrology, 29(5), 1549-1556. [15587]
Grosman-Rimon	2019	<100 participants	L. Grosman-Rimon, S. G. Hui, D. Freedman, G. Elbaz-Greener, D. Cherney and V. Rao. Biomarkers of Inflammation, Fibrosis, and Acute Kidney Injury in Patients with Heart Failure with and without Left Ventricular Assist Device Implantation. CardioRenal Medicine, 9(2), 108-116. [15592]

Gubhaju	2014	Not relevant type of population	L. Gubhaju, M. R. Sutherland, R. S. C. Horne, A. Medhurst, A. L. Kent, A. Ramsden, L. Moore, G. Singh, W. E. Hoy and M. J. Black. Assessment of renal functional maturation and injury in preterm neonates during the first month of life. American Journal of Physiology - Renal Physiology, 307(2), F149-F158. [15593]
Guerci	2018	<100 participants	P. Guerci, J. L. Claudot, E. Novy, N. Settembre, J. M. Lalot and M. R. Losser. Immediate postoperative plasma neutrophil gelatinase-associated lipocalin to predict acute kidney injury after major open abdominal aortic surgery: A prospective observational study. Anaesthesia Critical Care and Pain Medicine, 37(4), 327-334. [15594]
Guerrero-Orriach	2016	<100 participants	J. L. Guerrero-Orriach, D. Ariza-Villanueva, A. Florez-Vela, L. Garrido-Sanchez, M. I. Moreno-Cortes, M. Galan-Ortega, A. Ramirez-Fernandez, J. A. Torres, C. S. Fernandez, I. N. Arce, J. M. Melero-Tejedor, M. Rubio-Navarro and J. Cruz-Manas. Cardiac, renal, and neurological benefits of preoperative levosimendan administration in patients with right ventricular dysfunction and pulmonary hypertension undergoing cardiac surgery: Evaluation with two biomarkers neutrophil gelatinase-associated lipocalin and neuronal enolase. Therapeutics and Clinical Risk Management, 12(623-630. [15595]
Gunes	2016	<100 participants	A. Gunes, A. Ece, H. Akca, F. Aktar, S. Mete, S. Samanci, U. Uluca, V. Sen, I. Tan and I. Kaplan. Urinary kidney injury molecules in children with febrile seizures. Renal failure, 38(9), 1377-1382. [15598]
Gungor	2014	<100 participants	G. Gungor, H. Ataseven, A. Demir, Y. Solak, A. Gaipov, M. Biyik, B. Ozturk, I. Polat, A. Kiyici, O. O. Cakir and H. Polat. Neutrophil gelatinase-associated lipocalin in prediction of mortality in patients with hepatorenal syndrome: A prospective observational study. Liver International, 34(1), 49-57. [15600]
Gunnerson	2016	No relevant outcome. Subgroup analysis of already included study.	K. J. Gunnerson, A. D. Shaw, L. S. Chawla, A. Bihorac, A. Al-Khafaji, K. Kashani, M. Lissauer, J. Shi, M. G. Walker and J. A. Kellum. TIMP2*IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. Journal of Trauma and Acute Care Surgery, 80(2), 243-249. [15601]
Haase	2009	Meta-analysis - retained as background material	M. Haase, R. Bellomo, P. Devarajan, P. Schlattmann and A. Haase-Fielitz. Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis. American Journal of Kidney Diseases, 54(6), 1012-1024. [15624]
Haase	2011	Not a primary study	M. Haase, R. Bellomo and A. Haase-Fielitz. Neutrophil gelatinase-associated lipocalin: A superior biomarker for detection of subclinical acute kidney injury and poor prognosis. Biomarkers in Medicine, 5(4), 415-417. [15614]
Haase	2009	Not relevant biomarker assay or test	Haase M, Bellomo R, Devarajan P, Ma Q, Bennett MR, Möckel M, et al. . Novel biomarkers early predict the severity of acute kidney injury after cardiac surgery in adults.. Ann Thorac Surg 2009;88:124–30. https://doi.org/10.1016/j.athoracsur.2009.04.023. [15626]

Haase-Fielitz	2009	Not relevant biomarker assay or test	A. Haase-Fielitz, R. Bellomo, P. Devarajan, D. Story, G. Matalanis, D. Dragun and M. Haase. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery-A prospective cohort study. Critical Care Medicine, 37(2), 553-560. [15630]
Haase-Fielitz	2009	Not relevant biomarker assay or test	A. Haase-Fielitz, R. Bellomo, P. Devarajan, M. Bennett, D. Story, G. Matalanis, U. Frei, D. Dragun and M. Haase. The predictive performance of plasma neutrophil gelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. Nephrology Dialysis Transplantation, 24(11), 3349-3354. [15629]
Haase-Fielitz	2014	Systematic review - retained as background material	A. Haase-Fielitz, M. Haase and P. Devarajan. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: A critical evaluation of current status. Annals of Clinical Biochemistry, 51(3), 335-351. [15628]
Hahn	2017	Not a primary study	R. G. Hahn and J. Zdolsek. Nephrocheck results should be corrected for dilution. Acta anaesthesiologica Scandinavica, 61(2), 261-262. [15634]
Hall	2012	Not relevant type of population	I. E. Hall, M. D. Doshi, P. P. Reese, R. J. Marcus, H. Thiessen-Philbrook and C. R. Parikh. Association between peritransplant kidney injury biomarkers and 1-year allograft outcomes. Clinical Journal of the American Society of Nephrology, 7(8), 1224-1233. [15636]
Hall	2018	Systematic review - retained as background material	P. S. Hall, E. D. Mitchell, A. F. Smith, D. A. Cairns, M. Messenger, M. Hutchinson, J. Wright, K. Vinall-Collier, C. Corps, P. Hamilton, D. Meads and A. Lewington. The future for diagnostic tests of acute kidney injury in critical care: Evidence synthesis, care pathway analysis and research prioritisation. Health Technology Assessment, 22(32), 1-274. [15641]
Hamdy	2018	<100 participants	H. S. Hamdy, A. El-Ray, M. Salaheldin, M. Lasheen, M. Aboul-Ezz, A. S. Abdel-Moaty and A. Abdel-Rahim. Urinary neutrophil gelatinase-associated lipocalin in cirrhotic patients with acute kidney injury. Annals of Hepatology, 17(4), 624-630. [15642]
Hamishehkar	2017	Not relevant type of population	H. Hamishehkar, S. Sanaie, V. Fattahi, M. Mesgari and A. Mahmoodpoor. The effect of furosemide on the level of neutrophil gelatinase-associated lipocalin in critically hospitalized patients with acute kidney injury. Indian Journal of Critical Care Medicine, 21(7), 442-447. [15643]
Han	2009	<100 participants	W. K. Han, G. Wagener, Y. Zhu, S. Wang and H. T. Lee. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. Clinical Journal of the American Society of Nephrology, 4(5), 873-882. [15646]
Hang	2017	Not relevant biomarker assay or test	C. C. Hang, J. yang, S. Wang, C. S. Li and Z. R. Tang. Evaluation of serum neutrophil gelatinase-associated lipocalin in predicting acute kidney injury in critically ill patients. Journal of International Medical Research, 45(3), 1231-1244. [15648]
Hanna	2016	<100 participants	M. Hanna, P. D. Brophy, P. J. Giannone, M. S. Joshi, J. A. Bauer and S. Ramachandrarao. Early urinary biomarkers of acute kidney injury in preterm infants. Pediatric Research, 80(2), 218-223. [15649]
Hassan	2017	<100 participants	R. H. Hassan, S. M. Kandil, M. S. Zeid, M. E. Zaki and A. E. Fouda. Kidney injury in infants and children with iron-deficiency anemia before and after iron treatment. Hematology, 22(9), 565-570. [15654]

Hayashi	2017	<100 participants	H. Hayashi, W. Sato, T. Kosugi, K. Nishimura, D. Sugiyama, N. Asano, S. Ikematsu, K. Komori, K. Nishiwaki, K. Kadomatsu, S. Matsuo, S. Maruyama and Y. Yuzawa. Efficacy of urinary midkine as a biomarker in patients with acute kidney injury. Clinical and Experimental Nephrology, 21(4), 597-607. [15659]
Hazle	2013	<100 participants	M. A. Hazle, R. J. Gajarski, R. Aiyagari, S. Yu, A. Abraham, J. Donohue and N. B. Blatt. Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. Journal of Thoracic and Cardiovascular Surgery, 146(4), 861. [15660]
Heise	2011	<100 participants	D. Heise, K. Rentsch, A. Braeuer, M. Friedrich and M. Quintel. Comparison of urinary neutrophil glucosaminidase-associated lipocalin, cystatin C, and alpha1-microglobulin for early detection of acute renal injury after cardiac surgery. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery, 39(1), 38-43. [15661]
Heise	2011	<100 participants	D. Heise, K. Rentsch, A. Braeuer, M. Friedrich and M. Quintel. Comparison of urinary neutrophil glucosaminidase-associated lipocalin, cystatin C, and alpha1-microglobulin for early detection of acute renal injury after cardiac surgery. European Journal of Cardio-thoracic Surgery, 39(1), 38-43. [15662]
Helanova	2015	Not relevant type of population	K. Helanova, S. Littnerova, P. Kubena, E. Ganovska, M. Pavlusova, L. Kubkova, J. Jarkovsky, M. P. Goldbergova, J. Lipkova, J. Gottwaldova, P. Kala, O. Toman, M. Dastych, J. Spinar and J. Parenica. Prognostic impact of neutrophil gelatinase-associated lipocalin and B-type natriuretic in patients with ST-elevation myocardial infarction treated by primary PCI: a prospective observational cohort study. Bmj Open, 5(10), e006872-e006872. [18456]
Herbert	2015	No focus on DTA for AKI	C. Herbert, M. Patel, A. Nugent, V. V. Dimas, K. J. Guleserian, R. Quigley and V. Modem. Serum Cystatin C as an Early Marker of Neutrophil Gelatinase-associated Lipocalin-positive Acute Kidney Injury Resulting from Cardiopulmonary Bypass in Infants with Congenital Heart Disease. Congenital Heart Disease, 10(4), E180-E188. [15667]
Heung	2016	No relevant outcome. Subgroup analysis of already included study.	M. Heung, L. M. Ortega, L. S. Chawla, R. G. Wunderink, W. H. Self, J. L. Koyner, J. Shi and J. A. Kellum. Common chronic conditions do not affect performance of cell cycle arrest biomarkers for risk stratification of acute kidney injury. Nephrology Dialysis Transplantation, 31(10), 1633-1640. [15671]
Heydari	2017	<100 participants	B. Heydari, H. Khalili, M. T. Beigmohammadi, A. Abdollahi and I. Karimzadeh. Effects of atorvastatin on biomarkers of acute kidney injury in amikacin recipients: A pilot, randomized, placebo-controlled, clinical trial. Journal of Research in Medical Sciences, 22(1), 39. [15672]

Hinck	2018	<100 participants	B. D. Hinck, R. Miyaoka, J. E. Lingeman, D. G. Assimos, B. R. Matlaga, R. Pramanik, J. Asplin, B. Cohen and M. Monga. Urine kidney injury markers do not increase following gastric bypass: a multi-center cross-sectional study. The Canadian journal of urology, 25(1), 9199-9204. [15674]
Hirsch	2013	Not relevant type of population	R. Hirsch, C. Dent, H. Pfriem, J. Allen, R. H. Beekman, 3rd, Q. Ma, S. Dastrala, M. Bennett, M. Mitsnefes and P. Devarajan. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatric Nephrology, 22(12), 2089-95. [4009]
Hjortrup	2013	Systematic review - retained as background material	P. B. Hjortrup, N. Haase, M. Wetterslev and A. Perner. Clinical review: Predictive value of neutrophil gelatinase-associated lipocalin for acute kidney injury in intensive care patients. Critical Care, 17(2), 211. [15677]
Ho	2009	<100 participants	J. Ho, M. Lucy, O. Krokhin, K. Hayglass, E. Pascoe, G. Darroch, D. Rush, P. Nickerson, C. Rigatto and M. Reslerova. Mass Spectrometry-Based Proteomic Analysis of Urine in Acute Kidney Injury Following Cardiopulmonary Bypass: A Nested Case-Control Study. American Journal of Kidney Diseases, 53(4), 584-595. [15683]
Ho	2015	Meta-analysis - retained as background material	J. Ho, N. Tangri, P. Komenda, A. Kaushal, M. Sood, R. Brar, K. Gill, S. Walker, K. Macdonald, B. M. Hiebert, R. C. Arora and C. Rigatto. Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: A meta-analysis. American Journal of Kidney Diseases, 66(6), 993-1005. [15679]
Hodgson	2019	<100 participants	L. E. Hodgson, R. M. Venn, S. Short, P. J. Roderick, D. Hargreaves, N. Selby and L. G. Forni. Improving clinical prediction rules in acute kidney injury with the use of biomarkers of cell cycle arrest: a pilot study. Biomarkers, 24(1), 23-28. [15685]
Hoffman	2013	<100 participants	S. B. Hoffman, A. N. Massaro, A. A. Soler-Garcia, S. Perazzo and P. E. Ray. A novel urinary biomarker profile to identify acute kidney injury (AKI) in critically ill neonates: A pilot study. Pediatric Nephrology, 28(11), 2179-2188. [15686]
Holderied	2018	Not relevant type of population	A. Holderied. IGFBP7/TIMP-2 based prevention of acute kidney injury: Does "time is nephron" apply in AKI?. Nephrologe, 13(3), 192-194. [15687]
Hollmen	2011	Not a primary study	M. Hollmen. Diagnostic test for early detection of acute kidney injury. Expert Review of Molecular Diagnostics, 11(6), 553-555. [15688]
Holzscheiter	2014	Not relevant type of population	L. Holzscheiter, C. Beck, S. Rutz, E. Manuilova, I. Domke, W. G. Guder and W. Hofmann. NGAL, L-FABP, and KIM-1 in comparison to established markers of renal dysfunction. Clinical Chemistry and Laboratory Medicine, 52(4), 537-546. [18461]
Hong	2013	<100 participants	D. Y. Hong, J. H. Lee, S. O. Park, K. J. Baek and K. R. Lee. Plasma neutrophil gelatinase-associated lipocalin as early biomarker for acute kidney injury in burn patients. Journal of Burn Care and Research, 34(6), e326-e332. [15694]

Honore	2016	No relevant outcome. Subgroup analysis of already included study.	P. M. Honore, H. B. Nguyen, M. Gong, L. S. Chawla, S. M. Bagshaw, A. Artigas, J. Shi, O. Joannes-Boyau, J. L. Vincent and J. A. Kellum. Urinary Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 for Risk Stratification of Acute Kidney Injury in Patients with Sepsis. Critical Care Medicine, 44(10), 1851-1860. [15695]
Honore	2016	Not a primary study	P. M. Honore and H. D. Spapen. Neutrophil gelatinase-associated lipocalin elimination by renal replacement therapy: Minding the membrane!. Critical Care, 20(1), 87. [15696]
Hoskova	2013	<100 participants	L. Hoskova, J. Franekova, I. Malek, P. Secnik Jr, J. Pirk, J. Kautzner, O. Szarszoi and A. Jabor. Relationship of cardiorenal biomarkers for prediction of renal dysfunction in patients after heart transplantation. Cor et Vasa, 55(4), E364-E369. [15707]
Hoskova	2016	No relevant outcome	L. Hoskova, J. Franekova, I. Malek, J. Kautzner, O. Szarszoi, A. Jabor, M. Pindak, O. Viklicky and V. Melenovsky. Comparison of cystatin C and NGAL in early diagnosis of acute kidney injury after heart transplantation. Annals of Transplantation, 21(239-245. [15706]
Hosohata	2016	<100 participants	K. Hosohata, S. Washino, T. Kubo, S. Natsui, A. Fujisaki, S. Kurokawa, H. Ando, A. Fujimura and T. Morita. Early prediction of cisplatin-induced nephrotoxicity by urinary vanin-1 in patients with urothelial carcinoma. Toxicology, 359-360(71-5. [15709]
Hoste	2018	Not a primary study	E. A. Hoste and W. Vandenberghe. Plasma neutrophil gelatinase-associated lipocalin (NGAL) for timing of initiation of renal replacement therapy for acute kidney injury?. Journal of Thoracic Disease, 10(Supplement33), S3989-S3993. [15710]
Howell	2015	<100 participants	E. Howell, S. Sen, T. Palmieri, Z. Godwin, J. Bockhold, D. Greenhalgh and N. K. Tran. Point-of-care B-type natriuretic peptide and neutrophil gelatinase-Associated lipocalin measurements for acute resuscitation: A pilot study. Journal of Burn Care and Research, 36(2 Supplement 2)), e26-e33. [15714]
Hryniewiecka	2014	No focus on DTA for AKI	E. Hryniewiecka, K. Gala, M. Krawczyk and L. Paczek. Is neutrophil gelatinase-associated lipocalin an optimal marker of renal function and injury in liver transplant recipients?. Transplantation Proceedings, 46(8), 2782-2785. [15715]
Hsiao	2012	<100 participants	P. G. Hsiao, C. A. Hsieh, C. F. Yeh, H. H. Wu, T. F. Shiu, Y. C. Chen and P. H. Chu. Early prediction of acute kidney injury in patients with acute myocardial injury. Journal of Critical Care, 27(5), 525. [15716]
Hsu	2012	Not a primary study	R. K. Hsu and C. Y. Hsu. We can diagnose AKI "early". Clinical Journal of the American Society of Nephrology, 7(11), 1741-1742. [15718]
Huang	2016	<100 participants	C. Y. Huang, C. C. Shih, K. Chung, K. C. Kao and H. P. Wu. Predictive value of plasma neutrophil gelatinase-associated lipocalin for acute renal failure in patients with severe sepsis. Journal of the Chinese Medical Association, 79(8), 428-434. [15722]

Huelin	2019	Not relevant type of population	P. Huelin, E. Sola, C. Elia, C. Sole, A. Risso, R. Moreira, M. Carol, N. Fabrellas, O. Bassegoda, A. Juanola, G. de Prada, S. Albertos, S. Piano, I. Graupera, X. Ariza, L. Napoleone, E. Pose, X. Filella, M. Morales-Ruiz, J. Rios, J. Fernandez, W. Jimenez, E. Poch, F. Torres and P. Gines. Neutrophil Gelatinase-Associated Lipocalin for Assessment of Acute Kidney Injury in Cirrhosis: A Prospective Study. Hepatology, . [15727]
Hui-Miao	2017	Meta-analysis - retained as background material	J. Hui-Miao, H. Li-Feng, Y. Zheng, L. Wen-Xiong, H.-M. Jia, L.-F. Huang, Y. Zheng and W.-X. Li. Diagnostic value of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for acute kidney injury: a meta-analysis. Critical Care, 21(1-11. [6130]
Hunsicker	2017	<100 participants	O. Hunsicker, A. Feldheiser, A. Weimann, D. Liehre, J. Sehouli, K. D. Wernecke and C. Spies. Diagnostic value of plasma NGAL and intraoperative diuresis for AKI after major gynecological surgery in patients treated within an intraoperative goal-directed hemodynamic algorithm. Medicine (United States), 96(28), e7357. [15729]
Hur	2014	Not relevant biomarker assay or test	M. Hur, H. Kim, S. Lee, F. Cristofano, L. Magrini, R. Marino, C. S. Gori, C. Bongiovanni, B. Zancla, P. Cardelli and S. Di Somma. Diagnostic and prognostic utilities of multimarkers approach using procalcitonin, B-type natriuretic peptide, and neutrophil gelatinase-associated lipocalin in critically ill patients with suspected sepsis. Bmc Infectious Diseases, 14(224-224. [18468]
Hurry	2017	<100 participants	P. K. Hurry, J. H. Poulsen, F. Bendtsen and S. Moller. Neutrophil gelatinase-associated lipocalin and cystatin C in cirrhosis and portal hypertension: Relations to organ extraction and dysfunction. Journal of gastroenterology and hepatology, 32(2), 473-481. [18469]
Hwang	2014	<100 participants	Y. J. Hwang, M. C. Hyun, B. S. Choi, S. Y. Chun and M. H. Cho. Acute kidney injury after using contrast during cardiac catheterization in children with heart disease. Journal of Korean medical science, 29(8), 1102-1107. [15733]
Ibrahim	2019	<100 participants	M. E. Ibrahim, C. Chang, Y. Hu, S. L. Hogan, N. Mercke, M. Gomez, C. L. O'Bryant, D. W. Bowles, B. George, X. Wen, B. Buckley, L. Aleksunes and M. S. Joy. Pharmacokinetic determinants of cisplatin-induced subclinical kidney injury in oncology patients. European Journal of Clinical Pharmacology, 75(1), 51-57. [15734]
Iguchi	2012	<100 participants	N. Iguchi, A. Uchiyama, K. Hosotsubo and Y. Fujino. Plasma neutrophil gelatinase-associated lipocalin clearance during venovenous hemodiafiltration. Clinical and experimental nephrology, 16(2), 356-7. [15735]
Iguchi	2015	<100 participants	N. Iguchi, A. Uchiyama, K. Ueta, Y. Sawa and Y. Fujino. Neutrophil gelatinase-associated lipocalin and liver-type fatty acid-binding protein as biomarkers for acute kidney injury after organ transplantation. Journal of Anesthesia, 29(2), 249-255. [15736]
In	2014	Not relevant type of population	J. W. In, J. E. Kim, J. S. Jeong, S. H. Song and H. K. Kim. Diagnostic and prognostic significance of neutrophil gelatinase-associated lipocalin in disseminated intravascular coagulation. Clinica Chimica Acta, 430(145-149. [15739]

Innami	2014	<100 participants	Y. Innami, N. Katori, K. Mori, S. Kosugi, T. Suzuki, N. Sakurai, H. Nagata, J. Takeda and H. Morisaki. Increased prothrombotic property as a risk factor of acute kidney injury after surgical repair of abdominal aortic aneurysm: A prospective observational study. Journal of Intensive Care, 2(1), 46. [15740]
Introcaso	2018	<100 participants	G. Introcaso, M. Nafi, A. Bonomi, C. L'Acqua, L. Salvi, R. Ceriani, D. Carcione, A. Cattaneo and M. T. Sandri. Improvement of neutrophil gelatinase-associated lipocalin sensitivity and specificity by two plasma measurements in predicting acute kidney injury aftecardiac surgery. Biochemia Medica, 28(3), 030701. [15741]
Isikkent	2018	<100 participants	A. Isikkent, S. Yilmaz, I. U. Ozturan, N. O. Dogan, E. Yaka, H. Gultekin, T. Kum and M. Pekdemir. Utility of neutrophil celatinase-associated lipocalin in the management of acute kidney injury: A prospective, observational study. Hong Kong Journal of Emergency Medicine, . [15743]
Isler	2018	<100 participants	Y. Isler, S. Ozdinc and H. Kaya. Can ngal be used as an early marker of contrast-induced nephropathy in emergency department. Acta Medica Mediterranea, 34(6), 1889-1894. [15744]
Ismail	2012	<100 participants	G. Ismail, R. Bobeica, S. Ioanitescu and R. Jurubita. Association of serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels with disease severity in patients with early-stage autosomal dominant polycystic kidney disease. Revista Romana De Medicina De Laborator, 20(2), 109-116. [18471]
Isshiki	2016	No relevant outcome	R. Isshiki, T. Asada, D. Sato, M. Sumida, Y. Hamasaki, R. Inokuchi, T. Matsubara, T. Ishii, N. Yahagi, M. Nangaku, E. Noiri and K. Doi. Association of Urinary Neutrophil Gelatinase-Associated Lipocalin with Long-Term Renal Outcomes in ICU Survivors: A Retrospective Observational Cohort Study. Shock, 46(1), 44-51. [15746]

Itenov	2014	No focus on DTA for AKI	T. S. Itenov, K. Bangert, P. H. Christensen, J. U. Jensen, M. H. Bestle, M. L. Jakobsen, S. S. Reilev, M. Kofoed-Djursner, M. B. Rasmussen, C. S. V. Hallas, M. Zacho, J. Iversen, T. Leerbeck, M. Jeppesen, K. S. Hansen, K. B. Jensen, J. D. Knudsen, A. Friis-Moller, K. Schonning, A. Lester, H. Westh, G. Lisby, J. K. Moller, B. Bruun, J. J. Christensen, M. Arpi, K. Astvad, M. D. Bartels, J. Engberg, H. Fjeldsoe-Nielsen, U. S. Jensen, L. Hein, T. Mohr, D. G. Strange, P. L. Petersen, A. O. Lauritsen, S. Hougaard, T. Mantoni, L. Nebrich, A. Bendtsen, L. H. Andersen, F. Baerentzen, A. Eversbusch, B. Bomler, R. Martusevicius, T. Nielsen, BadstolokkenP.M, C. Maschmann, P. Hallas, A. Lindhardt, T. Galle, K. Graeser, E. Hohwu-Christensen, P. Gregersen, H. C. Boesen, L. M. Pedersen, K. Thiesen, L. C. Hallengreen, I. Rye, J. Cordtz, K. R. Madsen, P. R. C. Kirkegaard, L. Findsen, L. H. Nielsen, D. H. Pedersen, J. H. Andersen, C. Albrechtsen, A. Jacobsen, T. Jansen, A. G. Jensen, H. H. Jorgensen, M. Vazin, L. Lipsius, K. Thornberg, J. Nielsen, K. Thormar, M. Skielboe, B. Thage, C. Thoft, M. Uldbjerg, E. Anderlo, M. Engsig, F. Hani, R. B. Jacobsen, L. Mulla, U. Skram, H. Tousi, P. Soe-Jensen, T. Waldau, T. Faber, B. Andersen, I. Gillesberg, A. Christensen, C. Hartmann, R. Albret, D. S. Dinesen, K. Gani, M. Ibsen, N. G. Holler, J. Loken, M. Steensen, J. A. Petersen, P. Carl, E. Gade, D. Solevad, C. Heiring, M. Jorgensen, K. Ekelund, A. Afshari, N. Hammer, M. Bitsch, J. S. Hansen, C. Wamberg, T. D. Clausen, R. Winkel, J. Huusom, D. L. Buck, U. Grevstad, E. Aasvang, K. Lenz, P. Mellado, H. Karacan, J. Hidestal, J. Hogagard, J. Hojbjerg, J. Hojlund, M. Johansen, S. Strande, M. Bestle, S. Hestad, M. Ostergaard, N. Wesche, S. A. Nielsen, H. Christensen, H. Blom, C. H. Jensen, K. Nielsen, I. B. Jensen, K. A. Jeppesen, M. H. Andersen, P. Fjeldborg, A. Vestergaard, O. Viborg, C. D. Rossau, N. Reiter, M. Glaeemose, M. B. Wraner, C. B. Thomsen, B. Rasmussen, C. Lund-Rasmussen, B. Bech, K. Bjerregaard, L. Spliid, L. L. W. Nielsen, N. E. Drenck, K. M. Larsen, M. Goldinger, D. Illum, C. Jessen, A. Christiansen, A. Berg, T. Elkmann, J. A. K. Pedersen, M. Simonsen, H. Joensen, H. Alstrom, C. Svane and A. Engquist. Serum and Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL) Levels are Not Equivalent in Patients Admitted to Intensive Care. Journal of Clinical Laboratory Analysis, 28(2), 163-167. [15748]
Izadi	2016	Systematic review - retained as background material	A. Izadi, M. Yousefifard, B. Nakhjavan-Shahraki, M. Baikpour, J. M. Razaz, N. Ataei and M. Hosseini. Value of Plasma/Serum Neutrophil Gelatinase-Associated Lipocalin in Detection of Pediatric Acute Kidney Injury; a Systematic Review and Meta-Analysis. International Journal of Pediatrics-Mashhad, 4(11), 3815-3836. [18472]

Jafari	2018	<100 participants	M. Jafari, S. Ala, K. Haddadi, A. Alipour, M. Mojtahedzadeh, S. Ehteshami, S. Abediankenari, M. Shafizad, E. Salehifar and F. Khalili. Cotreatment with furosemide and hypertonic saline decreases serum neutrophil gelatinase-associated lipocalin (NGAL) and serum creatinine concentrations in traumatic brain injury: A randomized, single-blind clinical trial. Iranian Journal of Pharmaceutical Research, 17(3), 1130-1140. [15753]
Jahnukainen	2018	<100 participants	T. Jahnukainen, J. Keski-Nisula, J. Tainio, H. Valkonen, T. Patila, H. Jalanko and P. Suominen. Efficacy of corticosteroids in prevention of acute kidney injury in neonates undergoing cardiac surgery-A randomized controlled trial. Acta Anaesthesiologica Scandinavica, 62(8), 1072-1079. [15755]
Jain	2016	<100 participants	V. Jain, Y. Mehta, A. Gupta, R. Sharma, A. Raizada and N. Trehan. The role of neutrophil gelatinase-associated lipocalin in predicting acute kidney injury in patients undergoing off-pump coronary artery bypass graft: A pilot study. Annals of Cardiac Anaesthesia, 19(2), 225-230. [15756]
Jayaraman	2014	Not relevant biomarker assay or test	R. Jayaraman, S. Sunder, S. Sathi, V. K. Gupta, N. Sharma, P. Kanchi, A. Gupta, S. K. Daksh, P. Ram and A. Mohamed. Post cardiac surgery acute kidney injury: A woebegone status rejuvenated by the novel biomarkers. Iranian Red Crescent Medical Journal, 16(7), e19598. [15763]
Jelinek	2018	Not relevant type of population	M. J. Jelinek, S. M. Lee, A. Wyche Okpareke, C. Wing, J. L. Koyner, P. T. Murray, W. M. Stadler and O. D. P.H. Predicting Acute Renal Injury in Cancer Patients Receiving Cisplatin Using Urinary Neutrophil Gelatinase-Associated Lipocalin and Cystatin C. Clinical and Translational Science, 11(4), 420-427. [15766]
Jeong	2012	<100 participants	T. D. Jeong, S. Kim, W. Lee, G. W. Song, Y. K. Kim, S. Chun, S. G. Lee and W. K. Min. Neutrophil gelatinase-associated lipocalin as an early biomarker of acute kidney injury in liver transplantation. Clinical Transplantation, 26(5), 775-781. [15768]
Je-Yeob	2013	Not relevant biomarker assay or test	L. E. E. Je-Yeob, K. I. M. Jin-Young, O. P. Sang, L. E. E. Kyeong-Ryong, B. Kwang-Je and H. Dae-Young. Plasma Neutrophil Gelatinase-associated Lipocalin is an Early Marker of Acute Kidney Injury. Journal of the Korean Society of Emergency Medicine, 157-163. [6172]
Jia	2017	Meta-analysis - retained as background material	H. M. Jia, L. F. Huang, Y. Zheng and W. X. Li. Diagnostic value of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for acute kidney injury: A meta-analysis. Critical Care, 21(1), 77. [15773]
Jia	2017	Meta-analysis - retained as background material	H. M. Jia, L. F. Huang, Y. Zheng and W. X. Li. Prognostic value of cell cycle arrest biomarkers in patients at high risk for acute kidney injury: A systematic review and meta-analysis. Nephrology, 22(11), 831-837. [15772]
Jiang	2015	Not relevant type of population	L. Jiang and H. Cui. Could Blood Neutrophil Gelatinase-Associated Lipocalin (NGAL) be a Diagnostic Marker for Acute Kidney Injury in Neonates? A Systemic Review and Meta-Analysis. Clinical laboratory, 61(12), 1815-1820. [15774]

Jiang	2018	No relevant outcome	Q. Q. Jiang, M. F. Han, K. Ma, G. Chen, X. Y. Wan, S. B. Kilonzo, W. Y. Wu, Y. L. Wang, J. You and Q. Ning. Acute kidney injury in acute-on-chronic liver failure is different from in decompensated cirrhosis. World Journal of Gastroenterology, 24(21), 2300-2310. [15775]
Joannes-Boyau	2012	Not a primary study	O. Joannes-Boyau and J. Fichet. NGAL and sepsis. Annales Francaises D Anesthesie Et De Reanimation, 31(8-9. [18476]
Jobs	2014	<100 participants	K. Jobs, E. Straz-Zebrowska, M. Placzynska, R. Zdanowski, B. Kalicki, S. Lewicki and A. Jung. Interleukin-18 and NGAL in assessment of ESWL treatment safety in children with urolithiasis. Central European Journal of Immunology, 39(3), 384-391. [15778]
Jochmans	2017	<100 participants	I. Jochmans, N. Meurisse, A. Neyrinck, M. Verhaegen, D. Monbaliu and J. Pirenne. Hepatic ischemia/reperfusion injury associates with acute kidney injury in liver transplantation: Prospective cohort study. Liver Transplantation, 23(5), 634-644. [15780]
Journois	2013	Not a primary study	D. Journois and L. Jacob. [NGAL more or less than a biomarker?]. NGAL plus ou moins qu'un biomarqueur ?, 32(3), 134-5. [15785]
Jungbauer	2011	No focus on DTA for AKI	C. G. Jungbauer, C. Birner, B. Jung, S. Buchner, M. Lubnow, C. Von Bary, D. Endemann, B. Banas, K. M. Mac, C. A. Boger, G. Riegger and A. Luchner. Kidney injury molecule-1 and N-acetyl-s-d-glucosaminidase in chronic heart failure: Possible biomarkers of cardiorenal syndrome. European Journal of Heart Failure, 13(10), 1104-1110. [15788]
Kaddourah	2016	<100 participants	A. Kaddourah, S. L. Goldstein, R. Basu, E. J. Nehus, T. C. Terrell, L. Brunner, M. R. Bennett, C. Haffner and J. L. Jefferies. Novel urinary tubular injury markers reveal an evidence of underlying kidney injury in children with reduced left ventricular systolic function: a pilot study. Pediatric nephrology (Berlin, Germany), 31(10), 1637-45. [15791]
Kafkas	2012	Not relevant type of population	N. Kafkas, C. Demponeras, F. Zouboulloglou, L. Spanou, D. Babalis and K. Makris. Serum levels of gelatinase associated lipocalin as indicator of the inflammatory status in coronary artery disease. International journal of inflammation, . [4711]
Kafkas	2016	Not relevant type of population	N. Kafkas, C. Liakos, F. Zouboulloglou, O. Dagadaki, S. Dragasis and K. Makris. Neutrophil Gelatinase-Associated Lipocalin as an Early Marker of Contrast-Induced Nephropathy After Elective Invasive Cardiac Procedures. Clinical Cardiology, 39(8), 464-470. [15792]
Kahli	2014	<100 participants	A. Kahli, C. Guenancia, M. Zeller, S. Grosjean, K. Stamboul, L. Rochette, C. Girard and C. Vergely. Growth Differentiation Factor-15 (GDF-15) levels are associated with cardiac and renal injury in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. PLoS ONE, 9(8), e105759. [15793]
Kalisnik	2017	<100 participants	J. M. Kalisnik, E. Hrovat, A. Hrastovec, J. Zibert, A. Jerin, M. Skitek, G. Santarpino and T. Klokocovnik. Creatinine, Neutrophil Gelatinase-Associated Lipocalin, and Cystatin C in Determining Acute Kidney Injury After Heart Operations Using Cardiopulmonary Bypass. Artificial Organs, 41(5), 481-489. [15796]

Kalisnik	2017	Not a primary study	J. M. Kalisnik, T. Fischlein and G. Santarpino. Cardiac surgery-associated neutrophil gelatinase-associated lipocalin score for postoperative acute kidney injury: What is the clinical implication?. Journal of Thoracic and Cardiovascular Surgery, 154(3), 938. [15797]
Kambhampat	2013	Not relevant biomarker assay or test	G. Kambhampat, N. I. Ejaz, A. Asmar, R. Aiyer, A. A. Arif, N. Pourafshar, V. R. Yalamanchili and A. Ahsan Ejaz. Fluid balance and conventional and novel biomarkers of acute kidney injury in cardiovascular surgery. Journal of Cardiovascular Surgery, 54(5), 639-646. [15798]
Kamis	2016	Not relevant biomarker assay or test	F. Kamis, I. Yegenaga, M. Musul, C. Baydemir, S. Bek, B. Kalender and N. Baykara. Neutrophil gelatinase-associated lipocalin levels during the first 48 hours of intensive care may indicate upcoming acute kidney injury. Journal of Critical Care, 34(89-94. [15802]
Kanchi	2017	<100 participants	M. Kanchi, R. Manjunath, J. Massen, L. Vincent and K. Belani. Neutrophil gelatinase-associated lipocalin as a biomarker for predicting acute kidney injury during off-pump coronary artery bypass grafting. Annals of Cardiac Anaesthesia, 20(3), 297-302. [15804]
Kandil	2017	<100 participants	M. A. Kandil, K. M. Abouelenain, A. Alsebaey, H. S. Rashed, M. H. Afifi, M. A. Mahmoud and K. A. Yassen. Impact of terlipressin infusion during and after live donor liver transplantation on incidence of acute kidney injury and neutrophil gelatinase-associated lipocalin serum levels: A randomized controlled trial. Clinical Transplantation, 31(8), e13019. [15805]
Kandur	2016	<100 participants	Y. Kandur, S. Gonen, K. Fidan and O. Soylemezoglu. Evaluation of urinary KIM-1, NGAL, and IL-18 levels in determining early renal injury in pediatric cases with hypercalciuria and/or renal calculi. Clinical Nephrology, 86(2), 62-69. [15806]
Karademir	2016	<100 participants	L. D. Karademir, F. Dogruel, I. Kocyigit, C. Yazici, A. Unal, M. H. Sipahioglu, O. Oymak and B. Tokgoz. The efficacy of theophylline in preventing cisplatin-related nephrotoxicity in patients with cancer. Renal Failure, 38(5), 806-814. [15810]
Karadeniz	2019	<100 participants	M. S. Karadeniz, I. A. EniÅŸte, H. Å. r. Ã‡iftÃ§i, S. Usta, T. Tefik, Ã. n. ÅžanlÄ±, K. Pembeci and K. M. TuÄŸrul. Neutrophil Gelatinase-associated Lipocalin Significantly Correlates with Ischemic Damage in Patients Undergoing Laparoscopic Partial Nephrectomy. Balkan Medical Journal, 36(2), 121-128. [6131]
Karaolanis	2015	<100 participants	G. Karaolanis, A. Katsaros, V. V. Palla, S. Lionaki, D. Moris, E. Karanikola, M. Kravaritou, V. Drossos, T. Psarros, K. Triantafillou, N. Aleksandropoulos and G. Zografos. Urine NGAL as a biomarker of kidney damage after on- and off-pump coronary artery bypass graft surgery: A prospective pilot study. Hellenic Journal of Cardiology, 56(2), 160-168. [15814]
Kardakos	2014	<100 participants	I. S. Kardakos, D. I. Volanis, A. Kalikaki, V. P. Tzortzis, E. N. Serafetinides, M. D. Melekos and D. S. Delakas. Evaluation of Neutrophil Gelatinase-associated Lipocalin, Interleukin-18, and Cystatin C as Molecular Markers Before and After Unilateral Shock Wave Lithotripsy. Urology, 84(4), 783-788. [18482]

