NICE advice

NephroCheck test to help assess the risk of acute kidney injury in critically ill patients

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is the NephroCheck (including VITROS NephroCheck) test. It is an in vitro diagnostic test used to measure urinary biomarkers of kidney injury as an aid in detecting acute kidney injury.
- The **innovative aspects** are that NephroCheck is claimed to predict the risk of kidney injury earlier than current clinical assessment and testing methods.
- The intended **place in therapy** would be in addition to standard care. It would be most likely to be used in critically ill patients.
- The **main points from the evidence** summarised in this briefing are from 3 validation and diagnostic accuracy studies (n=1,262) and 2 randomised controlled trials (n=397). The evidence suggests that an increase in urinary TIMP2 and IGFBP7 in the critically ill may be a predictor of acute kidney injury risk.
- **Key uncertainty** is that there are no studies comparing NephroCheck-guided implementation of preventive care with standard NHS practice.
- The **cost** of a NephroCheck test cartridge is £49.80 (excluding VAT; not including the cost of the platform for the test). This would represent an additional cost compared with standard clinical assessment. This might be offset if early recognition of acute kidney injury were to result in less resource-intensive preventive care and so reduce the costs of managing acute kidney injury.

The technology

The NephroCheck test (Ortho Clinical Diagnostics) measures urinary levels of tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7). The test is intended to be used in the early detection of acute kidney injury (AKI) because these markers are thought to be involved in the development of renal tubule injury. The company claims that TIMP-2 and IGFBP7 have an additive predictive value if used together.

The test procedure involves adding fresh urine samples to a buffer mixed with a fluorescent antibody conjugate. The sample is then applied to a cartridge and inserted into the platform for incubation, reading, result calculation and result display. The plastic cartridge is single use and contains sandwiched immunoassays for TIMP-2 and IGFBP7. It has a shelf life of 52 weeks and must be used on 1 of 2 specified platforms, either:

- NephroCheck test cartridge on a benchtop instrument (Astute140Meter) or
- VITROS NephroCheck test cartridge on a laboratory instrument (VITROS 3600 Immunodiagnostic System or VITROS 5600 Integrated System).

The procedure takes about 20 minutes and the output is a single number called the AKI risk score. The test score is derived from multiplying the concentrations of the 2 biomarker levels. An AKI risk score of 0.3 or less indicates a low risk of developing moderate to severe (AKI stage 2 and AKI stage 3) AKI within 12 hours of the assessment, while an AKI risk score of greater than 0.3 suggests a high risk of developing moderate to severe AKI within 12 hours.

Innovations

The company claims that the biomarkers measured by the NephroCheck test predict kidney injury earlier than current clinical assessment and tests. This enables appropriate intervention that may prevent progression to a more severe injury. The test differs from current markers of renal injury in that the 2 markers are claimed to be less likely to be elevated by common comorbidities such as diabetes, chronic kidney disease and sepsis.

Current care pathway

The definition of AKI covers a wide spectrum of injury and is typically characterised by increased serum creatinine (SCr) levels and decreased urine output. Attempts at defining and staging AKI as a set of functional criteria have led to the following classifications:

- RIFLE (risk, injury, failure, loss of kidney function, end-stage kidney disease)
- AKIN (Acute Kidney Injury Network)
- KDIGO (Kidney Disease: Improving Global Outcomes).

Early diagnosis of AKI remains a challenge; the NICE guideline on acute kidney injury: prevention, detection and management, which is being updated, puts emphasis on early intervention and stresses the importance of risk assessment and prevention. The guideline recommends using a multi-parameter approach including clinical indicators of functional decline such as raised SCr levels, estimated glomerular filtration rate (eGFR), reduced urine output and other factors such as age, use of nephrotoxic drugs and comorbidities to identify at-risk patients. Patients considered to be at risk are offered preventive therapy.

Increased SCr levels and reduced urine output are consequences of an earlier injury to the kidney and may not manifest for up to 48 hours after the injury has occurred.

It is suggested that TIMP-2 and IGFBP7 levels rise rapidly early in the process of injury to kidney cells, allowing earlier intervention when increased levels are found.

NICE has published a medtech innovation briefing on the NGAL test for early diagnosis of AKI.

Population, setting and intended user

The NephroCheck test system is intended to be used in addition to clinical evaluation and standard diagnostic tests, such as serum creatinine, as an aid to assess the risk of moderate or severe AKI. It is most likely to be used in critically ill patients, including those who have had major surgery. The test is intended to be done in a laboratory by a trained technician, or in a near-patient setting by a trained healthcare professional.

