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Assessment Group's Report

Point-of-care creatinine tests to assess kidney function before administering intravenous contrast for computed tomography (CT) imaging: systematic review, meta-analysis and economic evaluation

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List of abbreviations

AKI	Acute kidney injury
ACR	American College of Radiology
CHE	Centre for Health Economics
CIN	Contrast-induced nephropathy
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence interval
CI-AKI	Contrast induced acute kidney injury
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
eGFR	Estimated Glomerular Filtration Rate
ESUR	European Society of Urogenital Radiology
ICER	Incremental cost-effectiveness ratio
IV	Intravenous
IDMS	Isotope-dilution mass spectrometry
KDIGO	Kidney Disease Improving Global Outcomes
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic resonance imaging
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NR	Not reported
OR	Odds ratio
PC-AKI	Post contrast acute kidney injury
POC	Point of care
QALY	Quality-adjusted life-year
QoL	Quality of life
QUADAS	Quality assessment of diagnostic accuracy studies
RANZCR	Royal Australian and New Zealand College of Radiologists
RRT	Renal replacement therapy
SCr	Serum creatinine

Abstract

Background

Patients with low estimated Glomerular Filtration Rates (eGFR) may be at higher of risk post-contrast acute kidney injury (PC-AKI) following contrast-enhanced computed tomography (CT) imaging. Point-of-care (POC) devices allow rapid measurement of eGFR for patients referred without a recent eGFR result.

Objectives

To assess the clinical and cost-effectiveness of point-of-care creatinine tests to evaluate kidney function, for outpatients without a recent eGFR measurement who need contrast-enhanced CT imaging.

Methods

Three systematic reviews of: test accuracy, implementation and clinical outcomes, and economic analyses. Bibliographic databases were searched up to November 2018. Studies comparing the accuracy of POC creatinine tests with laboratory reference to assess kidney function in adults in a non-emergency setting, and studies reporting implementation and clinical outcomes were included. Probabilities of individuals having their eGFR correctly classified were estimated within a Bayesian framework and pooled using a fixed-effect model.

A *de-novo* probabilistic decision tree cohort model was developed to characterise the decision problem from a NHS and Personal Social Services (PSS) perspective. A range of alternative POC testing approaches were considered. A series of scenario analyses were conducted.

Results

Fifty-four studies were included in the clinical reviews. Twelve studies reported diagnostic accuracy for eGFR; half were at low risk of bias. There were concerns about the applicability of eGFR study results in all but two studies.

i-STAT and ABL devices had higher probabilities of correctly classifying individuals in the same eGFR categories as the reference laboratory compared with StatSensor devices. There was limited evidence for epoc and Piccolo Xpress devices and no studies of Dri-chem NX500. The review of implementation and clinical outcomes included six studies showing practice variation in the management decisions when a POC device indicated an abnormal eGFR.

The review of cost-effectiveness evidence identified no relevant studies. The de-novo decision model developed included a total of 14 strategies. Due to limited data the model only included i-STAT, ABL 800 Flex and StatSensor. Base case cost-effectiveness results showed the most cost-effective testing strategy was a three-step testing sequence involving initially screening all individuals for risk factors,

testing with POC those with at least one risk factor, and including a final confirmatory laboratory test for individuals with a POC test positive result. Within this testing approach the specific POC device with the highest net benefit was i-STAT, though differences in net benefit with StatSensor were very small.

Limitations

There was insufficient evidence for several POC devices, for patients with eGFRs below 30mLs/min/1.73 $m^{2,}$ and on the full potential health impact of delayed or rescheduled CT scans or the use of alternative imaging modalities.

Conclusions

A three-step testing sequence combining a risk factor questionnaire with a POC test and confirmatory laboratory testing appears a cost-effective use of NHS resources compared to current practice. The contribution of intravenous contrast media to acute kidney injury and benefits and harms of IV hydration, notably in patients with eGFR<30, remain uncertain. Cost-effectiveness of point of care testing appears largely driven by POC tests' potential to minimise delays within the current CT pathway.

Plain English Summary

Before CT scans are performed, a contrast agent is usually needed to improve image quality. After receiving contrast, some patients' kidneys may be damaged, especially in patients whose kidneys already do not work well. A blood test can help to identify these patients before a CT scan to minimise the risk of kidney injury. The blood test measures serum creatinine, which indicates how well the kidneys function.

