Aberdeen HTA Group

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

Erratum to the EAG Report

Date completed 25 November 2019

Does not contain CIC/AIC

This document is intended to replace the following pages of the original EAG assessment report for *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,* which contained minor inaccuracies:

- 21 (amendment of text to clarify that creatinine in the blood and urine output are used by health professionals to decide whether AKI is present)
- 24 (changing the text from "no evidence" to "limited evidence" to acknowledge the findings in the Gocze et al. study);
- 61 (amendment of text to ensure consistency of methods and results sections regarding the number of studies that provided the AUC values for prediction of mortality and RRT);
- 71 (addition of a table footnote);
- 77 (correction of the sensitivity and specificity values for the Di Leo 2018 study)
- 78 (correction of the number of NephroCheck studies in the critical care setting reported in the text);
- 79 (correction of the total number of participants in the seven NephroCheck studies)
- 86 (amendment of text regarding the timing of measurement for the Cho 2014 study)
- 128 (changing the text from "no evidence" to "limited evidence" to acknowledge the findings in the Gocze et al. study);
- 136 (clarification of text regarding the Meersch et al.'s study);
- 140 (amendment of text to ensure consistency of methods and results section regarding the use of Sawhney et al.'s data for HR of CKD);
- 141 (correction of typographical error and amended title heading in Table 21);
- 145 (amendment to the text to refer to the different VITROS instruments rather than a specific instrument);
- 176 (correction of reporting error in Table 34, scenario 1K (Column: "ICER vs. SC");
- 177 (correction of typographical error in Table 34 - Scenario 1M)
- 184 & 185 (correction of reporting error in Table 35 - Scenario 1M)
- 207 (amendment to the text regarding the uncertainty of the effects on health outcomes)

The amended pages follow in order of page number below.

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 and the urine output are 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 56 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.

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 limited 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,

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, 11 studies provided suitable data on prediction of mortality in critically ill patients at risk of AKI, and four 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-eight studies were conducted in Europe (4 in the UK, 6 in Germany, 3 in Italy, 3 in Spain, 2 in Greece, 2 in Denmark, 1 in the Netherlands, 1 in France, 1 in Belgium, 1 in France and Belgium, 1 in Finland, 1 in Norway, 1 in Switzerland and 1 in European countries); 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); 2 in North America and Europe; and 1 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.

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 1.4 years (0.2-2.7); 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 398	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);

‡ The Seitz 2013 study included also 20 adolescents or adults.

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 (0.09, 0.61)	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	0.64	0.56	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.

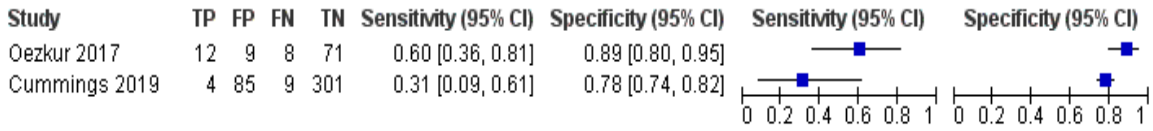

Figure 5 Forest plots of sensitivity and specificity for NephroCheck for detection of AKI in adults - cardiac surgery setting

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

Critical care - mixed population

Five 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).

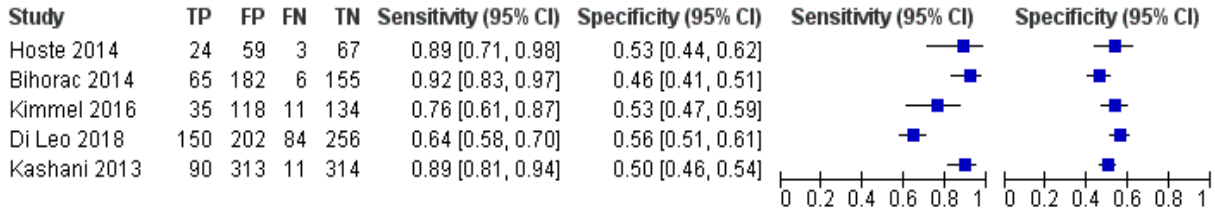

Figure 6 Forest plots of sensitivity and specificity for NephroCheck for detection of AKI in adults - critical care setting

