National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Tests to help assess risk of acute kidney injury for people being considered for critical care admission (ARCHITECT and Alinity i Urine NGAL assays, BioPorto NGAL test and NephroCheck test)

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read with the final scope issued by NICE for the assessment and the diagnostics assessment report. A glossary of terms can be found in appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of multiple neutrophil gelatinase-associated lipocalin (NGAL) assays (ARCHITECT and Alinity i Urine NGAL assays and the BioPorto NGAL test) and the NephroCheck test to help assess the risk of acute kidney injury.

The NephroCheck test is indicated for use in people who are critically ill, but the NGAL tests potentially have a broader indication. At the scoping workshop and assessment subgroup meeting, clinical experts considered the most relevant population for this assessment. They considered the different types of care for people who are critically ill to determine who could benefit from use of the tests in the NHS. People who are admitted to critical care in the NHS should already have a range of interventions designed to prevent acute kidney injury because they are extremely unwell. Therefore, the potential for the tests

to improve outcomes in this population is limited in the NHS because the results of the tests are unlikely to change management decisions. Clinical experts highlighted that the tests could be useful for people who are being considered for admission to critical care; that is, when a decision about admission has not been made and the test results could guide the use of acute kidney injury care bundles. The decision question for this assessment therefore focuses on this population.

The tests can potentially detect kidney injury earlier than current methods for monitoring kidney function: serum creatinine and urine levels. Serum creatinine levels are slow to rise after kidney injury. Also, the use of intravenous fluids and diuretics can cause issues when detecting kidney injury by measuring urine levels. Earlier identification of acute kidney injury could allow earlier adoption of measures, such as care bundles, that could prevent progression to more severe injury and reduce the risk of adverse outcomes for patients. This could include reducing the incidence of moderate to severe acute kidney injury, mortality while in critical care, the length of time a person has to stay in hospital, the need for temporary renal replacement therapy (RRT) and the risk of chronic kidney disease developing or progressing.

Abbott states that the ARCHITECT and Alinity i Urine NGAL assays are run on different (ARCHITECT or Alinity) immunoassay analysers, but both use the same reagents. The NephroCheck test and Abbott NGAL assays both use urine. The BioPorto NGAL test uses either urine or blood plasma.

Provisional recommendations on the use of the tests will be made by the diagnostics advisory committee at the committee meeting on 27 November 2019.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Do the ARCHITECT and Alinity i Urine NGAL assays, the NephroCheck test and BioPorto NGAL test represent a cost-effective use of NHS resources when used to assess the risk of acute kidney injury in people who are critically ill who are being assessed for possible critical care admission?
Populations	People who are critically ill and considered at risk of developing acute kidney injury (that is, who are having their serum creatinine and urine output monitored), and who are being assessed for possible critical care admission. If data permit, subgroup analyses could be done for children and young people. If data permit, subgroup analyses could be done for people with a different underlying risk of acute kidney injury. These subgroups include: • chronic kidney disease • sepsis • hip fracture • major trauma • chronic liver disease • post major surgery. In addition, the tests may perform differently in people with urinary tract infections and other inflammatory conditions. If data permit, results could be reported separately for this population.
Interventions	• ARCHITECT and Alinity i Urine NGAL assays (Abbott) • The NephroCheck test (Astute Medical) • The NGAL test – using plasma (BioPorto Diagnostics) • The NGAL test – using urine (BioPorto Diagnostics) Used alongside serum creatinine, urine output monitoring and clinical judgement
Comparator	Serum creatinine, urine output monitoring and clinical judgement only
Healthcare setting	Secondary or tertiary care
Outcomes	Intermediate measures for consideration may include: • predictive accuracy or diagnostic accuracy • length of stay in critical or intensive care • length of stay in hospital

	• incidence of acute kidney injury (and severity or stage of condition) • length of acute kidney injury episode • incidence or duration of acute renal replacement therapy within 7 days • incidence of chronic kidney disease-related renal replacement therapy post-acute kidney injury • impact on steady state estimated glomerular filtration rate at 90 days • impact of test result on clinical decision making • incidence of hospital readmission post-discharge • time to test result • equivalence of biomarkers (for example, the NGAL assays).
	Clinical outcomes for consideration may include: • mortality • acute kidney injury-associated morbidity (such as chronic kidney disease or end-stage renal disease).
	Patient-reported outcomes for consideration may include health-related quality of life.
	Costs will be considered from an NHS and personal social services perspective. Costs for consideration may include: • costs related to using the tests (including maintenance, controls, calibration, accreditation, staff time to run tests) • costs related to assessment for people diagnosed with acute kidney injury (such as nephrology consultations, scans and renal biopsies) • costs related to interventions used when acute kidney injury is predicted or diagnosed (such as optimising haemodynamics and fluid status) • costs related to hospital stays (including critical or intensive care) • costs related to renal replacement therapy during hospitalisation • costs related to treating chronic kidney disease; including renal replacement therapy for end-stage renal disease.
	The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.

Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details, including descriptions of the interventions, comparator, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review to identify evidence on the diagnostic accuracy and clinical effectiveness of the NephroCheck test and NGAL assays (Abbott ARCHITECT and Alinity assays and the BioPorto assay) to help assess, and reduce, the risk of acute kidney injury for critically ill hospitalised patients who are considered for critical care admission. For details of the systematic review see page 48 of the diagnostics assessment report.

For the full inclusion and exclusion criteria for the studies see table 2 on page 49 of the diagnostics assessment report. Although the population in the scope is people being considered for critical care admission, the EAG included data from studies of people in critical care to maximise the data available.

In total, 56 studies (reported in 71 articles) were included. Of these, 46 enrolled adults only, 8 enrolled children only and 2 enrolled both adults and children. Twenty-eight studies were done in Europe (4 in the UK), 15 in North America, 9 in Asia, 2 in North America and Europe, 1 in Australia and 1 study did not provide details of location. In most studies data were collected prospectively.

- 53 studies reported data on the use of the biomarkers to detect or predict acute kidney injury in critically ill patients admitted to hospital.
- 11 studies reported data on the ability of the tests to predict mortality, 4 reported data on the ability of the tests to predict the need for renal replacement therapy and 3 studies assessed the ability of the tests to predict worsening of acute kidney injury.
- No studies provided suitable data to assess the ability of the tests to predict chronic kidney disease.

No randomised controlled trials or controlled clinical trials were identified. No studies compared using the biomarkers with standard clinical care for clinical effectiveness outcomes.

The studies assessed the use of the tests in various clinical settings. For adults, the most common settings were after cardiac surgery (12 studies) and in intensive care (16 studies). For children, most were done after cardiac surgery (6 studies).

The EAG divided the studies in adults and children into 3 groups based on clinical setting:

- people who had cardiac surgery
- people who had major non-cardiac surgery
- people admitted to critical care (included critically ill patients presenting to the emergency department and patients admitted to intensive care or considered for critical care for various medical conditions).

For an overview of the included studies see tables 3 and 4 of the diagnostics assessment report page 63.

No studies were identified that used the Alinity i Urine NGAL assay.

Evidence on accuracy to detect emerging acute kidney injury

Test accuracy was determined by the ability of the tests to identify the presence of acute kidney injury according to current clinical criteria (that is, using serum creatinine and urine output). A rise in serum creatinine levels or fall in urine output, or both, occurring within a certain time after the NephroCheck or NGAL test was done (this varied between studies, from within 12 hours to within 8 days) were used to indicate if acute kidney injury occurred (reference standard). These typically used the KDIGO, RIFLE or AKIN systems to define acute kidney injury occurrence, and to stage its severity (see table 1 on page 38 of the diagnostics assessment report for further details). The definition of acute kidney injury varied between studies.

The EAG could extract or derive the necessary data for sensitivity and specificity (2 by 2 tables) to address this question from 33 of the included studies.

Quality assessment

The QUADAS-2 tool was used for quality assessment of the studies. The EAG commented that for most studies it was not clear if the tests were interpreted without knowledge of the reference standard (unclear risk of bias).

Studies that used NephroCheck were judged at low risk of bias for interpretation of the test because they used a common threshold. However, for the NGAL studies a common threshold for NGAL was not used. The EAG also commented that in the NGAL studies the threshold was not pre-specified before data were collected.

Two studies were assessed as being at high risk of bias on the patient flow domain because more than 50% of the participants were excluded from the analysis (Jaques et al. 2019) or because of poor reporting (Asada et al. 2016).

The EAG considered that the applicability of the index test results to the NHS was unclear in many studies because there was wide variation in the NGAL

threshold used to define a positive test result and in the timing of the test sample collection. The EAG commented that it had no major concerns that the patient population, index text and reference standard were not applicable to the review question. However, in some of the included studies people were already admitted to critical care. An overview of the QUADAS-2 results is shown in figure 1, which is reproduced from the diagnostics assessment report (see page 72).

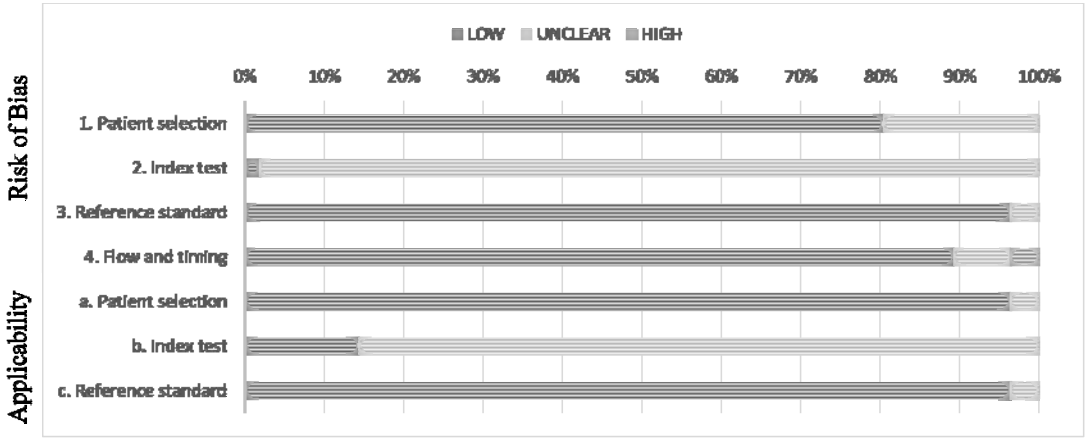


Figure 1 Risk of bias assessment of studies using the QUADAS-2 tool

Results

The EAG ran meta-analyses using the hierarchical summary ROC (HSROC) model to estimate summary values for sensitivity and specificity because the threshold used for a positive test result varied in the identified studies. If multiple thresholds were used in a study, the EAG selected 1 to use in their analysis. Meta-analysis was only done if data from 4 or more studies were available. Heterogeneity was assessed by a visual inspection of the forest plots of sensitivity and specificity estimates and of the size of the prediction region in the HSROC plots.

NephroCheck

All studies assessed used the NephroCheck test on urine samples. No studies were done in the UK, where the threshold for critical care admission may be higher.

Two studies assessed the use of NephroCheck to detect acute kidney injury after cardiac surgery and 5 studies assessed its use in hospitalised patients admitted to intensive or critical care for various clinical reasons (see table 2). No studies were identified in people who had major non-cardiac surgery.