Before a contrast-enhanced CT scan some patients already have a recent creatinine blood test result from a previous blood test. Their blood samples will have been analysed in a central laboratory but this can take at least an hour. Other patients do not have a recent creatinine measurement so their CT scan may be delayed or rescheduled. Sometimes, to avoid risking kidney injury, patients may have scans without a contrast agent. "Point-of-care" devices (handheld, table-top or portable) can rapidly measure creatinine, usually from finger-prick samples. Numerous point-of-care devices are available but they may not be as accurate as laboratory analysers so their benefit is unclear.

We reviewed all available evidence on the benefits and harms of point-of-care creatinine tests before CT scans and assessed whether they are a cost-effective use of NHS resources. We found that some devices (i-STAT and ABL) were more accurate than others (StatSensor). There was insufficient evidence for other devices. We found that, for outpatients, using a POC device after a screening questionnaire and then confirming this with a laboratory test appeared to be a cost-effective use of NHS resources. We found that the risk of kidney injury due to contrast media appears very low. The main benefit of point of care testing may be to reduce unnecessary delays or rescheduling of CT scan appointments.

1 Scientific Summary

1.1 Background

Intravenously administered contrast agents are thought to occasionally cause kidney damage or 'acute kidney injury' (AKI), particularly in patients with existing kidney disease. There is debate as to whether low-osmolar and iso-osmolar contrast agents pose any meaningful risk of AKI. Some guidelines recommend that patients with abnormal estimated Glomerular Filtration Rate (eGFR) may need prophylactic intravenous hydration to reduce the risk of post-contrast AKI (PC-AKI), or alternative imaging strategies may be used which do not require the use of a contrast agent. The risk of PC-AKI can be assessed in most hospital patients awaiting a CT scan or procedure: all inpatients should have a recent eGFR or creatinine measurement available as part of other hospital tests, as should many outpatients. However, some outpatients do not have a recent result available when their CT appointment is due. Although a blood sample could be taken and sent to the hospital laboratory, results typically only become available more than an hour after the blood is taken. Consequently, rather than being subject to an uncertain risk of PC-AKI, their CT appointment may be rescheduled or performed without a contrast agent. Point-of-care (POC) measurement devices allow rapid blood sampling and measurement of eGFR, enabling PC-AKI risk to be assessed and, if low, for the CT appointment to go ahead as planned.

1.2 Objectives

The purpose of this assessment is to evaluate the clinical and cost-effectiveness of point-of-care creatinine tests to estimate kidney function, for people who need contrast-enhanced computed tomography (CT) imaging in a non-emergency setting and who do not have a recent serum creatinine measurement.

1.3 Methods

1.3.1 Assessment of clinical effectiveness

Two systematic reviews were conducted, to evaluate the test accuracy of POC creatinine tests, and to assess their implementation outcomes and clinical impact. A wide range of bibliographic sources including MEDLINE and EMBASE were searched from inception to November 2018 for published and unpublished literature.

For test accuracy outcomes, observational studies that compared the results of POC creatinine tests with laboratory-based tests to assess kidney function in a non-emergency setting were included. Studies reporting sufficient data to allow the calculation of diagnostic accuracy estimates (expressed as or allowing calculation of sensitivity and specificity), correlation or measurement bias were included. For clinical and implementation outcomes, any studies of POC creatinine tests to assess

kidney function before CT imaging in a non-emergency, outpatient setting were included. Only studies of adults were included.

A range of POC devices were eligible, including StatSensor (Nova Biomedical), i-STAT (Abbott), ABL800 FLEX and ABL90 FLEX (Radiometer), Epoc Blood Analysis System (Siemens Healthineers), Piccolo Xpress (Abaxis), and Dri-chem NX500 (Fujifilm).

Two researchers independently screened the titles and abstracts of all reports identified by the bibliographic searches and of all full-text papers subsequently obtained for assessment. Data extraction and quality assessment were performed by at least one researcher and checked by a second. The quality of diagnostic accuracy studies was assessed using a modified version of the QUADAS-2 checklist. Where sufficient data were available, probabilities of individuals being correctly classified by the POC device according to risk categories defined by their eGFR laboratory measurement were estimated within a Bayesian framework using Markov chain Monte Carlo. Data from different studies were pooled using a fixed-effect model. Results were reported as posterior medians with 95% credible intervals (CrI) and plotted as density strips.