Kardakos	2014	<100 participants	I. S. Kardakos, D. I. Volanis, A. Kalikaki, V. P. Tzortzis, E. N. Serafetinides, M. D. Melekos and D. S. Delakas. Evaluation of neutrophil gelatinase-associated lipocalin, interleukin-18, and cystatin C as molecular markers before and after unilateral shock wave lithotripsy. Urology, 84(4), 783-788. [6132]
Kari	2018	<100 participants	J. A. Kari, M. A. Shalaby, K. Sofyani, A. S. Sanad, A. F. Ossra, R. S. Halabi, M. H. Aljuhani, W. M. Toffaha, F. A. Moria, S. Sabry, H. A. A. Ahmed, K. A. Alhasan, S. Sharief and O. Safdar. Urinary neutrophil gelatinase-associated lipocalin (NGAL) and serum cystatin C measurements for early diagnosis of acute kidney injury in children admitted to PICU. World Journal of Pediatrics, 14(2), 134-142. [15815]
Karimzadeh	2017	<100 participants	I. Karimzadeh, M. Heydari, M. Ramzi, M. M. Sagheb and K. Zomorodian. Urinary neutrophil gelatinase-associated lipocalin as a biomarker of kidney injury in hematologic-oncologic patients receiving amphotericin B. Iranian Journal of Kidney Diseases, 11(3), 201-208. [15816]
Katagiri	2012	<100 participants	D. Katagiri, K. Doi, K. Honda, K. Negishi, T. Fujita, M. Hisagi, M. Ono, T. Matsubara, N. Yahagi, M. Iwagami, T. Ohtake, S. Kobayashi, T. Sugaya and E. Noiri. Combination of two urinary biomarkers predicts acute kidney injury after adult cardiac surgery. Annals of Thoracic Surgery, 93(2), 577-583. [15825]
Katagiri	2013	Not relevant biomarker assay or test	D. Katagiri, K. Doi, T. Matsubara, K. Negishi, Y. Hamasaki, K. Nakamura, T. Ishii, N. Yahagi and E. Noiri. New biomarker panel of plasma neutrophil gelatinase-associated lipocalin and endotoxin activity assay for detecting sepsis in acute kidney injury. Journal of Critical Care, 28(5), 564-570. [15824]
Katagiri	2016	No relevant outcome	M. Katagiri, M. Takahashi, K. Doi, M. Myojo, A. Kiyosue, J. Ando, Y. Hirata and I. Komuro. Serum neutrophil gelatinase-associated lipocalin concentration reflects severity of coronary artery disease in patients without heart failure and chronic kidney disease. Heart and Vessels, 31(10), 1595-1602. [15826]
Kesik	2015	<100 participants	V. Kesik, E. Demirkaya and M. Buyukpamukcu. Urinary neutrophil gelatinase associated lipocalin as a biomarker in ifosfamide induced chronic renal failure. European Review for Medical and Pharmacological Sciences, 19(24), 4851-4857. [15836]
Khan	2014	No relevant outcome	U. A. Khan, S. G. Coca, K. Hong, J. L. Koyner, A. X. Garg, C. S. Passik, M. Swaminathan, S. Garwood, U. D. Patel, S. Hashim, M. A. Quantz and C. R. Parikh. Blood transfusions are associated with urinary biomarkers of kidney injury in cardiac surgery. Journal of Thoracic and Cardiovascular Surgery, 148(2), 726-732. [15840]
Khan	2014	<100 participants	M. Khan, N. Choudhry, M. F. U. Haq, Shahjahan, S. Mahmood, S. Sarmad and R. Yasmin. Evaluation of neutrophil gelatinase associated lipocalin, as a biomarker of renal injury in type 2 diabetic patients. Pakistan Journal of Medical and Health Sciences, 8(3), 612-615. [15839]
Khatami	2015	Not relevant type of population	M. R. Khatami, M. R. P. Sabbagh, N. Nikravan, Z. Khazaeipour, M. A. Boroumand, S. Sadeghian and B. Davoudi. The role of neutrophil-gelatinase-associated lipocalin in early diagnosis of contrast nephropathy. Indian Journal of Nephrology, 25(5), 292-296. [15841]

Khawaja	2019	<100 participants	S. Khawaja, L. Jafri, I. Siddiqui, M. Hashmi and F. Ghani. The utility of neutrophil gelatinase-associated Lipocalin (NGAL) as a marker of acute kidney injury (AKI) in critically ill patients. Biomarker Research, 7(1), 4. [15842]
Khosravi	2013	<100 participants	M. B. Khosravi, S. Milani and F. Kakaei. Serum neutrophil gelatinase-associated lipocalin versus serum creatinine for the prediction of acute kidney injury after liver transplantation. International Journal of Organ Transplantation Medicine, 4(3), 102-109. [15843]
Kidher	2014	<100 participants	E. Kidher, L. Harling, H. Ashrafian, H. Naase, A. Chukwuemeka, J. Anderson, D. P. Francis and T. Athanasiou. Pulse wave velocity and neutrophil gelatinase-associated lipocalin as predictors of acute kidney injury following aortic valve replacement. Journal of cardiothoracic surgery, 9(1), 89. [15844]
Kift	2013	<100 participants	R. L. Kift, M. P. Messenger, T. C. Wind, S. Hepburn, M. Wilson, D. Thompson, M. W. Smith, C. Sturgeon, A. J. Lewington, P. J. Selby and R. E. Banks. A comparison of the analytical performance of five commercially available assays for neutrophil gelatinase-associated lipocalin using urine. Annals of Clinical Biochemistry, 50(3), 236-244. [15845]
Kil	2018	<100 participants	H. K. Kil, J. Y. Kim, Y. D. Choi, H. S. Lee, T. K. Kim and J. E. Kim. Effect of combined treatment of ketorolac and remote Ischemic preconditioning on renal ischemia-reperfusion injury in patients undergoing partial nephrectomy: Pilot study. Journal of Clinical Medicine, 7(12), 470. [15846]
Kim	2011	<100 participants	T. Kim, G. J. Arnaoutakis, A. Bihorac, T. D. Martin, P. J. Hess Jr, C. T. Klodell, C. G. Tribble, A. A. Ejaz, L. L. Moldawer and T. M. Beaver. Early blood biomarkers predict organ injury and resource utilization following complex cardiac surgery. Journal of Surgical Research, 168(2), 168-172. [15859]
Kim	2013	Not relevant biomarker assay or test	H. Kim, M. Hur, D. N. Cruz, H. W. Moon and Y. M. Yun. Plasma neutrophil gelatinase-associated lipocalin as a biomarker for acute kidney injury in critically ill patients with suspected sepsis. Clinical Biochemistry, 46(15), 1414-1418. [15850]
Kim	2013	Not relevant type of population	S. M. Kim, J. S. Park, E. R. Norwitz, H. J. Jung, B. J. Kim, C. W. Park and J. K. Jun. Circulating levels of neutrophil gelatinase-associated lipocalin (NGAL) correlate with the presence and severity of preeclampsia. Reproductive Sciences, 20(9), 1083-1089. [15858]
Kim	2014	No focus on DTA for AKI	B. H. Kim, N. Yu, H. R. Kim, K. W. Yun, I. S. Lim, T. H. Kim and M.-K. Lee. Evaluation of the Optimal Neutrophil Gelatinase-Associated Lipocalin Value as a Screening Biomarker for Urinary Tract Infections in Children. Annals of Laboratory Medicine, 34(5), 354-359. [18485]
Kim	2014	<100 participants	J. D. Kim, H. K. Chee, J. K. Shin, J. S. Kim, S. A. Lee, Y. H. Kim, W. S. Lee and H. Y. Kim. Novel Early Predictor of Acute Kidney Injury after Open Heart Surgery under Cadiopulmonary Bypass Using Plasma Neutrophil Gelatinase-Associated Lipocalin. The Korean journal of thoracic and cardiovascular surgery, 47(3), 240-8. [15856]

Kim	2016	Meta-analysis - retained as background material	S. Kim, H. J. Kim, H. S. Ahn, J. Y. Song, T. H. Um, C. R. Cho, H. Jung, H. K. Koo, J. H. Park, S. S. Lee and H. K. Park. Is plasma neutrophil gelatinase-associated lipocalin a predictive biomarker for acute kidney injury in sepsis patients? A systematic review and meta-analysis. Journal of Critical Care, 33(213-223. [15857]
Kim	2016	Not a primary study	J. E. Kim, S. W. Song, J. Y. Kim, H. J. Lee, K. H. Chung and Y. H. Shim. Effect of a Single Bolus of Erythropoietin on Renoprotection in Patients Undergoing Thoracic Aortic Surgery With Moderate Hypothermic Circulatory Arrest. Annals of Thoracic Surgery, 101(2), 690-696. [15855]
Kim	2017	Not relevant biomarker assay or test	H. Kim, M. Hur, S. Lee, R. Marino, L. Magrini, P. Cardelli, J. Struck, A. Bergmann, O. Hartmann and S. Di Somma. Proenkephalin, Neutrophil Gelatinase-Associated Lipocalin, and Estimated Glomerular Filtration Rates in Patients With Sepsis. Annals of laboratory medicine, 37(5), 388-397. [15849]
Kim	2018	<100 participants	Y. Kim, Y. S. Cho, D. Kym, J. Yoon, H. Yim, J. Hur and W. Chun. Diagnostic performance of plasma and urine neutrophil gelatinase-associated lipocalin, cystatin C, and creatinine for acute kidney injury in burn patients: A prospective cohort study. PLoS ONE, 13(6), e0199600. [15860]
Kim	2019	Not a primary study	H. Y. Kim, C. S. Kim, E. H. Bae, S. W. Kim and S. K. Ma. Clinical Significance of the Interval Change of Plasma Neutrophil Gelatinase-Associated Lipocalin in Acute Kidney Injury and Acute Kidney Injury Superimposed on Chronic Kidney Disease. Chonnam medical journal, 55(1), 68-69. [15851]
Kipnis	2016	Not a primary study	E. Kipnis. Predicting acute kidney injury after hip-fracture surgery: Join the (renal) resistance!. Anaesthesia Critical Care and Pain Medicine, 35(6), 369-370. [15865]
Kirbis	2015	<100 participants	S. Kirbis, M. Gorenjak and A. Sinkovic. The role of urine neutrophil gelatinase - associated lipocalin (NGAL) in acute heart failure in patients with ST - elevation myocardial infarction. BMC Cardiovascular Disorders, 15(1), 49. [15866]
Kiseli	2017	<100 participants	M. Kiseli, G. S. Caglar, H. Yilmaz, A. Y. Gursoy, T. Candar, E. G. Pabuccu, Z. K. Bengisun and F. Tuzuner. Neutrophil Gelatinase-Associated Lipocalin Levels During Pneumoperitoneum. Jsls-Journal of the Society of Laparoendoscopic Surgeons, 21(1), UNSP e2016.00091-UNSP e2016.00091. [18486]
Kisoon	2015	<100 participants	R. Y. U. Kisoon, A. H. N. Jae-Yun, L. E. E. Mi-Jin, N. H. O. Woo-Young and K. I. M. Seong-Hun. Early Detection and Staging of Acute Kidney Injury in Non-traumatic Rhabdomyolysis in Emergency Department. Journal of the Korean Society of Emergency Medicine, 370-378. [6170]
Kit	2015	<100 participants	O. I. Kit, E. M. Frantsiyants, S. N. Dimitriadi, I. V. Kaplieva, L. K. Trepitaki, N. D. Cheryarina and Y. A. Pogorelova. Role of markers for acute kidney injury in surgical management of patients with renal cancer. Onkourologiya, 11(3), 34-39. [18487]

Kit	2017	<100 participants	O. I. Kit, E. M. Frantsiyants, D. A. Rozenko, N. D. Ushakova, S. N. Dimitriadi, Y. A. Pogorelova, N. D. Cheryarina, L. S. Kozlova, K. P. Boyko and V. V. Gurnak. Dynamics of markers of markers of acute kidney injury when using epidural block during resection under warm ischemia. Onkourologiya, 13(4), 25-33. [18488]
Kitao	2015	<100 participants	T. Kitao, T. Kimata, S. Yamanouchi, S. Kato, S. Tsuji and K. Kaneko. Urinary Biomarkers for Screening for Renal Scarring in Children with Febrile Urinary Tract Infection: Pilot Study. Journal of Urology, 194(3), 766-771. [18489]
Klein	2018	Meta-analysis - retained as background material	S. J. Klein, A. K. Brandtner, G. F. Lehner, H. Ulmer, S. M. Bagshaw, C. J. Wiedermann and M. Joannidis. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Intensive Care Medicine, 44(3), 323-336. [15869]
Knafl	2017	<100 participants	D. Knafl, M. Muller, S. Pajenda, Z. Genc, M. Hecking and L. Wagner. The urine biomarker panel [IGFBP7]x[TIMP-2] (NephroCheck parameter) does not correlate with IGFBP7 and TIMP-2 gene expression in urinary sediment. PLoS ONE, 12(11), e0188316. [15870]
Ko	2018	Not relevant biomarker assay or test	S. W. Ko, N. H. Chi, C. H. Wu, T. M. Huang, S. C. J. Chueh, C. H. Wang, J. H. Lin, W. J. Wang, J. T. Ting, H. M. Chang, R. Connolly, C. H. Lai, L. J. Tseng, V. C. Wu and T. S. Chu. Hemojuvelin Predicts Acute Kidney Injury and Poor Outcomes Following Cardiac Surgery. Scientific reports, 8(1), 1938. [15871]
Koch	2011	Not relevant biomarker assay or test	A. M. Koch, S. Dittrich, R. Cesnjevar, A. Ruffer, C. Breuer and M. Glockler. Plasma neutrophil gelatinase-associated lipocalin measured in consecutive patients after congenital heart surgery using point-of-care technology. Interactive Cardiovascular and Thoracic Surgery, 13(2), 133-136. [15872]
Kohagura	2012	Not a primary study	K. Kohagura and Y. Ohya. Early detection and prediction by biomarkers of acute kidney injury after cardiac surgery. Circulation Journal, 76(1), 53-54. [15873]
Kokot	2012	<100 participants	M. Kokot, G. Biolik, D. Ziaja, T. Fojt, K. Cisak, K. Antoniak, T. Kowalewska-Twardela, K. Pawlicki, K. Ziaja and J. Dulawa. Acute kidney injury after abdominal aortic aneurysm surgery: Detailed assessment of early effects using novel markers. Polskie Archiwum Medycyny Wewnetrznej, 122(7-8), 353-360. [15878]
Konvalinka	2014	Not a primary study	A. Konvalinka. Urine proteomics for acute kidney injury prognosis: Another player and the long road ahead. Kidney International, 85(4), 735-738. [15881]
Koo	2015	No focus on DTA for AKI	K. C. Koo, J. H. Hong, H. S. Lee, S. U. Jeh, Y. D. Choi, K. H. Rha and W. S. Ham. Accuracy of urinary neutrophil gelatinase- Associated lipocalin in quantifying acute kidney injury after partial nephrectomy in patients with normal contralateral kidney. PLoS ONE, 10(7), e0133675. [15882]

Kooiman	2015	Not relevant type of population	J. Kooiman, W. R. van de Peppel, Y. W. J. Sijpkens, H. F. H. Brulez, P. M. de Vries, M. A. Nicolaie, H. Putter, M. V. Huisman, W. van der Kooij, C. van Kooten and T. J. Rabelink. No increase in Kidney Injury Molecule-1 and Neutrophil Gelatinase-Associated Lipocalin excretion following intravenous contrast enhanced-CT. European Radiology, 25(7), 1926-1934. [15884]
Kos	2013	<100 participants	F. T. Kos, M. A. N. Sendur, S. Aksoy, H. T. Celik, S. Sezer, B. Civelek, S. Yaman and N. Zengin. Evaluation of renal function using the level of neutrophil gelatinase-associated lipocalin is not predictive of nephrotoxicity associated with cisplatin-based chemotherapy. Asian Pacific journal of cancer prevention : APJCP, 14(2), 1111-4. [15887]
Kostic	2019	<100 participants	D. Kostic, G. P. N. dos Santos Beozzo, S. B. do Couto, A. H. T. Kato, L. Lima, P. Palmeira, V. L. J. Krebs, V. Bunduki, R. P. V. Francisco, M. Zugaib, W. B. de Carvalho and V. H. K. Koch. First-year profile of biomarkers for early detection of renal injury in infants with congenital urinary tract obstruction. Pediatric Nephrology, 34(6), 1117-1128. [15888]
Kostrubiec	2012	Not relevant type of population	M. Kostrubiec, A. Labyk, J. Pedowska-Wloszek, O. Dzikowska-Diduch, A. Wojciechowski, M. Garlinska, M. Ciurzynski and P. Pruszczyk. Neutrophil gelatinase-associated lipocalin, cystatin C and eGFR indicate acute kidney injury and predict prognosis of patients with acute pulmonary embolism. Heart, 98(16), 1221-1228. [15889]
Koukoulaki	2013	<100 participants	M. Koukoulaki, C. Spyropoulos, P. Hondrogiannis, E. Papachristou, E. Mitsi, F. Kalfarentzos and D. S. Goumenos. Neutrophil Gelatinase-Associated Lipocalin as a Biomarker of Acute Kidney Injury in Patients with Morbid Obesity Who Underwent Bariatric Surgery. Nephron extra, 3(1), 101-105. [15890]
Koyner	2010	Not relevant biomarker assay or test	J. L. Koyner, V. S. Vaidya, M. R. Bennett, Q. Ma, E. Worcester, S. A. Akhter, J. Raman, V. Jeevanandam, M. F. O'Connor, P. Devarajan, J. V. Bonventre and P. T. Murray. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. Clinical Journal of the American Society of Nephrology, 5(12), 2154-2165. [15899]
Koyner	2013	<100 participants	J. L. Koyner, M. R. Bennett, E. M. Worcester, Q. Ma, J. Raman, V. Jeevanandam, K. E. Kasza, M. F. O'Connor, D. J. Konczal, S. Trevino, P. Devarajan and P. T. Murray. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney International, 74(8), 1059-69. [3972]
Koyner	2014	<100 participants	J. L. Koyner, A. X. Garg, H. Thiessen-Philbrook, S. G. Coca, L. G. Cantley, A. Peixoto, C. S. Passik, K. Hong and C. R. Parikh. Adjudication of etiology of acute kidney injury: Experience from the TRIBE-AKI multi-center study. BMC Nephrology, 15(1), 105. [15895]
Krawczeski	2011	Not relevant biomarker assay or test	C. D. Krawczeski, S. L. Goldstein, J. G. Woo, Y. Wang, N. Piyaphanee, Q. Ma, M. Bennett and P. Devarajan. Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. Journal of the American College of Cardiology, 58(22), 2301-2309. [15902]

Krawczeski	2011	Not relevant biomarker assay or test	C. D. Krawczeski, J. G. Woo, Y. Wang, M. R. Bennett, Q. Ma and P. Devarajan. Neutrophil gelatinase-associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. Journal of Pediatrics, 158(6), 1009. [15903]
Kumar	2011	Not a primary study	A. B. Kumar and M. Suneja. Cardiopulmonary bypass-associated acute kidney injury. Anesthesiology, 114(4), 964-970. [15911]
Kunutsor	2018	Not relevant type of population	S. K. Kunutsor, J. L. Flores-Guerrero, L. M. Kieneker, T. Nilsen, C. Hidden, E. Sundrehagen, S. Seidu, R. P. F. Dullaart and S. J. L. Bakker. Plasma neutrophil gelatinase-associated lipocalin and risk of cardiovascular disease: Findings from the PREVEND prospective cohort study. Clinica Chimica Acta, 486(66-75. [15913]
Kuribayashi	2016	Not relevant type of population	R. Kuribayashi, H. Suzumura, T. Sairenchi, Y. Watabe, Y. Tsuboi, G. Imataka, H. Kurosawa and O. Arisaka. Urinary neutrophil gelatinase-associated lipocalin is an early predictor of acute kidney injury in premature infants. Experimental and Therapeutic Medicine, 12(6), 3706-3710. [15917]
Labr	2018	Not relevant biomarker assay or test	K. Labr, J. Spinar, J. Parenica, L. Spinarova, F. Malek, M. Spinarova, O. Ludka, J. Jarkovsky, K. Benesova, M. Goldbergova-Pavkova and R. Labrova. Renal functions and prognosis stratification in chronic heart failure patients and the importance of neutrophil gelatinase-associated lipocalin. Kidney and Blood Pressure Research, 43(6), 1865-1877. [15921]
Lacquaniti	2013	Not relevant type of population	A. Lacquaniti, F. Buemi, R. Lupica, C. Giardina, G. Mure, A. Arena, C. Visalli, S. Baldari, C. Aloisi and M. Buemi. Can neutrophil gelatinase-associated lipocalin help depict early contrast material-induced nephropathy?. Radiology, 267(1), 86-93. [15925]
Lacquaniti	2013	<100 participants	A. Lacquaniti, M. Giardina, S. Lucisano, R. Messina, A. Buemi, C. D. Risitano, V. Chirico, M. Buemi and A. David. Neutrophil gelatinase-associated lipocalin (NGAL) and Endothelial Progenitor Cells (EPCs) evaluation in aortic aneurysm repair. Current Vascular Pharmacology, 11(6), 1001-1010. [15926]
Lahoud	2015	<100 participants	Y. Lahoud, O. Hussein, A. Shalabi, H. Awad, M. Khamaisi, I. Matar, O. Nativ and Z. Abassi. Effects of phosphodiesterase-5 inhibitor on ischemic kidney injury during nephron sparing surgery: quantitative assessment by NGAL and KIM-1. World journal of urology, 33(12), 2053-2062. [15929]
Lane	2018	<100 participants	B. R. Lane, S. K. Babitz, K. Vlasakova, A. Wong, S. L. Noyes, W. Boshoven, P. Grady, C. Zimmerman, S. Engerman, M. Gebben, M. Tanen, W. E. Glaab and F. D. Sistare. Evaluation of Urinary Renal Biomarkers for Early Prediction of Acute Kidney Injury Following Partial Nephrectomy: A Feasibility Study. European Urology Focus, . [15937]
Lavery	2008	<100 participants	A. P. Lavery, J. K. Meinzen-Derr, E. Anderson, Q. Ma, M. R. Bennett, P. Devarajan and K. R. Schibler. Urinary NGAL in premature infants. Pediatric Research, 64(4), 423-8. [3977]
Lee	2014	<100 participants	H. E. Lee, D. K. Kim, H. K. Kang and K. Park. The diagnosis of febrile urinary tract infection in children may be facilitated by urinary biomarkers. Pediatric Nephrology, 30(1), 123-130. [15951]

Lee	2016	<100 participants	S. M. K. Lee, M. A. Lanaspa, L. G. Sanchez-Lozada and R. J. Johnson. Hyponatremia with Persistent Elevated Urinary Fractional Uric Acid Excretion: Evidence for Proximal Tubular Injury?. Kidney & blood pressure research, 41(5), 535-544. [18496]
Lee	2018	Not relevant biomarker assay or test	C. C. Lee, C. H. Chang, S. W. Chen, P. C. Fan, S. W. Chang, Y. T. Chen, Y. Y. Nan, P. J. Lin and F. C. Tsai. Preoperative risk assessment improves biomarker detection for predicting acute kidney injury after cardiac surgery. PLoS ONE, 13(9), e0203447. [15947]
Lee	2018	<100 participants	C. W. Lee, H. W. Kou, H. S. Chou, H. H. Chou, S. F. Huang, C. H. Chang, C. H. Wu, M. C. Yu and H. I. Tsai. A combination of SOFA score and biomarkers gives a better prediction of septic AKI and in-hospital mortality in critically ill surgical patients: a pilot study. World journal of emergency surgery : WJES, 13(41. [15948]
Lee	2019	<100 participants	N. M. Lee, L. Deriy, T. R. Petersen, V. O. Shah, M. P. Hutchens and N. S. Gerstein. Impact of Isolyte Versus 0.9% Saline on Postoperative Event of Acute Kidney Injury Assayed by Urinary [TIMP-2]x[IGFBP7] in Patients Undergoing Cardiac Surgery. Journal of Cardiothoracic and Vascular Anesthesia, 33(2), 348-356. [15953]
Legr	2014	<100 participants	M. Legr, B. D. Berardinis, H. K. Gaggin, L. Magrini, A. Belcher, B. Zancla, A. Femia, M. Simon, S. Motiwala, R. Sambhare, S. D. Somma, A. Mebazaa, V. S. Vaidya and J. L. Januzzi. Evidence of uncoupling between renal dysfunction and injury in cardiorenal syndrome: Insights from the BIONICS study. PLoS ONE, 9(11), e112313. [15956]
Legrand	2013	<100 participants	M. Legrand, C. Collet, E. Gayat, J. Henao, V. Giraudeaux, J. Mateo, J.-M. Launay and D. Payen. Accuracy of urine NGAL commercial assays in critically ill patients. Intensive care medicine, 39(3), 541-2. [15958]
Legrand	2013	Not a primary study	M. Legrand, M. Darmon and M. Joannidis. NGAL and AKI: The end of a myth?. Intensive Care Medicine, 39(10), 1861-1863. [15961]
Legrand	2015	Not relevant type of population	M. Legrand, A. Jacquemod, E. Gayat, C. Collet, V. Giraudeaux, J.-M. Launay and D. Payen. Failure of renal biomarkers to predict worsening renal function in high-risk patients presenting with oliguria. Intensive care medicine, 41(1), 68-76. [18497]
Lei	2018	Not relevant biomarker assay or test	L. Lei, L. P. Li, Z. Zeng, J. X. Mu, X. Yang, C. Zhou, Z. L. Wang and H. Zhang. Value of urinary KIM-1 and NGAL combined with serum Cys C for predicting acute kidney injury secondary to decompensated cirrhosis. Scientific reports, 8(1), 7962. [15966]
Lentini	2012	<100 participants	P. Lentini, M. de Cal, A. Clementi, A. D'Angelo and C. Ronco. Sepsis and AKI in ICU Patients: The Role of Plasma Biomarkers. Critical care research and practice, 2012(856401. [15969]
Leoncini	2011	Not relevant type of population	G. Leoncini, M. Mussap, F. Viazzi, M. Fravega, R. Degrandi, G. P. Bezante, G. Deferrari and R. Pontremoli. Combined use of urinary neutrophil gelatinase-associated lipocalin (uNGAL) and albumin as markers of early cardiac damage in primary hypertension. Clinica Chimica Acta, 412(21-22), 1951-1956. [15970]

Leung	2009	<100 participants	J. C. K. Leung, M. F. Lam, S. C. W. Tang, L. Y. Y. Chan, K. Y. Tam, T. P. S. Yip and K. N. Lai. Roles of Neutrophil Gelatinase-Associated Lipocalin in Continuous Ambulatory Peritoneal Dialysis-Related Peritonitis. Journal of clinical immunology, 29(3), 365-378. [18498]
Levante	2017	Pilot study or preliminary analysis only	C. Levante, F. Ferrari, C. Manenti, F. Husain-Syed, M. Scarpa, T. H. Danesi, M. de Cal, V. Corradi, G. M. Virzi, A. Brendolan, F. Nalesso, P. Bezerra, S. Lopez-Giacoman, S. Samoni, M. Senzolo, D. Giavarina, L. Salvador, R. Bonato, S. de Rosa, E. Rettore and C. Ronco. Routine adoption of TIMP2 and IGFBP7 biomarkers in cardiac surgery for early identification of acute kidney injury. International Journal of Artificial Organs, 40(12), 714-718. [15971]
Levitsky	2014	<100 participants	J. Levitsky, T. B. Baker, C. Jie, S. Ahya, M. Levin, J. Friedewald, P. Al-Saden, D. R. Salomon and M. M. Abecassis. Plasma protein biomarkers enhance the clinical prediction of kidney injury recovery in patients undergoing liver transplantation. Hepatology (Baltimore, Md.), 60(6), 2017-2026. [15973]
Lewandowska	2014	<100 participants	L. Lewandowska, J. Matuszkiewicz-Rowinska, C. Jayakumar, U. O. Jedynak, S. Looney, M. Galas, M. Dutkiewicz, M. Krawczyk and G. Ramesh. Netrin-1 and semaphorin 3A predict the development of acute kidney injury in liver transplant patients. PLoS ONE, 9(10), e107898. [15974]
Li	2012	<100 participants	Y. Li, M. Zhu, Q. Xia, S. Wang, J. Qian, R. Lu, M. Che, H. Dai, Q. Wu, Z. Ni, B. Lindholm, J. Axelsson and Y. Yan. Urinary neutrophil gelatinase-associated lipocalin and L-type fatty acid binding protein as diagnostic markers of early acute kidney injury after liver transplantation. Biomarkers, 17(4), 336-342. [15981]
Li	2014	Non-English publication	J. Li, H. Zhang, Y. Shang and S. Cao. [The study of early diagnosis and prognostic effect using detection of NGAL in community acquired pneumonia with acute kidney injury]. Zhonghua wei zhong bing ji jiu yi xue, 26(4), 269-71. [15979]
Li	2018	Not relevant type of population	H. Li, Z. Yu, L. Gan, L. Peng and Q. Zhou. Serum NGAL and FGF23 may have certain value in early diagnosis of CIN. Renal failure, 40(1), 547-553. [15977]
Liangos	2009	Not relevant biomarker assay or test	O. Liangos, H. Tighiouart, M. C. Perianayagam, A. Kolyada, W. K. Han, R. Wald, J. V. Bonventre and B. L. Jaber. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. Biomarkers, 14(6), 423-431. [15987]
Liangos	2009	Pilot study or preliminary analysis only	Liangos O, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, et al. . Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. . Biomarkers 2009;14:423–31. https://doi.org/10.1080/13547500903067744. [3938]
Liao	2019	Not relevant type of population	B. Liao, W. Nian, A. Xi and M. Zheng. Evaluation of a diagnostic test of serum neutrophil gelatinase-associated lipocalin (NGAL) and urine KIM-1 in contrast-induced nephropathy (CIN). Medical Science Monitor, 25(565-570. [15989]

Liborio	2015	<100 participants	A. B. Liborio, M. B. M. Braz, A. C. Seguro, G. C. Meneses, F. M. De Oliveira Neves, D. C. Pedrosa, L. P. De Goes Cavalcanti, A. M. C. Martins and E. De Francesco Daher. Endothelial glycocalyx damage is associated with leptospirosis acute kidney injury. American Journal of Tropical Medicine and Hygiene, 92(3), 611-616. [15990]
Lichosik	2015	<100 participants	M. Lichosik, A. Jung, K. Jobs, A. Mierzejewska, R. Zdanowski and B. Kalicki. Interleukin 18 and neutrophil-gelatinase associated lipocalin in assessment of the risk of contrast-induced nephropathy in children. Central European Journal of Immunology, 40(4), 447-453. [15991]
Lim	2017	Not relevant biomarker assay or test	Y.-M. Lim, J. Y. Moon, D. Min, S.-H. Kim, W.-I. Yang, W.-J. Kim, J.-H. Sung, I. J. Kim, S.-W. Lim and D.-H. Cha. Serial measurements of neutrophil gelatinase-associated lipocalin: prognostic value in patients with ST-segment elevation myocardial infarction treated with a primary percutaneous coronary intervention. Coronary artery disease, 28(8), 690-696. [18500]
Lin	2013	Not relevant type of population	H. Y. H. Lin, S. C. Lee, S. F. Lin, H. H. Hsiao, Y. C. Liu, W. C. Yang, D. Y. Hwang, C. C. Hung, H. C. Chen and J. Y. Guh. Urinary neutrophil gelatinase-associated lipocalin levels predict cisplatin-induced acute kidney injury better than albuminuria or urinary cystatin C levels. Kaohsiung Journal of Medical Sciences, 29(6), 304-311. [16001]
Lin	2018	Not a primary study	Q. Lin and J. H. Mao. Early prediction of acute kidney injury in children: Known biomarkers but novel combination. World Journal of Pediatrics, 14(6), 617-620. [16002]
Lindberg	2016	Not relevant type of population	S. Lindberg, J. S. Jensen, S. Hoffmann, A. Z. Iversen, S. H. Pedersen, T. Biering-Sorensen, S. Galatius, A. Flyvbjerg, R. Mogelvang and N. E. Magnusson. Plasma neutrophil gelatinase-associated lipocalin reflects both inflammation and kidney function in patients with myocardial infarction. CardioRenal Medicine, 6(3), 180-190. [16003]
Lindberg	2012	Not relevant type of population	S. Lindberg, S. H. Pedersen, R. Mogelvang, J. S. Jensen, A. Flyvbjerg, S. Galatius and N. E. Magnusson. Prognostic utility of neutrophil gelatinase-associated lipocalin in predicting mortality and cardiovascular events in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Journal of the American College of Cardiology, 60(4), 339-345. [16004]
Lindsey-Yoojin	2017	Not relevant biomarker assay or test	C. Lindsey-Yoojin, C. Won-Sik, C. Eui-Kyung, S. Jeonghee, Y. I. M. Hyung-Eun and C. Byung-Min. Clinical Utility of Rapid Plasma Neutrophil Gelatinase-Associated Lipocalin Assays for Diagnosing Acute Kidney Injury in Critically Ill Newborn Infants. Neonatal Medicine, 164-170. [6167]
Ling	2008	Not relevant type of population	W. Ling, N. Zhaohui, H. Ben, G. Leyi, L. Jianping, D. Huili and Q. Jiaqi. Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. Nephron - Clinical Practice, 108(3), c176-c181. [16005]

Ling	2008	Not relevant type of population	W. Ling, N. Zhaohui, H. Ben, G. Leyi, L. Jianping, D. Huili and Q. Jiaqi. Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. Nephron, 108(3), c176-81. [3990]
Linko	2013	Not relevant biomarker assay or test	R. Linko, V. Pettila, A. Kuitunen, A. M. Korhonen, S. Nisula, S. Alila, O. Kiviniemi, R. Laru-Sompa, T. Varpula and S. Karlsson. Plasma neutrophil gelatinase-associated lipocalin and adverse outcome in critically ill patients with ventilatory support. Acta Anaesthesiologica Scandinavica, 57(7), 855-862. [16006]
Lipcsey	2014	No focus on DTA for AKI	M. Lipcsey, P. Hayward, M. Haase, A. Haase-Fielitz, G. Eastwood, L. Peck, G. Matalanis and R. Bellomo. Neutrophil gelatinase-associated lipocalin after off pump versus on pump coronary artery surgery. Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals, 19(1), 22-8. [16007]
Lipinski	2015	Not relevant type of population	M. Lipinski, A. Rydzewska-Rosolowska, A. Rydzewski and G. Rydzewska. Urinary Neutrophil Gelatinase-Associated Lipocalin as an Early Predictor of Disease Severity and Mortality in Acute Pancreatitis. Pancreas, 44(3), 448-452. [18502]
Lippi	2012	Not a primary study	G. Lippi and G. Cervellin. Neutrophil gelatinase-associated lipocalin: A more specific assay is needed for diagnosing renal injury. Clinica Chimica Acta, 413(13-14), 1160-1161. [16012]
Liu	2013	Not relevant biomarker assay or test	Liu S, Che M, Xue S, Xie B, Zhu M, Lu R, et al. . Urinary L-FABP and its combination with urinary NGAL in early diagnosis of acute kidney injury after cardiac surgery in adult patients. . Biomarkers 2013;18:95–101. https://doi.org/10.3109/1354750X.2012.740687. [16022]
Liu	2016	Compares clinical adjudication between nephrocheck and KDIGO - retained as background material	K. D. Liu, A. Vijayan, M. H. Rosner, J. Shi, L. S. Chawla and J. A. Kellum. Clinical adjudication in acute kidney injury studies: Findings from the pivotal TIMP-2*IGFBP7 biomarker study. Nephrology Dialysis Transplantation, 31(10), 1641-1646. [16019]
Liu	2017	Systematic review - retained as background material	C. Liu, X. Lu, Z. Mao, H. Kang, H. Liu, L. Pan, J. Hu, L. Wang and F. Zhou. The diagnostic accuracy of urinary [TIMP-2].[IGFBP7] for acute kidney injury in adults. Medicine (United States), 96(27), e7484. [16017]
Lu	2019	<100 participants	J. Lu, L. Lin, C. Ye, Q. Tao, M. Cui, S. Zheng, D. Zhu, L. Liu and Y. Xue. Serum NGAL Is Superior to Cystatin C in Predicting the Prognosis of Acute-on-Chronic Liver Failure. Annals of Hepatology, 18(1), 155-164. [18506]
Lubell	2017	No focus on DTA for AKI	T. R. Lubell, J. M. Barasch, K. Xu, M. Ieni, K. I. Cabrera and P. S. Dayan. Urinary Neutrophil Gelatinase-Associated Lipocalin for the Diagnosis of Urinary Tract Infections. Pediatrics, 140(6), e20171090-e20171090. [18507]
Luka	2013	<100 participants	C. C. W. Luka, K. M. Chowa, J. S. S. Kwok, B. C. H. Kwan, M. H. M. Chan, K. B. Lai, F. M. M. Lai, G. Wang, P. K. T. Li and C. C. Szeto. Urinary biomarkers for the prediction of reversibility in acute-on-chronic renal failure. Disease Markers, 34(3), 179-185. [16039]

Lukasz	2014	<100 participants	A. Lukasz, J. Beneke, J. Menne, F. Vetter, B. M. W. Schmidt, M. Schiffer, H. Haller, P. Kumpers and J. T. Kielstein. Serum neutrophil gelatinase-associated lipocalin (NGAL) in patients with shiga toxin mediated haemolytic uraemic syndrome (STEC-HUS). Thrombosis and Haemostasis, 111(2), 365-372. [16040]
Luo	2013	Not relevant type of population	Q. Luo, F. Zhou, H. Dong, L. Wu, L. Chai, K. Lan and M. Wu. Implication of combined urinary biomarkers in early diagnosis of acute kidney injury following percutaneous coronary intervention. Clinical Nephrology, 79(2), 85-92. [16041]
Luthra	2018	Not a primary study	A. Luthra and A. Tyagi. [TIMP-2]*[IGFBP7] for Predicting Early AKI. Anaesthesia, critical care & pain medicine, . [16042]
MacDonald	2012	<100 participants	S. Macdonald, G. Arendts, Y. Nagree and X. F. Xu. Neutrophil Gelatinase-Associated Lipocalin (NGAL) predicts renal injury in acute decompensated cardiac failure: A prospective observational study. BMC Cardiovascular Disorders, 12(8. [16044]
MacEdo	2013	Not a primary study	E. MacEdo and R. L. Mehta. Biomarkers for acute kidney injury: Combining the new silver with the old gold. Nephrology Dialysis Transplantation, 28(5), 1064-1067. [16045]
Madsen	2012	<100 participants	M. G. Madsen, R. Norregaard, J. Palmfeldt, L. H. Olsen, J. Frokiaer and T. M. Jorgensen. Urinary NGAL, cystatin C, beta 2-microglobulin, and osteopontin significance in hydronephrotic children. Pediatric Nephrology, 27(11), 2099-2106. [18508]
Maeda	2017	<100 participants	A. Maeda, H. Ando, T. Ura, K. Muro, M. Aoki, K. Saito, E. Kondo, S. Takahashi, Y. Ito, Y. Mizuno and A. Fujimura. Differences in urinary renal failure biomarkers in cancer patients initially treated with cisplatin. Anticancer Research, 37(9), 5235-5239. [16048]
Mahmoodpoor	2018	<100 participants	A. Mahmoodpoor, H. Hamishehkar, V. Fattahi, S. Sanaie, P. Arora and N. D. Nader. Urinary versus plasma neutrophil gelatinase-associated lipocalin (NGAL) as a predictor of mortality for acute kidney injury in intensive care unit patients. Journal of Clinical Anesthesia, 44(12-17. [16052]
Maisel	2011	Not relevant biomarker assay or test	A. S. Maisel, C. Mueller, R. Fitzgerald, R. Brikhan, B. C. Hiestand, N. Iqbal, P. Clopton and D. J. Van Veldhuisen. Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: The NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial. European Journal of Heart Failure, 13(8), 846-851. [16057]
Maisel	2016	Not relevant biomarker assay or test	A. S. Maisel, N. Wettersten, D. J. van Veldhuisen, C. Mueller, G. Filippatos, R. Nowak, C. Hogan, M. C. Kontos, C. M. Cannon, G. A. Muller, R. Birkhahn, P. Clopton, P. Taub, G. M. Vilke, K. McDonald, N. Mahon, J. Nunez, C. Briguori, C. Passino and P. T. Murray. Neutrophil Gelatinase-Associated Lipocalin for Acute Kidney Injury During Acute Heart Failure Hospitalizations: The AKINESIS Study. Journal of the American College of Cardiology, 68(13), 1420-1431. [16055]