Table 2 Overview of NephroCheck studies

Study	Timing of test	Cut-off	Definition of AKI	Prevalence of AKI
After cardiac surgery				
Oezkur 2017 (Germany; n=150)	ICU admission	0.3 ng/mL^2/1000	KDIGO	19%
Cummings 2019 (USA; n=400)	ICU admission	0.3 ng/mL^2/1000	KDIGO	4%
Critical care				
Kashani 2013 (North America and Europe; n=728)	ICU admission	0.3 ng/mL^2/1000	KDIGO	14%
Bihorac 2014 (USA; n=408)	Within 24 h of ICU admission	0.3 ng/mL^2/1000	KDIGO	17%
Hoste 2014 (USA; 153)	ICU admission	0.3 ng/mL^2/1000	KDIGO	18%
Kimmel 2016 (Germany; n=298)	Admission to the internal medicine service	Between 0.3 and 2.0 ng/mL^2/1000	KDIGO (modified version)	15%
Di Leo 2018 (Italy; n=719)	ICU admission	0.3 ng/mL^2/1000	KDIGO	34%

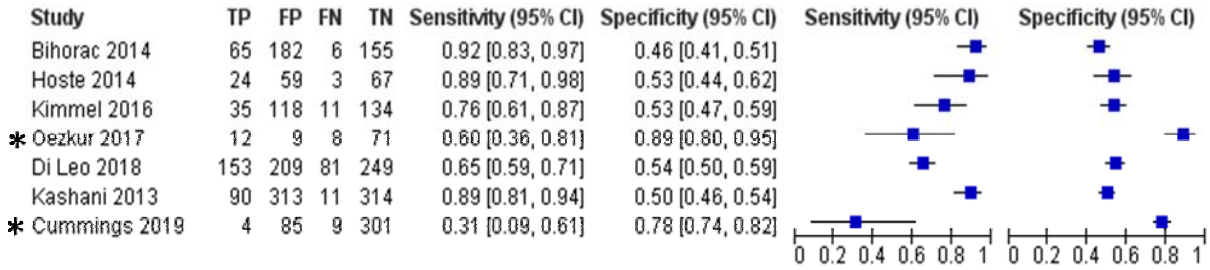
Abbreviations: AKI, acute kidney injury; ICU, intensive care unit

Individual sensitivity and specificity values for studies are shown in the forest plot (see figure 2) and HSROC (see figure 3). The summary estimate for sensitivity was 0.75 (95% confidence interval [CI] 0.58 to 0.87) and for specificity was 0.61 (95% CI 0.49 to 0.72). The EAG commented that there was heterogeneity between studies, and noted that estimates of specificity were generally low. Also, Cummings et al. appeared to be an outlier, and the

EAG highlighted the relatively low prevalence of acute kidney injury in this study (4%).

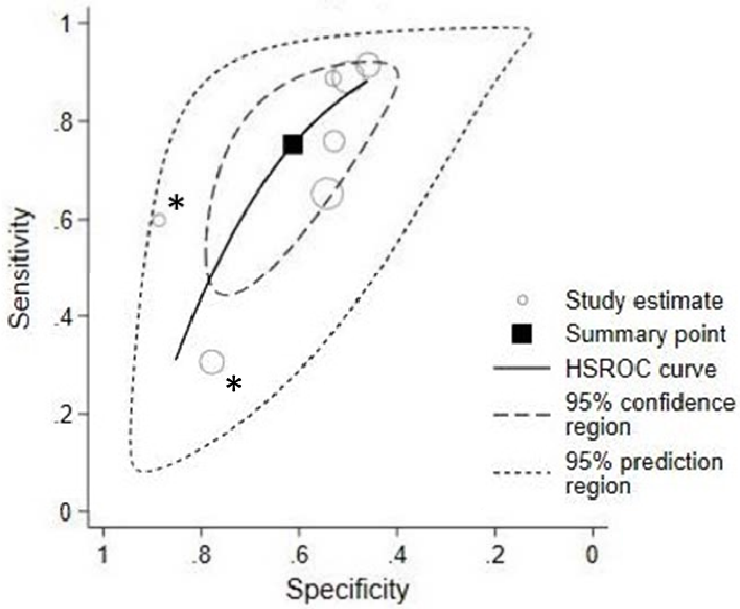
A meta-analysis for critical care studies alone was also done by the EAG. For the results see the diagnostics assessment report page 78.

Figure 2 Forest plot of sensitivity and specificity for NephroCheck for detecting acute kidney injury in adults – all settings.



* after cardiac surgery, all other studies done in critical care

Figure 3 HSROC for NephroCheck studies – all settings (adults)



* after cardiac surgery, all other studies done in critical care

ARCHITECT urine NGAL assay (adults)

Two studies provided test accuracy data on the use of the ARCHITECT NGAL assay for detecting acute kidney injury in patients who had cardiac surgery and 4 studies assessed its use in hospitalised patients admitted to intensive or critical care for various clinical reasons (see table 3). No studies were done in the UK or were identified in people who had major non-cardiac surgery.

Table 3 Overview of ARCHITECT NGAL assay studies

Study	Timing of test	Cut-off	Definition of AKI	Prevalence of AKI
After cardiac surgery				
Parikh 2011 (North America; n=1,200)	ICU admission	102 ng/mL	Acute dialysis or doubling of serum creatinine	5%
Thanakitcharu 2014 (Thailand; n=130)	Immediately after surgery	11.3 ng/mL	Increase in serum creatinine >0.3 mg/dL within 48 h	35%
Critical care				
Dupont 2012 (USE; n=141)	48 h after admission	32 microgram per g Cr [a]	Increase in serum creatinine >0.3 mg/dL	25%
Kokkoris 2012 (Greece; n=100)	ICU admission	58.5 ng/mL	RIFLE	36%
Nickolas 2012 (USA and Germany; n=1,635)	Admission to ED	104 ng/mL	RIFLE	6%
Treeprasertsuk 2015 (Thailand; n=121)	Within 72 h after admission	56 ng/mL	AKIN	29%

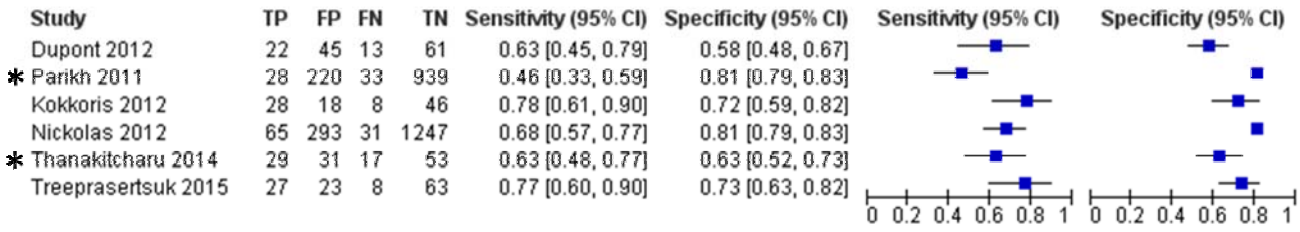
[a] Urine NGAL levels were expressed per unit of urine creatinine
Abbreviations: AKI, acute kidney injury; ICU, intensive care unit

Individual sensitivity and specificity values for studies are shown in the forest plot (see figure 4) and HSROC (see figure 5). The summary estimate for sensitivity was 0.67 (95% CI 0.58 to 0.76) and for specificity was 0.72 (95% CI

0.64 to 0.79). The EAG commented that there was heterogeneity between studies.

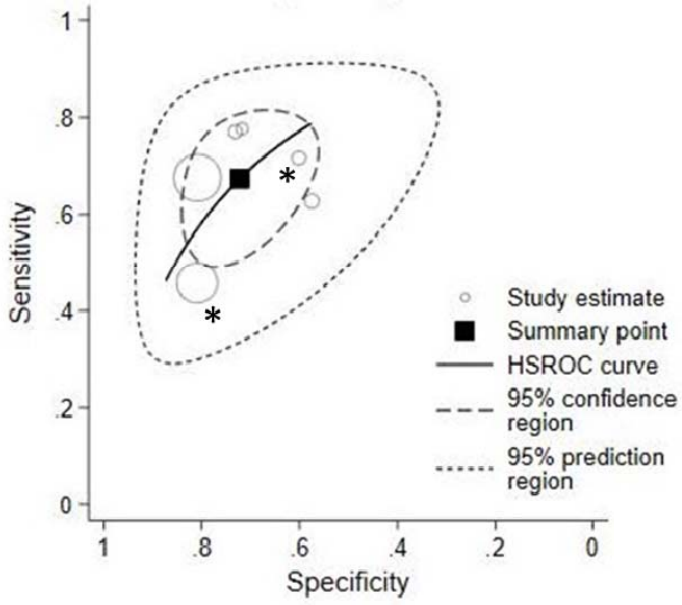
The EAG also did a meta-analysis for critical care studies alone. For the results see the diagnostics assessment report page 82.

Figure 4 Forest plots of sensitivity and specificity for the ARCHITECT urine NGAL assay for detecting acute kidney injury in adults – all settings



* after cardiac surgery, all other studies done in critical care

Figure 5 HSROC for urine NGAL ARCHITECT studies – all clinical settings (adults)



* after cardiac surgery, all other studies done in critical care

BioPorto NGAL test – urine (adults)

Eight studies assessed the use of the BioPorto NGAL test (using urine) for detecting acute kidney injury:

- 1 study in people who had cardiac surgery
- 1 study in people who had major non-cardiac surgery
- 6 studies in hospitalised patients admitted to intensive or critical care for various clinical reasons (see table 4).

One study was done in the UK (Matsa et al. 2014).

Table 4 Overview of BioPorto NGAL (urine) test studies

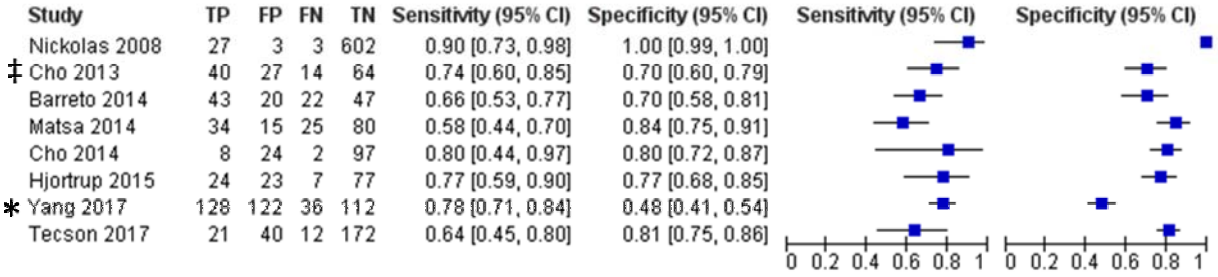
Study	Timing of test	Cut-off	Definition of AKI	Prevalence of AKI
After cardiac surgery				
Yang 2017 (China; n=398)	6 hours after surgery	98 microgram/g Cr	Acute dialysis or doubling of serum creatinine consistent with KDIGO stage 2 and 3 criteria	41%
After major non-cardiac surgery				
Cho 2014 (South Korea; n=131)	12 hours after hepatobiliary surgery	92.85 ng/mL	AKIN	8%
Critical care				
Nickolas 2008 (USA; n=635)	Admission to emergency department	130 µg/g Cr	RIFLE	5%
Cho 2013 (south Korea; n=145)	ICU admission	NR	AKIN	37%
Matsa 2014 (UK; n=194)	ICU admission	350 ng/mL	RIFLE	38%
Barreto 2014 (Spain; n=132)	When the infection was detected	51 µg/g Cr	AKIN	49%
Hjortrup 2015 (Denmark; n=151)	ICU admission	582 ng/mL	KDIGO	24%
Tecson 2017 (USA; n=245)	Within 48 hours of ICU admission	98 ng/mL	KDIGO (stage 2/3)	13%

In several studies NGAL levels were normalised by units of urine creatinine.
Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; Cr, creatinine; NR, not reported

Individual sensitivity and specificity values for studies are shown in the forest plot (see figure 6) and HSROC (see figure 7). The summary estimate for sensitivity was 0.73 (95% CI 0.65 to 0.80) and for specificity was 0.83 (95% CI 0.64 to 0.93). The EAG commented that there was heterogeneity between studies.