1.3.2 Economic assessment

A review of full economic evaluations was conducted. Two researchers independently screened the titles and abstracts of all reports identified by the bibliographic searches and of all full-text papers subsequently obtained. The main findings were narratively summarised.

A de novo decision model was developed to assess the cost-effectiveness of POC testing to assess kidney function, for people who need contrast-enhanced CT imaging in a non-emergency outpatient setting and who present without a recent eGFR measurement. The model provides a quantitative framework to link the diagnostic accuracy of POC creatinine tests to short-term costs and consequences (e.g. the impact on cancelled or delayed appointments, use of contrast media with and without IV hydration and associated risks such as PC-AKI) and final health outcomes expressed in terms of quality-adjusted life years (QALYs). Costs were estimated from the perspective of the NHS and Personal Social Services.

A decision tree cohort approach was used to estimate the costs and health outcomes of alternative testing and treatment strategies, based on: i) an individual's true eGFR status; ii) how these individuals are classified by different testing strategies; iii) clinical decisions aimed at reducing PC-AKI risk; (iv) the subsequent risk and consequences of PC-AKI.

A total of 14 strategies were evaluated, grouped into 6 general types: (i) laboratory testing only; (ii) risk factor screening combined with POC testing; (iii) risk factor screening combined with laboratory testing; (iv) risk factor screening combined with POC testing and laboratory testing; (v) POC testing

only and (vi) POC testing combined with laboratory testing. Only those POC devices that reported diagnostic accuracy data using eGFR thresholds were included (i-STAT Alinity, ABL 800 Flex and StatSensor).

1.4 Results

1.4.1 Diagnostic accuracy

A total of 54 studies were included. The systematic review of test accuracy included 12 studies that reported data for eGFR, seven that reported diagnostic accuracy data only for creatinine, and 50 studies that presented data on correlation and/or measurement bias between a POC device and a laboratory reference test. Most studies reported more than one type of outcome.

Only studies of i-STAT, StatSensor and ABL reported data on diagnostic accuracy. Few studies were available on the epoc and Piccolo Xpress devices, which only reported data on measurement bias or correlation. There were no studies of Dri-chem NX500.

Over half of the diagnostic accuracy studies of eGFR were considered to be at low risk of bias, although there were some concerns about the applicability of results to the outpatient CT setting in all but two studies.

Results of the eGFR data synthesis showed that i-STAT and ABL800/827 devices are more accurate than StatSensor devices at correctly detecting individuals with eGFR below 30 (better sensitivity). i-STAT and ABL devices also have higher probabilities of correctly classifying individuals in the same eGFR categories as the reference laboratory, compared with StatSensor devices. Additional analyses carried out using adjusted StatSensor data and including only studies which used the CKD-EPI equation confirmed these findings.

Of the studies reporting data on creatinine/eGFR measurement bias, results from the StatSensor studies demonstrated wide variation in both the size and direction of measurement bias. Although potentially important measurement bias was also identified in some studies of i-STAT and ABL devices, in most of these studies the concordance of results was generally better than in most of the StatSensor studies. Due to limited data, conclusions cannot be drawn about measurement biases for the epoc and Piccolo Xpress devices.

1.4.2 Implementation and clinical outcomes

The review of implementation and clinical outcomes included six studies. The results of these studies illustrated variation in practice in terms of both the proportions of patients who do not have a recent eGFR result and in the management decisions taken when a POC device indicates an abnormal eGFR.

1.4.3 Economic assessment

No previously published studies met the inclusion criteria for the cost-effectiveness review. One unpublished economic study was provided in academic confidence. [redacted]

From the 14 strategies evaluated in de novo model, the base case cost-effectiveness results showed that the strategy with highest net benefit (and most cost-effective) was a three-step testing sequence which involves initially screening all individuals for risk factors with a questionnaire, then testing those with at least one risk factor with a POC device and finally using a confirmatory laboratory test for those individuals who screen and test positive with POC. Within this testing approach type, the specific POC device within the highest net benefit was i-STAT. However, the differences in the net benefit between the i-STAT and StatSensor devices were found to be extremely small.