Maizel	2019	Not relevant type of population	J. Maizel, D. Daubin, L. Van Vong, D. Titeca-Beauport, M. Wetzstein, L. Kontar, M. Slama, K. Klouche and C. Vinsonneau. Urinary TIMP2 and IGFBP7 identifies high risk patients of short-term progression from mild and moderate to severe acute kidney injury during septic shock: A prospective cohort study. Disease Markers, 2019(3471215. [16060]
Makris	2009	<100 participants	K. Makris, N. Markou, E. Evodia, E. Dimopoulou, I. Drakopoulos, K. Ntetsika, D. Rizos, G. Baltopoulos and A. Haliassos. Urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early marker of acute kidney injury in critically ill multiple trauma patients. Clinical Chemistry and Laboratory Medicine, 47(1), 79-82. [16065]
Malyszko	2009	Not relevant type of population	J. Malyszko, H. Bachorzewska-Gajewska, B. Poniatowski, J. S. Malyszko and S. Dobrzycki. Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and without severe chronic kidney disease. Renal Failure, 31(10), 910-919. [16075]
Malyszko	2015	Not relevant type of population	J. Malyszko, H. Bachorzewska-Gajewska, E. Koc-Zorawska, J. S. Malyszko, G. Kobus and S. Dobrzycki. Midkine: A novel and early biomarker of contrast-induced acute kidney injury in patients undergoing percutaneous coronary interventions. BioMed Research International, 2015(879509. [16068]
Malyszko	2019	Not relevant type of population	J. Malyszko, H. Bachorzewska-Gajewska, J. S. Malyszko, E. Koc-Zorawska, J. Matuszkiewicz-Rowinska and S. Dobrzycki. Hepcidin - Potential biomarker of contrast-induced acute kidney injury in patients undergoing percutaneous coronary interventions. Advances in Medical Sciences, 64(2), 211-215. [16067]
Mamikonian	2014	<100 participants	L. S. Mamikonian, L. B. Mamo, P. B. Smith, J. Koo, A. J. Lodge and J. L. Turi. Cardiopulmonary bypass is associated with hemolysis and acute kidney injury in neonates, infants, and children*. Pediatric Critical Care Medicine, 15(3), e111-e119. [16077]
Mandei	2015	<100 participants	J. Mandei, E. Iskandar, A. Umboh and H. Lestari. Relationship between serum cystatin-C and urinary neutrophil gelatinase-associated lipocalin in septic children. Paediatrica Indonesiana, 55(2), 83-86. [18509]
Marcelino	2014	<100 participants	P. Marcelino, I. Tavares, D. Carvalho, C. Marques, M. J. Silvestre, R. Perdigoto and E. Barroso. Is urinary gamma-glutamyl transpeptidase superior to urinary neutrophil gelatinase-associated lipocalin for early prediction of acute kidney injury after liver transplantation?. Transplantation proceedings, 46(6), 1812-1818. [16080]
Martensson	2013	Not relevant biomarker assay or test	J. Martensson, M. Bell, S. Xu, M. Bottai, B. Ravn, P. Venge and C. R. Martling. Association of plasma neutrophil gelatinase-associated lipocalin (NGAL) with sepsis and acute kidney dysfunction. Biomarkers, 18(4), 349-356. [16089]
Martensson	2016	<100 participants	J. Martensson, N. Jonsson, N. J. Glassford, M. Bell, C. R. Martling, R. Bellomo and A. Larsson. Plasma endostatin may improve acute kidney injury risk prediction in critically ill patients. Annals of Intensive Care, 6(1), 1-9. [16085]

Martensson	2010	<100 participants	J. Martensson, M. Bell, A. Oldner, S. Xu, P. Venge and C. R. Martling. Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Medicine, 36(8), 1333-1340. [16092]
Martin-Moreno	2015	Not relevant type of population	P. L. Martin-Moreno, N. Varo, E. Martinez-Anso, N. Martin-Calvo, C. Sayon-Orea, J. I. Bilbao and N. Garcia-Fernandez. Comparison of Intravenous and Oral Hydration in the Prevention of Contrast-Induced Acute Kidney Injury in Low-Risk Patients: A Randomized Trial. Nephron, 131(1), 51-58. [16094]
Martino	2012	Pilot study or preliminary analysis only	F. K. Martino, I. Filippi, D. Giavarina, M. Kaushik, M. P. Rodighiero, C. Crepaldi, C. Teixeira, A. F. Nadal, M. H. Rosner and C. Ronco. Neutrophil gelatinase-associated lipocalin in the early diagnosis of peritonitis: The case of neutrophil gelatinase-associated lipocalin. Peritoneal Dialysis - State-of-the-Art 2012, 178(258-263. [16096]
Mathew	2008	Not relevant biomarker assay or test	A. Mathew and A. X. Garg. A single measure of urinary neutrophil gelatinase-associated lipocalin was accurate for diagnosing acute kidney injury. ACP Journal Club, 149(6), 13. [2814]
Matsuura	2018	<100 participants	R. Matsuura, Y. Komaru, Y. Miyamoto, T. Yoshida, K. Yoshimoto, R. Isshiki, K. Mayumi, T. Yamashita, Y. Hamasaki, M. Nangaku, E. Noiri, N. Morimura and K. Doi. Response to different furosemide doses predicts AKI progression in ICU patients with elevated plasma NGAL levels. Annals of Intensive Care, 8(1), 8. [16104]
Matys	2013	Not relevant type of population	U. Matys, H. Bachorzewska-Gajewska, J. Malyszko and S. Dobrzycki. Assessment of kidney function in diabetic patients. Is there a role for new biomarkers NGAL, cystatin C and KIM-1?. Advances in Medical Sciences, 58(2), 353-361. [18513]
Mawad	2016	<100 participants	H. Mawad, L.-P. Laurin, J.-F. Naud, F. A. Leblond, N. Henley, M. Vallee, V. Pichette and M. Leblanc. Changes in Urinary and Serum Levels of Novel Biomarkers after Administration of Gadolinium-based Contrast Agents. Biomarker Insights, 11(91-94. [18514]
Mayer	2017	Pilot study or preliminary analysis only	T. Mayer, D. Bolliger, M. Scholz, O. Reuthebuch, M. Gregor, P. Meier, M. Grapow, M. D. Seeberger and J. Fassl. Urine Biomarkers of Tubular Renal Cell Damage for the Prediction of Acute Kidney Injury After Cardiac Surgery-A Pilot Study. Journal of Cardiothoracic and Vascular Anesthesia, 31(6), 2072-2079. [16105]
Mazar	2014	No focus on DTA for AKI	M. Mazar, V. Ivancan, I. Segotic, Z. Colak, R. Gabelica, G. Rajsman, S. Uzun, S. Konosic, V. V. Brozovic and D. Strapajevic. A diagnosis of a renal injury by early biomarkers in patients exposed to cardiopulmonary bypass during cardiac surgery. Signa Vitae, 9(SUPPL. 1), 45-48. [16106]
Mazzeffi	2016	<100 participants	M. A. Mazzeffi, P. Stafford, K. Wallace, W. Bernstein, S. Deshpande, P. Odonkor, A. Grewal, E. Strauss, L. Stubbs, J. Gammie and P. Rock. Intra-abdominal Hypertension and Postoperative Kidney Dysfunction in Cardiac Surgery Patients. Journal of cardiothoracic and vascular anesthesia, 30(6), 1571-1577. [18515]
McCaffrey	2015	<100 participants	J. McCaffrey, B. Coupes, C. Chaloner, N. J. A. Webb, R. Barber and R. Lennon. Towards a biomarker panel for the assessment of AKI in children receiving intensive care. Pediatric Nephrology, 30(10), 1861-1871. [16108]

McCullough	2011	Not a primary study	P. A. McCullough, M. El-Ghoroury and H. Yamasaki. Early detection of acute kidney injury with neutrophil gelatinase- associated lipocalin. Journal of the American College of Cardiology, 57(17), 1762-1764. [16112]
McCullough	2012	Not relevant type of population	P. A. McCullough, F. J. Williams, D. N. Stivers, L. Cannon, S. Dixon, P. Alexander, D. Runyan and S. David. Neutrophil gelatinase-associated lipocalin: A novel marker of contrast nephropathy risk. American Journal of Nephrology, 35(6), 509-514. [16111]
McIlroy	2010	Not relevant biomarker assay or test	D. R. McIlroy, G. Wagener and H. T. Lee. Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery: The effect of baseline renal function on diagnostic performance. Clinical Journal of the American Society of Nephrology, 5(2), 211-219. [16122]
McIlroy	2010	Not a primary study	D. R. McIlroy, G. Wagener and H. T. Lee. Biomarkers of acute kidney injury: An evolving domain. Anesthesiology, 112(4), 998-1004. [16121]
McIlroy	2015	Not relevant biomarker assay or test	D. R. McIlroy, D. Farkas, M. Matto and H. T. Lee. Neutrophil gelatinase-associated lipocalin combined with delta serum creatinine provides early risk stratification for adverse outcomes after cardiac surgery: A prospective observational study. Critical Care Medicine, 43(5), 1043-1052. [16119]
McWilliam	2012	<100 participants	S. J. McWilliam, D. J. Antoine, V. Sabbisetti, M. A. Turner, T. Farragher, J. V. Bonventre, B. K. Park, R. L. Smyth and M. Pirmohamed. Mechanism-based urinary biomarkers to identify the potential for aminoglycoside-induced nephrotoxicity in premature neonates: a proof-of-concept study. PloS one, 7(8), e43809. [16128]
McWilliam	2018	Not relevant type of population	S. J. McWilliam, D. J. Antoine, A. L. Jorgensen, R. L. Smyth and M. Pirmohamed. Urinary Biomarkers of Aminoglycoside-Induced Nephrotoxicity in Cystic Fibrosis: Kidney Injury Molecule-1 and Neutrophil Gelatinase-Associated Lipocalin. Scientific reports, 8(1), 5094. [16126]
Md Ralib	2017	Not relevant type of population	A. Md Ralib, M. B. Mat Nor and J. W. Pickering. Plasma Neutrophil Gelatinase-Associated Lipocalin diagnosed acute kidney injury in patients with systemic inflammatory disease and sepsis. Nephrology, 22(5), 412-419. [16129]
Meersch	2018	Not a primary study	M. Meersch, A. Zarbock and M. KÃ¼llmar. Renal biomarkers for the initiation of renal replacement therapy--is this the future?...Srisawat N, Laoveeravat P, Limphunudom P, et al. The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: A feasibility study. J Crit Care 2018; 43:36-41. Journal of Thoracic Disease, 10(S3229-S3232. [6134]
Meersh	2014	<100 participants	M. Meersch, C. Schmidt, H. Van Aken, S. Martens, J. Rossaint, K. Singbartl, D. Gorlich, J. A. Kellum and A. Zarbock. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. PLoS ONE, 9(3), e93460. [16133]

Meersh	2017	No focus on DTA for AKI	M. Meersch, C. Schmidt, A. Hoffmeier, H. Van Aken, C. Wempe, J. Gerss and A. Zarbock. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Medicine, 43(11), 1551-1561. [16131]
Meersh	2014	<100 participants	M. Meersch, C. Schmidt, H. Van Aken, J. Rossaint, D. Gorlich, D. Stege, E. Malec, K. Januszewska and A. Zarbock. Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery. PLoS ONE, 9(10), e110865. [16132]
Meisner	2018	Not relevant biomarker assay or test	A. Meisner, K. F. Kerr, H. Thiessen-Philbrook, F. P. Wilson, A. X. Garg, M. G. Shlipak, P. Kavsak, R. P. Whitlock, S. G. Coca and C. R. Parikh. Development of biomarker combinations for postoperative acute kidney injury via Bayesian model selection in a multicenter cohort study. Biomarker Research, 6(1), 3. [16135]
Mellor	2012	<100 participants	A. J. Mellor and D. Woods. Serum neutrophil gelatinase-associated lipocalin in ballistic injuries: a comparison between blast injuries and gunshot wounds. Journal of critical care, 27(4), 419.e1-5. [16138]
Meneses	2018	<100 participants	G. C. Meneses, E. De Francesco Daher, G. B. da Silva Junior, G. F. Bezerra, T. P. da Rocha, I. E. P. de Azevedo, A. B. Liborio and A. M. C. Martins. Visceral leishmaniasis-associated nephropathy in hospitalised Brazilian patients: new insights based on kidney injury biomarkers. Tropical Medicine and International Health, 23(10), 1046-1057. [16139]
Menon	2016	Not relevant biomarker assay or test	S. Menon, S. L. Goldstein, T. Mottes, L. Fei, A. Kaddourah, T. Terrell, P. Arnold, M. R. Bennett and R. K. Basu. Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: A prospective cohort study. Nephrology Dialysis Transplantation, 31(4), 586-594. [16140]
Merrikhi	2014	<100 participants	A. Merrikhi, A. Gheissari and H. Mousazadeh. Urine and serum neutrophil gelatinase-associated lipocalin cut-off point for the prediction of acute kidney injury. Advanced biomedical research, 3(66. [16144]
Mertoglu	2018	<100 participants	C. Mertoglu, M. Gunay, A. Gurel and M. Gungor. Myo-inositol oxygenase as a novel marker in the diagnosis of acute kidney injury. Journal of Medical Biochemistry, 37(1), 1-6. [16145]
Metzger	2010	<100 participants	J. Metzger, T. Kirsch, E. Schiffer, P. Ulger, E. Mentes, K. Brand, E. M. Weissinger, M. Haubitz, H. Mischak and S. Herget-Rosenthal. Urinary excretion of twenty peptides forms an early and accurate diagnostic pattern of acute kidney injury. Kidney International, 78(12), 1252-1262. [16148]
Metzger	2016	Not relevant biomarker assay or test	J. Metzger, W. Mullen, H. Husi, A. Stalmach, S. Herget-Rosenthal, H. V. Groesdonk, H. Mischak and M. Klingele. Acute kidney injury prediction in cardiac surgery patients by a urinary peptide pattern: A case-control validation study. Critical Care, 20(1), 157. [16147]

Miah	2018	No focus on DTA for AKI	O. F. Miah, F. A. Dowel, A. Latif, A. N. Hai, M. A. Mahmud, M. A. Razzak and T. Ahammod. NGAL (Neutrophil Gelatinase-associated Lipocalin) is an Early Predictor of Acute Kidney Injury after Cardiac Surgery and Variation of NGAL Values in Homogenous Study Subject. Mymensingh medical journal : MMJ, 27(1), 212-215. [16152]
Miah	2018	<100 participants	O. F. Miah, D. K. Roy, A. A. Chowdhury, K. S. Alam, M. B. Alam, M. R. Anwar, F. A. Dowel, A. Latif, A. N. Hai, M. A. Mahmud, M. A. Razzak, T. Ahammod, S. U. Ahammed, H. Mahmud and R. S. Paul. Plasma Neutrophil Gelatinase Associated Lipocalin (pNGAL) Level to Identify AKI Early in Patients Undergoing Cardiac Valve Surgery. Mymensingh medical journal : MMJ, 27(2), 263-269. [16151]
Mironova	2019	Non-English publication	S. A. Mironova, Y. S. Yudina, M. V. Ionov, N. G. Avdonina, I. V. Emelyanov, E. Y. Vasilyeva, E. A. Kitaeva, N. E. Zvartau and A. O. Konradi. Novel biomarkers of kidney injury and fibrosis in patients with different severity of hypertension: Relation to vascular reactivity and stiffness. Russian Journal of Cardiology, 24(1), 44-51. [16159]
Mishra	2013	<100 participants	J. Mishra, C. Dent, R. Tarabishi, M. M. Mitsnefes, Q. Ma, C. Kelly, S. M. Ruff, K. Zahedi, M. Shao, J. Bean, K. Mori, J. Barasch and P. Devarajan. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet, 365(9466), 1231-8. [4031]
Mishra	2017	<100 participants	O. P. Mishra, A. K. Rai, P. Srivastava, K. Pandey, A. Abhinay, R. Prasad, R. N. Mishra and F. Schaefer. Predictive ability of urinary biomarkers for outcome in children with acute kidney injury. Pediatric Nephrology, 32(3), 521-527. [16162]
Mitsnefes	2013	<100 participants	M. M. Mitsnefes, T. S. Kathman, J. Mishra, J. Kartal, P. R. Khoury, T. L. Nickolas, J. Barasch and P. Devarajan. Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in children with chronic kidney disease. Pediatric Nephrology, 22(1), 101-8. [4017]
MohamadiSichani	2017	<100 participants	M. MohamadiSichani and Z. Tolou Ghamari. Investigation of urinary neutrophil gelatinase associated lipocalin (NGAL) for early diagnosis of acute kidney injury after percutaneous nephrolithotomy. African Journal of Urology, 23(3), 214-218. [16168]
Mohamed	2015	<100 participants	F. Mohamed, N. A. Buckley, S. Jayamanne, J. W. Pickering, P. Peake, C. Palangasinghe, T. Wijerathna, I. Ratnayake, F. Shihana and Z. H. Endre. Kidney damage biomarkers detect acute kidney injury but only functional markers predict mortality after paraquat ingestion. Toxicology Letters, 237(2), 140-150. [16169]
Mohamed	2016	<100 participants	Anonymous. Mechanism-specific injury biomarkers predict nephrotoxicity early following glyphosate surfactant herbicide (GPSH) poisoning. Toxicology letters.258 (pp 1-10), 2016.Date of publication: 06 sep 2016., . [4631]
Mohtat	2011	<100 participants	D. Mohtat, R. Thomas, Z. Du, Y. Boakye, T. Moulton, C. Driscoll and R. Woroniecki. Urinary transforming growth factor beta-1 as a marker of renal dysfunction in sickle cell disease. Pediatric Nephrology, 26(2), 275-280. [18523]

Mohtat	2011	Not relevant type of population	D. Mohtat, R. Thomas, Z. Du, Y. Boakye, T. Moulton, C. Driscoll and R. Woroniecki. Urinary transforming growth factor beta-1 as a marker of renal dysfunction in sickle cell disease. Pediatric Nephrology, 26(2), 275-280. [16173]
Moledina	2015	Not relevant biomarker assay or test	D. G. Moledina, C. R. Parikh, A. X. Garg, H. Thiessen-Philbrook, J. L. Koyner, U. D. Patel, P. Devarajan, M. G. Shlipak, S. G. Coca, J. Raman, V. Jeevanandam, S. Akhter, C. Edelstein, C. Passik, J. Nagy, M. Swaminathan, M. Chu, M. Goldbach, L. R. Guo, N. McKenzie, M. L. Myers, R. Novick, M. Quantz, M. Zappitelli, A. Palijan, M. Dewar, U. Darr, S. Hashim, J. Elefteriades, A. Geirsson, S. Garwood, I. Butrymowicz and H. Krumholz. Association of perioperative plasma neutrophil gelatinase-associated lipocalin levels with 3-year mortality after cardiac surgery: A prospective observational cohort study. PLoS ONE, 10(6), e0129619. [16178]
Moledina	2017	No focus on DTA for AKI	D. G. Moledina, I. E. Hall, H. Thiessen-Philbrook, P. P. Reese, F. L. Weng, B. Schroppel, M. D. Doshi, F. P. Wilson, S. G. Coca and C. R. Parikh. Performance of Serum Creatinine and Kidney Injury Biomarkers for Diagnosing Histologic Acute Tubular Injury. American Journal of Kidney Diseases, 70(6), 807-816. [16177]
Moon	2019	Not relevant type of population	J. M. Moon, B. J. Chun, M. H. Shin and Y. S. Cho. Predictive value of plasma neutrophil gelatinase-associated lipocalin in acute charcoal-burning carbon monoxide poisoning. Human & experimental toxicology, 960327119851259. [16180]
Morales-Buenrostro	2014	<100 participants	L. E. Morales-Buenrostro, O. I. Salas-Nolasco, J. Barrera-Chimal, G. C. Aparicio, S. Irizar-Santana, R. P. Rez-Villalva and N. A. Bobadilla. Hsp72 is a novel biomarker to predict acute kidney injury in critically ill patients. PLoS ONE, 9(10), e109407. [16186]
Moriyama	2016	<100 participants	T. Moriyama, S. Hagihara, T. Shiramomo, M. Nagaoka, S. Iwakawa and Y. Kanmura. Comparison of three early biomarkers for acute kidney injury after cardiac surgery under cardiopulmonary bypass. Journal of intensive care, 4(41. [16193]
Moriyama	2017	<100 participants	T. Moriyama, S. Hagihara, T. Shiramomo, M. Nagaoka, S. Iwakawa and Y. Kanmura. The protective effect of human atrial natriuretic peptide on renal damage during cardiac surgery. Journal of Anesthesia, 31(2), 163-169. [16194]
Mortara	2013	<100 participants	A. Mortara, M. Bonadies, S. Mazzetti, I. Fracchioni, P. Delfino, M. Chioffi, C. Bersano and G. Specchia. Neutrophil gelatinase-associated lipocalin predicts worsening of renal function in acute heart failure: methodological and clinical issues. Journal of Cardiovascular Medicine, 14(9), 629-634. [18528]
Mosa	2018	Not relevant biomarker assay or test	O. F. Mosa. Prognostic Significance of Serum NGAL and Troponin i against Acute Kidney Injury in Egyptian ICU Patients after Open Heart Surgery: A Pilot Study. Kidney Diseases, 4(4), 246-254. [16197]
Moyake	2016	Not relevant type of population	N. Moyake, E. Buchmann and N. J. Crowther. Neutrophil gelatinase-associated lipocalin as a diagnostic marker of acute kidney injury in pre-eclampsia. Journal of Obstetrics and Gynaecology Research, 42(11), 1483-1488. [16199]

Muhammad Usman	2013	<100 participants	M. Muhammad Usman, K. Dilshad Ahmed, K. Farooq Ahmad and N. Syed Muhammad Shahab. Comparison of urine with plasma neutrophil gelatinase-associated lipocalin in detecting acute kidney injury after cardiopulmonary bypass surgery. Pak. Armed Forces Med. J., 63(2), 179-183. [6175]
Munir	2013	<100 participants	Munir MU, Khan DA, Khan FA, Shahab Naqvi SM. . Rapid detection of acute kidney injury by urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass surgery.. J Coll Physicians Surg Pak 2013;23:103–6. [16206]
Munshi	2014	Not a primary study	R. Munshi and J. J. Zimmerman. Neutrophil gelatinase-associated lipocalin-can it predict the future?*. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 15(2), 173-4. [16207]
Muratoglu	2016	Not relevant type of population	M. Muratoglu, C. Kavalci, E. Kilicli, M. Findik, A. E. Kayipmaz and P. Durukan. Serum Neutrophil Gelatinase-Associated Lipocalin Levels In Early Detection Of Contrast-Induced Nephropathy. Clinical and investigative medicine. Medecine clinique et experimentale, 39(3), E88-E94. [16208]
Murphy	2014	<100 participants	N. Murphy, A. Vijayan, S. Frohlich, F. O'Farrell, M. Barry, S. Sheehan, J. Boylan and N. Conlon. Remote ischemic preconditioning does not affect the incidence of acute kidney injury after elective abdominal aortic aneurysm repair. Journal of Cardiothoracic and Vascular Anesthesia, 28(5), 1285-1292. [16209]
Musiol	2016	<100 participants	K. Musiol, G. Sobol-Milejska, L. Nowotka, K. Torba, M. Kniazewska and H. Wos. Renal function in children treated for central nervous system malignancies. Childs Nervous System, 32(8), 1431-1440. [18531]
Nadkarni	2017	No focus on DTA for AKI	G. N. Nadkarni, S. G. Coca, A. Meisner, S. Patel, K. F. Kerr, U. D. Patel, J. L. Koyner, A. X. Garg, H. T. Philbrook, C. L. Edelstein, M. Shlipak, J. El-Khoury, C. R. Parikh, J. Raman, V. Jeevanandam, S. Akhter, C. Passik, J. Nagy, M. Swaminathan, M. Chu, M. Goldbach, L. R. Guo, N. McKenzie, M. L. Myers, R. Novick, M. Quantz, M. Zappitelli, A. Palijan, M. Dewar, U. Darr, S. Hashim, J. Elefteriades, A. Geirsson, S. Garwood, I. Butrymowicz, H. Krumholz and S. Dixon. Urinalysis findings and urinary kidney injury biomarker concentrations. BMC Nephrology, 18(1), 218. [16216]
Nam	2015	Meta-analysis - retained as background material	M. J. Nam, C. H. Lim, H. J. Kim, Y. H. Kim, H. Choi, H. S. Son, H. J. Lim and K. Sun. A Meta-Analysis of Renal Function After Adult Cardiac Surgery With Pulsatile Perfusion. Artificial Organs, 39(9), 788-794. [16220]
Nasonova	2019	Non-English publication	S. N. Nasonova, I. V. Zhirov, M. V. Ledyakhova, T. V. Sharf, E. G. Bosykh, V. P. Masenko and S. N. Tereshchenko. Early diagnosis of acute renal injury in patients with acute decompensation of chronic heart failure. Terapevticheskii arkhiv, 91(4), 67-73. [16223]

Nayak	2016	Not relevant biomarker assay or test	N. M. Nayak, S. Madhumitha, R. A. Annigeri, R. Venkataraman, S. Balasubramaian, R. Seshadri, V. Vadamalai, B. S. Rao, P. C. Kowdle, N. Ramakrishnan and M. K. Mani. Clinical utility of urine neutrophil gelatinase-associated lipocalin measured at admission to predict outcomes in heterogeneous population of critically ill patients. Indian Journal of Nephrology, 26(2), 119-124. [16227]
Negrin	2018	<100 participants	L. L. Negrin, R. Hahn, T. Heinz and S. Hajdu. Diagnostic utility of serum neutrophil gelatinase-associated lipocalin in polytraumatized patients suffering acute kidney injury: A prospective study. BioMed Research International, 2018(2687584. [16229]
Nehus	2017	No focus on DTA for AKI	E. Nehus, A. Kaddourah, M. Bennett, O. Pyles and P. Devarajan. Subclinical Kidney Injury in Children Receiving Nonsteroidal Anti-Inflammatory Drugs After Cardiac Surgery. Journal of Pediatrics, 189(175-180. [16230]
Nejat	2012	No relevant outcome	M. Nejat, J. W. Pickering, P. Devarajan, J. V. Bonventre, C. L. Edelstein, R. J. Walker and Z. H. Endre. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. Kidney International, 81(12), 1254-1262. [16231]
Nguyen	2019	Not relevant type of population	L. S. Nguyen, V. Spagnoli, M. Kerneis, M. Hauguel-Moreau, O. Barthelemy, J. P. Collet, G. Montalescot and J. Silvain. Evaluation of neutrophil gelatinase-associated lipocalin and cystatin C as biomarkers of acute kidney injury after ST-segment elevation myocardial infarction treated by percutaneous coronary intervention. Archives of Cardiovascular Diseases, 112(3), 180-186. [16236]
Nickavar	2016	<100 participants	A. Nickavar, B. Safaeian, E. Valavi and F. Moradpour. Validity of Neutrophil Gelatinase Associated Lipocaline as a Biomarker for Diagnosis of Children with Acute Pyelonephritis. Urology journal, 13(5), 2860-2863. [16239]
Niemann	2009	<100 participants	C. U. Niemann, A. Walia, J. Waldman, M. Davio, J. P. Roberts, R. Hirose and J. Feiner. Acute kidney injury during liver transplantation as determined by neutrophil gelatinase-associated lipocalin. Liver Transplantation, 15(12), 1852-1860. [16243]
Ning	2018	Not relevant type of population	L. Ning, Z. Li, D. Wei, H. Chen, C. Yang, D. Wu, Y. Wang and J. Zhang. Urinary semaphorin 3A as an early biomarker to predict contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas, 51(4), e6487. [16249]
Nishida	2010	<100 participants	M. Nishida, H. Kawakatsu, Y. Okumura and K. Hamaoka. Serum and urinary neutrophil gelatinase-associated lipocalin levels in children with chronic renal diseases. Pediatrics International, 52(4), 563-568. [16251]
Noto	2019	<100 participants	A. Noto, A. Cortegiani and A. David. Nephrocheck: Should we consider urine osmolality?. Critical Care, 23(1), 23. [16255]
Noyan	2015	<100 participants	A. Noyan, G. Parmaksiz, H. Dursun, S. S. Ezer, R. Anarat and N. Cengiz. Urinary NGAL, KIM-1 and L-FABP concentrations in antenatal hydronephrosis. Journal of Pediatric Urology, . [16257]

Nusca	2018	Not relevant type of population	A. Nusca, M. Miglionico, C. Proscia, L. Ragni, M. Carassiti, F. L. Pepe and G. D. Sciascio. Early prediction of contrast-induced acute kidney injury by a "bedside" assessment of Neutrophil Gelatinase-Associated Lipocalin during elective percutaneous coronary interventions. PLoS ONE, 13(5), e0197833. [16258]
Nymo	2012	Not relevant biomarker assay or test	S. H. Nymo, T. Ueland, E. T. Askevold, T. H. Flo, J. Kjekshus, J. Hulthe, J. Wikstrand, J. McMurray, D. J. Van Veldhuisen, L. Gullestad, P. Aukrust and A. Yndestad. The association between neutrophil gelatinase-associated lipocalin and clinical outcome in chronic heart failure: results from CORONA. Journal of internal medicine, 271(5), 436-443. [18537]
Odum	2014	<100 participants	L. Odum, A. S. Andersen and T. V. F. Hviid. Urinary neutrophil gelatinase-associated lipocalin (NGAL) excretion increases in normal pregnancy but not in preeclampsia. Clinical Chemistry and Laboratory Medicine, 52(2), 221-225. [18539]
Oh	2012	<100 participants	S. W. Oh, H. J. Chin, D. W. Chae and K. Y. Na. Erythropoietin improves long-term outcomes in patients with acute kidney injury after coronary artery bypass grafting. Journal of Korean Medical Science, 27(5), 506-511. [16266]
Olvera-Posada	2017	<100 participants	D. Olvera-Posada, T. Dayarathna, M. Dion, H. Alenezi, A. Sener, J. D. Denstedt, S. E. Pautler and H. Razvi. KIM-1 Is a Potential Urinary Biomarker of Obstruction: Results from a Prospective Cohort Study. Journal of Endourology, 31(2), 111-118. [16268]
Omerika	2014	No focus on DTA for AKI	L. Omerika, S. Rasic and N. Serdarevic. Importance of determination of urine neutrophile gelatinase associated lipocalin in early detection of acute kidney injury. Collegium Antropologicum, 38(1), 161-166. [16269]
Oncel	2016	<100 participants	M. Y. Oncel, F. E. Canpolat, S. Arayici, E. Alyamac Dizdar, N. Uras and S. S. Oguz. Urinary markers of acute kidney injury in newborns with perinatal asphyxia (.). Renal failure, 38(6), 882-8. [16271]
Onk	2016	Not relevant biomarker assay or test	O. A. Onk, D. Onk, F. Ozcelik, M. Gunay and K. Turkmen. Risk factors for acute kidney injury after coronary artery bypass surgery and its detection using neutrophil gelatinase-associated lipocalin. CardioRenal Medicine, 6(3), 216-229. [16272]
Opotowsky	2017	No focus on DTA for AKI	A. R. Opotowsky, F. R. Baraona, F. R. Mc Causland, B. Loukas, E. Landzberg, M. J. Landzberg, V. Sabbisetti and S. S. Waikar. Estimated glomerular filtration rate and urine biomarkers in patients with single-ventricle Fontan circulation. Heart (British Cardiac Society), 103(6), 434-442. [16273]
Ordooei Javan	2017	<100 participants	Ordooei Javan, J. Salamzadeh, S. Shokouhi and Z. Sahraei. Evaluation of renal toxicity of colistin therapy with neutrophil gelatinase-associated lipocalin: A biomarker of renal tubular damage. Iranian Journal of Kidney Diseases, 11(6): 447-453 . [15762]
Orsolya	2015	No focus on DTA for AKI	M. Orsolya, M. Attila-Zoltan, V. Gherman, F. Zaharie, S. Bolboaca, C. Chira, C. Bodolea, C. Tomuleasa, A. Irimie, L. Coman and D. Ionescu. The effect of anaesthetic management on neutrophil gelatinase associated lipocalin (NGAL) levels after robotic surgical oncology. Journal of B.U.ON., 20(1), 317-324. [16276]

Osman	2014	Not relevant type of population	O. Osman, O. Ayee Deniz, E. Abdulkadir, S. Cihat, S. Husnu Oguz and C. Avse Banu. Cystatin C as biomarker of contrast-induced nephropathy in pediatric cardiac angiography. Turkish journal of medical sciences, 44(2), 178-85. [16280]
Ostermann	2015	Not a primary study	M. Ostermann and M. Joannidis. Biomarkers for AKI improve clinical practice: no. Intensive care medicine, 41(4), 618-22. [16281]
Ostermann	2018	Substudy measuring associations in nephrocheck levels and exposure to renal insult - retained as background material	M. Ostermann, P. A. McCullough, L. G. Forni, S. M. Bagshaw, M. Joannidis, J. Shi, K. Kashani, P. M. Honore, L. S. Chawla and J. A. Kellum. Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. Critical Care Medicine, 46(3), 375-383. [16283]
Owens	2011	<100 participants	G. E. Owens, K. King, J. G. Gurney and J. R. Charpie. Low Renal Oximetry Correlates With Acute Kidney Injury After Infant Cardiac Surgery. Pediatric cardiology, 32(2), 183-188. [18542]
Oz	2016	Not relevant biomarker assay or test	K. Oz, S. Gode, S. Basgoze, M. Koser, A. Oz, O. S. Goksel, M. Yeniterzi and I. Bakir. Cystatin C and NGAL as Biomarkers for Early Detection of Acute Kidney Injury in Geriatrics. International surgery, 101(7-8), 390-398. [18543]
Ozdemir	2014	Not relevant type of population	O. Ozdemir, A. D. Oguz, A. Eren, C. Sanli, H. O. Sylemezoglu and A. B. Cayci. Cystatin C as biomarker of contrast-induced nephropathy in pediatric cardiac angiography. Turkish Journal of Medical Sciences, 44(2), 178-185. [16290]
Ozkan	2014	<100 participants	S. Ozkan, P. Durukan, C. Kavalci, A. Duman, M. B. Sayhan, O. Salt and A. Ipekci. Importance of neutrophil gelatinase-associated lipocalin in differential diagnosis of acute and chronic renal failure. Iranian Red Crescent Medical Journal, 16(8), e14133. [16292]
Paapstel	2016	<100 participants	K. Paapstel, M. Zilmer, J. Eha, K. Tootsi, A. Piir and J. Kals. Early biomarkers of renal damage in relation to arterial stiffness and inflammation in male coronary artery disease patients. Kidney and Blood Pressure Research, 41(4), 488-497. [16293]
Paarmann	2013	Not relevant biomarker assay or test	H. Paarmann, E. I. Charitos, A. Beilharz, H. Heinze, J. Schon, A. Berggreen and M. Heringlake. Duration of cardiopulmonary bypass is an important confounder when using biomarkers for early diagnosis of acute kidney injury in cardiac surgical patients. Applied Cardiopulmonary Pathophysiology, 17(3), 284-297. [16294]
Padhy	2014	Not relevant type of population	M. Padhy, S. Kaushik, M. P. Girish, S. Mohapatra, S. Shah and B. C. Koner. Serum neutrophil gelatinase associated lipocalin (NGAL) and cystatin C as early predictors of contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention. Clinica Chimica Acta, 435(48-52. [16296]
Pajenda	2015	<100 participants	S. Pajenda, A. Ilhan-Mutlu, M. Preusser, S. Roka, W. Druml and L. Wagner. NephroCheck data compared to serum creatinine in various clinical settings. BMC Nephrology, 16(1), 0203-5. [16299]

Palazzuoli	2014	Not relevant biomarker assay or test	A. Palazzuoli, G. Ruocco, M. Beltrami, B. Franci, M. Pellegrini, B. Lucani, R. Nuti and C. Ronco. Admission plasma neutrophil gelatinase associated lipocalin (NGAL) predicts worsening renal function during hospitalization and post discharge outcome in patients with acute heart failure. Acute cardiac care, 16(3), 93-101. [16300]
Palazzuoli	2014	Not relevant biomarker assay or test	A. Palazzuoli, G. Ruocco, M. Pellegrini, S. Martini, G. Del Castillo, M. Beltrami, B. Franci, B. Lucani and R. Nuti. Patients with Cardiorenal Syndrome Revealed Increased Neurohormonal Activity, Tubular and Myocardial Damage Compared to Heart Failure Patients with Preserved Renal Function. Cardiorenal Medicine, 4(3-4), 257-268. [18544]
Palazzuoli	2015	Not relevant biomarker assay or test	A. Palazzuoli, G. Ruocco, M. Pellegrini, C. De Gori, G. Del Castillo, B. Franci, R. Nuti and C. Ronco. Comparison of neutrophil gelatinase-associated lipocalin versus B-type natriuretic peptide and cystatin C to predict early acute kidney injury and outcome in patients with acute heart failure. American Journal of Cardiology, 116(1), 104-111. [16301]
Palermo	2017	<100 participants	J. Palermo, A. B. Dart, A. De Mello, P. Devarajan, R. Gottesman, G. Garcia Guerra, G. Hansen, A. R. Joffe, C. Mammen, N. Majesic, C. Morgan, P. Skippen, M. Pizzi, A. Palijan and M. Zappitelli. Biomarkers for Early Acute Kidney Injury Diagnosis and Severity Prediction: A Pilot Multicenter Canadian Study of Children Admitted to the ICU. Pediatric Critical Care Medicine, 18(6), e235-e244. [16303]
Pan	2018	<100 participants	J. J. Pan, Z. Y. Sun, X. Y. Zhou, Y. H. Hu, R. Cheng, X. Q. Chen and Y. Yang. Is neutrophil gelatinase-associated lipocalin a good diagnostic marker for renal injury in asphyxiated preterm infants?. Journal of Research in Medical Sciences, 23(1), 90. [16306]
Pang	2016	Not relevant type of population	Y. Pang, Y. Tan, Y. Li, J. Zhang, Y. Guo, Z. Guo, C. Zhang, F. Yu and M. H. Zhao. Pentraxin 3 Is Closely Associated With Tubulointerstitial Injury in Lupus Nephritis: A Large Multicenter Cross-Sectional Study. Medicine, 95(3), e2520. [16309]
Pang	2017	<100 participants	H. M. Pang, X. L. Qin, T. T. Liu, W. X. Wei, D. H. Cheng, H. Lu, Q. Guo and L. Jing. Urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin as early biomarkers for predicting vancomycin-associated acute kidney injury: a prospective study. European review for medical and pharmacological sciences, 21(18), 4203-4213. [16308]
Papadopoulou-Marketou	2015	<100 participants	N. Papadopoulou-Marketou, C. Skevaki, I. Kosteria, M. Peppa, G. P. Chrousos, I. Papassotiriou and C. Kanaka-Gantenbein. NGAL and cystatin C: two possible early markers of diabetic nephropathy in young patients with type 1 diabetes mellitus: one year follow up. Hormones-International Journal of Endocrinology and Metabolism, 14(2), 232-240. [18546]