Costs

Technology costs

The VITROS 3600 Immunodiagnostic and VITROS 5600 integrated laboratory systems can be used for a variety of tests; it is not anticipated that a hospital will purchase either of these platforms solely to use NephroCheck. If neither of the laboratory systems, or an Astute140 meter is available, a hospital adopting the test is likely to purchase the benchtop Astute140, which costs £3,000 excluding VAT. Each single use NephroCheck cartridge costs £49.80 excluding VAT.

Resource consequences

NephroCheck would be an additional cost compared to standard diagnostic testing for AKI. These costs may be offset if early detection resulted in appropriate nephro-protective care and avoided resource-intensive treatments such as renal replacement therapy. Further cost savings may arise from avoiding unnecessary preventive care in patients not at risk, and so avoiding the cost of managing any adverse events arising from this. There is no published economic evidence to support this. Training for laboratory staff is provided by the company.

Currently, 3 NHS organisations have used the NephroCheck test.

Regulatory information

The NephroCheck test system is CE marked as follows:

- NephroCheck test/VITROS NephroCheck test: CE marked (non-annex II/general/GIVD [others]).
- Astute140 Meter: CE marked (non-annex II/general/GIVD [others]).
- VITROS 3600 Immunodiagnostic System: CE marked (non-annex II/general/GIVD [others]).
- VITROS 5600 Integrated System: CE marked (non-annex II/general/GIVD [others]).

Four manufacturer field safety notices for this technology were identified but have been resolved.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

No equality issues were identified.

Clinical and technical evidence

A literature search was carried out for this briefing in line with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Five studies are summarised in this briefing with a total of 1,659 critically ill patients admitted to an intensive care unit (ICU). The evidence suggests that increased levels of TIMP-2 and IGFBP7 can predict the risk of acute kidney injury (AKI) and that NephroCheck-guided intervention can reduce the incidence of moderate to severe AKI in critically ill patients. Evidence in 4 studies was generated using the NephroCheck test on a benchtop platform.

Table 1 summarises the clinical evidence as well as its strengths and limitations.

An NIHR HTA-funded systematic review (Hall et al. 2018) assessed a variety of in vitro diagnostic tests, including NephroCheck, for early detection of AKI in ICU patients. This review concluded that using in vitro diagnostic tests in ICU patients could potentially improve patient care. A meta-analysis done as part of the review highlighted limitations arising from between-study heterogeneity. Overall the evidence base was limited because there is no standard definition of AKI and there was a variation in the time of testing.

Overall assessment of the evidence

Diagnostic accuracy and validation

In the included studies, AKI was defined based on a variety of classifications: RIFLE, KDIGO and AKIN. Irrespective of the definition used, the 3 validation studies (Kashani et al. Bihorac et al. and Cuartero et al.) found that an increase in urinary IGFBP 7 and TIMP2 above a specified cut-off point is associated with an increased risk of AKI. However, these studies have not shown that a rise in urinary TIMP-2 and IGFBP7 is specific to the presence of AKI, considering that TIMP-2 and IGFBP7 levels can increase because of a variety of cellular trauma including oxidative stress, ultraviolet radiation, drugs and toxins.

A test specificity of ~50% for the NephroCheck test at a pre-selected cut-off of 0.3 suggests that ~50% of AKI negative patients would have a false-positive result and receive preventive care. This

may be an improvement from current standard care, where people who do not have AKI receive unnecessary preventive measures.

Clinical effectiveness and implementation

The Meersch (2017) and Gocze (2017) studies assessed the clinical effectiveness of implementing the KDIGO care bundle in cardiac and non-cardiac surgery patients assessed as being at increased risk of developing AKI based on TIMP-2·IGFBP7 of greater than 0.3. Results of both trials show that NephroCheck-guided care significantly reduced the incidence AKI in the intervention arm. However there was a non-significant difference between the intervention and control arms of both trials for the need for renal replacement therapy and mortality and major adverse kidney events by 30 days. It remains uncertain if reducing AKI incidence translates into any patient or system benefits.

A significant number of further studies are planned or in progress.