Differences in the cost and diagnostic specificity of the individual testing strategies appeared more important drivers than diagnostic sensitivity. The reduction of PC-AKI risk and associated consequences were not major drivers in the model due to the low risk of PC-AKI estimated for this population, the lack of evidence of an increased risk of PC-AKI associated with the use of contrast media and the lack of evidence on the impact of IV hydration in reducing the risk of PC-AKI.

The base-case findings appeared robust to a number of alternative assumptions explored using scenario analysis. The only exception to this was when an additional 'no testing and manage all with contrast enhanced CT strategy was included. This strategy was not considered in the base-case analysis as the clinical appropriateness of this strategy appears questionable given current clinical guidelines that advocate some form of testing or risk stratification prior to the administration of contrast media.

1.5 Discussion

The systematic reviews were performed using transparent, reproducible and robust methods. Our comprehensive literature searches sought to identify all relevant published and unpublished studies, which minimised the possibility of publication or language biases affecting the review results. Key review processes were performed in duplicate which minimised the possibility of reviewer errors and biases. Previously unpublished data from two important studies of diagnostic accuracy based on eGFR thresholds were obtained. Studies reporting measurement bias and clinical or workflow outcomes were included. Study quality was evaluated in studies reporting eGFR diagnostic accuracy

data using a modified version of the QUADAS-2 tool. Appropriate synthesis methods were used to evaluate the accuracy of the devices and provide the inputs needed for the economic evaluation in the form of probabilities. Uncertainty was accounted for, although it was not possible to fully account for between-study differences in results.

Most of the 54 studies which were eligible for inclusion in the systematic review reported only measurement bias or correlation outcomes and so were of limited relevance to the economic modelling part of the assessment. Correlation results data are limited because results which might appear impressive can sometimes hide imperfect agreement between methods.

Some studies were limited by small sample sizes and most studies had few patients with eGFRs below 30mLs/min/1.73 m^2. Although this is reflective of outpatient populations it limits the data available for analyses based on the more clinically relevant eGFR threshold of <30. Few studies directly compared different POC creatinine devices and eGFR diagnostic accuracy data were not available for the ABL90 FLEX PLUS, Dri-chem NX500, epoc Blood Analysis System and Piccolo Xpress POC devices.

There were few studies which reported data on the impact of POC devices in CT departments on the use (or rates of non-use) of contrast agents for diagnostic procedures nor were there many data on the use of prophylactic treatments or workflow outcomes such as cancelled appointments. No data were available on clinical outcomes such as need for renal replacement therapy or hospital admissions. The impact of POC on these important outcomes is therefore uncertain.

The de novo decision model is the first formal evaluation of the potential clinical benefits, risks and costs of incorporating POC testing to assess kidney function, for people who need contrast-enhanced CT imaging in a non-emergency outpatient setting and who present without a recent eGFR measurement. Our findings suggest that the use of POC devices may reduce costs to the health system arising from unecessary delays in CT scanning appointments for the majority of individuals. Any savings also need to be considered against the potential risks arising from misclassification. However, while the use of POC devices results in a marginal reduction in outcomes compared to a strategy of obtaining a laboratory measurement for all individuals, the loss in outcomes appears more than offset by the estimated cost savings.

A potential limitation of our findings is the assumption made in the base-case analsysis that all individuals will eventually proceed to a contrast enhanced CT scan. This simplification was considered necessary given the limited data available, the hetereogeneity in the overall population including underlying reasons for imaging, and challenges in linking these parameters to individualised

clinical decision making and associated outcomes. However, an extensive series of scenario analyses were undertaken to explore the potential impact of alternative assumptions.

The finding that a 'no testing and use of IV contrast for all' strategy had the highest net benefit suggests that additional testing costs required to obtain either a laboratory assessment or a POC test result may not provide sufficient improvements in patient outcomes to warrant routine testing. However, these findings also need to be considered alongside the limitations of the model assumptions and the uncertainties that clearly remain regarding the risks of contrast media and the benefits of appropriate prophylactic management to reduce the risk of PC-AKI.