Papassotiriou	2016	<100 participants	G. P. Papassotiriou, E. Kastritis, M. Gkotzamanidou, D. Christoulas, E. Eleutherakis-Papaiakovou, M. Migkou, M. Gavriatopoulou, M. Roussou, A. Margeli, I. Papassotiriou, M. A. Dimopoulos and E. Terpos. Neutrophil Gelatinase-Associated Lipocalin and Cystatin C Are Sensitive Markers of Renal Injury in Patients with Multiple Myeloma. Clinical Lymphoma, Myeloma and Leukemia, 16(1), 29-35. [16312]
Parekh	2013	<100 participants	D. J. Parekh, J. M. Weinberg, B. Ercole, K. C. Torkko, W. Hilton, M. Bennett, P. Devarajan and M. A. Venkatachalam. Tolerance of the human kidney to isolated controlled ischemia. Journal of the American Society of Nephrology, 24(3), 506-517. [16314]
Parikh	2012	Not a primary study	A. Parikh and A. Shaw. The Economics of Renal Failure and Kidney Disease in Critically Ill Patients. Critical Care Clinics, 28(1), 99-111. [16320]
Parikh	2013	<100 participants	C. R. Parikh, J. Mishra, H. Thiessen-Philbrook, B. Dursun, Q. Ma, C. Kelly, C. Dent, P. Devarajan and C. L. Edelstein. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney International, 70(1), 199-203. [4027]
Parikh	2013	Not a primary study	C. R. Parikh and G. Han. Variation in performance of kidney injury biomarkers due to cause of acute kidney injury. American Journal of Kidney Diseases, 62(6), 1023-1026. [16328]
Parikh	2016	Uses simulated data from the TRIBE AKI study - retained as background material	C. R. Parikh, D. G. Moledina, S. G. Coca, H. R. Thiessen-Philbrook and A. X. Garg. Application of new acute kidney injury biomarkers in human randomized controlled trials. Kidney International, 89(6), 1372-1379. [16324]
Parikh	2017	No relevant outcome	C. R. Parikh, J. Puthumana, M. G. Shlipak, J. L. Koyner, H. Thiessen-Philbrook, E. McArthur, K. Kerr, P. Kavsak, R. P. Whitlock, A. X. Garg and S. G. Coca. Relationship of kidney injury biomarkers with long-term cardiovascular outcomes after cardiac surgery. Journal of the American Society of Nephrology, 28(12), 3699-3707. [16321]
Parikh	2017	Not a primary study	A. Parikh, J. A. Rizzo, P. Canetta, C. Forster, M. Sise, O. Maarouf, E. Singer, A. Elger, S. Elitok, K. Schmidt-Ott, J. Barasch and T. L. Nickolas. Correction: Does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) & serum creatinine (sCr) for acute kidney injury (AKI) diagnosis. PloS one, 12(9), e0185772. [16317]
Parikh	2017	Not a primary study	A. Parikh, J. A. Rizzo, P. Canetta, C. Forster, M. Sise, O. Maarouf, E. Singer, A. Elger, S. Elitok, K. Schmidt-Ott, J. Barasch and T. L. Nickolas. Correction: Does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) & serum creatinine (sCr) for acute kidney injury (AKI) diagnosis (PLoS ONE (2017) 12:5 (e0178091) DOI: 10.1371/journal.pone.0178091). PLoS ONE, 12(9), e0185772. [16319]
Park	2012	<100 participants	H. D. Park, J. Y. Seo and S. Y. Lee. The Relationship between serum neutrophil gelatinase-associated lipocalin and renal function in patients with vancomycin treatment. Annals of Clinical and Laboratory Science, 42(1), 7-13. [16341]

Park	2015	<100 participants	G. Y. Park, C. H. Yu, J. S. Kim, Y. J. Kang, O. Kwon, J. Y. Choi, J. H. Cho, C. D. Kim, Y. L. Kim and S. H. Park. Plasma neutrophil gelatinase-associated lipocalin as a potential predictor of adverse renal outcomes in immunoglobulin a nephropathy. Korean Journal of Internal Medicine, 30(3), 345-353. [16340]
Park	2016	<100 participants	S. O. Park, J. Y. Ahn, Y. H. Lee, Y. J. Kim, Y. H. Min, H. C. Ahn, Y. D. Sohn, S. M. Park, Y. T. Oh and D. H. Shin. Plasma neutrophil gelatinase-associated lipocalin as an early predicting biomarker of acute kidney injury and clinical outcomes after recovery of spontaneous circulation in out-of-hospital cardiac arrest patients. Resuscitation, 101(84-90. [16345]
Park	2018	<100 participants	Y.-R. Park, J. S. Oh, H. Jeong, J. Park, Y. M. Oh, S. Choi and K. H. Choi. Predicting long-term outcomes after cardiac arrest by using serum neutrophil gelatinase-associated lipocalin. American Journal of Emergency Medicine, 36(4), 660-664. [18548]
Park	2018	Not relevant type of population	S. Y. Park, J. S. Eom, J. S. Lee, Y. S. Ju and J. Y. Park. Neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury in patients during treatment with colistimethate sodium. Infection and Chemotherapy, 50(2), 128-137. [16346]
Park	2015	Not relevant biomarker assay or test	C. M. Park, J. S. Kim, H. W. Moon, S. Park, H. Kim, M. Ji, M. Hur and Y. M. Yun. Usefulness of plasma neutrophil gelatinase-associated lipocalin as an early marker of acute kidney injury after cardiopulmonary bypass in Korean cardiac patients: A prospective observational study. Clinical Biochemistry, 48(1-2), 44-49. [16339]
Parr	2015	Not relevant type of population	S. K. Parr, A. J. Clark, A. Bian, A. K. Shintani, N. E. Wickersham, L. B. Ware, T. A. Ikizler and E. D. Siew. Urinary L-FABP predicts poor outcomes in critically ill patients with early acute kidney injury. Kidney International, 87(3), 640-648. [16347]
Parravicini	2010	<100 participants	E. Parravicini, S. L. Nemerofsky, K. A. Michelson, T. K. Huynh, M. E. Sise, D. A. Bateman, J. M. Lorenz and J. M. Barasch. Urinary Neutrophil Gelatinase-Associated Lipocalin Is a Promising Biomarker for Late Onset Culture-Positive Sepsis in Very Low Birth Weight Infants. Pediatric research, 67(6), 636-640. [18550]
Parravicini	2016	<100 participants	E. Parravicini, C. Locatelli, J. M. Lorenz, S. L. Nemerofsky and D. A. Bateman. Is urinary neutrophil gelatinase-associated lipocalin able to predict acute kidney injury episodes in very low birth weight infants in clinical settings?. Pediatric Research, 80(5), 663-667. [16348]
Passov	2019	Not relevant biomarker assay or test	A. Passov, L. Petaja, M. Pihlajoki, U.-S. Salminen, R. Suojaranta, A. Vento, S. Andersson, V. Pettila, A. Schramko and E. Pesonen. The origin of plasma neutrophil gelatinase-associated lipocalin in cardiac surgery. BMC nephrology, 20(1), 182. [16350]
Patel	2013	Not relevant type of population	M. L. Patel, R. Sachan, R. Gangwar, P. Sachan and S. M. Natu. Correlation of serum neutrophil gelatinase-associated lipocalin with acute kidney injury in hypertensive disorders of pregnancy. International Journal of Nephrology and Renovascular Disease, 6(181-186. [16352]

Patel	2016	Not relevant biomarker assay or test	M. L. Patel, R. Sachan, R. Shyam, S. Kumar, R. Kamal and A. Misra. Diagnostic accuracy of urinary neutrophil gelatinase-associated lipocalin in patients with septic acute kidney injury. International Journal of Nephrology and Renovascular Disease, 9(161-169. [16351]
Patschan	2014	<100 participants	D. Patschan, M. Heeg, M. Brier, G. Brandhorst, S. Schneider, G. A. Muller and M. J. Koziolek. CD4+ lymphocyte adenosine triphosphate--a new marker in sepsis with acute kidney injury?. BMC nephrology, 15(203. [16353]
Peco-Antic	2013	Not relevant biomarker assay or test	A. Peco-Antic, I. Ivanisevic, I. Vulicevic, J. Kotur-Stevuljevic, S. Ilic, J. Ivanisevic, M. Miljkovic and N. Kocev. Biomarkers of acute kidney injury in pediatric cardiac surgery. Clinical Biochemistry, 46(13-14), 1244-1251. [16358]
Pedersen	2010	<100 participants	K. R. Pedersen, H. B. Ravn, V. E. Hjortdal, R. Norregaard and J. V. Povlsen. Neutrophil Gelatinase-Associated Lipocalin (NGAL): Validation of commercially available ELISA. Scandinavian Journal of Clinical and Laboratory Investigation, 70(5), 374-382. [16360]
Pejovic	2015	Not relevant type of population	B. Pejovic, J. Eric-Marinkovic, M. Pejovic, J. Kotur-Stevuljevic and A. Peco-Antic. Detection of acute kidney injury in premature asphyxiated neonates by serum neutrophil gelatinase-associated lipocalin (sNGAL) - Sensitivity and specificity of a potential new biomarker. Biochemia Medica, 25(3), 450-459. [16361]
Peralta	2014	Not relevant type of population	C. A. Peralta, R. Scherzer, C. Grunfeld, A. Abraham, P. C. Tien, P. Devarajan, M. Bennett, A. W. Butch, K. Anastos, M. H. Cohen, M. Nowicki, A. Sharma, M. A. Young, M. J. Sarnak, C. R. Parikh and M. G. Shlipak. Urinary biomarkers of kidney injury are associated with all-cause mortality in the Women's Interagency HIV Study (WIHS). HIV Medicine, 15(5), 291-300. [16365]
Peres	2014	<100 participants	L. A. Peres, A. D. da Cunha, R. A. Assumpcao, A. Schafer, A. L. da Silva, A. D. Gaspar, D. F. Scarpari, J. B. Alves, R. Girelli Neto and T. F. de Oliveira. Evaluation of the cisplatin nephrotoxicity using the urinary neutrophil gelatinase-associated lipocalin (NGAL) in patients with head and neck cancer. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia, 36(3), 280-288. [16367]
Perrin	2013	Not relevant type of population	T. Perrin, E. Descombes, J. L. Magnin, M. Gachet, O. M. Hemett, D. Hayoz, V. Stolt, G. Baeriswyl, J. C. Stauffer, J. J. Goy, M. Togni and S. Cook. Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) and contrast-induced acute kidney injury after coronary angiogram. Swiss Medical Weekly, 143(13853. [16369]
Perrotti	2015	Not relevant biomarker assay or test	Perrotti A, Miltgen G, Chevet-Noel A, Durst C, Vernerey D, Bardonnet K, et al. . Neutrophil gelatinase-associated lipocalin as early predictor of acute kidney injury after cardiac surgery in adults with chronic kidney failure. . Ann Thorac Surg 2015;99:864–9. https://doi.org/10.1016/j.athoracsur.2014.10.011. [16372]

Perry	2010	Not relevant biomarker assay or test	T. E. Perry, J. D. Muehlschlegel, K. Y. Liu, A. A. Fox, C. D. Collard, S. K. Shernan and S. C. Body. Plasma neutrophil gelatinase-associated lipocalin and acute postoperative kidney injury in adult cardiac surgical patients. Anesthesia and Analgesia, 110(6), 1541-1547. [16373]
Pesonen	2016	<100 participants	E. J. Pesonen, P. K. Suominen, J. Keski-Nisula, I. P. Mattila, P. Rautiainen and T. Jahnukainen. The Effect of Methylprednisolone on Plasma Concentrations of Neutrophil Gelatinase-Associated Lipocalin in Pediatric Heart Surgery. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 17(2), 121-7. [16375]
Petrovic	2013	<100 participants	S. Petrovic, N. Bogavac-Stanojevic, A. Peco-Antic, I. Ivanisevic, J. Kotur-Stevuljevic, D. Paripovic, M. Sopic and Z. Jelic-Ivanovic. Clinical application neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 as indicators of inflammation persistence and acute kidney injury in children with urinary tract infection. BioMed Research International, 2013(947157. [16378]
Pezeshgi	2018	<100 participants	A. Pezeshgi, S. Ghodrati, M. Kiafar, K. Kamali and M. Asadi-Khiavi. Study of neutrophil gelatinase-associated lipocalin in patients with cardiovascular shock. Journal of Renal Injury Prevention, 7(3), 144-147. [18554]
Piccoli	2012	Not a primary study	G. B. Piccoli, M. Ferraresi, E. Aroasio, S. Gonella, A. De Pascale and A. Veltri. The search for perfect biomarkers in acute kidney damage: The case of NGAL, from AKI to acute pyelonephritis: Back to the clinic?. Nephrology Dialysis Transplantation, 27(9), 3665-3666. [16384]
Pickering	2012	<100 participants	J. W. Pickering, A. M. Ralib and Z. H. Endre. Combining creatinine and volume kinetics identifies missed cases of acute kidney injury following cardiac arrest. Critical Care, 17(1), R7. [16389]
Pickering	2013	Not relevant biomarker assay or test	J. W. Pickering and Z. H. Endre. Linking Injury to Outcome in Acute Kidney Injury: A Matter of Sensitivity. PLoS ONE, 8(4), e62691. [16387]
Pickering	2013	Not relevant biomarker assay or test	J. W. Pickering and Z. H. Endre. The clinical utility of plasma neutrophil gelatinase-associated lipocalin in acute kidney injury. Blood purification, 35(4), 295-302. [16388]
Piirainen	2018	<100 participants	A. Piirainen, J. Huopio, H. Kokki, A. Holopainen, T. Pajunen, K. Pulkki and M. Kokki. Novel renal markers for the assessment of renal integrity in patients undergoing knee arthroplasty - a pilot study. Journal of Experimental Orthopaedics, 5(1), 40. [16393]
Pilarczyk	2015	<100 participants	K. Pilarczyk, M. Edayadiyil-Dudasova, D. Wendt, E. Demircioglu, J. Benedik, D. S. Dohle, H. Jakob and F. Dusse. Urinary [TIMP-2]*[IGFBP7] for early prediction of acute kidney injury after coronary artery bypass surgery. Annals of Intensive Care, 5(1), 1-11. [16394]
Pisano	2018	Not a primary study	D. V. Pisano and M. F. Joyce. Plasma neutrophil gelatinase-associated lipocalin: Biomarker of the future or just another test?. Journal of clinical anesthesia, 45(37-38. [16398]
Plebani	2017	Not a primary study	M. Plebani. Biomarkers of acute kidney injury: A step forward. Clinical Chemistry and Laboratory Medicine, 55(8), 1071-1073. [16399]

Plewes	2014	Not relevant type of population	K. Plewes, A. A. Royakkers, J. Hanson, M. M. U. Hasan, S. Alam, A. Ghose, R. J. Maude, P. M. Stassen, P. Charunwatthana, S. J. Lee, G. D. Turner, A. M. Dondorp and M. J. Schultz. Correlation of biomarkers for parasite burden and immune activation with acute kidney injury in severe falciparum malaria. Malaria Journal, 13(1), 91. [16400]
Polat	2013	<100 participants	M. Polat, K. Fidan, O. Derinoz, S. Gonen and O. Soylemezoglu. Neutrophil gelatinase-associated lipocalin as a follow-up marker in critically ill pediatric patients with established acute kidney injury. Renal Failure, 35(3), 352-356. [16402]
Poorshahbaz	2015	<100 participants	F. Poorshahbaz, A. Karami, M. Jozpanahi, A. Pezeshki, S. Fagihzadeh, A. Esmailzadeh, R. Moosazadeh, M. Behmanesh, M. Kiafar and M. Kashkuli. Comparison of Changes in Serum Creatinine and PNGAL in Predicting Renal Damage in Brucellosis Patients Receiving Gentamycin. Crescent Journal of Medical and Biological Sciences, 2(4), 116-120. [18556]
Portal	2010	<100 participants	A. J. Portal, M. J. W. McPhail, M. Bruce, I. Coltart, A. Slack, R. Sherwood, N. D. Heaton, D. Shawcross, J. A. Wendon and M. A. Heneghan. Neutrophil gelatinase-Associated lipocalin predicts acute kidney injury in patients undergoing liver transplantation. Liver Transplantation, 16(11), 1257-1266. [16405]
Prabhu	2010	<100 participants	A. Prabhu, D. I. Sujatha, B. Ninan and M. A. Vijayalakshmi. Neutrophil Gelatinase Associated Lipocalin as a Biomarker for Acute Kidney Injury in Patients Undergoing Coronary Artery Bypass Grafting with Cardiopulmonary Bypass. Annals of Vascular Surgery, 24(4), 525-531. [16409]
Prasad	2014	Not a primary study	A. Prasad. Acute kidney injury following contrast administration in pediatric congenital heart disease patients: Time to move beyond the serum creatinine. Catheterization and Cardiovascular Interventions, 84(4), 620-621. [16411]
Prowle	2014	Not a primary study	J. R. Prowle and C. J. Kirwan. Acute kidney injury after cardiac surgery: The injury that keeps on hurting?. Critical Care Medicine, 42(9), 2142-2143. [16416]
Prowle	2015	Not a primary study	J. R. Prowle. Measurement of AKI biomarkers in the ICU: still striving for appropriate clinical indications. Intensive Care Medicine, 41(3), 541-543. [16414]
Prowle	2015	<100 participants	J. R. Prowle, P. Calzavacca, E. Licari, E. V. Ligabo, J. E. Echeverri, S. M. Bagshaw, A. Haase-Fielitz, M. Haase, V. Ostland, E. Noiri, M. Westerman, P. Devarajan and R. Bellomo. Combination of biomarkers for diagnosis of acute kidney injury after cardiopulmonary bypass. Renal Failure, 37(3), 408-416. [16415]
Przybylowski	2010	No focus on DTA for AKI	P. Przybylowski, J. Malyszko and J. S. Malyszko. Serum Neutrophil Gelatinase-Associated Lipocalin Correlates With Kidney Function in Heart Allograft Recipients. Transplantation Proceedings, 42(5), 1797-1802. [16421]
Przybylowski	2011	Not relevant type of population	P. Przybylowski, E. Koc-Zorawska, J. S. Malyszko, S. Kozlowska, M. Mysliwiec and J. Malyszko. Liver fatty-acid-binding protein in heart and kidney allograft recipients in relation to kidney function. Transplantation Proceedings, 43(8), 3064-3067. [16420]

Puiac	2017	<100 participants	C. Puiac, J. Szederjesi, A. Lazar, C. Bad and L. Puscasiu. Neutrophil Gelatinase-Associated Lipocalin as a Marker for Renal Dysfunction Detection in Critically Ill Patients with Increased Intraabdominal Pressure. Journal of Critical Care Medicine, 3(1), 24-28. [18561]
Puthumana	2017	Meta-analysis - retained as background material	J. Puthumana, X. Ariza, J. M. Belcher, I. Graupera, P. Gines and C. R. Parikh. Urine Interleukin 18 and Lipocalin 2 Are Biomarkers of Acute Tubular Necrosis in Patients With Cirrhosis: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology, 15(7), 1003. [16424]
Pynn	2015	No focus on DTA for AKI	J. M. Pynn, E. Parravicini, L. Saiman, D. A. Bateman, J. M. Barasch and J. M. Lorenz. Urinary neutrophil gelatinase-associated lipocalin: Potential biomarker for late-onset sepsis. Pediatric Research, 78(1), 76-81. [16425]
Qasem	2014	Not relevant biomarker assay or test	A. A. Qasem, S. E. Farag, E. Hamed, M. Emara, A. Bihery and H. Pasha. Urinary biomarkers of acute kidney injury in patients with liver cirrhosis. ISRN nephrology, 2014(376795. [16426]
Qiao	2015	Not relevant type of population	B. Qiao, J. Deng, Y. Li, X. Wang and Y. Han. Rosuvastatin attenuated contrast-induced nephropathy in diabetes patients with renal dysfunction. International Journal of Clinical and Experimental Medicine, 8(2), 2342-2349. [16427]
Quartin	2013	Not a primary study	A. Quartin, R. Schein and C. Cely. Accuracy of plasma neutrophil gelatinase-associated lipocalin in the early diagnosis of contrast-induced acute kidney injury in critical illness. Intensive Care Medicine, 39(9), 1670. [16428]
Quintavalle	2015	Not relevant type of population	C. Quintavalle, C. V. Anselmi, F. De Micco, G. Roscigno, G. Visconti, B. Golia, A. Focaccio, B. Ricciardelli, E. Perna, L. Papa, E. Donnarumma, G. Condorelli and C. Briguori. Neutrophil gelatinase-associated lipocalin and contrast-induced acute kidney injury. Circulation: Cardiovascular Interventions, 8(9), e002673. [16430]
Radovic	2019	No relevant outcome	M. Radovic, S. Bojic, J. Kotur-Stevuljevic, V. Lezaic, B. Milicic, M. Velinovic, R. Karan and S. Simic-Ogrizovic. Serum lactate as reliable biomarker of acute kidney injury in low-risk cardiac surgery patients. Journal of Medical Biochemistry, 38(2), 118-125. [16433]
Rafiei	2015	<100 participants	A. Rafiei, H. Mohammadjafari, S. Bazi and A. M. Mirabi. Urinary neutrophil gelatinase-associated lipocalin (NGAL) might be an independent marker for anticipating scar formation in children with acute pyelonephritis. Journal of Renal Injury Prevention, 4(2), 39-44. [18563]
Raggal	2013	<100 participants	N. E. Raggal, S. M. Khafagy, N. H. Mahmoud and S. E. Beltagy. Serum neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in asphyxiated neonates. Indian pediatrics, 50(5), 459-62. [16434]
Rakkolainen	2016	<100 participants	I. Rakkolainen and J. Vuola. Plasma NGAL predicts early acute kidney injury no earlier than s-creatinine or cystatin C in severely burned patients. Burns, 42(2), 322-328. [16435]

Ralib	2011	Not a primary study	A. M. Ralib, J. W. Pickering and Z. H. Endre. Predictor of early diagnosis, diagnosis, or progression of acute kidney injury. Annals of Emergency Medicine, 57(1), 75-76. [16437]
Ralib	2012	Not relevant biomarker assay or test	A. M. Ralib, J. W. Pickering, G. M. Shaw, P. Devarajan, C. L. Edelstein, J. V. Bonventre and Z. H. Endre. Test characteristics of urinary biomarkers depend on quantitation method in acute kidney injury. Journal of the American Society of Nephrology, 23(2), 322-333. [16438]
Ralib	2014	<100 participants	A. M. Ralib, J. W. Pickering, G. M. Shaw, M. P. Than, P. M. George and Z. H. Endre. The clinical utility window for acute kidney injury biomarkers in the critically ill. Critical Care, 18(6), 601. [16436]
Ralib	2017	Not relevant type of population	A. M. Ralib, S. Nanyan and M. B. M. Nor. Dynamic Changes of Plasma Neutrophil Gelatinase-Associated Lipocalin Predicted Mortality in Critically Ill Patients with Systemic Inflammatory Response Syndrome. Indian Journal of Critical Care Medicine, 21(1), 23-29. [18564]
Ramchandran	2013	Not a primary study	B. Ramchandran. Acute kidney injury in critically ill children: More than just urine output. Indian Journal of Critical Care Medicine, 17(4), 203-204. [16439]
Rampoldi	2018	<100 participants	B. Rampoldi, S. Tessarolo, P. Giubbilini, P. Gaia, S. D. Corino, S. Mazza, R. Rigolini, M. D. Poli, E. Vianello, M. M. Corsi Romanelli and E. Costa. Neutrophil gelatinase-associated lipocalin and acute kidney injury in endovascular aneurysm repair or open aortic repair: A pilot study. Biochemia Medica, 28(1), 010904. [16443]
Rauen	2011	Not a primary study	T. Rauen, R. Weiskirchen and J. Floege. In search of early events in the development of chronic kidney disease: The emerging role for lipocalin-2/NGAL*. Nephrology Dialysis Transplantation, 26(2), 445-447. [16447]
Redding	2013	Not a primary study	S. Redding. Distinct injury markers for the early detection and prognosis of incident acute kidney injury in critically ill adults with preserved kidney function. Annals of Clinical Biochemistry, 50(6), 625-626. [16449]
Reiter	2018	<100 participants	K. Reiter, G. Balling, V. Bonelli, J. Pabst Von Ohain, S. L. Braun, P. Ewert and B. Ruf. Neutrophil gelatinase-associated lipocalin reflects inflammation and is not a reliable renal biomarker in neonates and infants after cardiopulmonary bypass: A prospective case-control study. Cardiology in the Young, 28(2), 243-251. [16453]
Renhua	2014	Not relevant type of population	L. Renhua, C. Miaolin, W. Junlin, W. Qingwei, X. Xiaoping, D. Huili, Z. Weiming, N. Zhaohui, Q. Jiaqi and Y. Yan. The level of the biomarkers at the time of nephrology consultation might predict the prognosis of acute kidney injury in hospitalized patients. Blood Purification, 38(2), 89-95. [16455]
Rewa	2015	Not relevant biomarker assay or test	O. Rewa, R. Wald, N. K. J. Adhikari, M. Hladunewich, S. Lapinsky, J. Muscedere, S. M. Bagshaw, O. M. Smith, G. Lebovic, R. Kuint and D. J. Klein. Whole-blood neutrophil gelatinase-associated lipocalin to predict adverse events in acute kidney injury: A prospective observational cohort study. Journal of Critical Care, 30(6), 1359-1364. [16457]
Ribitsch	2011	Not a primary study	W. Ribitsch and A. R. Rosenkranz. Biomarkers in acute kidney injury: A never ending story?. Critical Care Medicine, 39(11), 2570-2571. [16460]

Ribitsch	2017	Not relevant type of population	W. Ribitsch, G. Schilcher, F. Quehenberger, S. Pilz, R. H. Portugaller, M. Truschnig-Wilders, R. Zweiker, M. Brodmann, P. Stiegler, A. R. Rosenkranz, J. W. Pickering and J. H. Horina. Neutrophil gelatinase-associated lipocalin (NGAL) fails as an early predictor of contrast induced nephropathy in chronic kidney disease (ANTI-CI-AKI study). Scientific reports, 7(41300. [16459]
Ricci	2012	Not relevant biomarker assay or test	Z. Ricci, R. Netto, C. Garisto, C. Iacoella, I. Favia and P. Cogo. Whole blood assessment of neutrophil gelatinase-associated lipocalin versus pediatricRIFLE for acute kidney injury diagnosis and prognosis after pediatric cardiac surgery: Cross-sectional study. Pediatric Critical Care Medicine, 13(6), 667-670. [16466]
Ricci	2015	No focus on DTA for AKI	Z. Ricci, R. Haiberger, C. Pezzella, C. Garisto, I. Favia and P. Cogo. Furosemide versus ethacrynic acid in pediatric patients undergoing cardiac surgery: A randomized controlled trial. Critical Care, 19(1), 2. [16465]
Roberts	2011	Not relevant type of population	D. M. Roberts, M. F. Wilks, M. S. Roberts, R. Swaminathan, F. Mohamed, A. H. Dawson and N. A. Buckley. Changes in the concentrations of creatinine, cystatin C and NGAL in patients with acute paraquat self-poisoning. Toxicology Letters, 202(1), 69-74. [16478]
Robertson	2019	<100 participants	F. P. Robertson, A. C. Yeung, V. Male, S. Rahman, S. Mallett, B. J. Fuller and B. R. Davidson. Urinary Neutrophil Gelatinase Associated Lipocalins (NGALs) predict acute kidney injury post liver transplant. HPB, 21(4), 473-481. [16479]
Rocha	2015	<100 participants	P. N. Rocha, M. N. Macedo, C. D. Kobayashi, L. Moreno, L. H. S. Guimaraes, P. R. L. Machado, R. Badaro, E. M. Carvalho and M. J. Glesby. Role of urine neutrophil gelatinase-associated lipocalin in the early diagnosis of amphotericin B-induced acute kidney injury. Antimicrobial Agents and Chemotherapy, 59(11), 6913-6921. [16481]
Ronco	2008	Not a primary study	C. Ronco. NGAL: an emerging biomarker of acute kidney injury. International Journal of Artificial Organs, 31(3), 199-200. [3983]
Ronco	2013	Not a primary study	C. Ronco. Kidney attack: Overdiagnosis of acute kidney injury or comprehensive definition of acute kidney syndromes?. Blood Purification, 36(2), 65-68. [16493]
Ronco	2017	Not a primary study	C. Ronco, L. Rizo-Topete, M. Serrano-Soto and K. Kashani. Pro: Prevention of acute kidney injury: Time for teamwork and new biomarkers. Nephrology Dialysis Transplantation, 32(3), 408-413. [16487]
Rostami	2010	Not a primary study	Z. Rostami and M. Lessan-Pezeshki. Role of NGAL for the early detection of acute kidney injury. International Journal of Nephrology & Urology, 2(3), 387-389. [6136]
Roudkenar	2008	<100 participants	M. H. Roudkenar, R. Halabian, A. Odi, A. M. Roushandeh, P. Yaghmai, M. R. Najar, N. Amirizadeh and M. A. Shokrgozar. Upregulation of neutrophil gelatinase-associated lipocalin, NGAL/Lcn2, in beta-thalassemia patients. Archives of Medical Research, 39(4), 402-407. [18572]

Roudkenar	2008	No focus on DTA for AKI	M. H. Roudkenar, R. Halabian, Z. Ghasemipour, A. M. Roushandeh, M. Rouhbakhsh, M. Nekogoftar, Y. Kuwahara, M. Fukumoto and M. A. Shokrgozar. Neutrophil gelatinase-associated lipocalin acts as a protective factor against H2O2 toxicity. Archives of Medical Research, 39(6), 560-566. [18571]
Rouve	2018	<100 participants	E. Rouve, K. Lakhal, C. Salmon Gandonniere, Y. Jouan, L. Bodet-Contentin and S. Ehrmann. Lack of impact of iodinated contrast media on kidney cell-cycle arrest biomarkers in critically ill patients 11 Medical and Health Sciences 1103 Clinical Sciences. BMC Nephrology, 19(1), 308. [16510]
Royakkers	2012	Not relevant biomarker assay or test	A. A. Royakkers, C. S. Bouman, P. M. Stassen, J. C. Korevaar, J. M. Binnekade, W. van de Hoek, M. A. Kuiper, P. E. Spronk and M. J. Schultz. Systemic and urinary neutrophil gelatinase-associated lipocalins are poor predictors of acute kidney injury in unselected critically ill patients. Critical care research and practice, 2012(712695. [16514]
Ruf	2015	<100 participants	B. Ruf, V. Bonelli, G. Balling, J. Horer, N. Nagdyman, S. L. Braun, P. Ewert and K. Reiter. Intraoperative renal near-infrared spectroscopy indicates developing acute kidney injury in infants undergoing cardiac surgery with cardiopulmonary bypass: A case-control study. Critical Care, 19(1), 27. [16517]
Saad	2016	<100 participants	A. Saad, W. Wang, S. M. S. Herrmann, J. F. Glockner, M. A. McKusick, S. Misra, H. Bjarnason, L. O. Lerman and S. C. Textor. Atherosclerotic renal artery stenosis is associated with elevated cell cycle arrest markers related to reduced renal blood flow and postcontrast hypoxia. Nephrology Dialysis Transplantation, 31(11), 1855-1863. [16523]
Sagatov	2019	No focus on DTA for AKI	I. Y. Sagatov and U. S. Medeubekov. Dynamics of urine neutrophil gelatinase-associated lipocalin in cardiac surgery patients in the near term after surgery. Chirurgia (Turin), 32(2), 59-61. [16525]
Saleena	2015	Not relevant type of population	U. V. Saleena, K. Nalini, K. Gopalakrishna, R. Prabhu, B. M. Vadhiraja, M. S. Athiyamaan, A. Kamath and M. S. Vidyasagar. Early prediction of cisplatin nephrotoxicity in head and neck cancer patients - an evaluation with urinary biomarkers. International Journal of Pharmaceutical Sciences and Research, 6(7), 2893-2901. [16529]
Saleh	2017	Not relevant biomarker assay or test	N. Y. Saleh, W. M. M. A. El Fotoh and M. A. El-Hawy. Serum Neutrophil Gelatinase-Associated Lipocalin: A Diagnostic Marker in Pediatric Sepsis. Pediatric Critical Care Medicine, 18(6), E245-E252. [18577]
Sarafidis	2009	<100 participants	K. Sarafidis, E. Tsepkentzi, E. Agakidou, E. Diamanti, A. Taparkou, V. Soubasi, F. Papachristou and V. Drossou. Serum and urine acute kidney injury biomarkers in asphyxiated neonates. Pediatric Nephrology, 27(9), 1575-1582. [16535]
Sarafidis	2014	<100 participants	K. Sarafidis, E. Tsepkentzi, E. Diamanti, E. Agakidou, A. Taparkou, V. Soubasi, F. Papachristou and V. Drossou. Urine neutrophil gelatinase-associated lipocalin to predict acute kidney injury in preterm neonates. A pilot study. Pediatric Nephrology, 29(2), 305-310. [16534]

Sargentini	2012	<100 participants	Sargentini V, Mariani P, D'Alessandro M, Pistolesi V, Lauretta MP, Pacini F, et al. x. Assessment of NGAL as an early biomarker of acute kidney injury in adult cardiac surgery patients. . Assessment of NGAL as an early biomarker of acute kidney injury in adult cardiac surgery patients. . [16536]
Sarlak	2014	Not a primary study	H. Sarlak, M. Dinc, S. Balta, M. Cakar, E. Arslan and S. Demirbas. Early detection of urinary NGAL and plasma CysC may prevent progression to overt acute renal failure. Swiss Medical Weekly, 144(w13949. [16537]
Sarnak	2014	Not relevant type of population	M. J. Sarnak, R. Katz, A. Newman, T. Harris, C. A. Peralta, P. Devarajan, M. R. Bennett, L. Fried, J. H. Ix, S. Satterfield, E. M. Simonsick, C. R. Parikh, M. G. Shlipak and A. B. C. S. Hlth. Association of Urinary Injury Biomarkers with Mortality and Cardiovascular Events. Journal of the American Society of Nephrology, 25(7), 1545-1553. [18578]
Satirapoj	2016	Not relevant type of population	B. Satirapoj, K. Aramsaowapak, T. Tangwonglert and O. Supasyndh. Novel Tubular Biomarkers Predict Renal Progression in Type 2 Diabetes Mellitus: A Prospective Cohort Study. Journal of Diabetes Research, 2016(3102962. [16540]
Savran Karadeniz	2019	<100 participants	M. Savran Karadeniz, I. Alp Eniste, H. Senturk Ciftci, S. Usta, T. Tefik, O. Sanli, K. Pembeci and K. M. Tugrul. Neutrophil gelatinase-associated lipocalin significantly correlates with ischemic damage in patients undergoing laparoscopic partial nephrectomy. Balkan Medical Journal, 36(2), 121-128. [16541]
Saydam	2018	<100 participants	O. Saydam, E. Turkmen, O. Portakal, M. Arici, R. Dogan, M. Demircin, I. Pasaoglu and M. Yilmaz. Emerging biomarker for predicting acute kidney injury after cardiac surgery: Cystatin c. Turkish Journal of Medical Sciences, 48(6), 1096-1103. [16542]
Sayed	2015	<100 participants	S. Sayed, N. K. Idriss, A. Blann, H. G. Sayyed, D. M. Raafat, D. Fouad and M. S. K. Tawfeek. The Number of GT(n) Repeats in the Hemeoxygenase-1 Gene Promoter is Increased in Pediatric Heart Failure but is Unrelated to Renal, Antioxidant and Anti-inflammatory Markers. Pediatric cardiology, 36(6), 1204-1211. [18579]
Scazzochio	2014	<100 participants	E. Scazzochio, M. Munmany, L. Garcia, E. Meler, F. Crispi, E. Gratacos and F. Figueras. Prognostic role of maternal neutrophil gelatinase-associated lipocalin in women with severe early-onset preeclampsia. Fetal Diagnosis and Therapy, 35(2), 127-132. [16543]
Schanz	2017	<100 participants	M. Schanz, J. Shi, C. Wasser, M. D. Alscher and M. Kimmel. Urinary [TIMP-2] x [IGFBP7] for risk prediction of acute kidney injury in decompensated heart failure. Clinical Cardiology, 40(7), 485-491. [16545]
Schanz	2018	Not relevant type of population	M. Schanz, C. Wasser, S. Allgaeuer, S. Schricker, J. Dippon, M. D. Alscher and M. Kimmel. Urinary [TIMP-2].[IGFBP7]-guided randomized controlled intervention trial to prevent acute kidney injury in the emergency department. Nephrology, dialysis, transplantation, . [16544]
Schanz	2017	<100 participants	M. Schanz, A. Hoferer, J. Shi, M. D. Alscher and M. Kimmel. Urinary TIMP2.IGFBP7 for the prediction of platinum-induced acute renal injury. International Journal of Nephrology and Renovascular Disease, 10(175-181. [16546]

Schaub	2015	No focus on DTA for AKI	J. A. Schaub, A. X. Garg, S. G. Coca, J. M. Testani, M. G. Shlipak, J. Eikelboom, P. Kavsak, E. McArthur, C. Shortt, R. Whitlock and C. R. Parikh. Perioperative heart-type fatty acid binding protein is associated with acute kidney injury after cardiac surgery. Kidney International, 88(3), 576-583. [16549]
Schetz	2018	Not a primary study	M. Schetz and J. Prowle. Focus on acute kidney injury 2017. Intensive Care Medicine, 44(11), 1992-1994. [16550]
Schilcher	2011	Not a primary study	G. Schilcher, W. Ribitsch, R. Otto, R. H. Portugaller, F. Quehenberger, M. Truschnig-Wilders, R. Zweiker, P. Stiegler, M. Brodmann, K. Weinhandl and J. H. Horina. Early detection and intervention using neutrophil gelatinase-associated lipocalin (NGAL) may improve renal outcome of acute contrast media induced nephropathy: A randomized controlled trial in patients undergoing intra-arterial angiography (ANTI-CIN Study). BMC Nephrology, 12(1), 39. [16554]
Schinstock	2013	No relevant outcome	C. A. Schinstock, M. H. Semret, S. J. Wagner, T. M. Borland, S. C. Bryant, K. B. Kashani, T. S. Larson and J. C. Lieske. Urinalysis is more specific and urinary neutrophil gelatinase-associated lipocalin is more sensitive for early detection of acute kidney injury. Nephrology Dialysis Transplantation, 28(5), 1175-1185. [16556]
Schley	2015	Poster presentation - may be the same study as Schley 16558	G. Schley, C. Koberle, E. Manuilova, S. Rutz, R. Kientsch-Engel, K. U. Eckardt and C. Willam. Comparative analysis of diagnostic and predictive performance of novel renal biomarkers in plasma and urine of acute kidney injury patients. Intensive Care Medicine Experimental, 3(Supplement 1), A258. [16559]
Schneider	2013	Not a primary study	A. G. Schneider and R. Bellomo. Acute kidney injury: New studies. Intensive Care Medicine, 39(4), 569-571. [16565]
Schneider	2018	Not a primary study	A. G. Schneider, N. Mongardon and L. Muller. Biomarkers of renal injury, time for a grey-zone approach?. Anaesthesia Critical Care and Pain Medicine, 37(4), 307-309. [16564]
Schutz	2017	Not relevant type of population	C. Schutz, D. R. Boulware, K. Huppler-Hullsiek, M. von Hohenberg, J. Rhein, K. Taseera, F. Thienemann, C. Muzoora, D. B. Meya and G. Meintjes. Acute Kidney Injury and Urinary Biomarkers in Human Immunodeficiency Virus-Associated Cryptococcal Meningitis. Open forum infectious diseases, 4(3), ofx127. [16573]
Seibert	2013	<100 participants	F. S. Seibert, N. Pagonas, R. Arndt, F. Heller, D. Dragun, P. Persson, K. Schmidt-Ott, W. Zidek and T. H. Westhoff. Calprotectin and neutrophil gelatinase-associated lipocalin in the differentiation of pre-renal and intrinsic acute kidney injury. Acta Physiologica, 207(4), 700-708. [16578]
Seibert	2018	No focus on DTA for AKI	F. S. Seibert, M. Sitz, J. Passfall, M. Haesner, P. Laschinski, M. Buhl, F. Bauer, N. Babel, N. Pagonas and T. H. Westhoff. Prognostic value of urinary calprotectin, NGAL and KIM-1 in chronic kidney disease. Kidney and Blood Pressure Research, 43(4), 1255-1262. [16577]