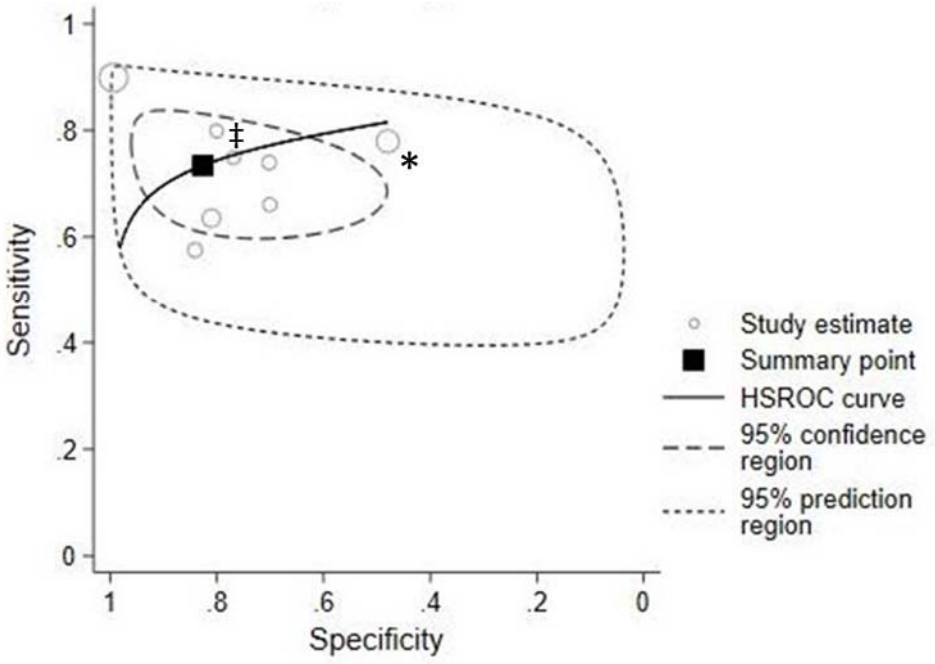
The EAG also did a meta-analysis for critical care studies alone. For the results see the diagnostics assessment report page 86.

Figure 6 Forest plots of sensitivity and specificity for BioPorto NGAL test (urine) for detecting acute kidney injury in adults – all settings



* after cardiac surgery ‡ after major non-cardiac surgery, all other studies done in critical care

Figure 7 HSROC for BioPorto NGAL test (urine) studies – all clinical settings (adults)



* after cardiac surgery ‡ after major non-cardiac surgery, all other studies done in critical care

BioPorto NGAL assay – plasma (adults)

The EAG only identified studies in the critical care setting for the BioPorto NGAL assay used with blood plasma (see table 5). One study was done in the UK (Matsa et al. 2014).

Table 5 Overview of BioPorto NGAL (plasma) test studies

Study	Timing of test	Cut-off	Definition of AKI	Prevalence of AKI
Matsa 2014	ICU admission	400 ng/mL	RIFLE	38%
Hjortrup 2015	ICU admission	558 ng/mL	KDIGO	24%
Tecson 2017	Within 48 hours of ICU admission	142 ng/mL	KDIGO (stage 2 and 3)	13%
Itenov 2017	ICU admission	185 ng/mL	KDIGO	36%

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit

Individual sensitivity and specificity values for studies are shown in the forest plot (see figure 8) and HSROC (see figure 9). The summary estimate for sensitivity was 0.76 (95% CI 0.56 to 0.89) and for specificity was 0.67 (95% CI 0.40 to 0.86). The EAG commented that there was heterogeneity across studies.

Figure 8 Forest plots of sensitivity and specificity for BioPorto NGAL (plasma) test for detecting acute kidney injury in adults – critical care

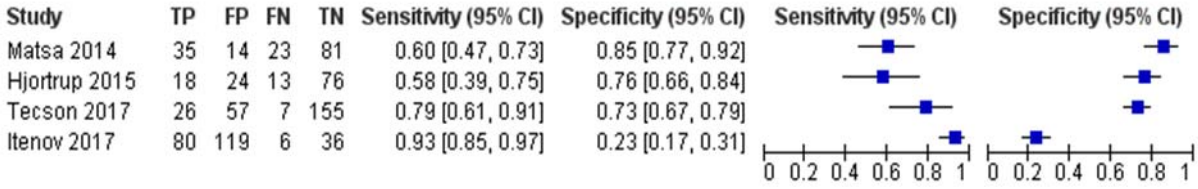
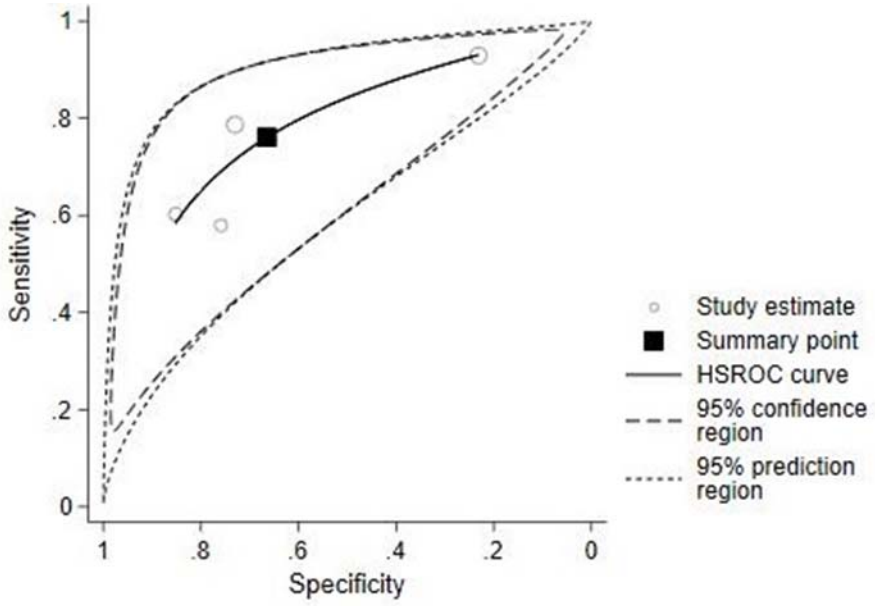


Figure 9 HSROC for BioPorto NGAL (plasma) test studies – critical care



Children

Seven studies assessed use of the NGAL assays using urine samples to detect acute kidney injury in children. No studies were done in the UK. No studies assessing the use of NephroCheck in children were identified. The

company has stated that this test is only marketed in the UK for use for people over 21 years.

ARCHITECT urine NGAL assay (children): After cardiac surgery

Five studies assessed the use of the ARCHITECT urine NGAL assay for detecting acute kidney injury in children who had cardiac surgery (see table 6). The summary estimate for sensitivity was 0.68 (95% CI 0.53 to 0.80) and for specificity 0.79 (95% CI 0.63 to 0.89). Estimates from individual studies can be seen in the forest plot (see figure 10) and HSROC (see figure 11). The EAG commented that there was considerable heterogeneity across studies.

No studies were identified in a population who had major non-cardiac surgery.

Table 6 Overview of ARCHITECT urine NGAL test (children) – after cardiac surgery

Study	Timing of test	Cut-off	Definition of AKI	Prevalence of AKI
Parikh 2011 (North America; n=311)	ICU admission	72 ng/mL	Acute dialysis, or doubling of serum creatinine from baseline	17%
Cantinotti 2012 (Italy; n=135)	2 h after surgery	49.9 ng/mL	pRIFLE	27%
Seitz 2013 (Not reported; n=139)	2h after end of surgery	27.6 ng/mL	pRIFLE	55%
Bennett 2013 (USA; n=196)	2 h after surgery	150 ng/mL	50% or greater increase in serum creatinine from baseline within 72 hours	50%
Alcaraz 2014 (Spain; n=106)	ICU admission	100 ng/mL	pRIFLE	34%

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit

Figure 10 Forest plots of sensitivity and specificity for ARCHITECT urine NGAL for detecting acute kidney injury in children – cardiac surgery

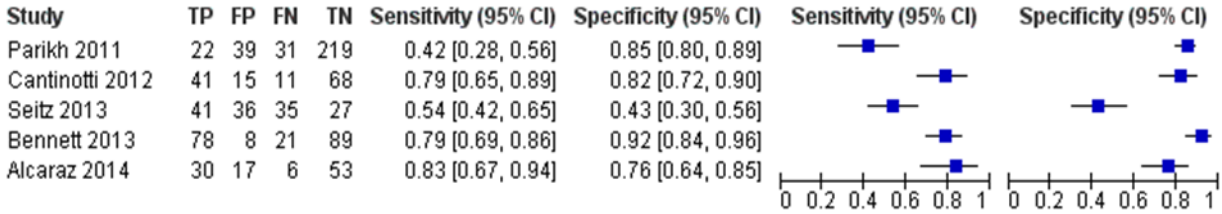
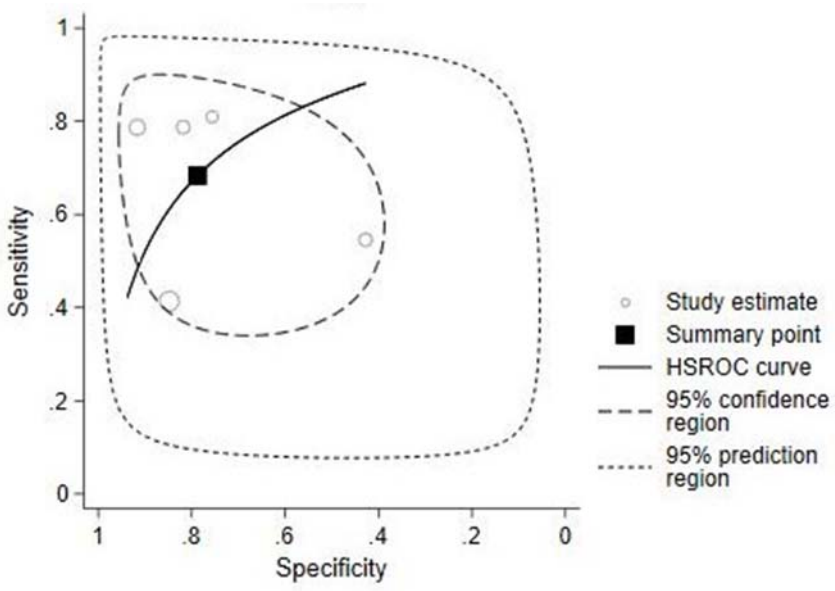


Figure 11 HSROC for ARCHITECT urine NGAL studies – cardiac surgery



ARCHITECT urine NGAL assay (children): Critical care

One study assessed the use of the ARCHITECT Urine NGAL assay for detecting acute kidney injury in children admitted to intensive or critical care for various clinical reasons (see table 7). The sensitivity and specificity were 0.77 (95% CI 0.60 to 0.90) and 0.85 (95% CI 0.74 to 0.92), respectively.

Table 7 Overview of ARCHITECT NGAL Urine test (children): Critical care

Study	Timing of test	Cut-off	Definition of AKI	Prevalence of AKI
Zwiers 2015 (Netherlands; n=100)	ICU admission	126 ng/mL	RIFLE	35%

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit

BioPorto NGAL assay – urine (children): After cardiac surgery

One study assessed the use of the BioPorto NGAL assay using urine for detecting acute kidney injury in children who had cardiac surgery (see table 8). NGAL was measured using a concentration normalised by units of creatinine. The sensitivity and specificity were 0.77 (95% CI 0.69 to 0.84) and 0.47 (95% CI 0.40 to 0.54), respectively.

No studies were identified in people who had major non-cardiac surgery.