Table 1 Summary of selected studies

Kashani et al. (2013)	
Study size, design and location	A prospective multicentre observational study across North America and Europe. This study was in 2 phases. Phase 1 was the discovery of novel biomarkers in adults admitted in ICU with at least 1 risk factor for AKI. Phase 2 (Sapphire study) was the validation phase involving 744 adults admitted in ICU with critical illness and no evidence of AKI at the time of enrolment.
Intervention	NephroCheck test on the benchtop instrument at a test cut-off of >0.3, referenced against clinical outcome of confirmed AKI as classified by KDIGO staging.

Key outcomes	In the discovery phase, urinary IGFBP7 and TIMP2 emerged as the best-performing biomarkers from 340 plasma and urinary markers examined (AUC=0.77 and 0.75, respectively, for RIFLE-I/F within 12 to 36 hours). The AUC for IGFBP7 and TIMP2 was significantly greater ($p<0.002$) than the AUC of previously known biomarkers (urine and plasma NGAL, plasma cystatin-C, and KIM-1, IL-18, pi-GST, and L-FABP in the urine) of AKI. Based on an analysis done for 728 patients in the validation cohort, 101 (14%) patients met the primary endpoint of moderate or severe AKI (11%-KDIGO stage 2 and 2.5% KDIGO – stage 3) within 12 hours. 218 (30%) patients developed AKI within 7 days (22% KDIGO stage 2 and 8% KDIGO stage 3) and 49 (6.7%) patients had renal replacement therapy during hospital stay. A total of 121 (17%) patients died before hospital discharge truncated at 30 days, 161 subjects (22%) met the MAKE30 endpoint.
Strengths and limitations	This large multicentre trial discovered new biomarkers and validated them in separate patient populations. Laboratory technicians were blinded to clinical data and reasons for loss to follow up were clearly stated. The study was funded by the manufacturer of the NephroCheck Test system (Astute Medical).
Bihorac et al. (2014)	
Study size, design and location	A prospective multicentre study of 420 critically ill patients admitted to both surgical and medical ICUs, with an indwelling urinary catheter in the US.
Intervention	NephroCheck test on the benchtop instrument at a test cut-off of >0.3, referenced against clinically confirmed AKI as judged by an independent clinical adjudication committee (CAC) of 3 nephrologists.

Key outcomes	The primary endpoint was the ability of urinary TIMP2 and IGFBP7 to predict moderate to severe AKI within 12 hours of test measurement as judged by the CAC. Of the 408 patients evaluated, 71 (17.4%) reached the key endpoint. The CAC agreed on the diagnosis of AKI in 94% of cases. Inter-rater reliability was excellent, Fleiss' Kappa: 0.86 (95% CI 0.80 to 0.91; p<0.001). Median urinary TIMP2 IGFBP7 was significantly higher in critically ill patients diagnosed with AKI 1.6 (0.7 to 2.8) than those without 0.3 (0.2 to 0.8), p<0.001. At a pre-selected cut-off of 2.0, specificity was 95% (95% CI 93 to 97) and sensitivity was 37% (95% CI 26 to 47). At a pre-selected cut-off of 0.3 sensitivity was 92% (95% CI 85 to 98), specificity was 46% (95% CI 41 to 52). Patients with TIMP2 IGFBP7 between 0.3 and 2.0 had 5 times more risk for AKI (95% CI 3 to 17) than critically ill patients with results below ≤0.3. Patients with test results greater than 2.0 had 17 times the risk for AKI (95% CI 9 to 54).
Strengths and limitations	This study was sufficiently powered for the endpoint and had a complete follow-up. The adjudication committee and laboratory technicians were blinded to the results of the test. Adjudication was based both on the test and a range of other clinical data. The study was funded by the company.
Cuartero et al. (2017)	
Study size, design and location	A prospective observational study of 98 critically ill patients with or without sepsis admitted to ICU with an expected stay of at least 48 hours. Spain.
Intervention	NephroCheck test on the benchtop instrument at a test cut-off of >0.3, referenced against clinical outcome of confirmed AKI as classified by AKIN staging.