Se-Jun	2017	<100 participants	P. Se-Jun, K. O. O. Hoseok, L. E. E. Kyoung-Jin, K. I. M. Seo-Hyun, Y. U. N. Seo-Young, K. I. M. Seunghyup, W. Dong-Hee, J. O. O. Shin-Young, L. E. E. Byungmo, C. HoJun and P. Sihyung. Usefulness of neutrophil gelatinase-associated lipocalin(NGAL) to confirm subclinical acute kidney injury and renal prognosis in patients following surgery. Kosin Medical Journal, 212-220. [6166]
Seker	2015	<100 participants	M. M. Seker, K. Deveci, A. Seker, E. Sancakdar, A. Yilmaz, A. K. Turesin, T. Kacan and N. A. Babacan. Predictive role of neutrophil gelatinase-associated lipocalin in early diagnosis of platin-induced renal injury. Asian Pacific journal of cancer prevention : APJCP, 16(2), 407-410. [16580]
Self	2010	Not a primary study	W. H. Self and T. W. Barrett. Novel Biomarkers: Help or Hindrance to Patient Care in the Emergency Department?. Annals of Emergency Medicine, 56(1), 60-61. [16581]
Sellmer	2017	No focus on DTA for AKI	A. Sellmer, B. H. Bech, J. V. Bjerre, M. R. Schmidt, V. E. Hjortdal, G. Esberg, S. Rittig and T. B. Henriksen. Urinary Neutrophil Gelatinase-associated Lipocalin in the evaluation of Patent Ductus Arteriosus and AKI in Very Preterm Neonates: A cohort study. BMC Pediatrics, 17(1), 7. [16582]
Sen	2015	<100 participants	S. Sen, Z. R. Godwin, T. Palmieri, D. Greenhalgh, A. N. Steele and N. K. Tran. Whole blood neutrophil gelatinase-associated lipocalin predicts acute kidney injury in burn patients. Journal of Surgical Research, 196(2), 382-387. [16583]
Sen	2015	Not relevant type of population	V. Sen, A. Ece, U. Uluca, M. Soker, A. Gunes, I. Kaplan, I. Tan, S. Yel, N. Mete and C. Sahin. Urinary early kidney injury molecules in children with beta-thalassemia major. Renal failure, 37(4), 607-13. [16584]
Seo	2014	<100 participants	W. H. Seo, S. W. Nam, E. H. Lee, B. K. Je, H. E. Yim and B. M. Choi. A rapid plasma neutrophil gelatinase-associated lipocalin assay for diagnosis of acute pyelonephritis in infants with acute febrile urinary tract infections: A preliminary study. European Journal of Pediatrics, 173(2), 229-232. [16586]
Shahbazi	2015	Not relevant type of population	F. Shahbazi, S. Sadighi, S. Dashti-Khavidaki, F. Shahi, M. Mirzania, A. Abdollahi and M. H. Ghahremani. Effect of Silymarin Administration on Cisplatin Nephrotoxicity: Report from A Pilot, Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Phytotherapy Research, 29(7), 1046-1053. [16591]
Shahbazi	2015	Not relevant type of population	F. Shahbazi, S. Sadighi, S. Dashti-Khavidaki, F. Shahi and M. Mirzania. Urine ratio of neutrophil gelatinase-associated lipocalin to creatinine as a marker for early detection of cisplatinassociated nephrotoxicity. Iranian Journal of Kidney Diseases, 9(4), 305-310. [16592]
Shaker	2010	<100 participants	O. Shaker, A. El-Shehaby and M. El-Khatib. Early Diagnostic Markers for Contrast Nephropathy in Patients Undergoing Coronary Angiography. Angiology, 61(8), 731-736. [18581]
Shaker	2018	<100 participants	A. M. Shaker, E. El Mohamed, H. H. Samir, M. M. Elnokeety, H. A. Sayed and T. A. Ramzy. Fibroblast growth factor-23 as a predictor biomarker of acute kidney injury after cardiac surgery. Saudi journal of kidney diseases and transplantation, 29(3), 531-539. [16593]

Shao	2017	Not relevant type of population	Y. Shao, Y. Fan, Y. Xie, L. Yin, Y. Zhang, L. Deng, X. Sun, X. Shao, X. Tan, J. He and S. Zhao. Effect of continuous renal replacement therapy on kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin in patients with septic acute kidney injury. Experimental and Therapeutic Medicine, 13(6): 3594-3602. [16597]
Shapiro	2010	Not relevant biomarker assay or test	N. I. Shapiro, S. Trzeciak, J. E. Hollander, R. Birkhahn, R. Otero, T. M. Osborn, E. Moretti, H. B. Nguyen, K. Gunnerson, D. Milzman, D. F. Gaieski, M. Goyal, C. B. Cairns, K. Kupfer, S. W. Lee and E. P. Rivers. The Diagnostic Accuracy of Plasma Neutrophil Gelatinase-Associated Lipocalin in the Prediction of Acute Kidney Injury in Emergency Department Patients With Suspected Sepsis. Annals of Emergency Medicine, 56(1), 52. [16598]
Sharma	2017	Not relevant type of population	A. Sharma, B. G. Demissei, J. Tromp, H. L. Hillege, J. G. Cleland, C. M. O'Connor, M. Metra, P. Ponikowski, J. R. Teerlink and B. A. Davison. A network analysis to compare biomarker profiles in patients with and without diabetes mellitus in acute heart failure. European journal of heart failure, 19(10), 1310â€ 1320. [4794]
Shavit	2011	<100 participants	L. Shavit, I. Dolgoker, H. Ivgi, M. Assous and I. Slotki. Neutrophil gelatinase-associated lipocalin as a predictor of complications and mortality in patients undergoing non-cardiac major surgery. Kidney and Blood Pressure Research, 34(2), 116-124. [16603]
Shavit	2013	Not relevant type of population	L. Shavit, R. Manilov, Y. Wiener-Well, N. Algur and I. Slotki. Urinary neutrophil gelatinase-associated lipocalin for early detection of acute kidney injury in geriatric patients with urinary tract infection treated by colistin. Clinical Nephrology, 80(6), 405-416. [16602]
Shaw	2011	Cost-effectiveness - retained as background material	A. D. Shaw, D. B. Chalfin and J. Kleintjens. The economic impact and cost-effectiveness of urinary neutrophil gelatinase-associated lipocalin after cardiac surgery. Clinical Therapeutics, 33(11), 1713-1725. [16605]
Shema-Didi	2016	Not relevant type of population	L. Shema-Didi, B. Kristal, S. Eizenberg, N. Marzuq, M. Sussan, Y. Feldman-Idov, P. Ofir and S. Atar. Prevention of contrast-induced nephropathy with single bolus erythropoietin in patients with diabetic kidney disease: A randomized controlled trial. Nephrology, 21(4), 295-300. [16607]
Shen	2014	<100 participants	S. J. Shen, Z. X. Hu, Q. H. Li, S. M. Wang, C. J. Song, D. D. Wu, J. L. He, J. C. Guan and J. P. Shan. Implications of the changes in serum neutrophil gelatinase-associated lipocalin and cystatin C in patients with chronic kidney disease. Nephrology, 19(3), 129-135. [16609]
Shin	2017	<100 participants	S. Shin, J. Ha, S. Lee, W. Lee and J. Park. Increased urinary neutrophil gelatinase-associated lipocalin in very-low-birth-weight infants with oliguria and normal serum creatinine. Pediatric Nephrology, 32(6), 1059-1065. [6138]

Shinke	2015	Not relevant type of population	H. Shinke, S. Masuda, Y. Togashi, Y. Ikemi, A. Ozawa, T. Sato, Y. H. Kim, M. Mishima, T. Ichimura, J. V. Bonventre and K. Matsubara. Urinary kidney injury molecule-1 and monocyte chemotactic protein-1 are noninvasive biomarkers of cisplatin-induced nephrotoxicity in lung cancer patients. Cancer Chemotherapy and Pharmacology, 76(5), 989-996. [16613]
Shirakabe	2014	Not relevant biomarker assay or test	A. Shirakabe, N. Hata, N. Kobayashi, H. Okazaki, T. Shinada, K. Tomita, M. Yamamoto, M. Tsurumi, M. Matsushita, Y. Yamamoto, S. Yokoyama, K. Asai and W. Shimizu. Serum heart-type fatty acid-binding protein level can be used to detect acute kidney injury on admission and predict an adverse outcome in patients with acute heart failure. Circulation Journal, 79(1), 119-128. [16616]
Shirakabe	2019	Not relevant biomarker assay or test	A. Shirakabe, N. Hata, N. Kobayashi, H. Okazaki, M. Matsushita, Y. Shibata, S. Uchiyama, T. Sawatani, K. Asai and W. Shimizu. Worsening renal failure in patients with acute heart failure: the importance of cardiac biomarkers. ESC Heart Failure, 6(2), 416-427. [16614]
Shlipak	2012	Not relevant type of population	M. G. Shlipak, R. Scherzer, A. Abraham, P. C. Tien, C. Grunfeld, C. A. Peralta, P. Devarajan, M. Bennett, A. W. Butch, K. Anastos, M. H. Cohen, M. Nowicki, A. Sharma, M. A. Young, M. J. Sarnak and C. R. Parikh. Urinary markers of kidney injury and kidney function decline in HIV-infected women. Journal of Acquired Immune Deficiency Syndromes, 61(5), 565-573. [16618]
Shoaib	2019	<100 participants	M. Shoaib, S. N. Mahmud and M. Safdar. Early Diagnosis Of Acute Kidney Injury By Urinary Neutrophil Gelatinase Associated Lipocalin In Adult Critically Ill Patients. Journal of Ayub Medical College, Abbottabad : JAMC, 31(1), 12-15. [16619]
Shrestha	2011	No relevant outcome	K. Shrestha, A. G. Borowski, R. W. Troughton, J. D. Thomas, A. L. Klein and W. H. W. Tang. Renal dysfunction is a stronger determinant of systemic neutrophil gelatinase-associated lipocalin levels than myocardial dysfunction in systolic heart failure. Journal of cardiac failure, 17(6), 472-8. [16621]
Shrestha	2012	<100 participants	K. Shrestha, Z. Shao, D. Singh, M. Dupont and W. H. W. Tang. Relation of systemic and urinary neutrophil gelatinase-associated lipocalin levels to different aspects of impaired renal function in patients with acute decompensated heart failure. American Journal of Cardiology, 110(9), 1329-1335. [16622]
Shukla	2017	Not relevant type of population	A Shukla, MK Rai, N Prasad, V Agarwal. Short-Term Non-Steroid Anti-Inflammatory Drug Use in Spondyloarthritis Patients Induces Subclinical Acute Kidney Injury: Biomarkers Study. Nephron, 135(4), 277-286. [16624]
Shulkina	2016	<100 participants	S. G. Shulkina, V. V. Schekotov, E. N. Smirnova and A. A. Antipova. Vascular endothelial growth factor and lipocalin-2 as markers of early nephron damage in patients with hypertension and obesity. Sovremennye Tehnologii v Medicine, 8(1), 148-151. [16627]

Shum	2015	Not relevant biomarker assay or test	H. P. Shum, N. Y. W. Leung, L. L. Chang, O. Y. Tam, A. M. C. Kwan, K. C. Chan, W. W. Yan and T. M. Chan. Predictive value of plasma neutrophil gelatinase-associated lipocalin for acute kidney injury in intensive care unit patients after major non-cardiac surgery. Nephrology, 20(5), 375-382. [16628]
Shyam	2017	<100 participants	R. Shyam, M. L. Patel, R. Sachan, S. Kumar and D. K. Pushkar. Role of urinary neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury in patients with circulatory shock. Indian Journal of Critical Care Medicine, 21(11), 740-745. [16630]
Si Nga	2015	Not relevant biomarker assay or test	H. Si Nga, P. Medeiros, P. Menezes, R. Bridi, A. Balbi and D. Ponce. Sepsis and AKI in Clinical Emergency Room Patients: The Role of Urinary NGAL. BioMed Research International, 2015(1-8. [6139]
Si Nga	2015	Not relevant biomarker assay or test	H. Si Nga, P. Medeiros, P. Menezes, R. Bridi, A. Balbi and D. Ponce. Sepsis and AKI in Clinical Emergency Room Patients: The Role of Urinary NGAL. BioMed Research International, 2015(413751. [16631]
Siddappa	2019	<100 participants	P. K. Siddappa, R. Kochhar, P. Sarotra, B. Medhi, V. Jha and V. Gupta. Neutrophil gelatinase-associated lipocalin: An early biomarker for predicting acute kidney injury and severity in patients with acute pancreatitis. JGH Open, 3(2), 105-110. [16632]
Sidoti	2014	<100 participants	A. Sidoti, M. Giacalone, A. Abramo, M. Anselmino, C. Donadio, C. D. Salvo, F. Giunta and F. Forfori. Early identification of acute kidney injury after bariatric surgery: Role of NGAL and cystatin C. Open Obesity Journal, 6(1), 50-59. [16634]
Siew	2009	Not relevant biomarker assay or test	E. D. Siew, L. B. Ware, T. Gebretsadik, A. Shintani, K. G. M. Moons, N. Wickersham, F. Bossert and T. A. Ikizler. Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. Journal of the American Society of Nephrology, 20(8), 1823-1832. [16639]
Siew	2010	Not relevant biomarker assay or test	E. D. Siew, T. A. Ikizler, T. Gebretsadik, A. Shintani, N. Wickersham, F. Bossert, J. F. Peterson, C. R. Parikh, A. K. May and L. B. Ware. Elevated urinary IL-18 levels at the time of ICU admission predict adverse clinical outcomes. Clinical Journal of the American Society of Nephrology, 5(8), 1497-1505. [16638]
Siew	2013	Not relevant biomarker assay or test	E. D. Siew, L. B. Ware, A. Bian, A. Shintani, S. K. Eden, N. Wickersham, B. Cripps and T. A. Ikizler. Distinct injury markers for the early detection and prognosis of incident acute kidney injury in critically ill adults with preserved kidney function. Kidney International, 84(4), 786-794. [16635]
Silvetti	2014	<100 participants	S. Silvetti, R. Meroni, E. Bignami, T. Bove, G. Landoni, A. Zangrillo, R. Bellomo and F. Pappalardo. Preoperative urinary neutrophil gelatinase-associated lipocalin and outcome in high-risk heart failure patients undergoing cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia, 28(2), 323-327. [16640]
Sim	2015	Not relevant type of population	J. H. Sim, H. E. Yim, B. M. Choi, J. H. Lee and K. H. Yoo. Plasma neutrophil gelatinase-associated lipocalin predicts acute pyelonephritis in children with urinary tract infections. Pediatric research, 78(1), 48-55. [16641]

Simonazzi	2015	<100 participants	G. Simonazzi, I. Capelli, A. Curti, G. Comai, N. Rizzo and G. La Manna. Serum and Urinary Neutrophil Gelatinase-associated Lipocalin Monitoring in Normal Pregnancy Versus Pregnancies Complicated by Pre-eclampsia. In Vivo, 29(1), 117-121. [18587]
Singal	2018	No focus on DTA for AKI	A. K. Singal, B. Jackson, G. B. Pereira, K. B. Russ, P. S. Fitzmorris, D. Kakati, P. Axley, S. Ravi, T. Seay, S. P. Ramachandra Rao, R. Mehta, Y. F. Kuo, K. P. Singh and A. Agarwal. Biomarkers of Renal Injury in Cirrhosis: Association with Acute Kidney Injury and Recovery after Liver Transplantation. Nephron, 138(1), 1-12. [16644]
Singer	2016	Not relevant type of population	E. Singer, E. V. Schrezenmeier, A. Elger, E. R. Seelow, A. Krannich, F. C. Luft and K. M. Schmidt-Ott. Urinary NGAL-Positive Acute Kidney Injury and Poor Long-term Outcomes in Hospitalized Patients. Kidney international reports, 1(3), 114-124. [16645]
Singh	2016	Not relevant type of population	G. B. Singh, S. H. Ann, J. Park, H. C. Chung, J. S. Lee, E. S. Kim, J. I. Choi, J. Lee, S. J. Kim and E. S. Shin. Remote ischemic preconditioning for the prevention of contrast-induced acute kidney injury in diabetics receiving elective percutaneous coronary intervention. PLoS ONE, 11(10), e0164256. [16650]
Singh	2018	Not relevant type of population	A. Singh, R. Kamal, R. Tiwari, V. K. Gaur, V. Bihari, G. N. V. Satyanarayana, D. K. Patel, P. A. Azeez, V. Srivastava, A. Ansari and C. N. Kesavachandran. Association between PAHs biomarkers and kidney injury biomarkers among kitchen workers with microalbuminuria: A cross-sectional pilot study. Clinica Chimica Acta, 487(349-356. [16649]
Sinna	2019	<100 participants	M. M. Sinna, F. M. Altaf and O. F. Mosa. The study of Serum and urinary NGAL and Cystatin C levels as biomarker tools for diagnosis of both AKI and CKD: A histobiochemical comparative study. Current pharmaceutical design, . [16655]
Sirisopha	2016	<100 participants	A. Sirisopha, S. Vanavanan, A. Chittamma, B. Phakdeekitcharoen, A. Thakkinstian, A. Lertrit, N. Sathirapongsasuti and C. Kitiyakara. Effects of Therapy on Urine Neutrophil Gelatinase-Associated Lipocalin in Nondiabetic Glomerular Diseases with Proteinuria. International journal of nephrology, 2016(4904502. [16656]
Sirota	2013	<100 participants	J. C. Sirota, A. Walcher, S. Faubel, A. Jani, K. McFann, P. Devarajan, C. L. Davis and C. L. Edelstein. Urine IL-18, NGAL, IL-8 and serum IL-8 are biomarkers of acute kidney injury following liver transplantation. BMC Nephrology, 14(1), 17. [16657]
Sise	2009	Not a primary study	M. E. Sise, J. Barasch, P. Devarajan and T. L. Nickolas. Elevated urine neutrophil gelatinase-associated lipocalin can diagnose acute kidney injury in patients with chronic kidney diseases. Kidney International, 75(1), 115-116. [16659]
Slack	2013	<100 participants	A. J. Slack, M. J. W. McPhail, M. Ostermann, M. Bruce, R. Sherwood, R. Musto, T. Dew, G. Auzinger, W. Bernal, J. O'Grady, M. A. Heneghan, K. Moore and J. A. Wendon. Predicting the development of acute kidney injury in liver cirrhosis - An analysis of glomerular filtration rate, proteinuria and kidney injury biomarkers. Alimentary Pharmacology and Therapeutics, 37(10), 989-997. [16662]

Smertka	2014	<100 participants	M. Smertka, J. Wroblewska, A. Suchojad, M. Majcherczyk, D. Jadamus-Niebroj, T. Owsianka-Podlesny, A. Brzozowska and I. Maruniak-Chudek. Serum and urinary NGAL in septic newborns. BioMed Research International, 2014(717318. [16665]
Sokolski	2017	Not relevant biomarker assay or test	M. Sokolski, R. Zymlinski, J. Biegus, P. Siwolowski, S. Nawrocka-Millward, J. Todd, M. R. Yerramilli, J. Estis, E. A. Jankowska, W. Banasiak and P. Ponikowski. Urinary levels of novel kidney biomarkers and risk of true worsening renal function and mortality in patients with acute heart failure. European journal of heart failure, 19(6), 760-767. [16670]
Solak	2015	Not relevant biomarker assay or test	Y. Solak, M. I. Yilmaz, D. Siriopol, M. Saglam, H. U. Unal, H. Yaman, M. Gok, H. Cetinkaya, A. Gaipov, T. Eyileten, S. Sari, A. O. Yildirim, H. Z. Tonbul, S. Turk, A. Covic and M. Kanbay. Serum neutrophil gelatinase-associated lipocalin is associated with cardiovascular events in patients with chronic kidney disease. International Urology and Nephrology, 47(12), 1993-2001. [16671]
Song	2017	Meta-analysis - retained as background material	Z. Song, Z. Ma, K. Qu, S. Liu, W. Niu and T. Lin. Diagnostic prediction of urinary [TIMP-2] x [IGFBP7] for acute kidney injury: A meta-analysis exploring detection time and cutoff levels. Oncotarget, 8(59), 100631-100639. [16676]
Song	2017	Not relevant type of population	Y. Song, S. Sun, Y. Yu, G. Li, J. Song, H. Zhang and C. Yan. Diagnostic value of neutrophil gelatinase-associated lipocalin for renal injury in asphyxiated preterm infants. Experimental and Therapeutic Medicine, 13(4), 1245-1248. [16675]
Song	2018	No focus on DTA for AKI	Y. Song, D. H. Kim, T. D. Kwon, D. W. Han, S. H. Baik, H. H. Jung and J. Y. Kim. Effect of intraoperative dexmedetomidine on renal function after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a randomized, placebo-controlled trial. International Journal of Hyperthermia, . [16674]
Soto	2013	Not relevant biomarker assay or test	K. Soto, A. L. Papoila, S. Coelho, M. Bennett, Q. Ma, B. Rodrigues, P. Fidalgo, F. Frade and P. Devarajan. Plasma NGAL for the diagnosis of AKI in patients admitted from the emergency department setting. Clinical Journal of the American Society of Nephrology, 8(12), 2053-2063. [16681]
Soto	2016	Not relevant biomarker assay or test	K. Soto, P. Campos, I. Pinto, B. Rodrigues, F. Frade, A. L. Papoila and P. Devarajan. The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury. Kidney International, 90(5), 1090-1099. [16680]
Souza	2015	Not relevant type of population	D. F. Souza, S. S. A. Reis, R. V. Botelho and S. R. Ferreira-Filho. Relative and Absolute Changes in Urinary Neutrophil Gelatinase-Associated Lipocalin and Correlation with Small Increases in Serum Creatinine Levels after Coronary Angiography: An Observational Study. Nephron, 129(2), 84-90. [16682]
Soyler	2015	Not relevant biomarker assay or test	C. Soyler, M. D. Tanriover, S. Ascioglu, N. M. Aksu and M. Arici. Urine neutrophil gelatinase-associated lipocalin levels predict acute kidney injury in acute decompensated heart failure patients. Renal Failure, 37(5), 772-776. [16683]

Spasojevic-Dimitrijeva	2017	Not relevant type of population	B. Spasojevic-Dimitrijeva, J. Kotur-Stevuljevic, M. Dukic, D. Paripovic, G. Milosevski-Lomic, V. Spasojevic-Kalimanovska, P. Pavicevic, J. Mitrovic and M. Kostic. Serum neutrophil gelatinase-associated lipocalin and urinary kidney injury molecule-1 as potential biomarkers of subclinical nephrotoxicity after gadolinium-based and iodinated-based contrast media exposure in pediatric patients with normal kidney function. Medical Science Monitor, 23(4299-4305. [16685]
Sporek	2016	<100 participants	M. Sporek, A. Gala-Bladzinska, P. Dumnicka, M. Mazur-Laskowska, S. Kielczewski, J. Walocha, P. Ceranowicz, M. Kuzniewski, J. Mitus and B. Kusnierz-Cabala. Urine NGAL is useful in the clinical evaluation of renal function in the early course of acute pancreatitis. Folia medica Cracoviensia, 56(1), 13-25. [16688]
Sprenkle	2013	No focus on DTA for AKI	P. C. Sprenkle, J. Wren, A. C. Maschino, A. Feifer, N. Power, T. Ghoneim, I. Sternberg, M. Fleisher and P. Russo. Urine neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after kidney surgery. Journal of Urology, 190(1), 159-164. [16690]
Srisawat	2008	Not relevant type of population	N. Srisawat, R. Murugan, M. Lee, L. Kong, M. Carter, D. C. Angus and J. A. Kellum. Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. Kidney International, 80(5), 545-552. [16696]
Srisawat	2015	Not relevant type of population	N. Srisawat, K. Praditpornsilpa, K. Patarakul, M. Techapornrung, T. Daraswang, T. Sukmark, K. Khositrangsikun, A. Fakthongyoo, P. Oranrigsupak, L. Praderm, U. Suwattanasilpa, S. Peerapornratana, P. Loahaveeravat, N. Suwachittanont, T. O. Wirotwan, C. Phonork, S. Kumpunya, K. Tiranathanagul, C. Chirathaworn, S. Eiam-Ong, K. Tungsanga, V. Sitprija, J. A. Kellum and N. Townamchai. Neutrophil gelatinase associated lipocalin (NGAL) in leptospirosis acute kidney injury: A multicenter study in Thailand. PLoS ONE, 10(12), e0143367. [16694]
Srisawat	2018	<100 participants	N. Srisawat, P. Laoveeravat, P. Limphunudom, N. Lumlertgul, S. Peerapornratana, K. Tiranathanagul, P. Susantitaphong, K. Praditpornsilpa, K. Tungsanga and S. Eiam-Ong. The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: a feasibility study. Journal of critical care, 43(36-41). [4627]
Srisawat	2018	<100 participants	N. Srisawat, M. Kongwibulwut, P. Laoveeravat, N. Lumplertgul, P. Chatkaew, P. Saeyub, K. Latthaprecha, S. Peerapornratana, K. Tiranathanagul, S. Eiam-Ong and K. Tungsanga. The role of intraoperative parameters on predicting laparoscopic abdominal surgery associated acute kidney injury. BMC Nephrology, 19(1), 289. [16692]
Srisawat	2018	<100 participants	N. Srisawat, P. Laoveeravat, P. Limphunudom, N. Lumlertgul, S. Peerapornratana, K. Tiranathanagul, P. Susantitaphong, K. Praditpornsilpa, K. Tungsanga and S. Eiam-Ong. The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: A feasibility study. Journal of Critical Care, 43(36-41. [16693]

Srisawat	2018	Not a primary study	N. Srisawat, K. Tangvoraphonkchai, N. Lumlertgul, K. Tungsanga and S. Eiam-Ong. Role of acute kidney injury biomarkers to guide renal replacement therapy initiation, what we learn from EARLY-RRT trial and FST trial?. Journal of Thoracic Disease, 10(12), E835-E838. [16691]
Stads	2019	<100 participants	S. Stads, K. M. Kant, M. F. C. De Jong, W. De Ruijter, C. M. Cobbaert, M. G. H. Betjes, D. Gommers and H. M. Oudemans-Van Straaten. Predictors of short-term successful discontinuation of continuous renal replacement therapy: Results from a prospective multicentre study. BMC Nephrology, 20(1), 129. [16699]
Sterling	2017	<100 participants	M. Sterling, Z. Al-Ismaili, K. R. McMahon, M. Piccioni, M. Pizzi, T. Mottes, L. C. Lands, S. Abish, A. J. Fleming, M. R. Bennett, A. Palijan, P. Devarajan, S. L. Goldstein, M. M. O'Brien and M. Zappitelli. Urine biomarkers of acute kidney injury in noncritically ill, hospitalized children treated with chemotherapy. Pediatric Blood and Cancer, 64(10), e26538. [16706]
Stewart	2015	<100 participants	I. J. Stewart, K. R. Glass, J. T. Howard, B. D. Morrow, J. A. Sosnov, E. D. Siew, N. Wickersham, W. Latack, H. K. Kwan, K. D. Heegard, C. Diaz, A. T. Henderson, K. K. Saenz, Ikizler and K. K. Chung. The potential utility of urinary biomarkers for risk prediction in combat casualties: A prospective observational cohort study. Critical Care, 19(1), 252. [16708]
Strazzulla	2016	<100 participants	A. Strazzulla, G. Coppolino, C. Di Fatta, F. Giancotti, G. D'Onofrio, M. C. Postorino, M. Mazzitelli, S. V. Mammone, I. Gentile, L. Rivoli, E. Palella, T. Gravina, C. Costa, V. Pisani, V. De Maria, G. S. Barreca, N. Marascio, A. Foca, G. Fuiano, E. Gulletta and C. Torti. Is neutrophil gelatinase associated lipocalin useful in hepatitis C virus infection?. World Journal of Hepatology, 8(19), 815-824. [18592]
Stypmann	2015	No focus on DTA for AKI	J. Stypmann, M. Fobker, K. Rosing, M. Engelen, S. Gunia, A. M. Dell'Aquila and J. R. Nofer. Neutrophil gelatinase-associated lipocalin (NGAL) in heart transplant recipients after conversion to everolimus therapy. Journal of Cardiology, 66(4), 347-352. [16711]
Su	2017	Meta-analysis - retained as background material	Y. Su, Z. Gong, Y. Wu, Y. Tian and X. Liao. Diagnostic value of urine tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 for acute kidney injury: A meta-analysis. PLoS ONE, 12(1), e0170214. [16714]
Su	2018	Meta-analysis - retained as background material	L. J. Su, Y. M. Li, J. A. Kellum and Z. Y. Peng. Predictive value of cell cycle arrest biomarkers for cardiac surgery-associated acute kidney injury: a meta-analysis. British Journal of Anaesthesia, 121(2), 350-357. [16713]
Suchojad	2015	<100 participants	A. Suchojad, A. Tarko, M. Smertka, M. Majcherczyk, A. Brzozowska, J. Wroblewska and I. Maruniak-Chudek. Factors limiting usefulness of serum and urinary NGAL as a marker of acute kidney injury in preterm newborns. Renal Failure, 37(3), 439-445. [16715]
Sueud	2019	<100 participants	T. Sueud, N. R. Hadi, R. Abdulameer, D. A. Jamil and H. A. Al-Aubaidy. Assessing urinary levels of IL-18, NGAL and albumin creatinine ratio in patients with diabetic nephropathy. Diabetes & Metabolic Syndrome-Clinical Research & Reviews, 13(1), 564-568. [18593]

Sumida	2014	<100 participants	M. Sumida, K. Doi, O. Kinoshita, M. Kimura, M. Ono, Y. Hamasaki, T. Matsubara, T. Ishii, N. Yahagi, M. Nangaku and E. Noiri. Perioperative Plasma Neutrophil Gelatinase-associated lipocalin measurement in patients who undergo left ventricular assist device implantation surgery. Circulation Journal, 78(8), 1891-1899. [16717]
Sun	2017	Not relevant type of population	I. O. Sun, S. H. Shin, A. Y. Cho, H. J. Yoon, M. Y. Chang and K. Y. Lee. Clinical significance of NGAL and KIM-1 for acute kidney injury in patients with scrub typhus. PLoS ONE, 12(4), e0175890. [16718]
Surmiak	2015	<100 participants	P. Surmiak, M. Baumert, M. Fiala, Z. Walencka and A. Wiecek. Umbilical neutrophil gelatinase-associated Lipocalin level as an early predictor of acute kidney injury in neonates with hypoplastic left heart syndrome. BioMed Research International, 2015(360209. [16721]
Suzuki	2008	<100 participants	M. Suzuki, K. M. Wiers, M. S. Klein-Gitelman, K. A. Haines, J. Olson, K. B. Onel, K. O'Neil, M. H. Passo, N. G. Singer, L. Tucker, J. Ying, P. Devarajan and H. I. Brunner. Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. Pediatric Nephrology, 23(3), 403-412. [18594]
Sweetman	2016	<100 participants	D. U. Sweetman, C. Onwuneme, W. R. Watson, A. O'Neill, J. F. A. Murphy and E. J. Molloy. Renal function and novel urinary biomarkers in infants with neonatal encephalopathy. Acta Paediatrica, International Journal of Paediatrics, 105(11), e513-e519. [16725]
Szeto	2008	<100 participants	C. C. Szeto, B. C. H. Kwan, K. B. Lai, F. M. M. Lai, K. M. Chow, G. Wang, C. C. W. Luk and P. K. T. Li. Urinary expression of kidney injury markers in renal transplant recipients. Clinical Journal of the American Society of Nephrology, 5(12), 2329-2337. [16730]
Szewczyk	2009	<100 participants	M. Szewczyk, T. Wielkoszynski, M. Zakliczynski and M. Zembala. Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) Correlations With Cystatin C, Serum Creatinine, and Glomerular Filtration Rate in Patients After Heart and Lung Transplantation. Transplantation Proceedings, 41(8), 3242-3243. [16731]
Taghizadeh-Ghehi	2015	<100 participants	M. Taghizadeh-Ghehi, A. Sarayani, A. Ashouri, S. Ataei, A. Moslehi and M. Hadjibabaie. Urine neutrophil gelatinase associated lipocalin as an early marker of acute kidney injury in hematopoietic stem cell transplantation patients. Renal Failure, 37(6), 994-998. [16734]
Tai	2018	Meta-analysis - retained as background material	Q. Tai, H. Yi, X. Wei, W. Xie, O. Zeng, D. Zheng, J. Sun, G. Wang, S. Wang and G. Liu. The Accuracy of Urinary TIMP-2 and IGFBP7 for the Diagnosis of Cardiac Surgery-Associated Acute Kidney Injury: A Systematic Review and Meta-Analysis. Journal of Intensive Care Medicine, . [16735]
Takahashi	2016	<100 participants	G. Takahashi, S. Shibata, Y. Fukui, Y. Okamura and Y. Inoue. Diagnostic accuracy of procalcitonin and presepsin for infectious disease in patients with acute kidney injury. Diagnostic Microbiology and Infectious Disease, 86(2), 205-210. [16736]
Tamimi	2018	<100 participants	A. Tamimi, E. Kord, Y. H. Rappaport, A. Cooper, R. Abu Hamad, S. Efrati, R. S. Kenett, A. Zisman and Y. I. Siegel. Salivary Neutrophil Gelatinase-Associated Lipocalin Sampling Feasibility in Acute Renal Colic. Journal of Endourology, 32(6), 566-571. [16737]

Tanigasalam	2016	Not relevant biomarker assay or test	V. Tanigasalam, B. V. Bhat, B. Adhisivam, M. G. Sridhar and K. T. Harichandrakumar. Predicting Severity of Acute Kidney Injury in Term Neonates with Perinatal Asphyxia Using Urinary Neutrophil Gelatinase Associated Lipocalin. Indian Journal of Pediatrics, 83(12-13), 1374-1378. [16742]
Tanzil	2016	<100 participants	W. L. Tanzil, R. Wilar, M. F. J. Mantik, A. Umboh and S. N. N. Tatura. Comparison of urine neutrophil gelatinase-associated lipocalin to serum creatinine to assess kidney function in neonatal asphyxia. Paediatrica Indonesiana, 56(6), 356-359. [18597]
Tasanarong	2013	Not relevant type of population	A. Tasanarong, P. Hutayanon and D. Piyayotai. Urinary Neutrophil Gelatinase-Associated Lipocalin predicts the severity of contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. BMC Nephrology, 14(1), 270. [16743]
Tavakoli	2018	Not a primary study	R. Tavakoli and G. Lebreton. Biomarkers for early detection of cardiac surgery-associated acute kidney injury. Journal of Thoracic Disease, 10(Supplement33), S3914-S3918. [16746]
Tawfik	2015	<100 participants	Y. Tawfik, R. M. Shaat, S. R. El-Bassiony, S. Hawas and N. Effat. Urinary and serum neutrophil gelatinase-associated lipocalin as a biomarker in Egyptian systemic lupus erythematosus patients: Relation to lupus nephritis and disease activity. Egyptian Rheumatologist, 37(4), S25-S31. [16747]
ter Maaten	2016	No focus on DTA for AKI	J. M. ter Maaten, M. A. E. Valente, M. Metra, N. Bruno, C. M. O'Connor, P. Ponikowski, J. R. Teerlink, G. Cotter, B. Davison, J. G. Cleland, M. M. Givertz, D. M. Bloomfield, H. C. Dittrich, D. J. van Veldhuisen, H. L. Hillege, K. Damman and A. A. Voors. A combined clinical and biomarker approach to predict diuretic response in acute heart failure. Clinical research in cardiology : official journal of the German Cardiac Society, 105(2), 145-53. [16752]
Teresa Torres-Salido	2014	Not relevant type of population	M. Teresa Torres-Salido, J. Cortes-Hernandez, X. Vidal, A. Pedrosa, M. Vilardell-Tarres and J. Ordi-Ros. Neutrophil gelatinase-associated lipocalin as a biomarker for lupus nephritis. Nephrology Dialysis Transplantation, 29(9), 1740-1749. [18598]
Testani	2013	Not a primary study	J. M. Testani and W. H. W. Tang. Biomarkers of acute kidney injury in chronic heart failure: What do the signals mean?. JACC: Heart Failure, 1(5), 425-426. [16754]
Tiranathanagul	2013	<100 participants	K. Tiranathanagul, S. Amornsuntorn, Y. Avihingsanon, N. Srisawat, P. Susantitaphong, K. Praditpornsilpa, K. Tungsanga and S. Eiam-Ong. Potential role of neutrophil gelatinase-associated lipocalin in identifying critically ill patients with acute kidney injury stage 2-3 who subsequently require renal replacement therapy. Therapeutic Apheresis and Dialysis, 17(3), 332-338. [16766]

Tkaczyk	2018	<100 participants	M. Tkaczyk, D. Tomczyk, A. Jander, S. Goreczny, T. Moszura, P. Dryzek, W. Krajewski, E. Glowacka and A. Wosiak. Glomerular filtration decrease after diagnostic cardiac catheterisation in children with congenital cardiac malformation - the role of serum creatinine, cystatin C, neutrophil gelatinase and urine output monitoring. Postepy w Kardiologii Interwencyjnej, 14(1), 67-74. [16767]
Tomczyk	2016	<100 participants	D. Tomczyk, A. Jander, S. Chrul, T. Moszura, P. Dryzek, W. Krajewski, E. Glowacka and M. Tkaczyk. Contrast-induced acute kidney injury in children with cardiovascular defects - Results of a pilot study. Pediatria i Medycyna Rodzinna, 12(4), 436-444. [16771]
Tong	2015	Meta-analysis - retained as background material	J. Tong, H. Li, H. Zhang, Z. Luo, Y. Huang, J. Huang, F. He and J. Fu. Neutrophil Gelatinase-associated Lipocalin in the Prediction of Contrast-induced Nephropathy: A Systemic Review and Meta-analysis. Journal of Cardiovascular Pharmacology, 66(3), 239-245. [16773]
Toprak	2017	Not relevant type of population	Z. Toprak, E. Cebeci, S. A. Helvaci, I. D. Toprak, Y. Kutlu, A. Sakin and T. Tukek. Cisplatin nephrotoxicity is not detected by urinary cell-cycle arrest biomarkers in lung cancer patients. International Urology and Nephrology, 49(6), 1041-1047. [16775]
Torregrosa	2012	Not relevant biomarker assay or test	I. Torregrosa, C. Montoliu, A. Urios, N. Elmlili, I. Juan, M. J. Puchades, M. A. Solis, R. Sanjuan, M. L. Blasco, C. Ramos, P. Tomas, J. Ribes, A. Carratala and A. Miguel. Early biomarkers of acute kidney failure after heart angiography or heart surgery in patients with acute coronary syndrome or acute heart failure. Nefrologia, 32(1), 44-52. [16777]
Torregrosa	2015	Not relevant type of population	I. Torregrosa, C. Montoliu, A. Urios, M. J. Andres-Costa, C. Gimenez-Garzo, I. Juan, M. J. Puchades, M. L. Blasco, A. Carratala, R. Sanjuan and A. Miguel. Urinary KIM-1, NGAL and L-FABP for the diagnosis of AKI in patients with acute coronary syndrome or heart failure undergoing coronary angiography. Heart and Vessels, 30(6), 703-711. [16776]
Trachtman	2013	<100 participants	H. Trachtman, E. Christen, A. Cnaan, J. Patrick, V. Mai, J. Mishra, A. Jain, N. Bullington, P. Devarajan and H. U. S. S. P. M. C. T. Investigators of the. Urinary neutrophil gelatinase-associated lipocalcin in D+HUS: a novel marker of renal injury. Pediatric Nephrology, 21(7), 989-94. [4024]
Tsuchimoto	2014	<100 participants	A. Tsuchimoto, H. Shinke, M. Uesugi, M. Kikuchi, E. Hashimoto, T. Sato, Y. Ogura, K. Hata, Y. Fujimoto, T. Kaido, J. Kishimoto, M. Yanagita, K. Matsubara, S. Uemoto and S. Masuda. Urinary neutrophil gelatinase-associated lipocalin: A useful biomarker for tacrolimus-induced acute kidney injury in liver transplant patients. PLoS ONE, 9(10), e110527. [16785]
Tugba Kos	2013	<100 participants	F. Tugba Kos, M. A. N. Sendur, S. Aksoy, H. T. Celik, S. Sezer, B. Civelek, S. Yaman and N. Zengin. Evaluation of renal function using the level of neutrophil gelatinase-associated lipocalin is not predictive of nephrotoxicity associated with cisplatin-based chemotherapy. Asian Pacific Journal of Cancer Prevention, 14(2), 1111-1114. [16786]