Table 8 Overview of BioPorto NGAL test (children): After cardiac surgery

Study	Timing of test	Cut-off	Definition of AKI	Prevalence of AKI
Yang 2017 (China; n=323)	6 hours after surgery	186 microgram per g Cr	Acute dialysis or doubling of serum creatinine consistent with KDIGO stage 2 and 3 criteria	39%

Abbreviations: AKI, acute kidney injury; Cr, creatinine

Test accuracy assessed by area under ROC curve

The EAG also presented data on area under the ROC curve (AUC) for the tests for detecting acute kidney injury reported in studies. AUC summary estimates are shown in table 9. The EAG commented that the summary estimates had relatively large 95% prediction intervals, indicating heterogeneity between studies. For details see the diagnostics assessment report, page 100.

Table 9 Pooled AUC for detecting acute kidney injury

Test	Setting	AUC summary estimate (95% CI)
Adults		
NephroCheck (urine)	All settings	0.76 (0.50 to 0.91)
ARCHITECT NGAL (urine)	All settings	0.73 (0.68 to 0.78)
BioPorto NGAL (urine)	All settings	0.70 (0.65 to 0.74)
BioPorto NGAL (plasma)	All settings	0.72 (0.66 to 0.77)
Children		
ARCHITECT NGAL (urine)	After cardiac surgery	0.80 (0.65 to 0.90)
BioPorto NGAL (urine)	After cardiac surgery	0.88 (0.47 to 0.98)

Abbreviations: AUC, area under the curve; CI, confidence interval

In individual studies where a direct comparison was made, the AUC of the tests was higher than serum creatinine levels or conventional clinical assessment in most studies, but not all. For full details see table 12 in the diagnostics assessment report, page 104.

Evidence on ability to predict intermediate outcomes

The EAG identified 11 studies with data on the ability of the tests to predict mortality, 4 studies with data on predicting the need for renal replacement therapy (RRT) and 3 studies that assessed the ability of the tests to predict worsening of acute kidney injury. All studies were in critically ill patients at risk of acute kidney injury.

Quality assessment

The EAG used the PROBAST tool to assess risk of bias in studies assessing the tests for predicting relevant clinical outcomes. Overall, risk of bias was considered to be unclear for most studies (58%), largely because many studies were assessed as being at high risk of bias in the analysis domain. This was because most studies were published before the PROBAST tool was developed and did not comply with the new recommended standards (little information on selecting predictors, on model validation and whether the complexity in the data was accounted for appropriately). For applicability 75% of studies were judged by the EAG to be at low risk, with the remaining

studies at unclear risk. For details see the diagnostics assessment report, page 73.

Results

When possible, the EAG did meta-analyses of AUC values using a random-effects model to measure the performance of each test for predicting each relevant outcome. The EAG considered that an AUC of more than 0.70 indicated a useful risk predictor.

For predicting mortality, AUC values varied from 0.55 to 0.91. For predicting the need for RRT, AUC values varied from 0.68 to 0.86. For predicting worsening of acute kidney injury, AUC values varied from 0.66 to 0.71. For results see table 13 on page 107 of the diagnostics assessment report.

The EAG commented that adding the tests to existing clinical models generally improved risk prediction of newly developed acute kidney injury, or worsening of acute kidney injury, and mortality. However, it cautioned that there were limited data available, statistical models used varied between studies and information on potential candidate variables considered in studies was often not provided. For the results see table 14 on page 109 of the diagnostics assessment report.

Evidence on clinical outcomes

No studies were identified.

Evidence on patient-reported outcomes

No studies were identified.

2.2 Costs and cost effectiveness

The EAG did a search to identify existing studies investigating the cost effectiveness of the ARCHITECT and Alinity i Urine NGAL assays, the NephroCheck test and the BioPorto NGAL test when used (with standard clinical assessment) to assess the risk of acute kidney injury in people who

are critically ill and are being assessed for critical care admission. The EAG also built a de novo economic model to assess the cost effectiveness of the tests in this population.

Systematic review of cost-effectiveness evidence

The EAG did a systematic review to identify any published economic evaluations of the NephroCheck test, the ARCHITECT and Alinity urine NGAL assays and the BioPorto NGAL test (plasma and urine) for evaluating critically ill people at risk of developing acute kidney injury. For details of the review see the diagnostics assessment report, page 114. There were 4 studies that met the EAG's inclusion criteria. For an overview of the study characteristics see table 15 of the diagnostics assessment report, page 117.

Two of the studies used modelling strategies that were similar, and that the EAG considered appropriate for the current decision problem. But only 1 of these (Hall et al. 2018) was done in the UK. The EAG considered that Hall et al. was a comprehensive and high-quality assessment. But because the setting was outside the scope of this assessment, the EAG adapted the model for critically ill patients who are at risk of acute kidney injury and are being considered for admission to critical care.

Economic analysis

The EAG developed a de novo economic model designed to assess the cost effectiveness of using the tests (in addition to standard clinical monitoring) to help detect the risk of developing acute kidney injury and to help start early preventative care.

This was a 2-stage model using TreeAge Pro software. Because no direct evidence was identified showing the effect of using the tests (compared with standard monitoring alone) on health outcomes (such as acute kidney injury status, mortality, development of chronic kidney disease), the EAG used observational associations to infer how preventing or reducing the severity of

acute kidney injury may affect changes in health outcomes (a linked-evidence approach). An initial decision tree phase modelled:

- The accuracy of the tests to identify people with emerging acute kidney injury.
- For people with a positive biomarker test result, the effect of preventative measures (a KDIGO care bundle) on reducing the probability that they develop acute kidney injury, or reducing the severity of the condition if they develop it.
- The impact of developing acute kidney injury, and its severity, on short-term outcomes (within 90 days): whether a person is admitted to intensive care, length of stay in intensive care or hospital, whether RRT is needed while in hospital, development of chronic kidney disease and 90-day mortality.

After this initial 90-day period, a longer-term Markov model was used to model the effect of developing acute kidney injury while in hospital on the risk of developing chronic kidney disease, and the impact of this condition on the rest of a person's life. The model structure is described in more detail below.

Population

The modelled population was people who were critically ill in hospital, at risk of developing acute kidney injury and having their serum creatinine and urine output monitored. The EAG used the Grampian population register of hospitalisations to characterise this population. This dataset includes 17,630 adults admitted to hospital in Grampian in 2003. It is the complete population of all patients who had an abnormal kidney function blood test on hospital admission and had at least an overnight stay in hospital, including all patients who developed acute kidney injury. This population was considered appropriate because everyone had a blood test for kidney function at the point of hospital admission and was considered to be at risk of acute kidney injury. The model starting base-case cohort is therefore 63 years old, 54.3% women,

with about 11% having chronic kidney disease (more can develop this condition over time in the model). The base-case prevalence of acute kidney injury (that is, people who will develop the condition while in hospital under standard monitoring) was assumed to be 9.2%.

Model structure

Initial decision tree phase

In the decision tree (see figure 12), people who were critically ill in hospital, at risk of developing acute kidney injury, and were having their serum creatinine and urine output monitored, were divided into 2 cohorts: those who will develop acute kidney injury (under standard monitoring) and those who will not. People without acute kidney injury can either be admitted to intensive care or stay on a ward. For people who can develop acute kidney injury, this can either be prevented or not. If acute kidney injury is not prevented, people develop acute kidney injury stage 1, 2 or 3 (increasing severity). For people with stage 3 acute kidney injury, some need renal replacement therapy (RRT) while in hospital. People with acute kidney injury can also be admitted to intensive care or stay on a ward; having acute kidney injury (or a more severe form) can increase the probability of admission to intensive care. All people can also die within the 90-day period of the decision tree phase.

The decision tree was run separately for people having standard monitoring (serum creatinine and urine output monitoring alone) and people having the additional tests (NephroCheck or NGAL; as well as serum creatinine and urine output monitoring). For standard monitoring, no acute kidney injury was detected 'early' and prevented in the decision tree (although once serum creatinine rises or urine output falls later, or both, preventative measures were started). For people having the NephroCheck or NGAL tests, the model assumed that in the event of a positive test result, preventative measures were employed (a KDIGO care bundle) which prevents some people from developing acute kidney injury (for true positive results). In addition, for people

who develop acute kidney injury after having a care bundle, a larger proportion develop less severe acute kidney injury (stage 1). For false positive results from the tests (that is, people who will not develop acute kidney injury), the cost of the KDIGO care bundle was incurred, but they get no clinical benefit from it. For people with negative test results, no care bundle was assumed to be used. The accuracy estimates for the tests (NephroCheck and NGAL tests), which determine the proportions of true and false positives and negatives, were taken from the EAG's clinical effectiveness review (described below).

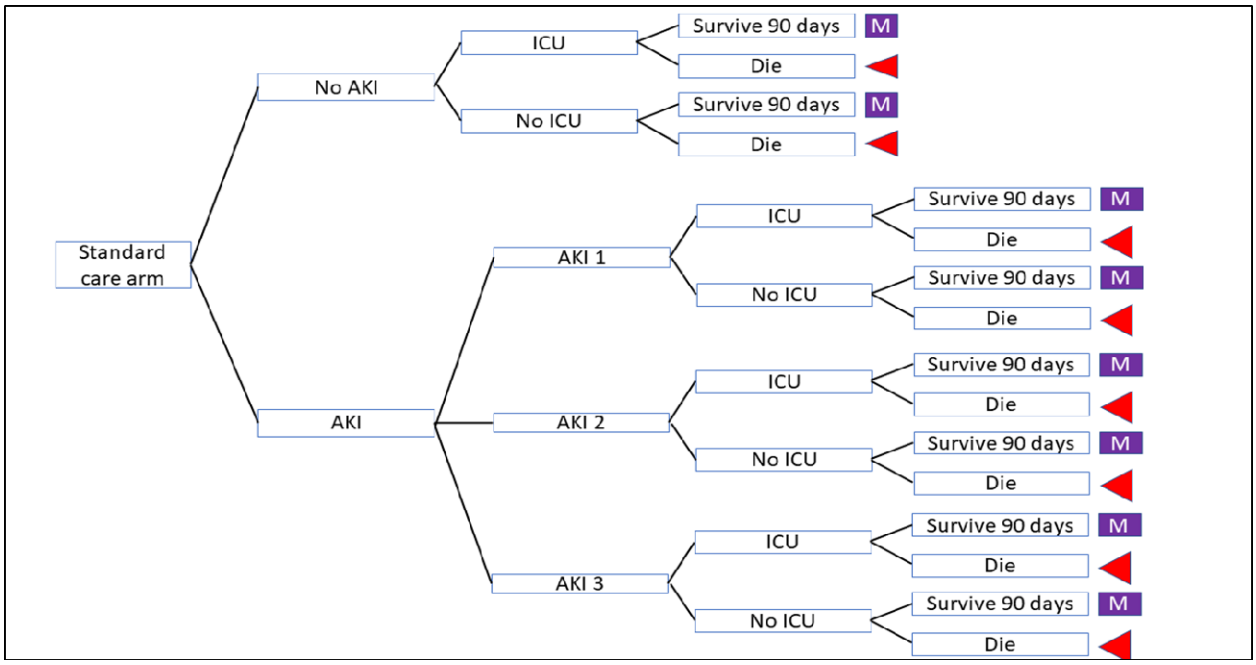


Figure 12 Simplified decision tree structure (figure 32 from the diagnostics assessment report)

The tests were assumed to act in the model by reducing the number of people who develop acute kidney injury while in hospital or, if a person does develop acute kidney injury, reducing its severity. The model has several options for how preventing acute kidney injury (or a more severe form of the condition) decreases the chance of adverse clinical outcomes occurring ('associative effects'). Preventing acute kidney injury can reduce:

- the probability of being admitted to intensive care while in hospital, and reduce the length of stay once admitted
- the overall length of time in hospital
- the risk of mortality (within the 90-day decision tree model)
- the number of people with stage 3 acute kidney injury, which means fewer people have RRT in hospital
- the risk of developing chronic kidney disease.