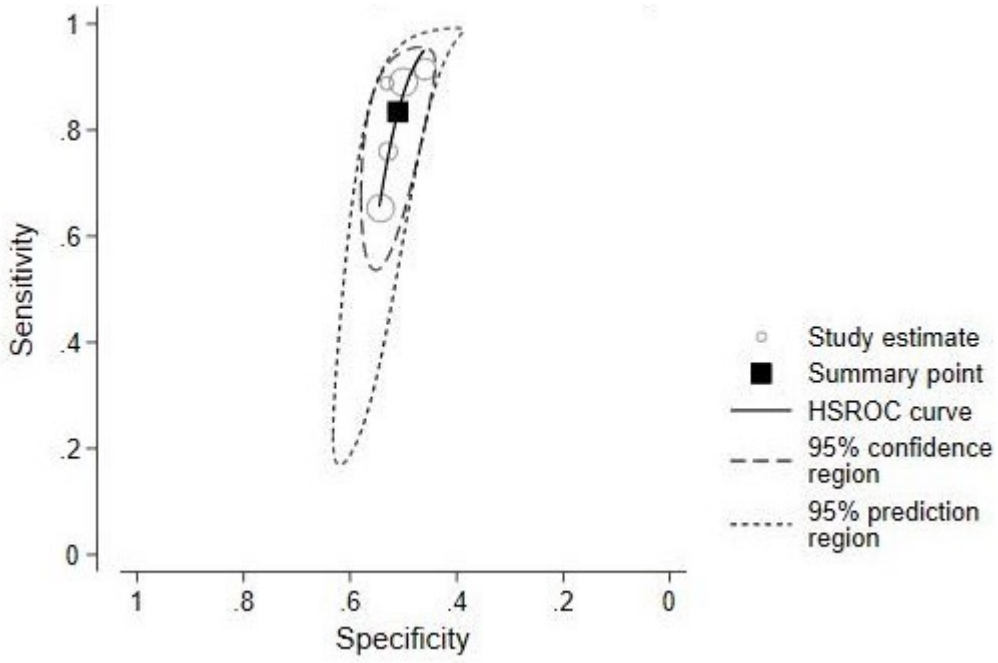

Figure 7 HSROC for NephroCheck studies - critical care setting

Figure 8 shows the forest plots of sensitivity and specificity estimates for all NephroCheck studies (2778 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

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 12 hours after 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.

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 limited 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

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. It is unclear whether knowledge of the NephroCheck test result was 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 (Göcze 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

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 US 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. An alternative source reporting the HR for the association between AKI and CKD that is constant across all AKI stages, is 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	Parameter value	HR	Standard error	Distribution	Source
Prevalence of CKD (starting proportion)	5,935	53,691	0.1105	--	--	Beta	Grampian data
Baseline incidence of CKD[A]	--	--	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]

[A] Note: rate converted to probability for application in the economic model.

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.

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 Immunodiagnostic Systems, although currently, there is a limited installed base in UK hospitals (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

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	6.07086	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	£48,020,759	£56,351	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	--	--	Dominant	42.3%	79.0%
Test 2 (NGAL plasma - BioPorto)	£23,055	£5	5.85837	0.00002	£256,153	Dominant	30.7%	77.3%

Test 4 (NGAL urine - ARCHITECT)	£23,084	Dominated	5.85827	Dominated	Dominated	Dominant	1.2%	75.2%
Test 1 (Nephrocheck)	£23,093	£39	5.85837	0.00000	£20,956,862	Dominant	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)	£22,884	Dominated	6.07564	Dominated	Dominated	£227,155	0.1%	19.2%
Test 1 (Nephrocheck)	£22,936	£71	6.07567	0.00000	£69,489,954	£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 1 (Nephrocheck)	£22,522	--	5.93563	--	--	£3,072	0%	0%
Test 2 (NGAL plasma - BioPorto)	£22,545	£22	5.95376	0.01813	£1,240	£3,344	0%	0%
Test 4 (NGAL urine - ARCHITECT)	£22,630	£86	5.97629	0.02253	£3,814	£3,238	0%	0%
Test 3 (NGAL urine - BioPorto)	£22,718	£88	6.01026	0.03397	£2,582	£3,576	0.1%	0.10%
Standard care (Scr)	£22,954	£235	6.07608	0.06582	£3,576	--	99.9%	--
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%

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)	£22,746	--	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	£1,370,281	0.0%	0.7%
Scenario 2M: Apply an additional risk of mortality to those with a false positive test (RR=1.5)								
Test 1 (Nephrocheck)	£22,533	--	5.93052	0.00000	--	£3,062	0%	0%
Test 2 (NGAL plasma - BioPorto)	£22,632	£99	5.94584	0.01532	£6,478	£2,644	0%	0%
Test 4 (NGAL urine - ARCHITECT)	£22,715	£83	5.97024	0.02440	£3,389	£2,464	0%	0%
Test 3 (NGAL urine - BioPorto)	£22,809	£94	6.00383	0.03360	£2,801	£2,297	0.0%	0.00%
Standard care (Scr)	£22,963	£155	6.07124	0.06740	£2,297	--	100.0%	--

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 regarding effects on health outcomes, particularly when used in the pre-critical care setting. 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 where 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