Tuladhar	2009	<100 participants	Tuladhar SM, Puntmann VO, Soni M, Punjabi PP, Bogle RG. Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass. J Cardiovasc Pharmacol 2009;53:261–6. https://doi.org/10.1097/FJC.0b013e31819d6139. . . [3952]
Tuladhar	2009	<100 participants	S. M. Tuladhar, V. O. Puntmann, M. Soni, P. P. Punjabi and R. G. Bogle. Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass. Journal of Cardiovascular Pharmacology, 53(3), 261-266. [16787]
Tung	2015	Not relevant type of population	Y. C. Tung, C. H. Chang, Y. C. Chen and P. H. Chu. Combined biomarker analysis for risk of acute kidney injury in patients with ST-segment elevation myocardial infarction. PLoS ONE, 10(4), e0125282. [16788]
Tyagi	2018	<100 participants	A. Tyagi, A. Luthra, M. Kumar and S. Das. Epidemiology of acute kidney injury and the role of urinary [TIMP-2].[IGFBP7]: a prospective cohort study in critically ill obstetric patients. International Journal of Obstetric Anesthesia, 36(77-84. [16789]
Tyagi	2018	<100 participants	A. Tyagi, S. Lahan, G. Verma, S. Das and M. Kumar. Role of intra-abdominal pressure in early acute kidney injury: A prospective cohort study in critically Ill obstetric patients. Indian Journal of Critical Care Medicine, 22(8), 602-607. [16791]
Tziakas	2015	Not relevant biomarker assay or test	D. Tziakas, G. Chalikias, D. Kareli, C. Tsigalou, A. Risgits, P. Kikas, D. Makrygiannis, S. Chatzikyriakou, G. Kampouromiti, D. Symeonidis, V. Voudris and S. Konstantinides. Spot urine albumin to creatinine ratio outperforms novel acute kidney injury biomarkers in patients with acute myocardial infarction. International Journal of Cardiology, 197(48-55. [16792]
Uehara	2009	Not relevant type of population	Y. Uehara, H. Makino, K. Seiki and Y. Urade. Urinary excretions of lipocalin-type prostaglandin D synthase predict renal injury in type-2 diabetes: A cross-sectional and prospective multicentre study. Nephrology Dialysis Transplantation, 24(2), 475-482. [2034]
Ueta	2014	<100 participants	K. Ueta, M. Watanabe, N. Iguchi, A. Uchiyama, Y. Shirakawa, T. Kuratani, Y. Sawa and Y. Fujino. Early prediction of acute kidney injury biomarkers after endovascular stent graft repair of aortic aneurysm: A prospective observational study. Journal of Intensive Care, 2(1), 45. [16797]
Uettwiller-Geiger	2016	<100 participants	D. L. Uettwiller-Geiger, R. Vijayendran, J. A. Kellum and R. L. Fitzgerald. Analytical characteristics of a biomarker-based risk assessment test for acute kidney injury (AKI). Clinica Chimica Acta, 455(93-98. [16798]
Urbschat	2014	No focus on DTA for AKI	A. Urbschat, S. Gauer, P. Paulus, M. Reissig, C. Weipert, E. Ramos-Lopez, R. Hofmann, P. Hadji, H. Geiger and N. Obermuller. Serum and urinary NGAL but not KIM-1 raises in human postrenal AKI. European Journal of Clinical Investigation, 44(7), 652-659. [16801]
Vaidya	2008	Not relevant type of population	V. S. Vaidya, S. S. Waikar, M. A. Ferguson, F. B. Collings, K. Sunderland, C. Gioules, G. Bradwin, R. Matsouaka, R. A. Betensky, G. C. Curhan and J. V. Bonventre. Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. Clinical and translational science, 1(3), 200-8. [3962]

Valero	2016	Not relevant type of population	E. Valero, J. C. Rodriguez, P. Moyano, G. Minana, J. Sanchis and J. Nunez. Role of Neutrophil Gelatinase-associated Lipocalin in the Detection of Contrast-induced Nephropathy in Patients Undergoing a Coronary Angiography. Revista Espanola de Cardiologia, 69(5), 524-525. [16813]
Valette	2013	<100 participants	X. Valette, B. Savary, M. Nowoczyn, C. Daubin, V. Pottier, N. Terzi, A. Seguin, S. Fradin, P. Charbonneau, J. L. Hanouz and D. Du Cheyron. Accuracy of plasma neutrophil gelatinase-associated lipocalin in the early diagnosis of contrast-induced acute kidney injury in critical illness. Intensive Care Medicine, 39(5), 857-865. [16814]
Van Biesen	2012	Not a primary study	W. Van Biesen, J. Van Massenhove, N. Lameire and R. Vanholder. Does urinary neutrophil gelatinase-associated lipocalin really solve the issue of discriminating prerenal from intrinsic acute kidney injury. Kidney International, 81(3), 321. [16817]
van Deursen	2014	No focus on DTA for AKI	V. M. van Deursen, K. Damman, A. A. Voors, M. H. van der Wal, T. Jaarsma, D. J. van Veldhuisen and H. L. Hillege. Prognostic Value of Plasma Neutrophil Gelatinase-Associated Lipocalin for Mortality in Patients With Heart Failure. Circulation-Heart Failure, 7(1), 35-42. [18602]
Van Wolfswinkel	2016	<100 participants	M. E. Van Wolfswinkel, L. C. Koopmans, D. A. Hesselink, E. J. Hoorn, R. Koelewijn, J. J. Van Hellemond and P. J. J. Van Genderen. Neutrophil gelatinase-associated lipocalin (NGAL) predicts the occurrence of malaria-induced acute kidney injury. Malaria Journal, 15(1), 464. [16823]
Vandenberghe	2017	Review - retained as background material	W. Vandenberghe, J. De Loor and E. A. J. Hoste. Diagnosis of cardiac surgery-associated acute kidney injury from functional to damage biomarkers. Current Opinion in Anaesthesiology, 30(1), 66-75. [16824]
Vanmassenhove	2013	No relevant outcome	J. Vanmassenhove, G. Glorieux, E. Hoste, A. Dhondt, R. Vanholder and W. Van Biesen. Urinary output and fractional excretion of sodium and urea as indicators of transient versus intrinsic acute kidney injury during early sepsis. Critical Care, 17(5), R234. [16828]
Vanmassenhove	2014	No focus on DTA for AKI	J. Vanmassenhove, G. Glorieux, E. Hoste, A. Dhondt, R. Vanholder and W. Van Biesen. AKI in early sepsis is a continuum from transient AKI without tubular damage over transient AKI with minor tubular damage to intrinsic AKI with severe tubular damage. International Urology and Nephrology, 46(10), 2003-2008. [16827]
Vanmassenhove	2015	No focus on DTA for AKI	J. Vanmassenhove, G. Glorieux, N. Lameire, E. Hoste, A. Dhondt, R. Vanholder and W. Van Biesen. Influence of severity of illness on neutrophil gelatinase-associated lipocalin performance as a marker of acute kidney injury a prospective cohort study of patients with sepsis. BMC Nephrology, 16(1), 18. [16826]
Varela	2015	<100 participants	C. F. Varela, G. Greloni, C. Schreck, G. Bratti, A. Medina, R. Marenchino, R. Pizarro, C. Belziti and G. Rosa-Diez. Assessment of fractional excretion of urea for early diagnosis of cardiac surgery associated acute kidney injury. Renal Failure, 37(10), 327-331. [16830]

Varnell	2017	Not a primary study	C. D. Varnell, Jr., S. L. Goldstein, P. Devarajan and R. K. Basu. Impact of Near Real-Time Urine Neutrophil Gelatinase-Associated Lipocalin Assessment on Clinical Practice. Kidney International Reports, 2(6), 1243-1249. [18603]
Verbrugge	2013	<100 participants	F. H. Verbrugge, M. Dupont, Z. Shao, K. Shrestha, D. Singh, M. Finucan, W. Mullens and W. H. W. Tang. Novel urinary biomarkers in detecting acute kidney injury, persistent renal impairment, and all-cause mortality following decongestive therapy in acute decompensated heart failure. Journal of Cardiac Failure, 19(9), 621-628. [16831]
Vermi	2014	<100 participants	A. C. Vermi, C. Costopoulos, A. Latib, D. Piraino, F. Maisano, C. Naim, T. Naganuma, F. Figini, A. Chieffo, F. Ceriotti, M. Montorfano and A. Colombo. Urinary neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury after transcatheter aortic valve implantation. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese, 55(1), 77-9. [16832]
Vesnina	2016	<100 participants	Z. V. Vesnina, Y. B. Lishmanov, E. A. Alexandrova and E. A. Nesterov. Evaluation of nephroprotective efficacy of hypoxic preconditioning in patients undergoing coronary artery bypass surgery. CardioRenal Medicine, 6(4), 328-336. [16835]
Virzi	2015	<100 participants	G. M. Virzi, M. De Cal, S. Day, A. Brocca, D. N. Cruz, C. Castellani, V. Cantaluppi, C. Bolin, M. Fedrigo, G. Thiene, M. Valente, A. Angelini, G. Vescovo and C. Ronco. Pro-apoptotic effects of plasma from patients with cardiorenal syndrome on human tubular cells. American Journal of Nephrology, 41(6), 474-484. [16840]
Virzi	2018	<100 participants	G. M. Virzi, A. Breglia, A. Brocca, M. De Cal, C. Bolin, G. Vescovo and C. Ronco. Levels of Proinflammatory Cytokines, Oxidative Stress, and Tissue Damage Markers in Patients with Acute Heart Failure with and without Cardiorenal Syndrome Type 1. CardioRenal Medicine, 8(4), 321-331. [16839]
Vives	2012	Not a primary study	M. Vives, G. Lockwood, P. P. Punjabi and D. Krahne. Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Anesthesiology, 116(2), 490-491. [16844]
Volovelsky	2018	<100 participants	O. Volovelsky, K. M. Gist, T. C. Terrell, M. R. Bennett, D. S. Cooper, J. A. Alten and S. L. Goldstein. Early postoperative measurement of fibroblast growth factor 23 predicts severe acute kidney injury in infants after cardiac surgery. Clinical Nephrology, 90(3), 165-171. [16845]
von Jeinsen	2017	No relevant outcome	B. von Jeinsen, D. Kraus, L. Palapies, S. Tzikas, T. Zeller, A. Schauer, C. Drechsler, C. Bickel, S. Baldus, K. J. Lackner, T. Munzel, S. Blankenberg, A. M. Zeiher and T. Keller. Urinary neutrophil gelatinase-associated lipocalin and cystatin C compared to the estimated glomerular filtration rate to predict risk in patients with suspected acute myocardial infarction. International Journal of Cardiology, 245(6-12. [16846]
Wagener	2008	Not relevant biomarker assay or test	G. Wagener, G. Gubitosa, S. Wang, N. Borregaard, M. Kim and H. T. Lee. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. American Journal of Kidney Diseases, 52(3), 425-33. [3973]

Wagener	2008	Not a primary study	G. Wagener and H. T. Lee. Aprotinin and urinary neutrophil gelatinase-associated lipocalin after cardiac surgery. Anesthesia & Analgesia, 106(5), 1593. [3980]
Wagener	2011	<100 participants	G. Wagener, M. Minhaz, F. A. Mattis, M. Kim, J. C. Emond and H. T. Lee. Urinary neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after orthotopic liver transplantation. Nephrology Dialysis Transplantation, 26(5), 1717-1723. [16848]
Wagener	2013	<100 participants	G. Wagener, M. Jan, M. Kim, K. Mori, J. M. Barasch, R. N. Sladen and H. T. Lee. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology, 105(3), 485-91. [4019]
Wai	2013	<100 participants	K. Wai, A. A. Soler-Garcia, S. Perazzo, P. Mattison and P. E. Ray. A pilot study of urinary fibroblast growth factor-2 and epithelial growth factor as potential biomarkers of acute kidney injury in critically ill children. Pediatric Nephrology, 28(11), 2189-2198. [16854]
Waldherr	2019	<100 participants	S. Waldherr, A. Fichtner, B. Beedgen, T. Bruckner, F. Schaefer, B. Tonshoff, J. Poschl, T. H. Westhoff and J. H. Westhoff. Urinary acute kidney injury biomarkers in very low-birth-weight infants on indomethacin for patent ductus arteriosus. Pediatric Research, 85(5), 678-686. [16859]
Wang	2014	Not relevant biomarker assay or test	M. Wang, Q. Zhang, X. Zhao, G. Dong and C. Li. Diagnostic and prognostic value of neutrophil gelatinase-associated lipocalin, matrix metalloproteinase-9, and tissue inhibitor of matrix metalloproteinases-1 for sepsis in the Emergency Department: An observational study. Critical Care, 18(6), 634. [16873]
Wang	2015	Not relevant biomarker assay or test	B. Wang, G. Chen, J. Zhang, J. Xue, Y. Cao and Y. Wu. Increased Neutrophil Gelatinase-Associated Lipocalin is Associated with Mortality and Multiple Organ Dysfunction Syndrome in Severe Sepsis and Septic Shock. Shock (Augusta, Ga.), 44(3), 234-8. [16863]
Wang	2016	<100 participants	W. Wang, A. Saad, S. M. Herrmann, A. E. Massat, M. A. McKusick, S. Misra, L. O. Lerman and S. C. Textor. Changes in inflammatory biomarkers after renal revascularization in atherosclerotic renal artery stenosis. Nephrology Dialysis Transplantation, 31(9), 1437-1443. [16875]
Wang	2016	No focus on DTA for AKI	Z. Wang, S. Ma, M. Zappitelli, C. Parikh, C. Y. Wang and P. Devarajan. Penalized count data regression with application to hospital stay after pediatric cardiac surgery. Statistical Methods in Medical Research, 25(6), 2685-2703. [16880]
Wang	2017	Not relevant biomarker assay or test	C. Wang, J. Zhang, J. Han, Q. Yang, J. Liu and B. Liang. The level of urinary IL-18 in acute kidney injury after cardiopulmonary bypass. Experimental and Therapeutic Medicine, 14(6), 6047-6051. [16864]
Wang	2017	<100 participants	Y. Wang, Z. Zou, J. Jin, J. Teng, J. Xu, B. Shen, W. Jiang, Y. Zhuang, L. Liu, Z. Luo, C. Wang and X. Ding. Urinary TIMP-2 and IGFBP7 for the prediction of acute kidney injury following cardiac surgery. BMC Nephrology, 18(1), 177. [16878]

Wang	2017	Not relevant type of population	H. J. Wang, P. Wang, N. Li, C. Wan, C. M. Jiang, J. He, D. J. Wang, M. Zhang and L. Sun. Effects of continuous renal replacement therapy on serum cytokines, neutrophil gelatinase-associated lipocalin, and prognosis in patients with severe acute kidney injury after cardiac surgery. Oncotarget, 8(6), 10628-10636. [16868]
Wang	2018	Not relevant biomarker assay or test	J. J. Wang, N. H. Chi, T. M. Huang, R. Connolly, L. W. Chen, S. C. J. Chueh, W. C. Kan, C. C. Lai, V. C. Wu, J. T. Fang, T. S. Chu and K. D. Wu. Urinary biomarkers predict advanced acute kidney injury after cardiovascular surgery. Critical Care, 22(1), 108. [16869]
Washino	2019	<100 participants	S. Washino, K. Hosohata, M. Oshima, T. Okochi, T. Konishi, Y. Nakamura, K. Saito and T. Miyagawa. A Novel Biomarker for Acute Kidney Injury, Vanin-1, for Obstructive Nephropathy: A Prospective Cohort Pilot Study. International journal of molecular sciences, 20(4), . [16882]
Wasilewska	2010	<100 participants	A. Wasilewska, W. Zoch-Zwierz, K. Taranta-Janusz and J. Michaluk-Skutnik. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of cyclosporine nephrotoxicity?. Pediatric Nephrology, 25(5), 889-897. [18612]
Watanabe	2014	<100 participants	M. Watanabe, G. F. Silva, C. D. Fonseca and F. Vattimo Md.e. Urinary NGAL in patients with and without acute kidney injury in a cardiology intensive care unit. Revista Brasileira de terapia intensiva, 26(4), 347-354. [16884]
Weber	2011	Not relevant type of population	C. L. Weber, M. Bennett, L. Er, M. T. Bennett and A. Levin. Urinary NGAL levels before and after coronary angiography: a complex story. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 26(10), 3207-3211. [16886]
Wen	2017	Non-English publication	Y. Wen, Z. Li, C. Chang, P. Zhang and Y. Lyu. Diagnostic significance of urinary neutrophil gelatin enzyme-related lipid delivery protein and kidney injury molecule-1 in acute kidney injury after cardiac operation with cardiopulmonary bypass operation in children. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue, 29(12), 1112-1116. [16890]
Westhoff	2015	<100 participants	J. H. Westhoff, B. Tonshoff, S. Waldherr, J. Poschl, U. Teufel, T. H. Westhoff and A. Fichtner. Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) . insulin-like growth factor-binding protein 7 (IGFBP7) predicts adverse outcome in pediatric acute kidney injury. PLoS ONE, 10(11), e0143628. [16895]
Westhoff	2016	<100 participants	J. H. Westhoff, A. Fichtner, S. Waldherr, N. Pagonas, F. S. Seibert, N. Babel, B. Tonshoff, F. Bauer and T. H. Westhoff. Urinary biomarkers for the differentiation of prerenal and intrinsic pediatric acute kidney injury. Pediatric Nephrology, 31(12), 2353-2363. [16894]
Westhoff	2017	<100 participants	J. H. Westhoff, F. S. Seibert, S. Waldherr, F. Bauer, B. Tonshoff, A. Fichtner and T. H. Westhoff. Urinary calprotectin, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin for the prediction of adverse outcome in pediatric acute kidney injury. European Journal of Pediatrics, 176(6), 745-755. [16893]

Wetz	2015	<100 participants	A. J. Wetz, E. M. Richardt, S. Wand, N. Kunze, H. Schotola, M. Quintel, A. Brauer and O. Moerer. Quantification of urinary TIMP-2 and IGFBP-7: An adequate diagnostic test to predict acute kidney injury after cardiac surgery?. Critical Care, 19(1), 3. [16897]
Wheeler	2008	Not relevant biomarker assay or test	D. S. Wheeler, P. Devarajan, Q. Ma, K. Harmon, M. Monaco, N. Cvijanovich and H. R. Wong. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Critical Care Medicine, 36(4), 1297-303. [2425]
Wijerathna	2018	<100 participants	T. M. Wijerathna, F. Mohamed, D. Dissanayaka, I. Gawarammana, C. Palangasinghe, F. Shihana, Z. Endre, S. Shahmy and N. A. Buckley. Albuminuria and other renal damage biomarkers detect acute kidney injury soon after acute ingestion of oxalic acid and potassium permanganate. Toxicology Letters, 299(182-190. [16900]
Wijerathna	2019	Not relevant type of population	T. M. Wijerathna, I. B. Gawarammana, F. Mohamed, D. M. Dissanayaka, P. I. Dargan, U. Chathuranga, C. Jayathilaka and N. A. Buckley. Epidemiology, toxicokinetics and biomarkers after self-poisoning with Gloriosa superba. Clinical Toxicology, . [16899]
Woitas	2017	Not relevant type of population	R. P. Woitas, H. Scharnagl, M. E. Kleber, G. E. Delgado, T. B. Grammer, M. Pichler, B. K. Kraemer, W. Maerz and T. Stojakovic. Neutrophil gelatinase-associated lipocalin levels are U-shaped in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study-Impact for mortality. Plos One, 12(2), e0171574-e0171574. [18614]
Wong	2014	Not a primary study	F. Wong and P. Murray. Kidney damage biomarkers: Novel tools for the diagnostic assessment of acute kidney injury in cirrhosis. Hepatology, 60(2), 455-457. [16905]
Woo	2012	Not relevant type of population	K.-S. Woo, J.-L. Choi, B.-R. Kim, J.-E. Kim, W.-S. An and J.-Y. Han. Urinary neutrophil gelatinase-associated lipocalin levels in comparison with glomerular filtration rate for evaluation of renal function in patients with diabetic chronic kidney disease. Diabetes & metabolism journal, 36(4), 307-13. [16907]
Wu	2010	<100 participants	Y. Wu, T. Su, L. Yang, S.-N. Zhu and X.-M. Li. Urinary Neutrophil Gelatinase-Associated Lipocalin: A Potential Biomarker for Predicting Rapid Progression of Drug-Induced Chronic Tubulointerstitial Nephritis. American Journal of the Medical Sciences, 339(6), 537-542. [18617]
Wu	2013	Not relevant type of population	J. Wu, Y. Ding, C. Zhu, X. Shao, X. Xie, K. Lu and R. Wang. Urinary TNF-alpha and NGAL are correlated with the progression of nephropathy in patients with type 2 diabetes. Experimental and Therapeutic Medicine, 6(6), 1482-1488. [18616]
Wu	2018	Not relevant type of population	V. C. Wu, C. C. Shiao, N. H. Chi, C. H. Wang, S. C. J. Chueh, H. H. Liou, H. D. Spapen, P. M. Honore and T. S. Chu. Outcome prediction of acute kidney injury biomarkers at initiation of dialysis in critical units. Journal of Clinical Medicine, 7(8), 202. [16910]
Xiao	2013	<100 participants	J. Xiao, J. Niu, X. Ye, Q. Yu and Y. Gu. Combined biomarkers evaluation for diagnosing kidney injury in preeclampsia. Hypertension in Pregnancy, 32(4), 439-449. [16917]

Xiao	2015	<100 participants	N. Xiao, P. Devarajan, T. H. Inge, T. M. Jenkins, M. Bennett and M. M. Mitsnefes. Subclinical kidney injury before and 1 year after bariatric surgery among adolescents with severe obesity. Obesity, 23(6), 1234-1238. [16918]
Xiao	2019	Not relevant biomarker assay or test	W. Xiao, W. Chen, H. Hu, X. Huang and Y. Luo. The clinical significance of neutrophil gelatinase-associated lipocalin in ischemic stroke patients with acute kidney injury. Journal of clinical laboratory analysis, e22907. [16919]
Xie	2014	<100 participants	Y. Xie, W. Xu, Q. Wang, X. Shao, Z. Ni and S. Mou. Urinary excretion of liver-type FABP as a new clinical marker for the progression of obstructive nephropathy. Biomarkers in medicine, 8(4), 543-56. [16922]
Ximenes	2015	<100 participants	R. O. Ximenes, A. Q. Farias and C. M. B. Helou. Early predictors of acute kidney injury in patients with cirrhosis and bacterial infection: Urinary neutrophil gelatinase-associated lipocalin and cardiac output as reliable tools. Kidney Research and Clinical Practice, 34(3), 140-145. [16924]
Xin	2013	<100 participants	C. Xin, X. Yulong, C. Yu, C. Changchun, Z. Feng and M. Xinwei. Urine neutrophil gelatinase-associated lipocalin and interleukin-18 predict acute kidney injury after cardiac surgery. Renal Failure, 30(9), 904-13. [3966]
Xue	2014	<100 participants	W. Xue, Y. Xie, Q. Wang, W. Xu, S. Mou and Z. Ni. Diagnostic performance of urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin for acute kidney injury in an obstructive nephropathy patient. Nephrology, 19(4), 186-194. [16928]
Yamanouchi	2018	<100 participants	S. Yamanouchi, T. Kimata, J. Kino, T. Kitao, C. Suruda, S. Tsuji, H. Kurosawa, Y. Hirayama, A. Saito and K. Kaneko. Urinary C-megalin for screening of renal scarring in children after febrile urinary tract infection. Pediatric Research, 83(3), 662-668. [16930]
Yamashita	2014	<100 participants	T. Yamashita, K. Doi, Y. Hamasaki, T. Matsubara, T. Ishii, N. Yahagi, M. Nangaku and E. Noiri. Evaluation of urinary tissue inhibitor of metalloproteinase-2 in acute kidney injury: A prospective observational study. Critical Care, 18(1), 716. [16932]
Yamashita	2016	<100 participants	T. Yamashita, E. Noiri, Y. Hamasaki, T. Matsubara, T. Ishii, N. Yahagi, M. Nangaku and K. Doi. Erythropoietin concentration in acute kidney injury is associated with insulin-like growth factor-binding protein-1. Nephrology, 21(8), 693-699. [16931]
Yang	2009	Not relevant type of population	Y.-H. Yang, X.-J. He, S.-R. Chen, L. Wang, E.-M. Li and L.-Y. Xu. Changes of serum and urine neutrophil gelatinase-associated lipocalin in type-2 diabetic patients with nephropathy: one year observational follow-up study. Endocrine, 36(1), 45-51. [18618]
Yang	2012	<100 participants	C. C. Yang, S. C. Hsieh, K. J. Li, C. H. Wu, M. C. Lu, C. Y. Tsai and C. L. Yu. Urinary neutrophil gelatinase-associated lipocalin is a potential biomarker for renal damage in patients with systemic lupus erythematosus. Journal of Biomedicine and Biotechnology, 2012(759313. [16934]

Yang	2014	<100 participants	H. T. Yang, H. Yim, Y. S. Cho, D. Kym, J. Hur, J. H. Kim, W. Chun and H. S. Kim. Assessment of biochemical markers in the early post-burn period for predicting acute kidney injury and mortality in patients with major burn injury: Comparison of serum creatinine, serum cystatin-C, plasma and urine neutrophil gelatinase-associated lipocalin. Critical Care, 18(4), R151. [16939]
Yang	2015	Not relevant biomarker assay or test	X. Yang, C. Chen, J. Tian, Y. Zha, Y. Xiong, Z. Sun, P. Chen, J. Li, T. Yang, C. Ma, H. Liu, X. Wang and F. F. Hou. Urinary angiotensinogen level predicts AKI in acute decompensated heart failure: A prospective, two-stage study. Journal of the American Society of Nephrology, 26(8), 2032-2041. [16946]
Yang	2016	Not relevant biomarker assay or test	C. H. Yang, C. H. Chang, T. H. Chen, P. C. Fan, S. W. Chang, C. C. Chen, P. H. Chu, Y. T. Chen, H. Y. Yang, C. W. Yang and Y. C. Chen. Combination of urinary biomarkers improves early detection of acute kidney injury in patients with heart failure. Circulation Journal, 80(4), 1017-1023. [16935]
Yang	2017	<100 participants	J. Yang, S. Y. Lim, M. G. Kim, C. W. Jung, W. Y. Cho and S. K. Jo. Urinary Tissue Inhibitor of Metalloproteinase and Insulin-like Growth Factor-7 as Early Biomarkers of Delayed Graft Function After Kidney Transplantation. Transplantation Proceedings, 49(9), 2050-2054. [16940]
Yap	2017	<100 participants	D. Y. H. Yap, W. K. Seto, J. Fung, S. H. Chok, S. C. Chan, G. C. W. Chan, M. F. Yuen and T. M. Chan. Serum and urinary biomarkers that predict hepatorenal syndrome in patients with advanced cirrhosis. Digestive and Liver Disease, 49(2), 202-206. [18620]
Yavas	2013	<100 participants	H. Yavas, O. Z. Sahin, R. Ersoy, F. Tasli, D. Gibyeli Genek, A. Uzum and M. Cirit. Prognostic value of NGAL staining in patients with IgA nephropathy. Renal Failure, 35(4), 472-476. [16949]
Yavuz	2014	<100 participants	S. Yavuz, A. Anarat, S. Acarturk, A. C. Dalay, E. Kesiktas, M. Yavuz and T. O. Acarturk. Neutrophil gelatinase associated lipocalin as an indicator of acute kidney injury and inflammation in burned children. Burns, 40(4), 648-654. [16950]
Ye	2018	Not relevant type of population	H.-H. Ye, G. Shen, Q. Luo, F.-F. Zhou, X.-L. Xie, C.-Y. Wang and L.-N. Han. Early diagnosis of acute kidney injury in aged patients undergoing percutaneous coronary intervention. Journal of Zhejiang University. Science. B, 19(5), 342-348. [16951]
Yegenaga	2018	Not relevant biomarker assay or test	I. Yegenaga, F. Kamis, C. Baydemir, E. Erdem, K. Celebi, N. Eren and N. Baykara. Neutrophil gelatinase-associated lipocalin is a better biomarker than cystatin C for the prediction of imminent acute kidney injury in critically ill patients. Annals of Clinical Biochemistry, 55(2), 190-197. [16952]
Yeh	2013	<100 participants	Y.-H. Yeh, J.-L. Chang, P.-C. Hsiao, S.-M. Tsao, C. H. Lin, S.-J. Kao, M.-C. Chou, S.-F. Yang and M.-H. Chien. Circulating Level of Lipocalin 2 As a Predictor of Severity in Patients With Community-Acquired Pneumonia. Journal of clinical laboratory analysis, 27(4), 253-260. [18621]

Yeung	2018	Systematic review - retained as background material	A. C. Y. Yeung, A. Morozov, F. P. Robertson, B. J. Fuller and B. R. Davidson. Neutrophil Gelatinase-Associated Lipocalin (NGAL) in predicting acute kidney injury following orthotopic liver transplantation: A systematic review. International Journal of Surgery, 59(48-54. [16955]
Yilmaz	2013	<100 participants	A. Yilmaz, E. Sevketoglu, A. Gedikbasi, S. Karyagar, A. Kiyak, M. Mulazimoglu, G. Aydogan, T. Ozpacaci and S. Hatipoglu. Early prediction of urinary tract infection with urinary neutrophil gelatinase associated lipocalin. Pediatric Nephrology, 24(12), 2387-92. [3935]
Ylinen	2014	<100 participants	E. Ylinen, K. Jahnukainen, U. M. Saarinen-Pihkala and T. Jahnukainen. Assessment of Renal Function During High-Dose Methotrexate Treatment in Children With Acute Lymphoblastic Leukemia. Pediatric Blood & Cancer, 61(12), 2199-2202. [18622]
Yndestad	2009	Not relevant biomarker assay or test	A. Yndestad, L. LandrÃ¸, T. Ueland, C. P. Dahl, T. H. Flo, L. E. Vinge, T. Espevik, S. S. FrÃ¸land, C. Husberg and G. Christensen. Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. European heart journal, 30(10), 1229â€ 1236. [4801]
Yoon	2018	<100 participants	K. C. Yoon, K. W. Lee, S. C. Oh, H. Kim, H. S. Kim, S. K. Hong, S. W. Ahn, N. J. Yi and K. S. Suh. Urinary Neutrophil Gelatinase-Associated Lipocalin as a Biomarker for Renal Injury in Liver Transplant Recipients Using Calcineurin Inhibitors. Transplantation Proceedings, 50(10), 3667-3672. [16959]
Young-Min	2014	<100 participants	J. Young-Min, H. A. Cheul-Min, N. O. H. Ki-Cheul and P. Y. O. Chang-Hae. The Usefulness of Plasma Neutrophil Gelatinase-Associated Lipocalin in Acute Pyelonephritis. Journal of the Korean Society of Emergency Medicine, 137-144. [6171]
Youssef	2012	<100 participants	D. M. Youssef and A. S. El-Shal. Urinary neutrophil gelatinase-associated lipocalin and kidney injury in children with focal segmental glomerulosclerosis. Iranian Journal of Kidney Diseases, 6(5), 355-360. [16963]
Youssef	2013	<100 participants	D. M. Youssef, A. M. Esh, E. Helmy Hassan and T. M. Ahmed. Serum NGAL in Critically Ill Children in ICU from a Single Center in Egypt. ISRN nephrology, 2013(140905. [16964]
Yuan	2014	Non-English publication	F. Yuan, H. Liu, W. X. Wang, J. J. Dai, L. Y. Dai, X. X. Yang and W. Y. Fang. Study on early diagnosis of acute decompensated heart failure combined with acute renal injury. Journal of Shanghai Jiaotong University (Medical Science), 34(12), . [16966]
Zaleska-Kociecka	2017	<100 participants	M. Zaleska-Kociecka, A. Skrobisz, I. Wojtkowska, M. Grabowski, M. Dabrowski, K. Kusmierski, K. Piotrowska, J. Imiela and J. Stepinska. Serum beta-2 microglobulin levels for predicting acute kidney injury complicating aortic valve replacement. Interactive Cardiovascular and Thoracic Surgery, 25(4), 533-540. [16972]
Zaouter	2018	<100 participants	C. Zaouter, F. Priem, L. Leroux, G. Bonnet, M. L. Bats, M. C. Beauvieux, A. Remy and A. Ouattara. New markers for early detection of acute kidney injury after transcatheter aortic valve implantation. Anaesthesia Critical Care and Pain Medicine, 37(4), 319-326. [16976]

Zaouter	2018	<100 participants	C. Zaouter, J. Potvin, M. L. Bats, M. C. Beauvieux, A. Remy and A. Ouattara. A combined approach for the early recognition of acute kidney injury after adult cardiac surgery. Anaesthesia Critical Care and Pain Medicine, 37(4), 335-341. [16975]
Zappitelli	2007	Not relevant biomarker assay or test	M. Zappitelli, K. K. Washburn, A. A. Arikan, L. Loftis, Q. Ma, P. Devarajan, C. R. Parikh and S. L. Goldstein. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: A prospective cohort study. Critical Care, 11(no pagination), . [2102]
Zappitelli	2007	Duplicate of a study that had already been assessedlicate of a study that had already been assessed	M. Zappitelli, K. K. Washburn, A. A. Arikan, L. Loftis, Q. Ma, P. Devarajan, C. R. Parikh and S. L. Goldstein. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Critical Care, 11(4), R84-R84. [18624]
Zappitelli	2012	No focus on DTA for AKI	M. Zappitelli, S. G. Coca, A. X. Garg, C. D. Krawczeski, H. T. Philbrook, K. Sint, S. Li, C. R. Parikh and P. Devarajan. The association of albumin/creatinine ratio with postoperative AKI in children undergoing cardiac surgery. Clinical Journal of the American Society of Nephrology, 7(11), 1761-1769. [16979]
Zarbock	2015	No focus on DTA for AKI	A. Zarbock, C. Schmidt, H. Van Aken, C. Wempe, S. Martens, P. K. Zahn, B. Wolf, U. Goebel, C. I. Schwer, P. Rosenberger, H. Haeberle, D. Gorlich, J. A. Kellum, M. Meersch and R. I. Renal. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA, 313(21), 2133-41. [16981]
Zarbock	2016	Not relevant type of population	A. Zarbock, J. A. Kellum, C. Schmidt, H. Van Aken, C. Wempe, H. Pavenstadt, A. Boanta, J. Gerss and M. Meersch. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The elain randomized clinical trial. JAMA - Journal of the American Medical Association, 315(20), 2190-2199. [16984]
Zelt	2018	Duplicate of a study that had already been assessedlicate of a study that had already been assessed	J. G. E. Zelt, L. M. Mielniczuk, P. P. Liu, J.-Y. Dupuis, S. Chih, A. Akbari and L. Y. Sun. Utility of Novel Cardiorenal Biomarkers in the Prediction and Early Detection of Congestive Kidney Injury Following Cardiac Surgery. Journal of Clinical Medicine, 7(12), 540-540. [18625]
Zeng	2014	Not relevant biomarker assay or test	X. F. Zeng, J. M. Li, Y. Tan, Z. F. Wang, Y. He, J. Chang, H. Zhang, H. Zhao, X. Bai, F. Xie, J. Sun and Y. Zhang. Performance of urinary NGAL and L-FABP in predicting acute kidney injury and subsequent renal recovery: A cohort study based on major surgeries. Clinical Chemistry and Laboratory Medicine, 52(5), 671-678. [16989]
Zhang	2015	Not relevant type of population	M. Zhang, X. Zhao, Y. Deng, B. Tang, Q. Sun, Q. Zhang, W. Chen, D. Yao, J. Yang, L. Cao and H. Guo. Neutrophil gelatinase associated lipocalin is an independent predictor of poor prognosis in cases of papillary renal cell carcinoma. Journal of Urology, 194(3), 647-652. [16996]
Zhang	2015	Not a primary study	Z. Zhang. Biomarkers, diagnosis and management of sepsis-induced acute kidney injury: a narrative review. Heart, lung and vessels, 7(1), 64-73. [17004]

Zhang	2016	Meta-analysis - retained as background material	A. Zhang, Y. Cai, P. F. Wang, J. N. Qu, Z. C. Luo, X. D. Chen, B. Huang, Y. Liu, W. Q. Huang, J. Wu and Y. H. Yin. Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: A systematic review and meta-analysis. Critical Care, 20(1), 41. [16991]
Zhang	2017	No focus on DTA for AKI	Y. Zhang, Y. Yu, J. Jia, W. Yu, R. Xu, L. Geng and Y. Wei. Administration of HES in elderly patients undergoing hip arthroplasty under spinal anesthesia is not associated with an increase in renal injury. BMC Anesthesiology, 17(1), 29. [17003]
Zhang	2017	<100 participants	J. Zhang, J. Han, J. Liu, B. Liang, X. Wang and C. Wang. Clinical significance of novel biomarker NGAL in early diagnosis of acute renal injury. Experimental and Therapeutic Medicine, 14(5), 5017-5021. [16994]
Zhang	2018	Not relevant type of population	Y. Zhang, J. Li, F. Li, X. Qi and J. Zhang. Neutrophil gelatinase-associated lipocalin accurately predicts renal tubular injury in patients with chronic hepatitis B treated with nucleos(t)ide analogs. Hepatology Research, 48(2), 144-152. [17002]
Zhang	2018	<100 participants	D. Zhang, Q. X. Han, M. H. Wu, W. J. Shen, X. L. Yang, J. Guo, S. K. Pan, Z. S. Liu, L. Tang, G. Y. Cai, X. M. Chen and H. Y. Zhu. Diagnostic Value of Sensitive Biomarkers for Early Kidney Damage in Diabetic Patients with Normoalbuminuria. Chinese Medical Journal, 131(23), 2891-2892. [16992]
Zhang	2018	Not relevant type of population	J. Zhang, X. Lin, B. Tian and C. Liu. Evaluation of the efficacy of ischemic post-conditioning for the improvement of contrast induced nephropathy on patients with acute coronary syndrome. International Journal of Clinical and Experimental Medicine, 11(5), 4663-4669. [16993]
Zhang	2018	Not relevant type of population	W. R. Zhang, T. E. Craven, R. Malhotra, A. K. Cheung, M. Chonchol, P. Drawz, M. J. Sarnak, C. R. Parikh, M. G. Shlipak and J. H. Ix. Kidney damage biomarkers and incident chronic kidney disease during blood pressure reduction: A case-control study. Annals of Internal Medicine, 169(9), 610-618. [16999]
Zheng	2013	<100 participants	J. Zheng, Y. Xiao, Y. Yao, G. Xu, C. Li, Q. Zhang, H. Li and L. Han. Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. Pediatric Cardiology, 34(4), 880-886. [17010]
Zhou	2016	Not relevant biomarker assay or test	L. Z. Zhou, X. B. Yang, Y. Guan, X. Xu, M. T. Tan, F. F. Hou and P. Y. Chen. Development and Validation of a Risk Score for Prediction of Acute Kidney Injury in Patients With Acute Decompensated Heart Failure: A Prospective Cohort Study in China. Journal of the American Heart Association, 5(11), . [17013]
Zhou	2016	Meta-analysis - retained as background material	F. Zhou, Q. Luo, L. Wang and L. Han. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: A meta-analysis. European Journal of Cardio-thoracic Surgery, 49(3), 746-755. [17012]
Zhou	2018	Not relevant type of population	F. Zhou, W. Song, Z. Wang, L. Yin, S. Yang, F. Yang, Z. Song, Y. Song, H. Zhang, F. Qiao and Z. Zhang. Effects of remote ischemic preconditioning on contrast induced nephropathy after percutaneous coronary intervention in patients with acute coronary syndrome. Medicine (United States), 97(2), 9579. [17011]

Zhu	2014	<100 participants	W. Zhu, M. Liu, G.-C. Wang, J.-P. Che, Y.-F. Xu, B. Peng and J.-H. Zheng. Urinary neutrophil gelatinase-associated lipocalin, a biomarker for systemic inflammatory response syndrome in patients with nephrolithiasis. Journal of Surgical Research, 187(1), 237-243. [18626]
Zhu	2016	Non-English publication	L. Zhu and D. Shi. Early diagnostic value of neutrophil gelatinase-associated lipocalin and interleukin-18 in patients with sepsis-induced acute kidney injury. Zhonghua wei zhong bing ji jiu yi xue, 28(8), 718-722. [17014]
Zughaier	2013	<100 participants	S. M. Zughaier, V. Tangpricha, T. Leong, A. A. Stecenko and N. A. McCarty. Peripheral Monocytes Derived From Patients With Cystic Fibrosis and Healthy Donors Secrete NGAL in Response to Pseudomonas aeruginosa Infection. Journal of Investigative Medicine, 61(6), 1018-1025. [18627]
Zwaag	2019	No focus on DTA for AKI	J. Zwaag, R. Beunders, M. C. Warle, J. A. Kellum, N. P. Riksen, P. Pickkers and M. Kox. Remote ischaemic preconditioning does not modulate the systemic inflammatory response or renal tubular stress biomarkers after endotoxaemia in healthy human volunteers: a single-centre, mechanistic, randomised controlled trial. British Journal of Anaesthesia, . [17017]
Zwiers	2015	<100 participants	A. J. M. Zwiers, K. Cransberg, Y. B. De Rijke, J. Van Rosmalen, D. Tibboel and S. N. De Wildt. Urinary neutrophil gelatinase-associated lipocalin predicts renal injury following extracorporeal membrane oxygenation. Pediatric Critical Care Medicine, 16(7), 663-670. [17020]