The model can switch on and off these potential benefits of preventing acute kidney injury, or reducing severity, on clinical outcomes. Not all are present in the base-case model (discussed below), and effects are investigated in scenario analyses. The model can also reduce the size of effect that developing acute kidney injury has on these clinical outcomes: no effect, full effect or partial effect.

Longer-term Markov model

People who do not die in the initial decision tree model enter the longer-term Markov model (see figure 13). In this model people discharged from hospital have either developed chronic kidney disease (stages 1 to 4; enter in state 2) or not (enter in state 1). The model is then run for the rest of their lifetime. During this time, they can develop stage 1 to 4 chronic kidney disease (if they do not already have it), progress to end-stage renal disease (ESRD) potentially needing dialysis and kidney transplant (which can either succeed or fail).

Developing acute kidney injury in the initial decision tree model increases the probability that a person will develop chronic kidney disease (stages 1 to 4) and enter the Markov model in this state. Having a more severe stage of acute kidney injury increases this probability even further. In the base case for the first cycle of the Markov model (1 year), people who have had acute kidney injury while in hospital have a higher risk of developing chronic kidney disease (with higher risk for more severe acute kidney injury). A scenario

analysis investigated the impact of this effect lasting for a full lifetime (as in Hall et al. 2018).

People can die in each model state, the probability of all-cause mortality used population values adjusted for age and sex. However, if disease state-specific mortality was higher this was used instead:

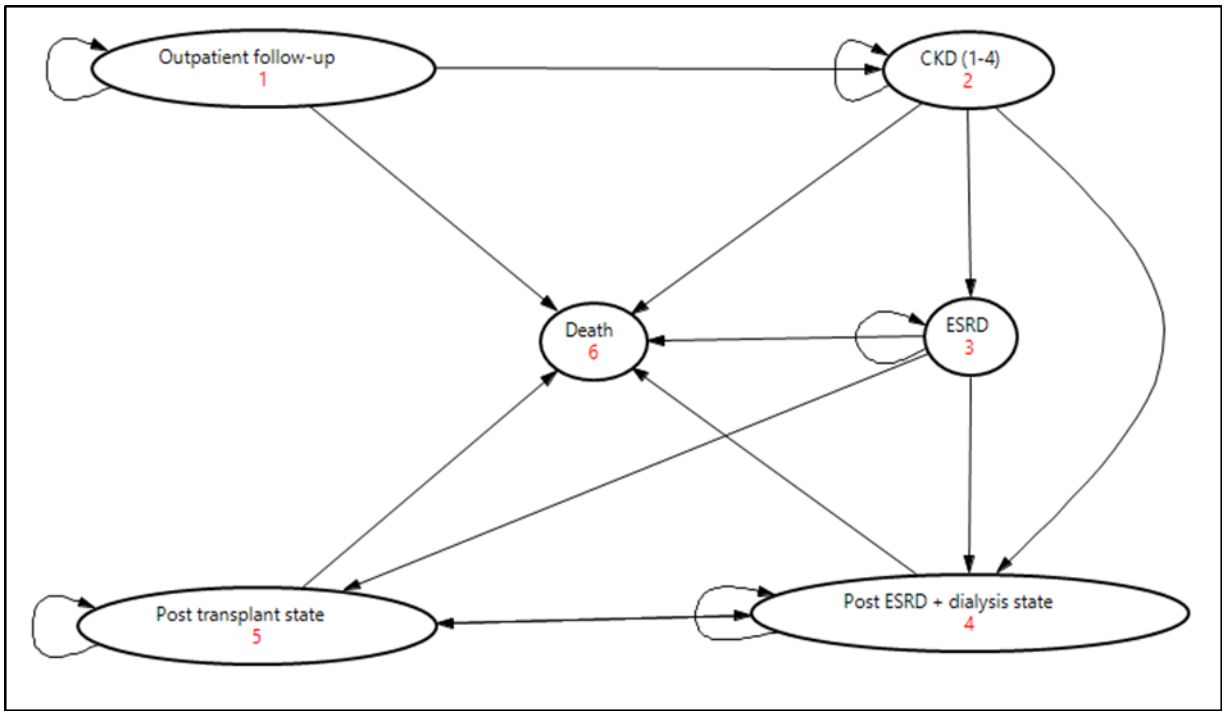


Figure 13 Markov chronic model phase structure (figure 33 in the diagnostics assessment report)

Model inputs

Initial decision tree phase

Accuracy of tests to detect emerging acute kidney injury

The sensitivity and specificity of the tests to identify people who will develop acute kidney injury (as shown by a later increase in serum creatinine or drop in urine output, or both) was taken from the systematic review and meta-analysis done in the clinical effectiveness section (see table 10). The EAG used values pooled from all studies identified for each of the tests (that is,

across all clinical settings). Accuracy estimates from populations who had cardiac surgery and in critical care were used in subgroup analyses. The EAG took account of the correlation between sensitivity and specificity values in the model; for details see page 126 and table 17 of the diagnostics assessment report.

Table 10 Sensitivity and specificity values for tests used in the model

Test parameter		Mean value (95% confidence interval)	Source
NephroCheck (urine)	Sensitivity	0.75 (0.58 to 0.87)	EAG's meta-analysis
	Specificity	0.61 (0.49 to 0.72)	
ARCHITECT NGAL (urine)	Sensitivity	0.67 (0.58 to 0.76)	
	Specificity	0.72 (0.64 to 0.79)	
BioPorto NGAL (urine)	Sensitivity	0.73 (0.65 to 0.80)	
	Specificity	0.83 (0.64 to 0.93)	
BioPorto NGAL (plasma)	Sensitivity	0.76 (0.56 to 0.89)	
	Specificity	0.67 (0.40 to 0.86)	
For children only population (scenario analysis Q)			
ARCHITECT NGAL (urine)	Sensitivity	0.68 (0.53 to 0.80)	EAG's meta-analysis
	Specificity	0.79 (0.63 to 0.89)	
BioPorto NGAL (urine)	Sensitivity	0.77 (0.70 to 0.84)	Yang et al. (2017)
	Specificity	0.47 (0.40 to 0.54)	

The EAG highlighted that the meta-analyses combined data from heterogeneous studies. For NGAL, the summary estimates combined data from studies which used different test thresholds. The EAG commented that the results of the economic model, particularly for comparisons between different NGAL assays, should be interpreted cautiously.

Tests were assumed to be done alongside standard monitoring (that is, serum creatinine and urine output monitoring) based on advice from clinical experts. Each test was assumed to be done only once in the base case.

Parameters for the effect of acute kidney injury on clinical outcomes

The incidence of acute kidney injury and the effect of developing the condition on clinical outcomes (admission to intensive care, 90-day mortality, need for RRT) was estimated by the EAG largely using data from the Grampian observational dataset (see table 11). The EAG highlighted that the extent of any impact of acute kidney injury status and consequent effect on clinical outcomes was uncertain and potentially controversial. The model could vary which clinical outcomes acute kidney injury status had an effect on, and the size of this effect.

Table 11 Model parameters for effect of acute kidney injury on subsequent outcomes

		Percentage	Relative risk	Distribution	Source
Incidence of AKI					
No AKI		90.8%	-	Remainder	Grampian data (2012 cohort)
AKI (any)		9.2%	-	Beta	
If AKI, probability it is:	AKI 1	68.7%	-	Dirichlet	
	AKI 2	19.4%	-	Dirichlet	
	AKI 3	11.9%	-	Dirichlet	
Probability of admission to ICU (during hospitalisation)					
No AKI		1.4%	-	Beta	Grampian data (2003 cohort)
AKI 1		10%	-	Beta	
AKI 2		14.3%	1.42	Log normal (versus AKI 1)	
AKI 3		19.4%	1.93	Log normal (versus AKI 1)	
Probability of mortality (by 90 days)					
No AKI		4.9%	-	Beta	Grampian data (2003 cohort)
AKI 1		21.5%	-	Beta	
AKI 2		34.5%	1.60	Log normal (versus AKI 1)	
AKI 3		46.3%	2.15	Log normal (versus AKI 1)	
Probability of requiring RRT (during hospitalisation)					
No AKI, AKI 1 or AKI 2		0%	-	-	Assumption
AKI 3		55.0%	-	Beta	Truche et al. (2018)

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy

The EAG cautioned that these data should not be interpreted as definitive causative effects. Scenario analyses explore the application of different assumptions around these highly uncertain associations.

Developing acute kidney injury could also affect length of hospital stay (see table 12). Data on length of stay in intensive care were not available from the Grampian dataset, so the EAG used Bastin et al. (2013). This was a cohort study (n=1,881) of people who had cardiac surgery, which reported median length of stay in intensive care by stage of acute kidney injury. As the length of stay in hospital includes time spent in intensive care, the time on the hospital ward was obtained by subtracting intensive care length of stay from total hospital length of stay for applying costs and utilities in the model. It was assumed that the need for RRT would not extend length of stay in hospital further.

A log normal distribution was used for all length of stay parameters.

Table 12 Effect of acute kidney injury status on length of stay in hospital and ICU

	Mean (SD)	Median (IQR)	Source
Length of stay in hospital			
No AKI	8.1 days (22.8)	3 days (1 to 8)	Grampian data
AKI 1	26.3 days (38.1)	14 days (7 to 31)	
AKI 2	32.4 days (56.5)	18 days (8 to 36)	
AKI 3	28.4 days (32.5)	17 days (9 to 35)	
Length of stay in ICU			
No AKI	2 days (-) [a]	1 day (1 to 2)	Bastin et al. (2013)
AKI 1	4 days (-) [a]	2 days (1 to 3)	
AKI 2	8 days (-) [a]	4 days (1 to 8)	
AKI 3	26 days (-) [a]	13 days (6 to 27)	

[a] Only median data were available for intensive care length of stay. The EAG parameterised the log normal distribution by assuming the mean was twice the median (ratio obtained from data in Hall et al.). See diagnostics assessment report page 133 for further details.
Abbreviations: SD, standard deviation; IQR, interquartile range

Parameters for the effect of adopting a KDIGO care bundle on developing acute kidney injury

The EAG assumed that a KDIGO care bundle would be the preventative care used if the tests were positive.

The EAG did a literature search for studies (published since searches were done for Hall et al. 2018) assessing the effect of the KDIGO care bundle on the probability of developing acute kidney injury, or the severity of the condition that occurs. For details see page 135 of the diagnostics assessment report. Three trials (Meersch et al. 2017; Göcze et al. 2018; Schanz et al. 2018) assessed the effect of NephroCheck-guided application of a KDIGO care bundle compared with standard care (that is, no use of a care bundle). No studies were identified that assessed NGAL test-guided treatment.

All 3 studies were done in Germany and reported the effect of KDIGO bundles on developing acute kidney injury (compared with standard monitoring):

- Meersch et al. (n=276): Incidence of acute kidney injury within 72 hours (primary outcome): absolute risk reduction of 16.6% (95% CI 5.5% to 28.0%) when KDIGO bundle used.
- Göcze et al. (n=121): Odds ratio of acute kidney injury for standard care compared with NephroCheck-guided use of KDIGO bundle of 1.96 (95% CI 0.93 to 4.10). The odds ratio of developing stage 2 or 3 acute kidney injury was statistically significant: 3.43 (95% CI 1.04 to 11.32).
- Schanz et al. (n=100): Proportion of people developing acute kidney injury (stage 2 and 3) was similar in both arms (38.9% and 39.1% at 3 days).