Key outcomes	AKI was classified in this study based on the AKIN classification. Test result scores of TIMP2 IGFBP7 were significantly higher in patients with AKI (1.03, IQR 0.38 to 3.29) compared to those without AKI (0.24, IQR 0.11 to 0.48; p<0.001). These differences were not related to the presence of sepsis. Patients who developed AKI had higher median test result scores (1.05 [IQR 0.41 to 2.31] for patients without sepsis and 0.98 [IQR 0.36 to 3.94] for patients with sepsis) than those without AKI (0.21 [IQR 0.10 to 0.40] in non-septic patients and 0.32 [IQR 0.15 to 0.63] for those with sepsis) with p<0.001 between subgroups with and without AKI. In patients with high TIMP2 IGFBP7 test result >2.0, there was a 3.15-fold risk for AKI and a 1.85-fold risk that AKI would be AKIN ≥2.
Strengths and limitations	In this study healthcare providers were blinded to the test results. This study had a small sample size and was funded by the company.
Meersch et al. (2017)	
Study size, design and location	A single-centre unblinded randomised study of 276 adults with an increased AKI risk (as measured by increased TIMP2 IGFBP7 levels) after cardiac surgery in Germany.
Intervention Comparator	NephroCheck-guided implementation of the KDIGO care bundle. Standard care for AKI prevention.
Key outcomes	The primary endpoint was the incidence of AKI as defined by KDIGO guidelines within the first 72 hours after surgery. There was a significantly lower incidence of AKI 72 hours after surgery in the intervention group than in the control (55.1% versus 71.7%, p=0.004). Within this, the incidence of moderate to severe AKI was significantly lower in the intervention group (29.7% versus 44.9%, p=0.009). The implementation of the bundle resulted in significantly improved hemodynamic parameters at different time points (p<0.05), less hyperglycaemia (p<0.001) and use of ACEi/ARBs (p<0.001) compared to controls. At 30, 60 and 90 days of follow-up there was no significant difference in requirement for RRT, all-cause mortality, MAKE, ICU length of stay and hospital length of stay between the intervention and control groups.

Strengths and limitations	Randomisation in this study reduces the risk of bias. The study design is suitable to test the effect of the intervention. The study was funded by the manufacturer of the NephroCheck test system (Astute Medical) and was not blinded. Standard care may not be generalisable to the UK.
Gocze et al. 2017	
Study size, design and location	A single-centre unblinded randomised clinical trial of 121 patients with an increased AKI risk after major non-urgent, non-cardiac surgery in Germany.
Intervention Comparator	NephroCheck-guided implementation of the KDIGO care bundle. Standard care for AKI prevention.
Key outcomes	The primary endpoint was the incidence of AKI according to the KDIGO guidelines during the first 7 days after surgery. The difference in the primary endpoint (all stages of AKI) between the intervention group and the control group was not statistically significant (31.7% versus 47.5% p=0.076). However, the incidence of moderate to severe AKI was significantly lower in the intervention group compared to the control group (6.7% versus 19.7%, p=0.035). The hospital length of stay (p=0.036) and the ICU length of stay (p=0.035) were also significantly shorter in the intervention group compared to the control group. There was no significant difference in the need for RRT, in-hospital mortality or MAKE at discharge between the intervention and control groups.
Strengths and limitations	The study was ended prematurely after an interim data analysis indicated planned recruitment (n=138) would not result in a statistically significant difference in the primary outcome. This might affect the size of the effect measured in the primary outcome. There was not direct financial involvement from the company stated in this study, this could minimise any bias towards the outcomes reported. The standard care in this study may not be generalisable to the UK.

Abbreviations: ACEi/ARBs, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AUC, area under the curve; ICU, intensive care unit; IGFBP 7, insulin-like growth factor binding protein 7; IL-18, interleukin-18; KDIGO, Kidney Disease: Improving Global Outcomes; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid-binding protein; MAKE30, Major Adverse Kidney Events by 30 day; NGAL, neutrophil gelatinase-associated lipocalin; pi-GST, pi-glutathione S-transferase; RIFLE-I/F, Risk, Injury, Failure, Loss, End stage; RRT, renal replacement therapy; TIMP 2 metalloproteinase 2.