Appendix 8 Characteristics of included studies

Table 41 Characteristics of included studies

Study ID	Assay	Age (Range or SD)	Sample size	AKI events	AKI Definition	Sex (% of male)	sCr	eGFR	SOFA Mean Score	CKD (%)	Inclusion Criteria	Exclusion Criteria
Cummings 2019, USA	NephC, Astute Medical	67 (58, 75)*	400	14	KDIGO	67%	NR	NR	NR	6	Patients who were originally enrolled in the AKI Cardiac Surgery RCT	Acute coronary syndrome, liver dysfunction, use of cyclosporine, current RRT, history of kidney transplant, pregnancy
Oezkur 2017, Germany	NephC, Astute Medical	AKI 65 (59, 73); No AKI 71 (64,76)*	150	35	KDIGO	72%	0.89** (IQR 0.75 to 1.02)	NR	NR	NR	Adult patients were eligible if they were undergoing elective cardiac surgery (coronary artery bypass graft [CABG] with or without mammary artery bypass, valve surgery with or without removal of the atrial auricle, combined CABG and valve surgery, or surgery of the thoracic aorta) involving cardiopulmonary bypass (CPB)	Patients with advanced stages of chronic kidney disease; signs of active infection; on medication with COMT inhibitors, MAO inhibitors or with immunosuppressive therapy and women during pregnancy and lactation.
Beitland 2016, Norway	NephC, Astute Medical	60 (13)	195	88	KDIGO	AKI: 83.0% No AKI: 86.0%;	NR	NR	NR	AKI 22 No AKI 9	Adult (≥18 years) comatose out-of-hospital cardiac arrest patients with return of spontaneous circulation	Patients with known chronic kidney disease, or who died within 24 h of ICU stay, or for some reason did not receive active treatment, were excluded
Kashani 2013, 21 sites in North America, 15	NephC, Astute Medical	64 (53, 73)	728	101	KDIGO	62%	NR	NR	NR	NR	Critically ill patients who were at least 21 years of age, admitted to the ICU within 24 hours of enrolment, expected to	Patients with known existing moderate or severe AKI

sites in Europe											remain in the ICU with a urinary catheter for at least 48 hours and were critically ill	
Bihorac 2014, USA	NephC, Astute Medical	63 (17)	408	71	KDIGO	54%	NR	NR	NR	NR	All enrolled patients were considered critically ill because of significant respiratory or cardiovascular dysfunction. The presence of an indwelling urinary catheter was also a prerequisite for inclusion.	Patients with documented moderate to severe AKI (KDIGO stage 2 to 3) at the time of enrolment
Hoste 2014, USA	NephC, Astute Medical	AKI stage 2/3 64 (54, 75); AKI stage 0/1 65 (54, 78)	153	27	KDIGO	AKI stage 2/3 44%; AKI stage 0/1 60%	NR	NR	NR	20	Patients at least 21 years of age, admitted to ICU within 24 h of enrolment and expected to remain in the ICU with a urinary catheter for at least 48 h after enrolment	NR
Di Leo 2018, Italy	NephC, Astute Medical	68 (51, 78)	719	234	KDIGO	NC(+) 63% NC(–) 59%	NR	NR	NR	AKI Stage 2/3: 33	All patients ≥18 years old were included in the study	Patients on chronic dialysis and with a life expectancy less than 24 h were excluded
Kimmel 2016, Germany	NephC, Astute Medical, uNGAL, BioPorto & pNGAL BioPorto	63 (14)	298	46	KDIGO (modified version)	72%	NR	NR	NR	NR	Age ≥18 years, willingness to sign an informed consent form, admission to the internal medicine service of the hospital, and haemoglobin level ≥9.5 g/dl (women) or ≥10.5 g/dl (men)	Dialysis requirement, pregnancy, or failure to meet any of the inclusion criteria
Gayat 2018, France	NephC, Astute Medical	65 (54, 75)	200	Unclear	KDIGO	78%	NR	NR	NR	NR	NR	NR

Zelt 2018, USA	pNGAL, BioPorto	67 (61, 73)	178	35	AKIN	NR	NR	NR	NR	NR	All patients having elective cardiac surgery requiring CPB	End stage renal disease; renal transplantation; solitary kidney, emergent operative status, off-pump procedures, procedures involving circulatory arrest, heart transplantation and left ventricular assist divide implantation
Lee 2018, Republic of Korea	pNGAL, BioPorto	59 (50, 71)	279	111	KDIGO	66%	NR	NR	NR	25	Nontraumatic CA survivors over 18 years of age who were treated with TH and obtained plasma NGAL level results were enrolled	Transferred to another facility or died during TH, they had a pre-arrest cognitive impairment on the CPC scale greater than 3, they had pre-arrest end-stage renal disease with RRT, they had CA as a result of AKI, extracorporeal membrane oxygenation was applied during the post-CA care, or there were missing data regarding their NGAL level
Itenov 2017, Denmark	pNGAL, BioPorto	67 (60, 76)	454	87	KDIGO or MDRD (in patients without sCr samples before admission)	60%	NR	NR	NR	21	Patients (18 years old or older) enrolled within 24 h of ICU admission and expected to stay in ICU at least 24 h. For the present cohort study, the authors included patients without CKD who survived >24 h after admission and with plasma samples from admission available for biomarker analysis	Patients with high plasma concentrations of bilirubin (40 mg/dL), and/or triglycerides (1,000 mg/dL) or patients at an increased risk from blood sampling were not eligible

Marino 2015, Italy	pNGAL, BioPorto	77 (72, 83)	101	49	RIFLE	60%	NR	NR	NR	NR	Patients arriving in the ED with the diagnosis of sepsis, severe sepsis or septic shock between December 2011 and April 2012	Exclusion criteria were age <18 years and the patient's inability to give informed consent
Parikh 2011, North America	uNGAL, ARCHITECT, Abbott	71 (10)	1200	60	Acute dialysis or doubling of sCr at a median of 3 days after surgery (IQR 2 to 4)	68%	1.0** (IQR 0.9 to 1.20)	NR	NR	20	High risk for AKI was defined by the presence of one or more of the following: emergency surgery, preoperative serum creatinine > 2 mg/dl (>177 μmol/L), ejection fraction < 35% or grade 3 or 4 left ventricular dysfunction, age > 70 years, diabetes mellitus, concomitant CABG and valve surgery, or repeat revascularization surgery.	Patients with evidence of AKI before surgery, prior kidney transplantation, preoperative serum creatinine level > 4.5 mg/dl (>398 μmol/L), or end-stage renal disease. Participants with multiple surgeries could only be enrolled in the study once.
Albert 2018, Germany	uNGAL, ARCHITECT, Abbott	70 (61,77)	101	15	RIFLE	72%	NR	NR	NR	NR	Nonemergency open-heart surgery with cardiopulmonary bypass	Emergency operation or off-pump surgery, CKD or kidney transplant; pts <18 y and pts on immunosuppression
Haase 2014, Germany	uNGAL, ARCHITECT, Abbott & pNGAL BioPorto	72 (65,77)	100	23	RIFLE	75%	NR	NR	NR	NR	Age above 70 y, pre-existing renal impairment (pre-operative creatinine >120 μmol/l, left ventricular ejection fraction <35%, insulin-dependent Type 2 diabetes, valvular surgery or valvular and coronary artery bypass surgery, redo cardiac surgery	Patients with chronic renal impairment (preoperative creatinine >300 μmol/L), those undergoing an emergency cardiac surgery procedure, patients on immunosuppression therapy, and those enrolled in a conflicting research study).
De Loor 2017, Belgium	uNGAL, BioPorto	69 (61, 76)	203	95	KDIGO	66%	NR	NR	NR	NR	Elective cardiac surgery	AKI stage ≥1, CKD stage 5; recent kidney transplant; surgery Sat and Sun.

Garcia-Alvarez 2015, Spain	uNGAL, ARCHITECT, Abbott	AKI 74 (68, 80); No AKI 69 (59, 76)	288	104	sCr ≥200% or eGFR <50% from baseline	AKI: 54%; No AKI: 46%	NR	NR	NR	NR	All patients admitted to ICU after cardiac surgery and provided informed consent	If patients required preoperative chronic or acute haemodialysis; previously undergone renal transplant or had coronary angiography in 7 days before surgery
Thanakitcharu 2014, Thailand	uNGAL, ARCHITECT, Abbott	51 (15.6)	130	46	sCr ≥0.3mg/dL within 48 h	59%	1.0 *mg/dl (SD 0.3)	74.1 (25.9)	NR	NR	All patients who underwent cardiac surgery with CPB	Pre-existing renal dysfunction with baseline sCr>3mg/dl; Kidney transplant patients; Hx of using nephrotoxic agents such as aminoglycoside, NSAIDs, radiocontrast agent within 2 weeks before Sx; Patients with sepsis; Patients undergoing emergency operation <24 hrs after admission
Tidbury 2019, UK	uNGAL, BioPorto	AKI 73 (54-87); No AKI 75 (59-85)	125	54	RIFLE	AKI: 63%; No AKI: 47%	NR	NR	NR	NR	High risk patients undergoing elective surgery for on-pump such as valve replacement, CABG or combined valve and CABG. All had impaired renal function pre-op established by an eGFR <60ml/min.	Excluded if they were scheduled to undergo surgery with anticipated CPB time less than 60 min; undergoing surgery on great vessels such as aortic surgery; had impaired liver function; renal failure or were on dialysis; malignancy; being pregnant.
Schley 2015, Germany	uNGAL, BioPorto & pNGAL BioPorto	70 (10)	110	37	AKIN	76%	1.2* mg/dl (SD 0.5)	NR	NR	NR	All patients undergoing cardiac surgery using CPB	Pre-existing haemodialysis-dependent end stage renal disease, previous kidney transplantation, immunosuppressive medication and pregnancy

Collins 2012, USA	uNGAL, ARCHITECT, Abbott	NR	399	20	sCr ≥0.3mg/dL or RIFLE	65%	NR	NR	NR	NR	Modified Framingham criteria for AHF; enrolled within 3 h of first physician contact; received vasodilators or diuretics in the ED for treatment of AHF.	NR
Dupont 2012, USA	uNGAL, ARCHITECT, Abbott	NR	141	35	sCr increase ≥0.3mg/dL	58%	NR	NR	NR	NR	>18 years of age, clinical evidence of congestion, planned strategy for treatment with intravenous furosemide	Acute coronary syndrome; end-stage renal disease or RRT; exposure to nephrotoxic agents; planned surgery at the time of enrolment; haemoglobin <9 mg/dL or active bleeding.
Cullen 2014, UK	uNGAL, ARCHITECT, Abbott	68 (11)	109	16	AKIN	NR	NR	NR	NR	NR	Patients admitted to critical care following major abdominal surgery	Refusal of consent, concurrent lithium therapy, acute myocardial ischemia, acute arrhythmias, pregnancy, patients receiving palliative treatment only and weight less than 40 kg.
Nisula 2015, Finland	uNGAL, BioPorto	62 (50,73)	855	379	KDIGO	64%	NR	NR	NR	NR	Emergency ICU admissions and postop patients admitted for more than 24 h	Patients <18 years of age, readmitted patients who received RRT during their previous admission, patients electively admitted with an ICU length of stay of <24 h if discharged alive, patients on chronic dialysis, organ donors, patients without permanent residency in Finland or without sufficient language skills, patients transferred between study ICUs if included in the study for 5 days already, and patients

												receiving intermediate care.
Doi 2014, Japan	uNGAL, BioPorto	AKI 65 (53, 74); No AKI 66 (55,73)	339	131	RIFLE	AKI: 70% No AKI: 64%;	NR	NR	NR	NR	patients >20 years who had been admitted to the mixed ICU	Patients with end-stage renal disease or renal transplant were excluded
Cho 2013, Korea	uNGAL, BioPorto	AKI 65.4 (14.8); No AKI 60.4 (17.4)	145	54	AKIN	AKI: 61%; No AKI: 57%	NR	NR	NR	NR	adult patients older than 18 years who were admitted to the medical or surgical ICU	end-stage renal disease or kidney transplantation and those with life expectancy of < 48 hr
Pipili 2014, Greece	uNGAL, ARCHITECT, Abbott	64 (18)	106	44	RIFLE	64%	1.0 mg/dL (SD 1.3)	NR	9 (3)	NR	All consecutive, mechanically ventilated patients admitted to the ICU were considered eligible for inclusion	Age <18 years, BMI more than 35 kg/m^2, end-stage renal disease on chronic haemodialysis, pregnancy, brain death, metastatic cancer and readmission to ICU or missing baseline creatinine within 6 months before admission
Martensson 2015, Australia	uNGAL, ARCHITECT, Abbott	Mild AKI 69 (59,74) Severe AKI 68 (54,76) No AKI 62 (48,72)	102	28	RIFLE	Mild AKI: 69% Severe AKI: 64% No AKI: 42%	NR	NR	NR	NR	>18 years, the presence of two or more systemic inflammatory response criteria, the presence of oliguria for ≥2 consecutive hours and/or a 25 μmol/L increase in creatinine from baseline.	NR

Isshiki 2018, Japan	uNGAL, ARCHITECT, Abbott	62 (51,73)	148	33	KDIGO	60%	NR	NR	NR	NR	>18 years who were admitted to the ICU	Anuria patients at ICU admission, those deceased within 24 h of ICU admission and end stage renal disease
Tecson 2017, USA	uNGAL, BioPorto & pNGAL BioPorto	AKI Stage 2/3 68 (56, 74) No AKI stage 0/1 63 (54,73)	245	33	KDIGO	AKI Stage 2/3 67% AKI Stage 0/1 64%	NR	NR	NR	NR	NR	NR
Matsa 2014, UK	uNGAL, BioPorto & pNGAL BioPorto	60 (15)	194	59	RIFLE	66%	80.8 mol/L (29.1)	NR	NR	NR	Consecutive adult (>18 years) patients admitted to the ICU were screened for inclusion	Refused consent, end-stage renal disease, previous renal transplant, patients already on RRT, patients referred to the ICU for RRT and patients with AKI as defined by RIFLE criteria for risk, injury or failure.
Kokkoris 2012, Greece	uNGAL, ARCHITECT, Abbott	AKI 63 (50, 81); No AKI 49 (35, 66)	100	36	RIFLE	57%	NR	NR	NR	0	All consecutive patients admitted to the ICU were screened for eligibility	end-stage renal disease, chronic kidney disease or nephrectomy or renal transplantation, Expected ICA stay or imminent death in less than 48 h, transfer from another ICA to high-dependency unit, Brain death, Age < 18 years, Inability to draw blood or urine
Asada 2016, Japan	uNGAL, ARCHITECT, Abbott	AKI 62 (48, 74); No AKI 63 (51,73)	133	31	KDIGO	AKI 68%; No AKI 58%	NR	NR	NR	0	Patients aged 18 years or older who were admitted to the ICU	Presence of end-stage renal disease

Nickolas 2012, USA and Germany	uNGAL, ARCHITECT, Abbott	64 (19)	1635	96	RIFLE	52%	0.9 (0.4) mg/dL	70.5 (33.2)	NR	0	Patients older than 18 years of age irrespective of their condition who were in the process of admission to the hospital from the ED	Patients who had 24 h of follow-up or were on long-term renal replacement therapy
Hjortrup 2015, Denmark	uNGAL, BioPorto & pNGAL BioPorto	66 (57, 75)	151	91	KDIGO	57%	NR	NR	NR	0	Need of fluid resuscitation in the ICU, the fulfilment of severe sepsis criteria within the previous 24 h and the consent from patient or proxy	< 18 years; allergy towards HES or malic acid; any form of RRT; acute burn injury > 10% of body surface area; severe hyperkalaemia within the last 6 hrs; liver or kidney transplantation or intracranial bleeding during current hospital admission; enrolment into another ICU trial of drugs with potential action on circulation, renal function or coagulation.
Park 2017, USA	uNGAL, ARCHITECT, Abbott	59 (11)	2466	NR	sCr (criteria not clearly defined)	54%	NR	43 (18)	NR	0	Adults with an eGFR of 20–70 ml/ min per 1.73 m2 were enrolled	Polycystic kidney disease, multiple myeloma, or GN on active immunosuppression
Smith 2013, UK	uNGAL, BioPorto	69 (12)	158	40	KDIGO	75%	NR	31 (11)	NR	0	NR	NR
Ariza 2016, European Countries	uNGAL, BioPorto	ACLF 57 (11); No ACLF 57 (12)	716	NR	sCr levels between ≥1.5 and <2 mg/dL	ACLF 66% No ACLF 65%,	NR	NR	NR	0	NR	Urinary tract infection at the time of urine collection were excluded because the urine levels of NGAL may be increased due to high leukocyte concentration in urine

Treepraserts uk 2015, Thailand	uNGAL, ARCHITECT, Abbott	57 (15)	121	35	AKIN	62%	NR	NR	NR	0	Cirrhotic patients who were admitted with AKI-prone conditions. All patients had normal baseline serum creatinine within 3 months prior to admission with cirrhosis, aged >18 years	Exclusion criteria were chronic kidney disease, or previous liver or kidney transplantation. The diagnosis of cirrhosis was based on a combination of clinical, biochemical and imaging assessments or liver biopsy
Barreto 2014, Spain	uNGAL, BioPorto	58 (12)	132	65	AKIN	70%	1.5 (1.0) mg/dL	NR	NR	0	Cirrhotic patients with a bacterial infection	Chronic haemodialysis before admission; previous liver and/or kidney transplantation; hepatocellular carcinoma outside the Milan criteria or any other advanced malignancy; lack of informed consent; and patients with urinary tract infection; these latter patients were excluded because uNGAL levels are increased in these patients and may therefore not reflect any impairment of kidney function.
Jaques 2019, Switzerland	uNGAL, BioPorto & pNGAL BioPorto	58 (10)	105	55	AKIN	71%	NR	NR	NR	0	Inclusion criteria were age ≥ 18 years and known or suspected cirrhosis with ascites confirmed by ultrasonography.	Exclusion criteria were proven multifocal hepatocellular carcinoma, known CKD stage V or dialysis before admission, prior kidney or liver transplantation, recent upper gastrointestinal bleeding, or more than 24 h delay between the admission and inclusion. Informed consent was

												sought from all eligible patients, or from a surrogate decision maker if the patient was unable to provide consent.
Cho 2014, Korea	uNGAL, BioPorto	57 (12)	135	54	AKIN	63%	NR	NR	NR	0	Patients who planned to undergo elective hepatobiliary surgery	Patients <18 years of age, with baseline estimated glomerular filtration rate of <60 ml/min/1.73 m2, on maintenance RRT, developed AKI preoperatively
Nickolas 2008, USA	uNGAL, BioPorto	60 (18)	635	30	RIFLE	51%	1.4 (1.8) mg/dL	NR	NR	0	>18 years admitted to emergency department	Patients who were receiving hemodialysis and patients without subsequent creatinine measurements
Verna 2012, USA	uNGAL, BioPorto	56 (49, 62)	118	52	Scr to >1.5 and 0.3 mg/dL above baseline, not responding with 48 h of volume resuscitation and not meeting the criteria for hepatorenal syndrome	61%	NR	NR	NR	0	Adults with cirrhosis	Patients on chronic haemodialysis, anuria for the first 24 h, urinary tract infection, proteinuria>500 mg/day, or urinary obstruction
Liebetrau 2013, Germany	uNGAL, ARCHITECT, Abbott	AKI 74 (8); No AKI 68 (11)	141	47	KDIGO	AKI 60% Non-AKI 73%,	NR	NR	NR	0	Consecutive patients scheduled to undergo elective major cardiac surgery (coronary artery bypass grafting and/or valve replacement) with the use of extracorporeal circulation	Patients with a preoperative estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m2 body surface
Parikh 2011, North America	uNGAL, ARCHITECT, Abbott	4 (5) years	311	53	Receipt of acute dialysis, or doubling	55%	NR	90 (26)	NR	0	All paediatric patients ages 1 month to 18 years undergoing cardiopulmonary bypass	Prior renal transplantation or dialysis

					of sCr from baseline to ostoperative value consistent with RIFLE stage 1 or AKIN stage 2							
Dong 2017, USA	uNGAL, BioPorto	AKI 1.4 years (0.2-2.7); No AKI 5 years (4.1-5.9)	150	50	KDIGO	AKI: 40%; No AKI: 57%	NR	NR	NR	0	All patients receiving CPB as long as the baseline SCr is normal for age	Pre-existing CKD
Bojan 2014, France	uNGAL, ARCHITECT, Abbott	<1 year	100	NR	AKIN	NR	NR	NR	NR	0	Surgery with CPB	NR
Bennett 2013, USA	uNGAL, ARCHITECT, Abbott	4 years	196	99	50% or greater increase in sCr from baseline within 72 hours	54%	NR	NR	NR	0	Elective CPB surgery	Pre-existing renal insufficiency, diabetes mellitus, peripheral vascular disease and use of nephrotoxic drugs before and during the study.
Cantinotti 2012, Italy	uNGAL, ARCHITECT, Abbott	6 months (1, 49)	135	52	RIFLE	58%	NR	NR	NR	0	All patients undergoing cardiac surgery for correction/ palliation of congenital heart defects	History of prior renal transplantation or dialysis requirements
Alcaraz 2014, Spain	uNGAL, ARCHITECT, Abbott	25 months (6.0-72.0)	106	36	Paediatric RIFLE criteria	59%	NR	NR	NR	0	Cardiac surgery for congenital lesions	Pre-existing renal dysfunction and heart transplantation
Lagos-Arevalo 2015, Canada	uNGAL, BioPorto	SCr-AKI 4.0 years (5); No SCr-AKI 5.0 years (6)	160	70	KDIGO	NR	NR	NR	NR	0	Children between 1 month and 18 years old who were not immediately post-operative from cardiac surgery admitted to PICU	Known end-stage renal disease, having received a renal transplant, a high likelihood of death in the following 48 h (determined by the PICU attending staff) and presence of <25%

												of PICU days with both a CysC and a SCr value available (determined by dividing number of available daily values by PICU admission days)
Zwiers 2015, Netherlands	uNGAL, ARCHITECT, Abbott	27 (1, 85) days	100	35	RIFLE	66%	N	NR	NR	0	Children (born later than 37 weeks of gestational age) between the ages of 1 day and 1 year admitted to the ICU and requiring endotracheal intubation and mechanical ventilation.	Congenital abnormalities of the kidney or urinary tract, death was anticipated within 24 hours or they received mechanical ventilation for other reasons. Patients were excluded when treatment with extracorporeal membrane oxygenation was required within the study period.
Yang 2017, China	uNGAL, BioPorto	C: 22 months (31); A: 46 years (15)	C: 323; A: 398	C: 126; A: 164	Acute dialysis or doubling of sCr consistent with KDIGO stage 2 and 3 criteria	C: 62%; A: 43%	C: 29.3µmol/L (SD 9.8); A: 76.6 µmol/L (SD 24.2)	C: 101.6 (35); A: 93.5 (23.7)	NR	0	Patients receiving elective cardiac surgery (cardio pulmonary bypass).	Exposure to nephrotoxin within 4 weeks before surgery, pre-existing advanced and urinary tract infection or obstruction
Seitz 2013, NR	uNGAL, ARCHITECT, Abbott	0 years (0-8)	139	76	RIFLE	55%	0.38*mg/dl (SD NR)	NR	NR	0	Patients undergoing CPB for surgical correction or palliation of congenital heart disease.	Patients with pre-existing renal insufficiency, patients with history of nephrotoxin use during pre-op days.

C: Children, A: Adults, *Mean, **Median.