Meersch et al. had a larger sample size and reported data for both the probability of acute kidney injury and the distribution of condition severity, so the EAG used these data in its model. Meersch et al. was a single-centre study in people who had cardiac surgery. If they tested positive on the

NephroCheck tests (using a score of over 0.3 as in the diagnostic accuracy studies in the clinical effectiveness review) they were randomised to either standard care or standard care plus a KDIGO care bundle. The EAG commented that the nature of the kidney insult caused by cardiac surgery may differ to that caused in other clinical settings, so the study results may not be generalisable to other settings. Support for the trial included a grant from Astute Medical. The KDIGO care bundle used in the study included:

- avoiding nephrotoxic agents
- discontinuing angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs)
- close monitoring of urine output and serum creatinine
- avoiding hyperglycaemia (for 72 hours)
- considering alternatives to radiocontrast agents
- fluid optimisation.

The EAG judged Meersch et al. as being at low risk of bias on most domains of the Cochrane Risk of Bias tool. The main limitation was that investigators were not blinded to the intervention groups, but the EAG considered this impractical.

The treatment effect was applied as a relative risk to baseline probabilities of developing acute kidney injury, and severity of condition, used for standard monitoring (see table 13).

Table 13 Effects of early NephroCheck-guided initiation of a KDIGO care bundle used in the model

		Mean relative risk [a]	Parameter distribution	Source
Any AKI		0.77	Log normal	Meersch et al. (2017)
If AKI does occur, relative risk that it is:	AKI 1	1.23		
	AKI 2	0.87		
	AKI 3	0.84		

[a] Calculated by the EAG using data from Meersch et al.
Abbreviation: AKI, acute kidney injury

No data on NGAL test-guided use of preventative care were identified. In base case 1, the EAG assumed that NGAL-guided care had the same effect as NephroCheck-guided care (on preventing acute kidney injury and on reducing its severity). The EAG commented that the NGAL and NephroCheck tests measure different markers; NGAL measures kidney injury and the NephroCheck markers identify kidney stress, which may allow intervention before acute kidney injury occurs. Therefore, the EAG did an alternative base-case analysis (base case 2) in which NGAL-guided care is assumed not to prevent acute kidney injury (relative risk is 1.0) but the same effect on reducing severity remains.

Meersch et al. also reported the effect of NephroCheck-guided KDIGO bundle use on other clinical outcomes. Although there was a significant reduction in occurrence of acute kidney injury by 72 hours for the KDIGO arm compared with standard care (odds ratio 0.48 [95% CI 0.29 to 0.80]), the EAG commented that this did not appear to translate to other clinical outcomes:

- need for RRT in hospital: odds ratio: 1.62 (95% CI 0.68 to 3.9)
- 90-day all-cause mortality, odds ratio: 1.21 (95% CI 0.49 to 3.03)
- length of stay in intensive care: median difference: 0 days (95% CI -1 to 0)
- length of stay in hospital, median difference: 0 days (95% CI -1 to 1).

The EAG commented that although the study was not powered to detect differences in these outcomes, there were no trends in the data that suggested an effect size (for example, for need for RRT and 90-day mortality, a higher proportion of people in the intervention arm had the clinical event).

Incidence of chronic kidney disease was not measured in the 3 studies.

Longer-term Markov model parameters

People entering the longer-term Markov model in the 'outpatient follow-up' state can develop chronic kidney disease (stages 1 to 4) over time, with an

annual probability derived from a cohort study of 97,782 intensive care patients enrolled on the Swedish intensive care register (baseline incidence of chronic kidney disease). For people who had acute kidney disease in the initial decision tree phase, this probability of developing chronic kidney disease (stages 1 to 4) is higher for the first year, before reverting to the baseline probability. This was based on clinical opinion that there is unlikely to be any longer-term effect of acute kidney injury on developing chronic kidney disease if it has not occurred in the first year after hospital discharge (a scenario analysis investigates a longer-term effect). The increased risk of developing chronic kidney disease (stages 1 to 4) for people with acute kidney injury was also applied in the decision tree phase.

Hazard ratios for the increased risk of developing chronic kidney disease for people with acute kidney injury (see table 14) were taken from a systematic review (See et al. 2019). This review included 3 studies that reported the effect of acute kidney injury stage on chronic kidney disease development (defined as chronic kidney disease stage 3 or higher), none of which were done in the UK. For details see the diagnostics assessment report, page 140.

Table 14 Parameters used in the model to link incidence of acute kidney injury to increased risk of chronic kidney disease

		Parameter value	HR	Distribution	Source
Baseline incidence of CKD per year		0.0044	-	Beta	Rimes-Stigare et al. (2015)
HR of CKD given the occurrence of:	AKI 1	-	2.32	Log normal	See et al. (2019)
	AKI 2	-	4.00		
	AKI 3	-	7.98		

Abbreviations: HR, hazard ratio; CKD, chronic kidney disease; AKI, acute kidney injury

People who develop chronic kidney disease (stage 1 to 4) in the Markov model then have an annual risk of developing ESRD, potentially with dialysis or a transplant (see figure 13 for health states and transitions between them). Transition probabilities to ESRD and to dialysis were taken from Kent et al.

(2015), which reported data on progression of kidney disease from an international (Europe, North America and Australasia) randomised controlled Study of Heart and Renal Protection (SHARP; n=7,246). Transition probabilities relating to kidney transplants were taken from the 2018 UK Renal Registry report.

People can die in all states in the Markov model. The probability of all-cause mortality was the average mortality risk of people discharged from hospital and intensive care (age- and sex-adjusted) for the first 5 years after discharge (Lone et al. 2016), unless health-state specific mortality was higher. After 5 years, the population reverted to general population mortality risks. A scenario analysis investigated longer-term effects on mortality caused by being admitted to intensive care while in hospital.

For details of the Markov model transition probabilities see the diagnostics assessment report, table 22 page 144.

Costs

All costs were included from a UK NHS perspective and were reported as 2017/18 values.

Test costs

The costs of using the tests included the cost of the test itself, equipment needed to run it, staff time to prepare the sample, run the test and interpret the result and training costs (see table 15). In its base-case analysis, the EAG assumed that to use the NephroCheck an Astute 140 Meter would also need to be purchased and included the cost of this. The EAG assumed that the NGAL tests are run on platforms that are already available in hospital laboratories, so the cost of these analysers was assumed to be negligible and was not included in the analysis. A scenario analysis in which no capital costs (including an analyser) or training costs were included for the tests was done.

For details of included staff costs related to using the tests see the diagnostics assessment report on page 145.

Table 15 Test-related costs

Cost per test	NephroCheck	BioPorto NGAL [a]	Abbott NGAL	
			ARCHITECT	Alinity [b]
Platform cost	£0.53	-	-	-
Equipment cost	£49.80	£20.00	£25.71	£28.29
Maintenance/ consumables	£4.23	£1.90	£3.51	£3.51
Staff costs	£37.62	£37.62	£37.62	£37.62
Staff training costs	£0.08	£0.03	£0.03	£0.03
Total cost	**£92.26**	**£59.55**	**£66.87**	**£69.44**

For details see table 24 of the diagnostics assessment report.

[a] Costs assumed to be the same for plasma and urine samples

[b] The Alinity NGAL assay was not included in the base-case analysis because of a lack of data for this assay

Cost of KDIGO bundle

The EAG assumed that the KDIGO care bundle would be applied for an additional 3 days over and above standard care for people who tested positive on the NephroCheck or NGAL tests (based on clinical opinion and consistent with the primary outcome measure from Meersch et al. 2017). Resources included in the care bundle costs included intravenous fluids (including nurse time), nephrologist and pharmacist review time and stopping blood pressure medication. For details see table 25 of the diagnostics assessment report on page 151. The total additional cost of applying the KDIGO bundle was assumed to be £106.36 per person.

Initial decision tree phase costs

Costs related to time in hospital and intensive care were taken from NHS reference costs (2017/18). An excess of £298 per day was applied for people with acute kidney injury in a scenario analysis. Costs of acute RRT while in

hospital were taken from NHS reference costs (2017/18) with the proportion having continuous RRT and intermittent dialysis taken from the 'Adding Insult to Injury' report. For details see page 151 of the diagnostics assessment report.

Longer-term Markov model costs

Outpatient follow-up costs after hospital discharge were taken from Lone et al. (2016), which used a matched cohort analysis from Scottish registries data, using an average of post-intensive care and post-non-intensive care admission costs for the first 5 years. Scenario analysis G investigates the effect of different long-term costs (having acute kidney injury while in hospital affects long-term costs). No annual costs were assumed after 5 years (this is explored in a scenario analysis; see table 27 in the diagnostics assessment report).

In the base case there was no increase in follow-up costs caused by having acute kidney injury in the initial 90-day hospitalisation period. A scenario analysis investigated the effect of added costs in follow up caused by acute kidney injury.

Costs related to chronic kidney disease, dialysis and kidney transplant were taken from Kent et al. (2015; SHARP trial data), NICE guidance and the BNF. For details see the diagnostics assessment report, page 156.

Health-related quality of life and QALY decrements

The EAG updated the searches run in Hall et al. (2018) to identify any additional source of utility data for its model for both the initial phase decision tree (see table 16) and longer-term Markov model (see table 17). The age- and sex-matched EQ-5D UK population norms were calculated using an equation published by Ara and Brazier (2010). These were used to derive age- and sex-adjusted utility multipliers from the raw pooled estimates from

studies, based on the age and sex distribution of the source studies. For details see the diagnostics assessment report, page 158.

For people admitted to intensive care in the initial decision tree phase of the model, the EAG used the utility value of an unconscious patient (-0.40; from Kind et al. 1999). The EAG highlighted substantial uncertainty about this parameter and tested it in a scenario analysis, using an average of this utility and another from a population discharged from intensive care (average utility value of 0.02).

Table 16 Health state utility values used in the initial decision tree phase

Decision tree branch	Utility used in model [a]	Distribution	Source
ICU	-0.40	Normal	Kind et al. (1999)
Ward	0.43	Beta	Hernandez et al. (2014)
Discharge	0.61	Beta	
Death	0	-	-

[a] Calculated using starting cohort age of 63 years and 0.457 proportion of men
For details see table 30 of the diagnostics assessment report

A utility decrement of 0.11 was also applied for people having RRT while in hospital (only applied to people on the ward, not in intensive care because utility here was already very low).

Table 17 Health state utility values used in the longer-term Markov model

Health state		Utility used in model at start [a]	Distribution	Source
After discharge	Year 1	0.66	Beta	Cuthbertson et al. (2010)
	Years 2 to 4	0.69		
	Year 5 onwards	0.67		
CKD (stages 1 to 4)		0.58		Nguyen et al. (2018)
ESRD		0.40		
ESRD (with HD)		0.55		Liem et al. (2008); Ara and Brazier (2010)
ESRD (with PD)		0.56		

[a] Calculated using starting cohort age of 63 years and 0.457 proportion of men

For details see table 32 of the diagnostics assessment report

Abbreviations: CKD, chronic kidney disease; HD, haemodialysis, PD, peritoneal dialysis; ESRD, end-stage renal disease

In addition to assumptions described above, the following assumptions were also applied in the base-case analysis:

- Acute kidney injury can be prevented by earlier NephroCheck or NGAL-guided use of a KDIGO care bundle (for people who would otherwise develop it with standard monitoring alone).
- The NephroCheck biomarkers and NGAL rise at similar times and the earlier identification of emerging kidney injury (relative to serum creatinine and urine output changes) is the same for both tests.
- There are no adverse effects on health caused by a false positive NephroCheck or NGAL test result.
- No adaptions to standard monitoring were made for people testing negative on NephroCheck or NGAL tests (although standard monitoring done alongside would detect acute kidney injury for false negative tests, just at a later time). This was because the EAG assumed that de-escalation of care would not occur solely because of a negative test result.
- Everyone with a positive NephroCheck or NGAL test immediately had a KDIGO care bundle.
- After 5 years post-transplant, mortality reverted to the general population all-cause mortality probability and the annual probability of transplant failure remained as that reported from years 3 to 5 in the UK renal registry.
- The proportion of the cohort with a transplant failure returned to dialysis, where their probability of progressing from ESRD on dialysis to a second transplant was the same as for progressing to the first transplant.