Recent and ongoing studies

- Variation IGFBP7 Markers and TIMP2 Induced by Injection of Contrast Iodized Drug at the Intensive Care Patient. ClinicalTrials.gov identifier: NCT02881710. Completed in August 2016. Devices: NephroCheck test. Location: France.
- Renal Resistive Index Compared with NephroCheck to Predict Postoperative Acute Renal Failure in Patients Undergoing Cardiac Surgery. ClinicalTrials.gov identifier: NCT02325726. Status: Completed: November 2014. Devices: NephroCheck test. Location: France.
- A pilot study evaluating novel biomarkers of AKI in postoperative patients undergoing major intra-abdominal surgery. ClinicalTrials.gov identifier: NCT02499185. Status: Recruiting. Device: NephroCheck test. Location: Belgium.
- Effectiveness of the NephroCheck to Predict Postoperative Acute Kidney Injury in Patients Undergoing a Transcatheter Aortic Valve Implantation. ClinicalTrials.gov identifier: NCT02976792. Status: Recruiting. Device: NephroCheck test. Location: France.
- Predicting Acute Kidney Injury in Critically Ill Trauma Patients Using Metalloproteinase 2 (TIMP2) and Insulin-like Growth Factor Binding Protein7 (IGFBP 7). ClinicalTrials.gov identifier: NCT02765464 Status: Recruiting. Location: US.
- Influence of individual hemolysis, haptoglobin-genotype and CD 163 Receptor-activity on AKI in cardiac surgery patients. Trial Identifier: DRKS00005457 Status: Recruiting. Location: Germany.
- Biomarker-guided Implementation of the AKI Bundle (PrevAKI-mc). ClinicalTrials.gov identifier: NCT03244514. Status: Recruiting. Device: NephroCheck test. Location: Germany and Italy; UK and Belgium are currently undergoing ethics approval.

- Acute Kidney Injury After Cardiac Surgery (NEPHROCAR). ClinicalTrials.gov identifier: NCT03396770. Status: Recruiting. Device: NephroCheck test. Location: France.

Specialist commentator comments

Comments on this technology were invited from clinical specialists working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Six specialists 3 of whom were familiar with this technology contributed to this briefing. One of the experts had used the technology only in research.

Level of innovation

All the specialists agreed that the technology was innovative. Two experts noted that the novelty was the development of a commercial product given that many putative markers of kidney injury have been investigated. Another expert noted that NephroCheck test is novel in its ability to predict the development of acute kidney injury (AKI) stage 2 and stage 3. Another expert felt that the prospect of using a preventive 'bundle' for patients with a positive NephroCheck test is novel. One expert noted that to show true clinical innovation, evidence needs to show that the use of NephroCheck test alters outcomes and allows changes in care pathways. One expert stated that potentially NephroCheck had some clinical application but requires analytical and clinical validation.

Potential patient impact

All experts agreed that early detection of AKI would allow early introduction of AKI care. One expert noted that early application of corrective measures may reduce the likelihood of requiring temporary dialysis. Another expert felt that if appropriate evidence is generated, NephroCheck test may potentially decrease morbidity, mortality, length of stay and risk of chronic kidney disease. This expert further stated NephroCheck may be useful in triaging patients. Two experts noted that early identification of patients at higher risk will help with close monitoring of these patients. One expert highlighted the need to give further consideration to identifying the cause of AKI. Another expert noted the importance of monitoring the clinicians' response to the test results and how this influences the start of treatment, as the technology could potentially change current practice.

Potential system impact

Three experts noted that if there were evidence to prove that NephroCheck influences outcomes, its use could potentially result in significant resource savings, reduced length of hospital stay, reduced use of critical care beds and reduced requirement for dialysis. However, 1 expert felt that given the low specificity of the test, it may be potentially resource intensive. Another expert felt NephroCheck could potentially allow clinicians to make an earlier diagnosis on patients at risk of progressing to AKI stage 2 and 3. One expert noted that the benefit to the system would include a reduction in the need for renal replacement therapy and avoiding hyperkalaemia. Another expert noted that a negative test had potential to change a patient's management.

Specialist commentators

The following clinicians contributed to this briefing:

- Prof Alastair Hutchison, professor of renal medicine, Manchester Royal Infirmary. No conflict of interest.
- Dr Nicholas Selby, associate professor of nephrology, Centre for Kidney Research and Innovation, division of medical sciences and graduate-entry medicine, University of Nottingham. Dr Selby has provided speaker services for the company.
- Dr Andrew AJP Lewington, consultant renal physician/honorary clinical associate professor, St James's University Hospital. No relevant conflict of interest.
- Dr Edward J Sharples, consultant renal and transplant medicine, Oxford kidney unit, Churchill Hospital. No relevant conflict of interest.
- Dr Stewart Pattman, consultant chemical pathologist, Northumbria Healthcare NHS Foundation Trust. No conflict of interest.
- Dr Marlies Ostermann, consultant in nephrology and critical care, Guy's and St Thomas' NHS Foundation Trust. Dr Ostermann was a co-investigator for 1 study in this briefing.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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