Appendix 9 Forest plots of AUC meta-analyses

Forest plots of AUC meta-analyses for detection of AKI

Figure 38 Adults NephroCheck across all settings

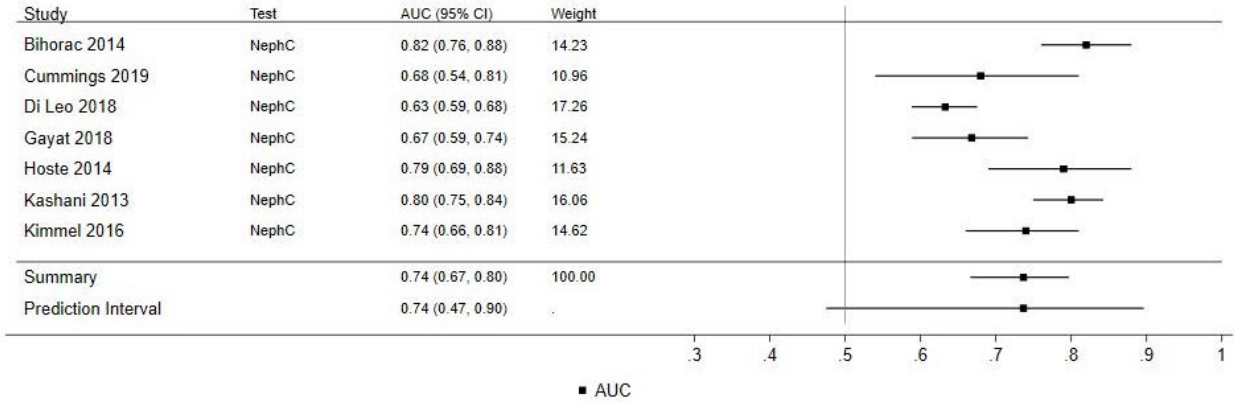


Figure 39 Adults NephroCheck critical care

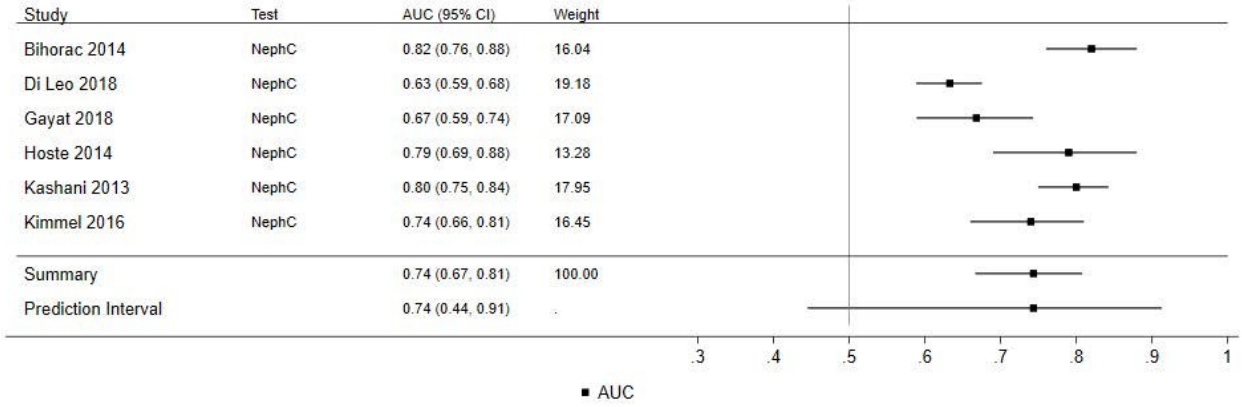


Figure 40 Adults uNGAL ARCHITECT (Abbott) all settings

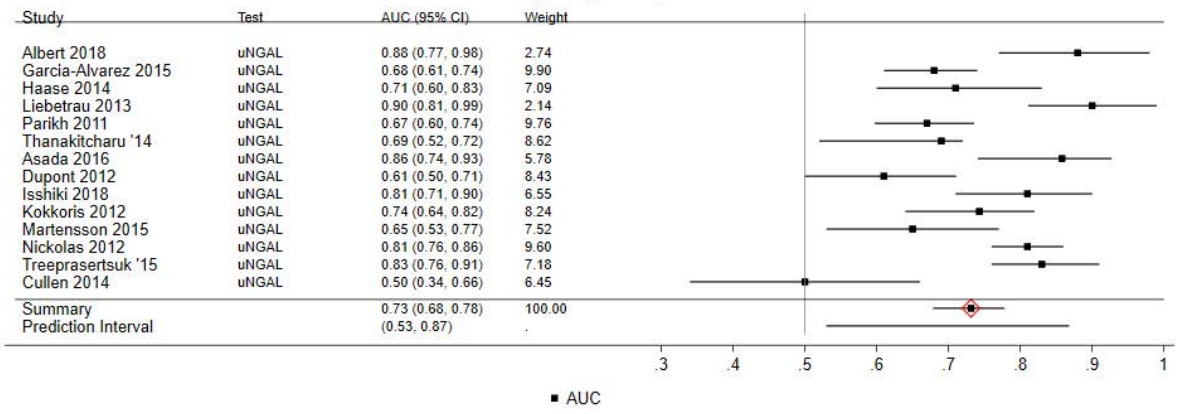


Figure 41 Adults uNGAL ARCHITECT (Abbott) cardiac surgery

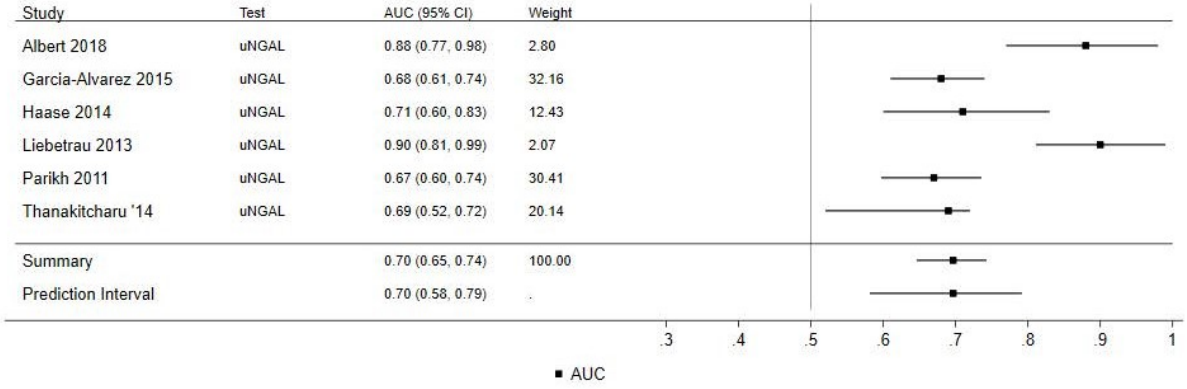


Figure 42 Adults uNGAL ARCHITECT (Abbott) critical care

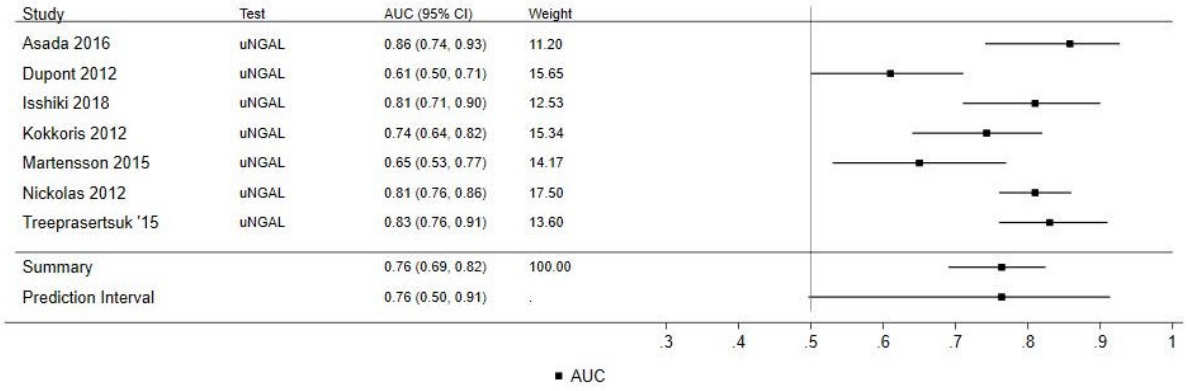


Figure 43 Adults uNGAL BioPorto across settings

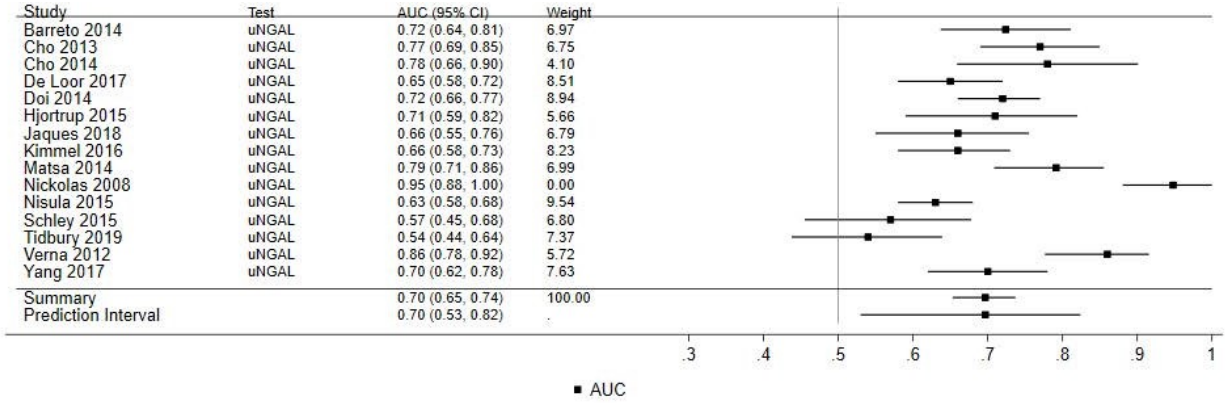


Figure 44 Adults uNGAL BioPorto cardiac surgery

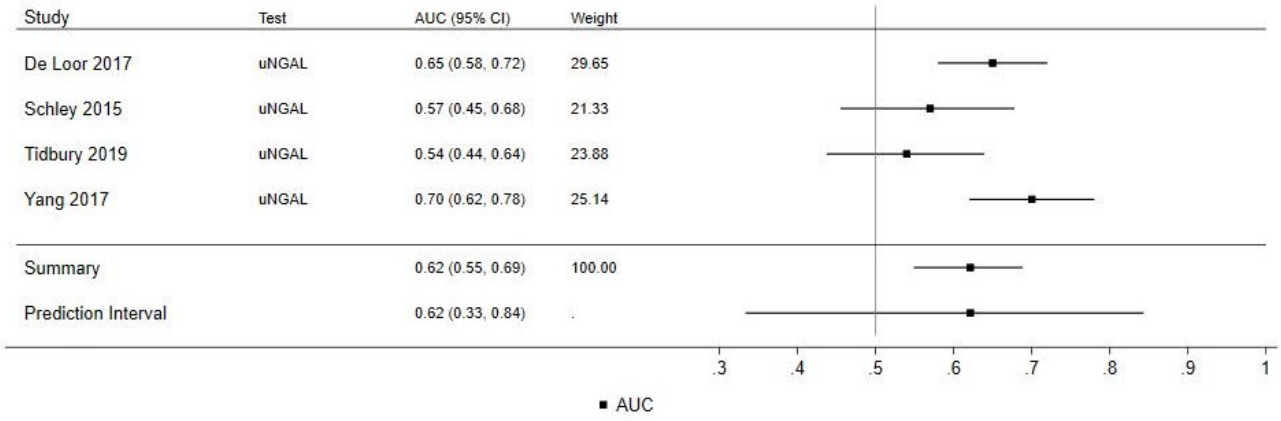


Figure 45 Adults uNGAL BioPorto critical care

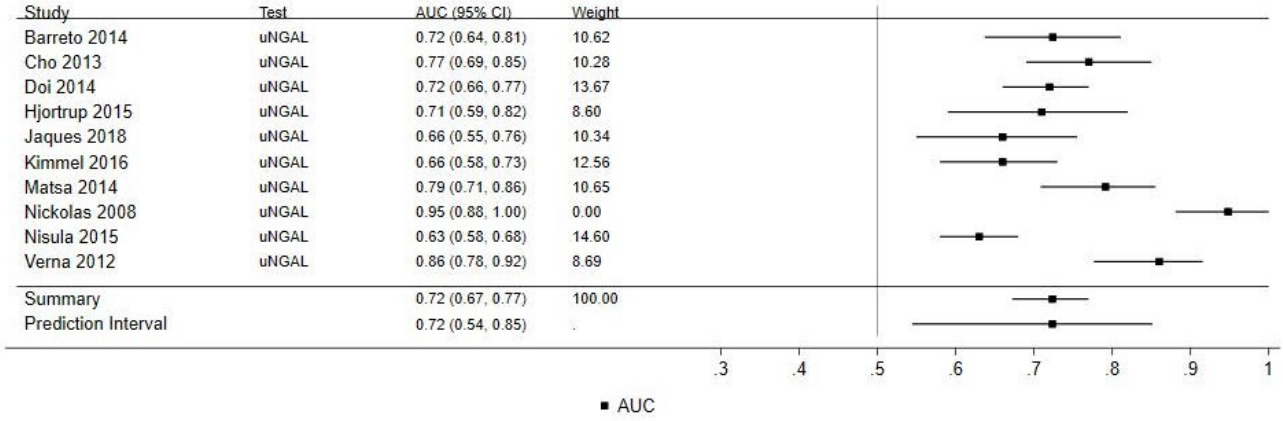


Figure 46 Adult uNGAL (Abbott and BioPorto) cardiac surgery

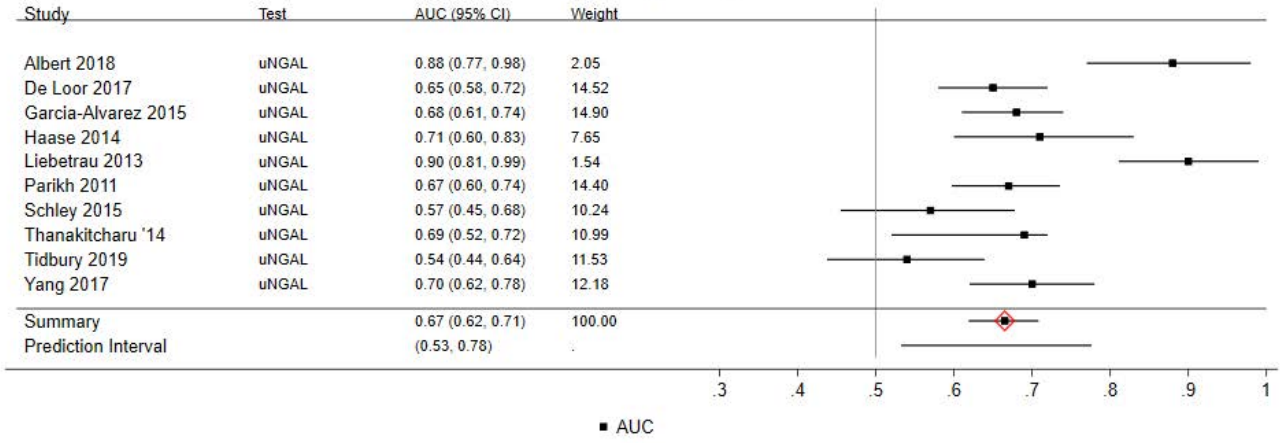


Figure 47 Adult uNGAL (Abbott and BioPorto) critical care

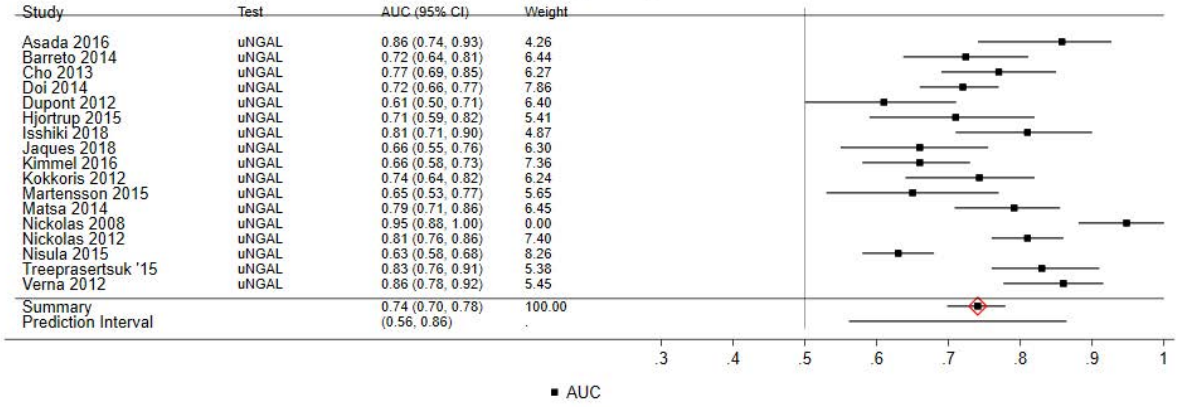


Figure 48 Adult uNGAL (Abbott and BioPorto) all settings

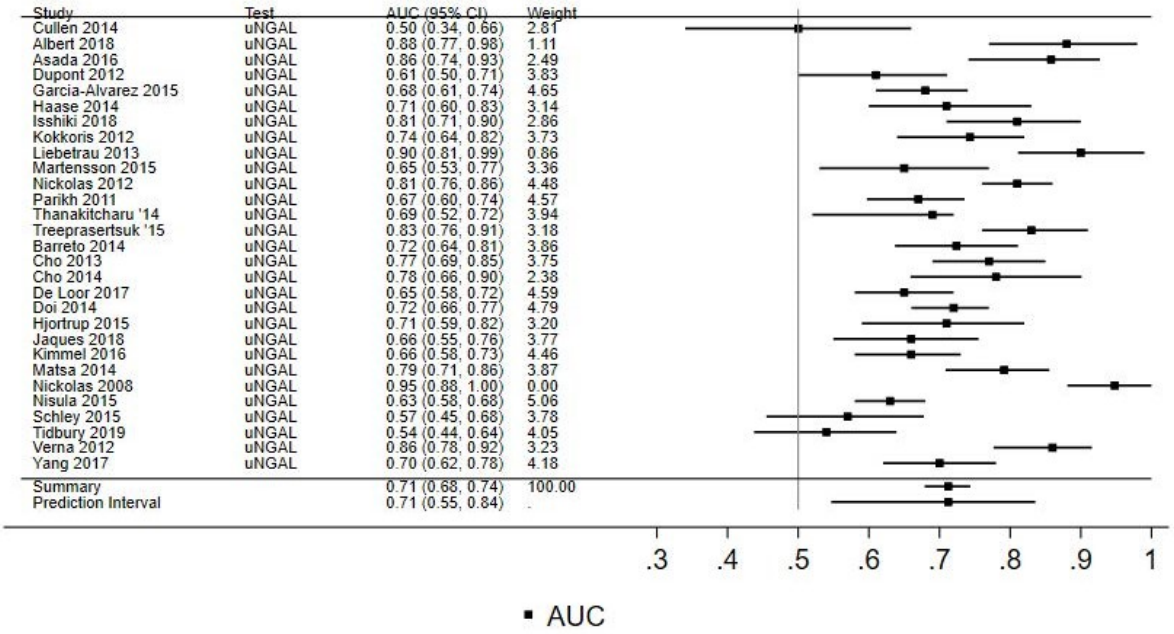


Figure 49 Adults pNGAL BioPorto across all settings

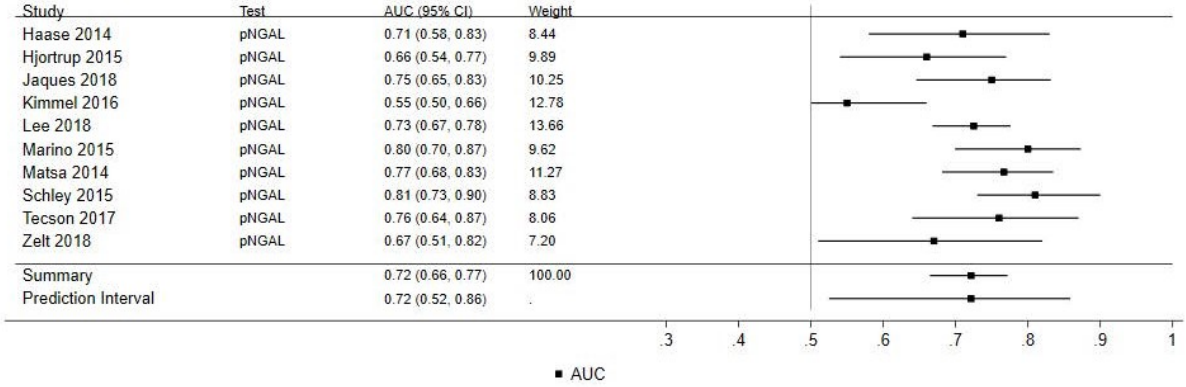


Figure 50 Adults pNGAL BioPorto cardiac surgery

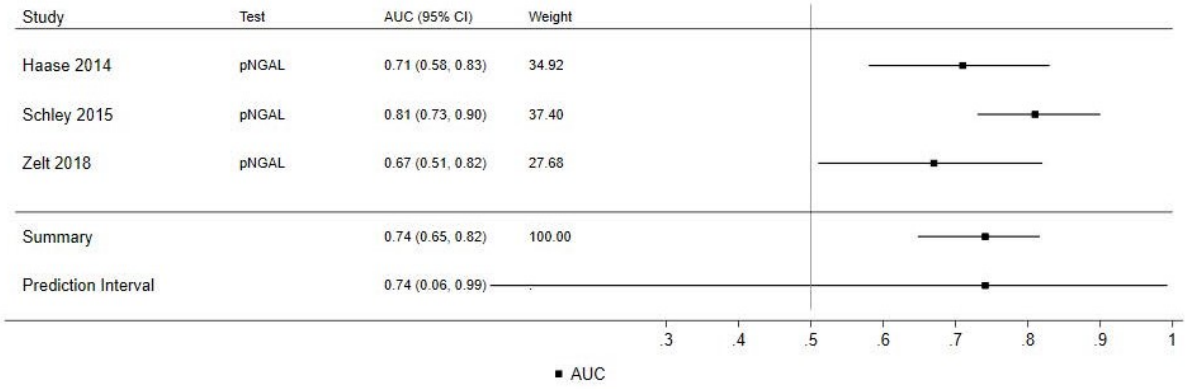


Figure 51 Adults pNGAL BioPorto critical care

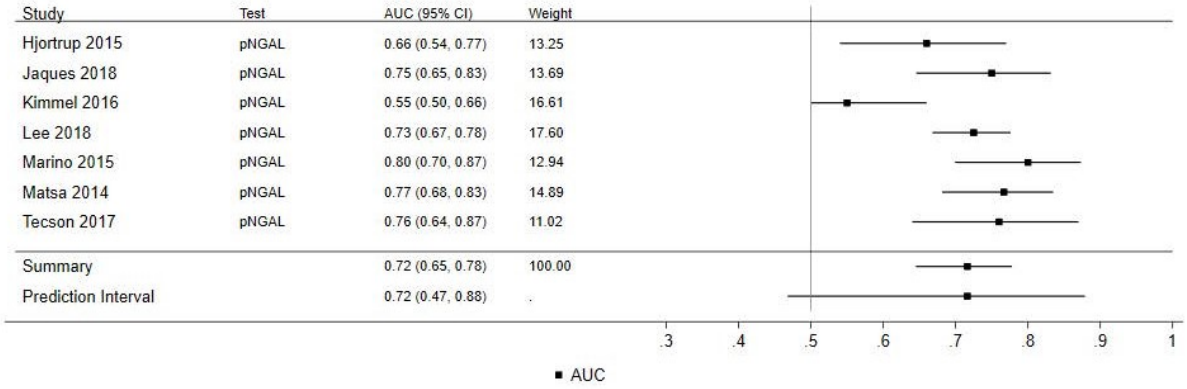


Figure 52 Child uNGAL (Abbott and BioPorto) across settings

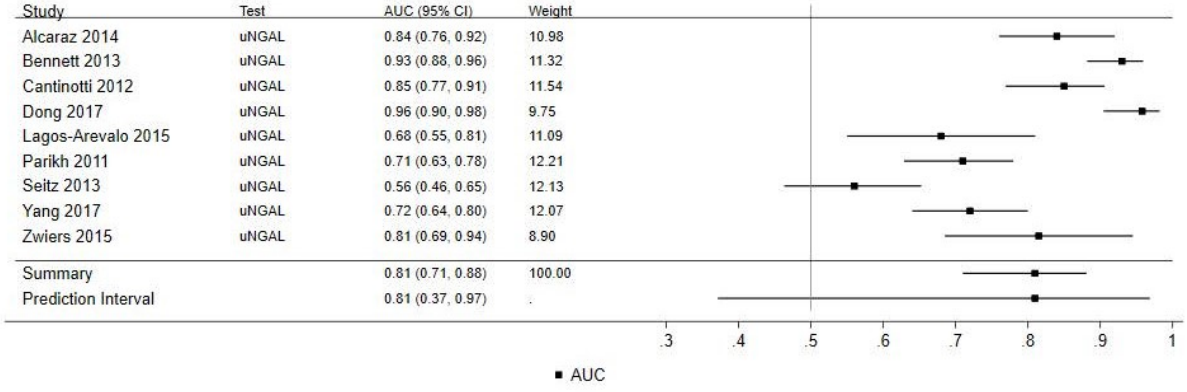


Figure 53 Child uNGAL ARCHITECT (Abbott) cardiac surgery

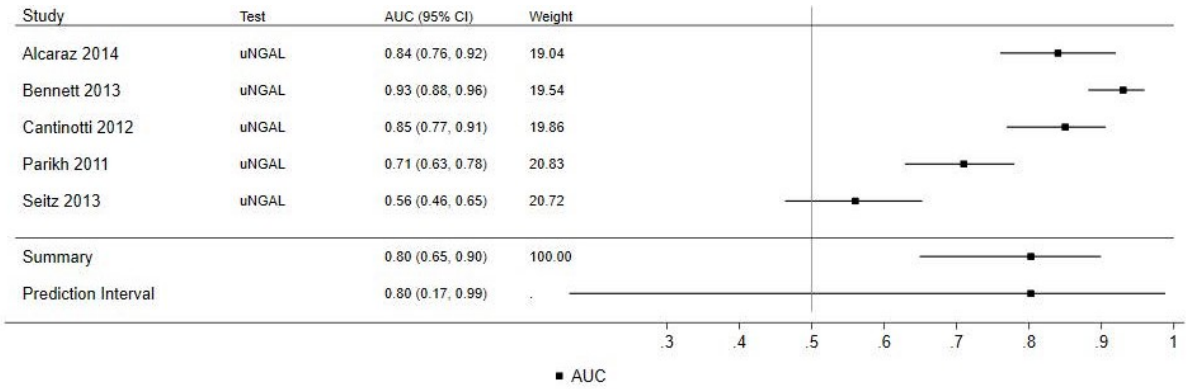
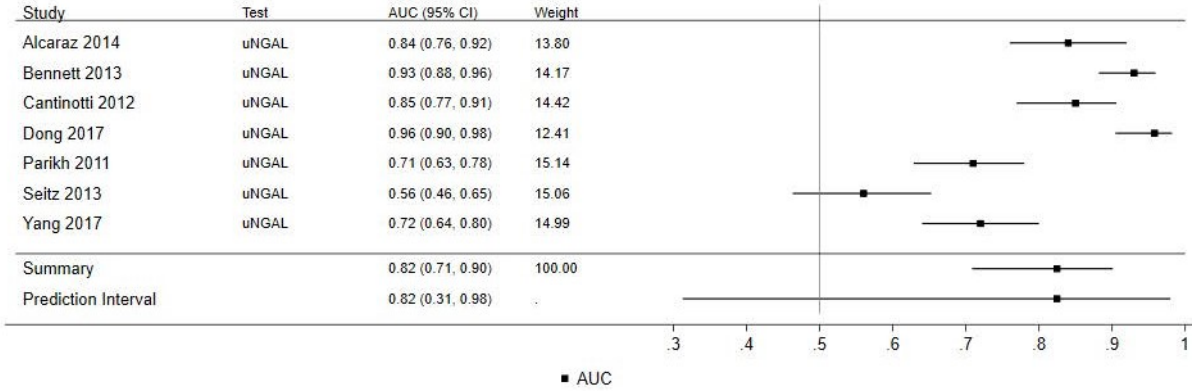


Figure 54 Child uNGAL (Abbott and BioPorto) all cardiac surgery



Forest plots of AUC meta-analyses for prediction of worsening of AKI, mortality and renal replacement therapy

Figure 55 Prediction of AKI Adults uNGAL ARCHITECT (Abbott) Critical care

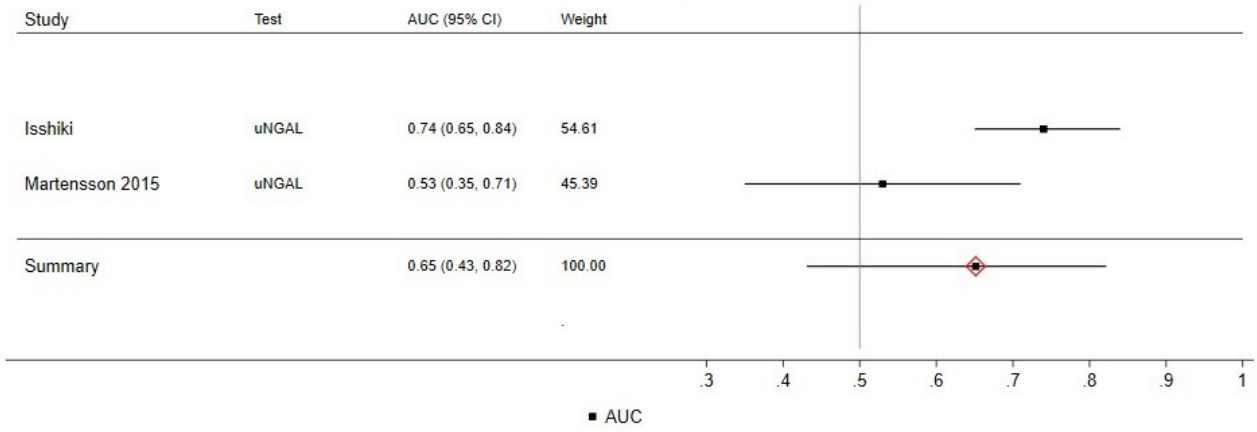


Figure 56 Prediction of mortality Adults uNGAL BioPorto critical care

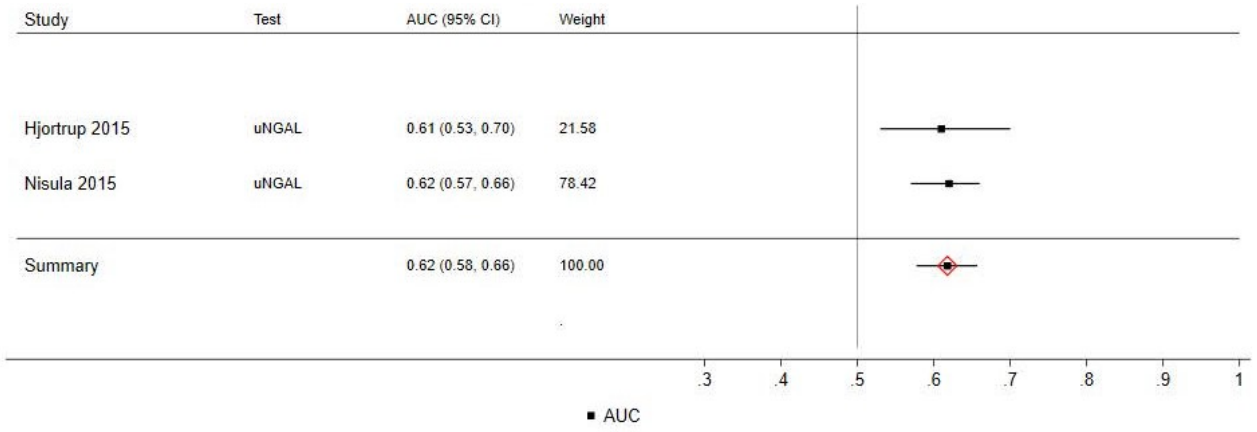


Figure 57 Prediction of mortality Adults pNGAL BioPorto critical care

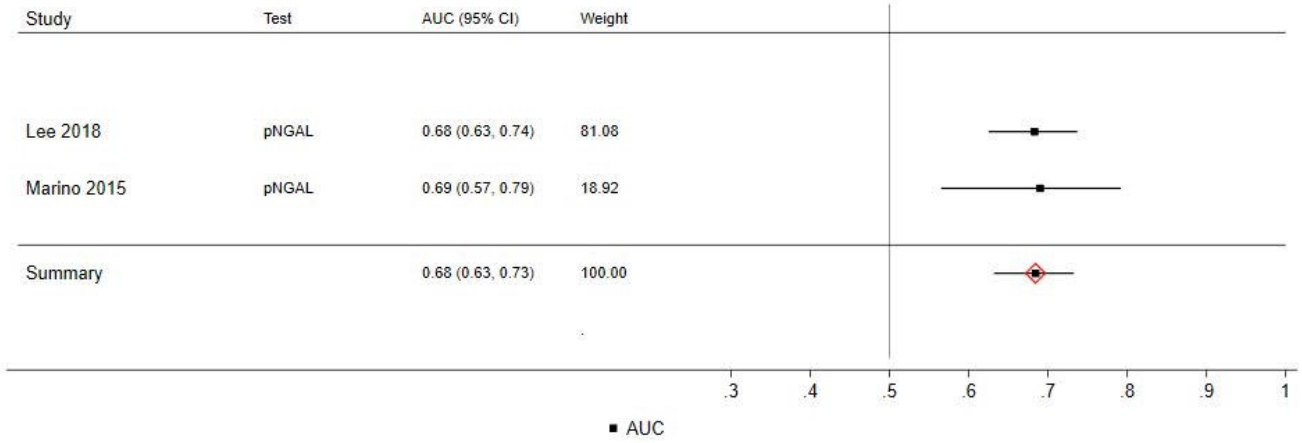


Figure 58 Prediction of mortality Adults uNGAL (Abbott and BioPorto) critical care

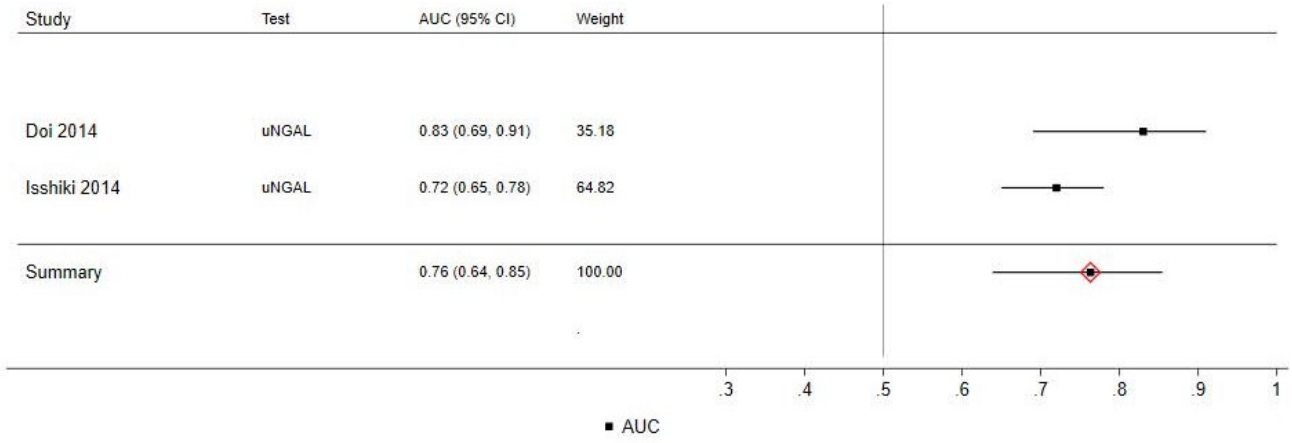
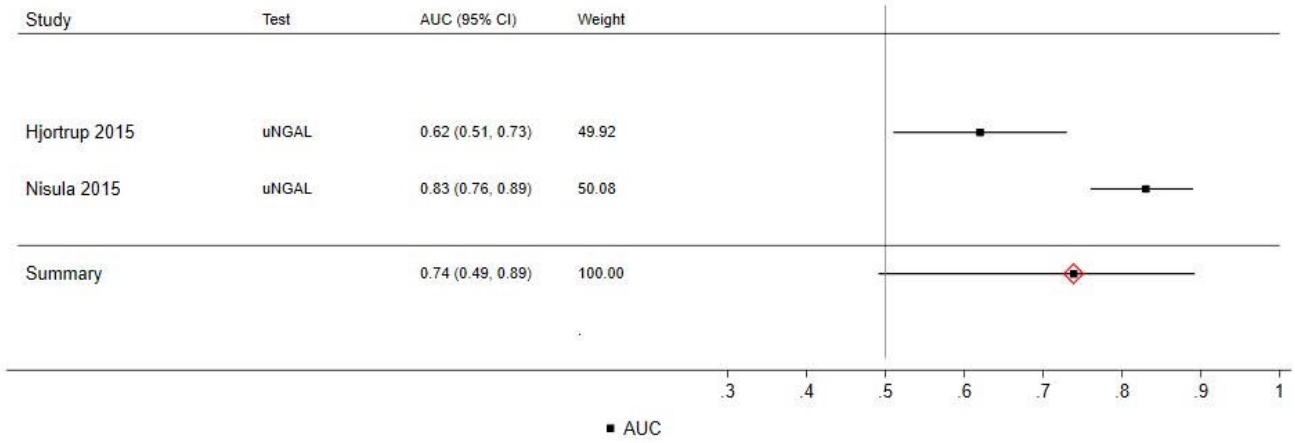


Figure 59 Prediction of RRT Adults uNGAL BioPorto critical care



Appendix 10 QUADAS2 risk of bias and applicability assessment

Table 42 QUADAS2 risk of bias and applicability assessment

Study ID	Assay	Risk of bias				Applicability		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Albert 2018	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Alcaraz 2014	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Ariza 2016	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Asada 2016	uNGAL	Unclear	Unclear	Low	High	Unclear	Unclear	Low
Barreto 2014	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Beitland 2016	NephC	Low	Unclear	Low	Low	Low	Low	Low
Bennett 2013	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Bihorac 2014	NephC	Low	Unclear	Low	Low	Low	Low	Low
Bojan 2014	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cantinotti 2012	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cho 2013	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cho 2014	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Collins 2012	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cullen 2014	uNGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Cummings 2019	NephC	Low	Unclear	Low	Low	Low	Low	Low
De Loor 2017	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Di Leo 2018	NephC	Low	Unclear	Low	Low	Low	Low	Low
Doi 2014	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Dong 2017	uNGAL	Low	Unclear	Low	Unclear	Low	Unclear	Low
Dupont 2012	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Garcia-Alvarez 2015	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Gayat 2018	NephC	Unclear	Unclear	Low	Low	Low	Low	Low
Haase 2014	uNGAL, pNGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Hjortrup 2015	uNGAL, pNGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Hoste 2014	NephC	Unclear	Unclear	Low	Low	Low	Low	Low
Isshiki 2018	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Itenov 2017	pNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Jaques 2019	uNGAL, pNGAL	Low	Unclear	Low	High	Unclear	Unclear	Low
Kashani 2013	NephC	Low	Unclear	Low	Low	Low	Low	Low
Kimmel 2016	NephC, uNGAL, pNGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low

Study ID	Assay	Risk of bias				Applicability		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Kokkoris 2012	uNGAL, pNGAL	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Lagos-Arevalo 2015	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Lee 2018	pNGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Liebetrau 2013	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Marino 2015	pNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Martensson 2015	uNGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Matsa 2014	uNGAL, pNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Nickolas 2008	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Nickolas 2012	uNGAL	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Nisula 2015	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Oezkur 2017	NephC	Low	Unclear	Low	Low	Low	Low	Low
Parikh 2011	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Parikh 2011	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Park 2017	uNGAL	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
Pipili 2014	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Schley 2015	uNGAL, pNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Seitz 2013	uNGAL	Low	Low	Low	Low	Low	Unclear	Low
Smith 2013	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Tecson 2017	uNGAL, pNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Thanakitcharu 2014	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Tidbury 2019	uNGAL	Low	Unclear	Low	Unclear	Low	Unclear	Low
Treeprasertsuk 2015	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Verna 2012	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Yang 2017	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Zelt 2018	pNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Zwiers 2015	uNGAL	Low	Unclear	Low	Low	Low	Unclear	Low
LOW		45 (80%)	1 (2%)	54 (96%)	50 (89%)	54 (96%)	8 (14%)	54 (96%)
UNCLEAR		11 (20%)	55 (98%)	2 (4%)	4 (7%)	2 (4%)	48 (86%)	2 (4%)
HIGH		0 (0%)	0 (0%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)

NephC = NephroCheck; uNGAL = urine NGAL; pNGAL = plasma NGAL

Appendix 11 PROBAST risk of bias and applicability assessment

Table 43 PROBAST risk of bias and applicability assessment

Study	Test	Risk of bias					Applicability			
		Participants	Predictors	Outcome	Analysis	Overall judgement	Participants	Predictors	Outcome	Overall judgement
Garcia-Alvarez 2015	uNGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Bennett 2013	uNGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Cullen 2014	uNGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Doi 2014	uNGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Nisula 2015	uNGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Marino 2015	pNGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Hjortrup 2015	uNGAL, pNGAL	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Treeprasertsuk 2015	uNGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Gayat 2018	NephC	Unclear	Unclear	Unclear	High	High	Unclear	Low	Low	Unclear
Martensson 2015	uNGAL	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Isshiki 2018	uNGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Lee 2018	pNGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low

Appendix 12 Health economics appendices

Table 44 Summary of studies identified from supplementary searches of the literature post-Hall

Author	Year	Population	Country	Utility measure	Valuation set	N	Age	Proportion male	Utility values reported	Mean	Median	SE	SD	CI low	CI high	IQR low	IQR high
Afiatin	2017	ESRD with PD and HD	Indonesia	EQ-5D-3L	Thailand	68	18+	55.9%	PD (no comp) HD (no compl) PD (+comp) HD (+comp)	0.82 0.70 0.31 0.37		0.03 0.04 0.09 0.11					
Chang	2016	ESRD with PD and HD	Taiwan	EQ-5D-3L	UK	Total: 1687 HD: 1403 PD: 284	Total: NR HD: 57.1 (13.6) PD: 46.7 (13.2)	HD: 49.9% PD: 51.1%	HD PD	0.83 0.90		0.19 0.16					
Cho	2018	CKD requiring dialysis	South Korea	EQ-5D-3L	Korean	50	NR	NR	CKD receiving dialysis	0.63		0.04					
Eriksson	2016	CKD patients (anemic and non-anemic) with / without dialysis	France, Germany, Italy, Spain, UK	EQ-5D-3L	Unclear, presume UK	Total: 1177 Non Anaemic: 313 (27%) Anaemic: 864 (73%)	63.7 (15.1)	60%	**Non-anaemic: (27%)** CKD 3 CKD 4 Dialysis Total **Anaemic: (73%)** CKD 3 CKD 4 Dialysis Total	**Non-an (27%):** 0.85 0.81 0.74 0.83 **Anaemic (73%):** 0.78 0.71 0.70 0.72			**Non-anaemic (27%):** 0.21 0.22 0.29 0.23 **Anaemic (73%):** 0.29 0.28 0.32 0.31				
Filali	2017	Chronic HD patients	Morocco	EQ-5D-3L	Unclear	103	49.7 (14.7)	45.60%	HD	0.41			0.36				
Hishii	2018	Chronic HD patients	Japan	EQ-5D-3L	Unclear	60	71.1 (12)	51.67%	HD	0.688			0.233				

Author	Year	Population	Country	Utility measure	Valuation set	N	Age	Proportion male	Utility values reported	Mean	Median	SE	SD	CI low	CI high	IQR low	IQR high
Jardine	2017	Maintenance HD	Australia (28%), canada (6%), china (62%), new zealand (4%)	EQ-5D-3L	Unclear	200	51.8 (12.1)	69.50%	HD	0.78			0.24				
Jesky	2016	pre-dialysis CKD (as per NICE guidance, CKD, 2008)	UK	EQ-5D-3L	UK	All CKD: 745 G1/2: 29 G3a: 45 G3b: 173 G4: 423 G5: 75	Median (IQR) All CKD 64; (50-76) G1/2 41; (34.5-55.5) G3a 55; (45-66.5) G3b 61.5; (48.3-73.8) G4: 69; (54-75.5) G5: 64; (53.5-75.5)	All CKD: 60.80% G1/2: 65.52% G3a: 71.11% G3b: 66.86% G4: 59.00% G5: 49.35%	All CKD G1/2 G3a G3b G4 G5		0.74 0.85 0.80 0.80 0.74 0.73					0.66 0.70 0.69 0.68 0.62 0.62	0.88 1 1 1 0.85 1
Katayama	2016	Chronic HD patients	Japan	EQ-5D-3L	unclear	Baseline: 71 1 year follow up: 43	70.9 (10.6) 69.1 (10.8)	58% 60%	HD (BL) HD (1yr)	0.720 0.790			0.224 0.181				
Kilshow	2016	ESRD (CM)	UK	EQ-5D-5L	None	41	82.7 (5.7)	56%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kularatna	2019	CKD	Sri Lanka	EQ-5D-3L	UK	Early Stage: 254 Stage 4: 614 Stage 5: 151 Dialysis: 38	Median approx age 41	56.10%	Early: Stage 4: Stage 5: Dialysis:	0.588 0.566 0.467 0.126			0.30 0.42 0.42 0.39				
Lee	2016	early to mid stage CKD	Korea	EQ-5D-3L	Korea	CKD 3/4: 75 CAPD: 75	61.4 (9.9) 59.1 (12.9)	41% 41%	CKD (3/4) CAPD	0.87 0.90			0.19 0.15				
Li	2017	Kidney transplant recipients and waiting list	UK	EQ-5D-5L	UK value set	Transplant recipients: 512 Waiting list: 1704	Median ~ 50 Median ~ 50	60% 58%	waiting list transplant (inc)	0.773 +0.054		0.005 0.011					
McNoe	2019	ESRD with or without dialysis	New Zealand	EQ-5D-3L	Vas only	No dialysis: 56 HD: 109 PD: 60	65+	66.1% 57.8% 73.3%	No dialysis HD PD		70 70 67.5					50 60 70	80 80 80
nagasawa	2018	Patients receiving dialysis	Japan	EQ-5D-3L	Japan	51	67.7 (12.1)	70.60%	Dialysis patients with CKD or ESRD	0.779			0.193				

Author	Year	Population	Country	Utility measure	Valuation set	N	Age	Proportion male	Utility values reported	Mean	Median	SE	SD	CI low	CI high	IQR low	IQR high
Nguyen	2018	CKD and ESRD	UK	EQ-5D-3L	UK	CKD1: 56 CKD2: 106 CKD3a: 155 CKD3b: 35 CKD 4/5: 5	44.6 (18.2) 60 (17.4) 65.3 (14.8) 74.1 (13.4) 72.2 (10.3)	33.9% 50.0% 46.5% 60.0% 40.0%	S1 S2 S3a S3b S4/5	base NR -0.112 -0.062 -0.185 -0.284				base NR -0.189 -0.128 -0.299 -0.408	base NR -0.034 +0.005 -0.071 -0.160		
Schlackow	2017	Moderate to advanced CKD	UK	EQ-5D-3L	UK	6356	62 (12)	63%	Regression Mean (intercept) Male Age +10y PFKT dialysis	0.86 +0.06 -0.05 -0.07 -0.06				0.84 +0.05 -0.05 -0.11 -0.07	0.88 +0.07 -0.04 -0.03 -0.04		
Sekercioglu	2017	CKD	Canada	SF-6D	Canada	All: 303 Dialysis: 101 Non dialysis: 202	62.7 (14.5) 60.6 (14.4) 63.8 (14.4)	58.8% 57.0% 61.0%	All CKD Dialysis no dialysis	0.720 0.670 0.740			0.110 0.110 0.100				
Senanayake	2019	pre-dialysis patients	Sri Lanka	EQ-5D-3L	Sri Lanka	1036	Median approx 60	62.40%	pre-dialysis CKD	0.52			0.33				
Shah	2019	ESRD (dialysis or conservative management)	UK and Australia	SF-6D	UK	Total: 129 Dialysis: 83 conservative: 46	75+	69% 59% 65%	Total Dialysis CM	0.62 0.61 0.65			0.14 0.13 0.15				
Shimizu	2018	HD patients	Japan	EQ-5D-5L	Japan	All: 717 age 60-69: 278 age 70-79: 311 age 80+: 118	72.9 (6.5)	62.50%	All HD age 60-69: age 70-79: age 80+:	0.738 0.784 0.744 0.616			0.207 0.179 0.202 0.231				

Author	Year	Population	Country	Utility measure	Valuation set	N	Age	Proportion male	Utility values reported	Mean	Median	SE	SD	CI low	CI high	IQR low	IQR high
Snowsill	2017	Kidney transplant recipients	UK	EQ-5D-3L	UK	N/A	N/A	N/A	Regression Mean (intercept) Age Age sq Male FG HD PD PTDM	0.968 -0.002 -0.000 +0.023 -0.053 -0.277 -0.264 -0.060		NR					
Tang	2017	ESRD	Taiwan	EQ-5D-5L	Japan	APD: 117 CAPD: 129	NR	NR	APD CAPD	0.82 0.82			0.19 0.21				
Thaweet-hamcharoen	2019	Patients receiving PD	Thailand	EQ-5D-5L	Thailand	64	63.44 (16.57)	68.75%	PD	0.801			0.228				
Van Loon	2019	ESRD	Netherlands	EQ-5D-3L	Dutch	CM: 89 Dialysis (23% PD): 192	82 (6) 75 (7)	NR	CM Dialysis	0.77 0.82			0.21 0.18				
Wee	2016	pre-dialysis, stage 3-5 CKD	Singapore	EQ-5D-3L	USA	309	62.6 (11.06)	58.20%	CKD 3-5, pre-dialysis	0.8			0.24				
Wolfgram	2017	Hypertensive CKD and non-CKD patients	USA	EQ-5D-3L	USA	All: 2620 Non-CKD: 1459 CKD: 1161 GFR 60+ (CKD s2 or better): 372 GFR 44-60 (CKD 3a): 781 GFR < 44 (CKD 3b or worse): 1449	79.85 (3.99) 79.39 (3.73) 80.42 (4.23) NR NR NR	62.1% 62% 62.3% NR NR NR	All: Non-CKD: CKD: GFR 60+ GFR 44-60 GFR < 44	0.85 0.85 0.84 0.85 0.85 0.82		0.00 0.01 0.01	0.13 0.13 0.13				
Wong	2019	ESRD on dialysis	China	SF-6D	China / Hong Kong	All: 397 PD: 103	57.3 (12.7) 63.1 (12.7)	61.9% 61.2%	All dialysis PD:	0.766 0.778			0.111 0.110				

Author	Year	Population	Country	Utility measure	Valuation set	N	Age	Proportion male	Utility values reported	Mean	Median	SE	SD	CI low	CI high	IQR low	IQR high
						Hosp. HD: 135 Home HD: 41 Comm. HD: 118	56.4 (12.6) 47.9 (8.5) 56.8 (11.6)	57.0% 67.4% 66.1%	Hospital HD: Home HD: Comm. HD:	0.731 0.778 0.790			0.114 0.091 0.107				
Yang	2019	ESRD on dialysis	Singapore	SF-12 mapped to EQ-5D-3L	unclear	Total: 266 CAPD: 145 APD: 121	59.3 (12.5) 60.8 (11.4) 57.4 (13.6)	45.5% 45.5% 45.5%	Total CAPD APD	0.59 0.58 0.60			0.21 0.21 0.22				
Yang	2018	Dialysis	France, Germany, Italy, Spain Singapore	EQ-5D-3L EQ-5D-5L	Country specific value sets	France: 299 Germany: 413 Italy: 278 Spain: 225 Singapore (5L): 163	66.6 (14.1) 61.8 (14.4) 60.8 (13.4) 60.6 (16.4) 60.5 (11.5)	62.5% 57.1% 54.7% 60.0% 52.2%	France: Germany: Italy: Spain: Singapore	0.622 0.796 0.864 0.746 0.621			0.383 0.224 0.185 0.292 0.447				
Zyoud	2016	ESRD on HD	Palestine	EQ-5D-5L	unclear	Age 60+ : 97	Mean NR	52.1%	ESRD	0.17			0.4				
Park	2016	CKD	Korea	EQ-5D-3L	Korean value set	All: 46,676 No CKD: 44,108 Stage 1 CKD: 793 Stage 2 CKD: 444 Stage 3a CKD: 1030 Stage 3b CKD: 211 Stage 4/5 CKD (ESRD): 90	45.4 (SE:0.1) 44.6 (SE:0.2) 38.7 (SE:2.8) 54.9 (SE:3.3) 72.8 (SE:0.5) 73.2 (SE:1.1) 64.0 (SE:1.8)	49.5% 49.9% 42.8% 56.6% 42.6% 44.9% 44%	All: No CKD: Stage 1: Stage 2: Stage 3a: Stage 3b: Stage 4/5:	0.943 0.946 0.955 0.901 0.826 0.787 0.793		0.001 0.001 0.011 0.017 0.005 0.011 0.018				

PFKT: Previous Failed Kidney Transplant; CM: Conservative Management

Table 45 Maintenance cost and consumables for the different tests

Maintenance/consumables	Price	Cost per test	Formula
Nephrocheck			
Paper roll	£2.50	£0.10	£2.5 / number of tests in kit (=25 tests)
Liquid quality control (one per kit)	£100.00	£4.00	£100 / number of tests in kit (=25 tests)
Electronic quality control (every 6 months)	£80.00	£0.13	£80*2 / number of tests performed per year in hospital laboratory (=1253, in St. James's University Hospital, Leeds, source: Hall et al. 2018)
BioPorto			
NGAL Calibrator	£385.00	£1.28	£385 / number of tests in kit (=300)
NGAL Control kit	£185.00	£0.62	£185 / number of tests in kit (=300)
Abbott			
ARCHITECT Urine Calibrator kit	£165	£2.06	£165 / number of tests a kit can produce (=80)
ARCHITECT Urine Control kit	£115	£1.44	£115 / number of tests a kit can produce (=80)
Reaction vessels and bulk solutions		0.01	Manufacturer estimation (sourced from NICE's Request for Information document)
Alinity			
Alinity Urine Calibrator kit	£165	£2.06	£165 / number of tests a kit can produce (=80)

Maintenance/consumables	**Price**	**Cost per test**	**Formula**
Alinity Urine Control kit	£115	£1.44	£115 / number of tests a kit can produce (=80)
Reaction vessels and bulk solutions		£0.01	Manufacturer estimation (sourced from NICE's Request for Information document)

Table 46 ESA medication

	NeoRecormon	Aranesp	Source
Price per IU	£0.007	£0.007	BNF 2019
	HD	**PD**	
Proportion taking ESAs (%)	92.6%	78.6%	UK Renal Registry (2019)
Dose (IU) per week	8000	4000	UK Renal Registry (2019)
Cost per year	£2,765	£1,174	
Proportion on HD	87.5%	12.5%	
Total cost per year (based on the proportion on HD and PD)	£2566		

Table 47 Blood pressure medication

	Unit cost per year (£)	Proportion of patients on each type of medication	Total average cost (£)	Source
ACE inhibitor	35.74	0.211	7.54	Tan et al., 2016, BNF 2019
ARBs	43.04	0.156	6.70	Tan et al., 2016, BNF 2019
Calcium-channel blockers	28.80	0.219	6.31	Tan et al., 2016, BNF 2019
Diuretics	21.92	0.487	10.66	Tan et al., 2016, BNF 2019
Beta-blockers	15.52	0.248	3.85	Tan et al., 2016, BNF 2019
Alpha-blockers	7.83	0.172	1.35	Tan et al., 2016, BNF 2019
Total average cost per year			36.41	Tan et al., 2016, BNF 2019