Base-case results

For the purposes of decision making, the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) gained or lost are considered. All results presented are probabilistic, produced from 1,000 simulations.

No evidence for NGAL test-guided implementation of preventative care for acute kidney injury on clinical outcomes was identified. Therefore, the EAG did 2 base cases:

- Base case 1: Using the NGAL test has the same effect as the NephroCheck test to prevent acute kidney injury and reduce severity of the condition if it occurs (based on Meersch et al.).
- Base case 2: Using the NGAL test can only reduce the severity of acute kidney injury (as for base case 1), not prevent it from occurring (NephroCheck effects are unchanged).

Because of uncertainty about the extent of any effect of acute kidney injury on other clinical outcomes, the EAG presented several scenario analyses (B, C and D). This was in addition to the base case varying which outcomes acute kidney injury occurrence (and severity) had an effect on, and the size of this effect. These are summarised in table 18. Scenario C was the most pessimistic (no effect of preventing acute kidney injury, or reducing severity, on clinical outcomes) and scenario D was the most optimistic (full effect of preventing acute kidney injury, or reducing severity, on clinical outcomes). In scenario B, preventing acute kidney injury had no effect on outcomes but reducing the severity of acute kidney injury improved clinical outcomes.

Table 18 Summary of effect of preventing acute kidney injury on outcomes used in the base case and scenarios B, C and D (based on table 33 in the diagnostics assessment report). Empty cells have the same value as the base case. '0' means no effect, '0.5' means partial effect, '1' means full effect

Effect of AKI on clinical outcome	Base case	Scenario B	Scenario C	Scenario D
Proportion of the RR of ICU admission (AKI vs. none) that can be achieved by averting AKI	***0.5***	0	0	1
Proportion of the HR of CKD (AKI vs. none) that can be achieved by averting AKI	***1***	0	0	1

Proportion of the RR of 90-day mortality (AKI vs. none) that can be achieved by averting AKI	***0***	0	0	1
Proportion of the difference in hospital and ICU length of stay (AKI vs. none) that can be achieved by averting AKI	***0.5***	0	0	1
Impact of AKI stage on hospital and ICU length of stay	***Increases by AKI stage***	-	Doesn't vary by AKI stage	-
Impact of AKI stage on the probability of ICU admission	***Increases by AKI stage***	-	Doesn't vary by AKI stage	-
Impact of AKI stage on the probability of developing CKD.	***Increases by AKI stage***	-	Doesn't vary by AKI stage	-
Impact of AKI stage on the probability of 90-day mortality	***Same for all AKI stages***	Increases by AKI stage	-	Increases by AKI stage

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; RR, relative risk

Full results from base case 1 and scenarios can be found in table 34 of the diagnostics assessment report. For cohort traces from the Markov model (base case configuration) see figure 34 of diagnostics assessment report.

Table 19 Cost-effectiveness results (probabilistic) for base case 1

Test	Total cost	Total QALYs	ICER [probability cost effective at £20,000 per QALY gained]	
			Fully incremental	Versus standard monitoring
BioPorto NGAL (urine)	£22,887	6.07332	- [43.5%]	Dominant [54.6%]
BioPorto NGAL (plasma)	£22,900	6.07332	£2,694,918 [11.1%]	Dominant [47.6%]
Standard monitoring only	£22,901	6.07296	Dominated [45.1%]	-
ARCHITECT NGAL	£22,912	6.07328	Dominated [0.1%]	£32,131 [41.4%]
NephroCheck	£22,938	6.07332	Dominated [0.2%]	£101,456 [31.9%]

The EAG commented that it was likely that the true estimate of cost effectiveness of the tests was somewhere between those produced by scenarios C and D.

Scenario C assumed no benefit of reducing acute kidney injury occurrence or severity on clinical outcomes (most pessimistic; see table 18). Standard care dominated all the tests in this scenario, with all tests having 0% probability of being cost effective at a maximum acceptable ICER of £20,000 per QALY gained.

Scenario D assumed full benefit of reducing acute kidney injury occurrence or severity on clinical outcomes (most optimistic; see table 18). Results are shown in table 20.

Table 20 Cost-effectiveness results (probabilistic) for scenario D (in base case 1)

Test	Total cost	Total QALYs	ICER [probability cost effective at £20,000 per QALY gained]	
			Fully incremental	Versus standard monitoring
Standard monitoring only	£22,959	6.08383	- [0.7%]	-
BioPorto NGAL (urine)	£23,013	6.11006	£2,052 [40.7%]	£2,052 [99.3%]
BioPorto NGAL (plasma)	£23,028	6.11091	£17,702 [47.5%]	£2,538 [99.1%]
ARCHITECT NGAL	£23,031	6.10799	Dominated [1.1%]	£2,981 [98.8%]
NephroCheck	£23,065	6.11064	Dominated [10.0%]	£3,955 [97.7%]

Analysis of alternative scenarios

In addition to scenarios B, C and D, the EAG did further scenario analyses in the base-case model to investigate parameter uncertainty (for details see table 33 of the diagnostics assessment report).

An overview of the additional scenarios is shown in table 21. A brief summary of cost effectiveness is also provided compared with standard monitoring only, for simplicity. In fully incremental analyses, the BioPorto NGAL test generally had the most favourable cost-effectiveness results of all the interventions (for results see table 33 in the diagnostics assessment report).

Table 21 Summary of scenario analyses and results for base case 1

Scenario	Effect on base case 1 cost-effectiveness results (versus standard monitoring)
Scenario E: Same as scenario D but with an additional cost applied in the initial decision tree for people with acute kidney injury while in hospital	Tests dominate standard monitoring or have a low ICER (NephroCheck)
Scenario F: No additional costs for RRT	BioPorto NGAL (urine) dominates

applied	standard monitoring, other tests have ICERs of over £17,500 per QALY gained
Scenario G: Having acute kidney injury while in hospital (initial decision tree phase) affected long-term costs and mortality risk in the longer-term Markov model	All tests dominate standard monitoring
Scenario H: The increased risk of developing chronic kidney disease caused by having acute kidney disease in hospital lasted for the rest of a person's life (rather than for just 1 year)	All tests dominate standard monitoring
Scenario I: Alternative discount rate for QALYs and costs used (0%)	The BioPorto NGAL tests (urine and plasma) dominate standard monitoring. The other tests have ICERs over £9,000 per QALY gained
Scenario J: Alternative discount rate for QALYs and costs used (6%)	BioPorto NGAL (urine) dominates standard monitoring. The other tests have ICERs of over £16,000 per QALY gained
Scenario K: Alternative prevalence of acute kidney injury used, based on studies included in systematic review: 23.2% (9.2% in base case)	All tests dominate standard monitoring
Scenario L: Tests were used twice (double the cost applied)	Tests all have ICERs over £110,000 per QALY gained compared with standard monitoring
Scenario M: Additional risk of 90-day mortality as a result of a false positive NephroCheck or NGAL test	Tests have lower incremental costs and QALYs compared with standard monitoring (South-West quadrant of cost-effectiveness plane); ICERs would not usually be considered cost effective
Scenario N: Excluded capital and training costs for tests	BioPorto NGAL (urine) dominates standard monitoring; other tests have ICERs of between £2,200 and £106,000 per QALY gained
Scenario O: Higher utility value (0.02) used for people in intensive care in decision tree phase (-0.40 used in base case)	BioPorto NGAL (urine) dominates standard monitoring; other tests have ICERs of between £1,500 and £118,000 per QALY gained
Scenario P: General population data was used for long-term outpatient utility (rather than utilities from people who had been admitted to hospital or intensive care)	BioPorto NGAL (urine) dominates standard monitoring; other tests have ICERs of between £1,100 and £65,000 per QALY gained

In **scenario Q**, the EAG used alternative accuracy estimates from studies that enrolled children only. Data were only available for the ARCHITECT NGAL and BioPorto NGAL (urine) tests (see table 22). The EAG cautioned that limited accuracy data for the tests in this population were available and that, because of lack of data, the model was not configured for a paediatric population, but used parameters from an adult population. Therefore, it considered the analysis to be exploratory only.

Table 22 Cost-effectiveness results (probabilistic) for scenario Q (for base case 1) – using accuracy estimates for children

Test	Total cost	Total QALYs	ICER [probability cost effective at £20,000 per QALY gained]	
			Fully incremental	Versus standard monitoring
Standard care (Scr)	£22,952	6.07678	- [55.1%]	-
ARCHITECT NGAL	£22,957	6.07709	£15,835 [24.2%]	£15,835 [43.3%]
BioPorto NGAL (urine)	£22,968	6.07713	£260,525 [20.6%]	£45,510 [40.4%]

For **base case 2**, the NGAL tests all had worse cost-effectiveness results than base case 1 because they were assumed to have no effect on preventing acute kidney injury.

Cost-effectiveness acceptability curves

For the cost-effectiveness acceptability curves for the 2 base cases see figures 35 and 36 of the diagnostics assessment report.

Subgroup analyses

The EAG did 2 subgroup analyses, based on using accuracy data for the tests from the cardiac surgery and critical care populations separately (data from

these settings were pooled for the base-case analysis; see table 10). All other parameters in the model were unchanged.

For the critical care subgroup, pooled sensitivity and specificity values were similar to those used in the base case (most identified studies were done in this setting). Cost-effectiveness results were therefore also similar to the base case. For the diagnostic accuracy data used for this subgroup see table 36 of the diagnostics assessment report and table 37 of the report for the cost-effectiveness results.

For the cardiac surgery subgroup, only single studies were available to inform sensitivity and specificity estimates for each test (table 23). Cost-effectiveness results are shown in table 24.

Table 23 Diagnostic accuracy data used for cardiac surgery subgroup

Test parameter		Mean value (95% confidence interval)	Source
NephroCheck (***urine***)	Sensitivity	0.31 (0.09 to 0.61)	Cummings et al. (2019)
	Specificity	0.78 (0.74 to 0.82)	
ARCHITECT NGAL (***urine)***	Sensitivity	0.46 (0.33 to 0.59)	Yang et al. (2017)
	Specificity	0.81 (0.79 to 0.83)	
BioPorto NGAL (***urine***)	Sensitivity	0.78 (0.72 to 0.84)	Parikh et al. (2017)
	Specificity	0.48 (0.42 to 0.54)	
BioPorto NGAL (***plasma***)	Sensitivity	0.62 (0.49 to 0.74)	Hall et al. (2018)
	Specificity	0.78 (0.75 to 0.81)	

Table 24 Cost-effectiveness results (probabilistic) for cardiac surgery subgroup

Test	Total cost	Total QALYs	ICER [probability cost effective at £20,000 per QALY gained]	
			Fully incremental	Versus standard monitoring
Standard monitoring	£22,912	6.07358	- [54.2%]	-
BioPorto NGAL (plasma)	£22,914	6.07387	£7,822 [17.8%]	£7,822 [45.5%]
BioPorto NGAL (urine)	£22,922	6.07394	£112,645 [28.0%]	£29,127 [41.9%]
ARCHITECT NGAL (urine)	£22,938	6.07380	Dominated [0.0%]	£120,552 [30.1%]
NephroCheck	£22,984	6.07373	Dominated [0.0%]	£484,944 [9.6%]

3 Summary

Clinical effectiveness

The EAG commented that the included studies varied in clinical settings, the time at which samples were collected, the definition of acute kidney injury and the time in which it had to occur, and the number of events. NGAL studies also varied considerably in the threshold value used for a positive result. The EAG stated that it had limited confidence in the validity and reliability of the results.

In general, the NephroCheck Test had higher sensitivity, but lower specificity than the other tests (see table 25). The pooled sensitivity of the BioPorto NGAL test was similar when urine and plasma were assessed, but the pooled specificity was higher for the assay when used with urine.

Table 25 Summary of pooled sensitivity and specificity values from meta-analyses

Test	Setting	Sensitivity	Specificity
NephroCheck (urine)	Critical care	0.83	0.51
	All	0.75	0.61
ARCHITECT NGAL (urine)	Critical care	0.70	0.72
	All	0.67	0.72
BioPorto NGAL (urine)	Critical care	0.72	0.87
	All	0.73	0.83
BioPorto NGAL (plasma)	Critical care	0.76	0.67

Most studies were done in a critical care setting. Too few studies were done after cardiac or major non-cardiac surgery for meta-analysis to be done for these settings alone. The EAG highlighted that results were notably different for studies with low prevalence of acute kidney injury.

Only 5 studies with the ARCHITECT NGAL test and 2 studies with the BioPorto NGAL test reported accuracy estimates from children.

Limited data were available on the ability of the tests to predict relevant clinical outcomes. Only a few studies were available for each test in each clinical setting so this limited the EAG's ability to do pooled analyses.

Cost effectiveness

The cost-effectiveness results were very sensitive to the extent that preventing, or reducing the severity of, acute kidney injury was assumed to affect clinical outcomes (admission to intensive care, length of stay in hospital or intensive care, 90-day mortality, need for RRT in hospital, effect on developing chronic kidney disease).

When assuming no benefit of preventing acute kidney injury (or reducing its severity) on clinical outcomes, the tests were dominated by standard monitoring (scenario C). When assuming that the benefit of preventing acute kidney injury (or reducing its severity) on clinical outcomes was the highest level possible ('full associative effect'; scenario D) the ICERs of the tests

compared with standard monitoring were all less than £4,000 per QALY gained (in base case 1).

Incremental differences between tests were generally small, particularly for incremental QALYs.

If acting on the results of the NGAL tests was assumed not to be able to prevent acute kidney injury (just to reduce its severity), cost-effectiveness estimates of the NGAL tests were substantially worse (base case 2).

For scenarios assessing the effect of additional parameters (that is, not relating to 'associative effect'; scenarios E to P), changes to several parameters improved the cost effectiveness of the tests:

- Increasing long-term costs and risk of mortality in the Markov model (scenario G) for people who were admitted to intensive care while in hospital (in the decision tree phase).
- Extending the time that having acute kidney injury while in hospital increases the risk of developing chronic kidney disease for the rest of a person's life (rather than for just 1 year; scenario H).
- Increasing the prevalence of acute kidney injury to 23% (from 9.2% in base case; scenario K).

Assuming false positive tests increase mortality (scenario M) worsened the cost effectiveness of the tests.

The EAG commented that the results were highly uncertain, with no clear optimal test. When the NGAL tests were assumed to be as effective as NephroCheck at preventing acute kidney injury (base case 1), the BioPorto NGAL tests generally had the greatest probability of cost effectiveness. This was because they were the cheapest and had slightly better diagnostic accuracy estimates from the meta-analyses. In contrast, NephroCheck was estimated to have poorer specificity compared with the NGAL tests, so generated additional costs of treatment for people with false positive tests.

However, if acting on the results of NGAL tests was assumed not to prevent acute kidney injury (base case 2), the probability of NephroCheck being the most cost-effective test rose considerably.

Few studies were available to inform estimates of test accuracy when used for children (and only for the ARCHITECT and BioPorto NGAL tests). The EAG cautioned that the scenario analysis using these estimates (scenario Q) should only be considered as speculative, because of a lack of data to inform model parameters for this population.

4 Issues for consideration

Clinical effectiveness

There was considerable heterogeneity in sensitivity and specificity results. The included studies varied considerably in terms of clinical setting, timing of sample collection, definition of acute kidney injury, prevalence of acute kidney injury and time of acute kidney injury diagnosis.

The target population for this assessment was people who are critically ill and considered at risk of developing acute kidney injury, who are being assessed for critical care admission. No studies were identified by the EAG in this population. Most included studies enrolled people already admitted to critical care, and only 1 study (that reported sensitivity and specificity) was done in the UK. The characteristics of people admitted to critical care are likely to vary across the world and may not be representative of the target population for this assessment. The EAG commented that it was unclear how well the findings of non-UK heterogeneous studies that are predominantly based in intensive care can be applied to the decision question for this assessment. It also commented that accuracy estimates were quite different for studies with higher and lower prevalence of acute kidney injury.

Studies using NGAL tests used a wide array of different thresholds to define a positive test result. Also, some NGAL studies used absolute urine

concentrations, while others used NGAL concentrations normalised for urine creatinine concentrations. This was likely to have contributed to differences in accuracy estimates between NGAL studies. In addition, the pooled estimate of sensitivity and specificity for the NGAL tests combined data from studies that used different thresholds (these pooled estimates were used in the economic model).

No direct evidence on the effect of using the tests on clinical outcomes was identified.

Cost effectiveness

Because no direct evidence of using the tests on clinical outcomes was identified, the EAG modelled the effect of using the tests to identify people who could benefit from a KDIGO care bundle, the effect of this on preventing or reducing the severity of acute kidney injury (data from Meersch et al.) and then the effect of this on clinical outcomes (using observational data).

The EAG highlighted that the pathways of presentation and care for acute kidney injury are complex. It is uncertain whether people could benefit from preventative treatment if emerging acute kidney injury is identified earlier. Meersch et al. was done in Germany, and it was uncertain whether the intervention assessed (a KDIGO care bundle) or the comparator (standard care in a German hospital) were sufficiently similar to NHS practice to make the results generalisable. People were enrolled in this study after cardiac surgery. The EAG cautioned that data from this study was unlikely to be generalisable to other populations.

In addition, although this study showed a potential benefit of NephroCheck-guided care on reducing acute kidney injury occurrence, no effect on other clinical outcomes was seen (length of stay in hospital or intensive care, need for RRT in hospital and 90-day mortality).

In its base-case model, the EAG had to make assumptions about which clinical outcomes (such as need for intensive care, length of intensive care or hospital stay, risk of 90-day mortality, developing chronic kidney disease) were affected by developing acute kidney injury, or a more severe form of the condition, or both. The EAG commented that the extent of any causal relationship between acute kidney injury and these clinical outcomes is uncertain and controversial.

Changing which clinical outcomes acute kidney injury occurrence, or severity, can affect in the model had a large impact on the cost effectiveness of the tests. For example, in scenarios B and C (in base case 1) which have a lower level of effect of acute kidney injury on clinical outcomes, the tests were either dominated by standard monitoring or had a relatively high ICER (over £45,000 per QALY gained). In contrast, for scenario D, which assumed a greater effect of acute kidney injury on clinical outcomes, the tests all had relatively low ICERs compared with standard care (less than £4,000 per QALY gained).

Across the scenarios (done in base case 1) the BioPorto NGAL tests generally had the greatest probability of cost effectiveness. However, the sensitivity and specificity estimates used in the model for the NGAL tests were produced by pooling data from studies that used different thresholds for a positive result.

Although published data show that NephroCheck-guided implementation of a KDIGO care bundle has the potential to prevent acute kidney injury, no such data exist for the NGAL tests. The EAG highlighted that the biomarkers used in the NephroCheck test (TIMP-2 and IGFBP-7) measure kidney stress, whereas NGAL measures kidney damage. Therefore, it is uncertain whether the effect of NGAL-guided preventative care on developing acute kidney injury would be the same as for NephroCheck. A second base case, which assumed a reduced effect of the NGAL tests on acute kidney injury (it could only reduce severity, not prevent it occurring), led to far worse cost-effectiveness estimates for the NGAL tests.

Higher prevalence of acute kidney injury also increased the cost effectiveness of the tests (23%; scenario K). A prevalence of 9.2% was used in the base case.

The longer that a patient is at increased risk of chronic kidney disease because they had acute kidney disease in hospital also increased the cost effectiveness of the tests. In the base case it was assumed this lasted for 1 year after discharge (acute kidney injury having occurred in hospital). In scenario analysis H this effect was assumed to last for the rest of a person's life, which caused all the tests to dominate standard monitoring.

The base case assumed no negative effect on health of a false positive result from the tests. However, an additional cost of preventative care with no benefit was incurred. If a false positive test does have an adverse effect on a person's health, for example by unnecessary fluid resuscitation or avoiding nephrotoxic treatments, the base-case analysis may overestimate the cost effectiveness of the tests (see scenario M, which included an additional 90-day mortality risk as a result of a false positive NephroCheck or NGAL test).

The EAG used data from a population register of hospitalisations from the Grampian region in 2003 to define the initial model cohort characteristics, and to estimate how much having acute kidney injury increased the risk of intensive care admission, 90-day mortality and length of stay in hospital. Clinical practice may have changed since 2003. Also, data from this region may not be generalisable to the NHS in England.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Chronic kidney disease is a major risk factor for acute kidney injury. Therefore populations with higher incidence of chronic kidney disease also have higher

incidence of acute kidney injury. These include older people, people with diabetes and certain ethnic groups, for example, people of south Asian family origin. Incidence is unlikely to be affected by using the tests but they may help earlier detection and slowing of disease progression.

The performance of the tests may be affected by inflammation in people who have inflammatory conditions or an infection such as a urinary tract infection. People with chronic kidney disease, diabetes or an inflammatory condition are likely to be protected by the disability provision of the Equality Act 2010.

6 Implementation

Several key considerations for adoption of the tests were highlighted during discussions with expert contributors during scoping.

Clinical experts highlighted uncertainty about what action to take when a test is positive. If used in critical care, people would already be having high intensity monitoring so there may be little benefit to any changes in care. A clinical expert also commented that people being tested for acute kidney injury would have been assumed to be at risk and should already be on a preventative management plan. Clinical experts also highlighted concern about tests producing false positive results, which would mean unnecessary over monitoring of patients with no change in outcome.

Clinical experts also highlighted that if an assay does not run on analysers currently in a hospital's laboratory, there are likely to be issues with space and cost if another company's analyser needs to be installed. Also, external quality assurance and accreditation would be needed if a new biomarker was introduced to a laboratory.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Aberdeen Health Technology Assessment (HTA) Group:

Brazzelli M, Aucott L, Aceves-Martins M et al.

The ARCHITECT and Alinity urine NGAL assays, urine NephroCheck test, and urine and plasma NGAL tests to help assess the risk of acute kidney injury for people who are being considered for admission to critical care. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2019.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers of technologies included in the final scope:

- Abbott Diagnostics
- BioMerieux
- BioPorto Diagnostics A/S
- Ortho Clinical Diagnostics

Other commercial organisations:

- None

Professional groups and patient/carer groups:

- British Renal Society
- Institute of Biomedical Sciences
- Faculty of Intensive Care Medicine
- Renal Association

- Royal College of Physicians
- Vasculitis UK

Research groups:

- None

Associated guideline groups:

- None

Others:

- Department of Health and Social Care
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Acute kidney injury
Acute kidney injury is a condition that affects the structure and function of the kidneys. It can be caused by many different conditions and is defined based on serum creatinine levels and urine output.

Chronic kidney disease
A long-term condition characterised by a loss of kidney function over time. It is normally asymptomatic.

Creatinine
Creatinine is the waste product of creatine, which the muscles use to make energy. Creatinine is excreted in the urine by the kidneys. High levels in the blood might indicate that the kidneys are not working correctly.

End-stage renal disease
End-stage renal disease occurs when chronic kidney disease reaches an advanced state. The kidneys do not work well enough to support the body, therefore dialysis or a kidney transplant is needed.

Glomerular filtration rate
A measure of the flow rate of blood passing through the kidneys.

Nephrotoxic drugs
Drugs that can cause damage to the kidneys.