1.6 Conclusions

A three step testing sequence that involves combining a risk factor questionnaire, POC testing and confirmatory laboratory testing would potentially reduce unnecessary delays or rescheduling of CT scans. This testing approach appears more cost-effective than the current approach which involves obtaining a recent laboratory based measurement prior to administering contrast media. However, the contribution of intravenous contrast media to the development of acute kidney injury, particularly in patients with an eGFR of <30, and the benefits and risks of IV hydration prophylaxis in this population, remain uncertain. While uncertainties remain, our findings suggest that these risks appear very low and that delaying contrast enhanced CT scans appears unnecessary for the vast majority of patients.

Evidence on the diagnostic accuracy of the Piccolo, ABL90 FLEX PLUS, Dri-chem NX500, and epoc Blood Analysis System devices is needed. A study which evaluates the impact of risk stratifying questionnaires on workflow outcomes in CT patients attending without recent eGFR results may also be worthwhile. Further research on the risk of contrast media and benefits and harms of IV hydration specifically in patients with eGFR<30 is warranted.

1.6.1 Study registration

The protocol for this review is registered on PROSPERO CRD42018115818

2 Background

2.1 Description of the health problem

The use of computed tomography (CT) imaging has transformed the way the body can be visualised to detect disease and inform treatment decisions across a range of diseases. This is illustrated by the increase in the number of CT scans performed in hospitals in England from just over 1 million in 1996-97 to almost 5 million in 2012-13.[1] Before CT imaging is performed, an iodine-based (iodinated) contrast agent is normally given to patients in order to enhance image quality and diagnostic performance. Different types of agent are available, with the dose varying depending on the type of scan or procedure required. However, intravenously administered contrast agents are thought to occasionally cause kidney damage or 'acute kidney injury' (AKI), particularly in patients with existing kidney disease. Historically, high-osmolar contrast agents were used for radiological examinations but they were considered to pose a significant risk of contrast induced AKI and other adverse events. The term contrast-induced AKI (CI-AKI) or contrast-induced nephropathy (CIN) describes an AKI occurring within a few days of receiving contrast which cannot be attributed to other causes. However, the development of safer contrast media (low-osmolar agents and iso-osmolar agents) and their widespread adoption in clinical practice, means it is now difficult to ascribe contrast as the cause of an AKI. Much of the research literature on the risks of CI-AKI is limited, being based on single-group cohorts, but the inclusion of adequate control populations in more recent studies has generated results which question the risk of AKI from contrast agents. This had led to current debate as to whether low-osmolar and iso-osmolar contrast agents pose *any* meaningful risk of AKI.[2-5] In light of this uncertainty, the term post-contrast AKI (PC-AKI) is now increasingly used to describe such events. Definitions of AKI vary, but often include absolute increases in baseline serum creatinine of ≥0.5mg/dl or relative increases of 25% to 50%.[6]

Although many possible clinical risk factors for PC-AKI have been suggested and studied, most relate to chronic kidney disease or AKI more broadly, rather than specifically to PC-AKI. Renal dysfunction appears to be the most important risk factor for PC-AKI. A creatinine blood test is used to identify patients at risk – elevated creatinine levels indicate likely kidney dysfunction. In clinical practice creatinine blood test results are often used to calculate eGFR (estimated Glomerular Filtration Rate) which is considered a better measure of kidney function than creatinine alone; eGFR is calculated using details on age, sex, race and creatinine level. Several different methods exist to calculate eGFR in adults, with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation and the MDRD (Modification of Diet in Renal Disease) equation frequently used in the NHS. eGFR results are used to evaluate patient risk of PC-AKI before a contrast agent is administered so that any risk from contrast agents can be minimised or removed. Patients with abnormal eGFR results may need

prophylactic intravenous hydration to reduce the risk of AKI, or alternative imaging strategies may be used which do not require the use of a contrast agent.

The risk of PC-AKI can be quickly assessed in most hospital patients awaiting a CT scan or procedure: all inpatients should have a recent eGFR or creatinine measurement available as part of other hospital tests, as should many outpatients. However, some outpatients do not have a recent result available when their CT appointment is due. Although a blood sample could be taken and sent to the hospital laboratory, results typically only become available more than an hour after the blood is taken. Moreover, some radiology services offer extended day and 7-day services, which may not be in line with laboratory provision. Kidney function will therefore be unknown in these patients at the time of their appointment, so their risk of PC-AKI will be more difficult to evaluate. Consequently, rather than being subject to an uncertain risk of PC-AKI, their CT appointment may be rescheduled or performed without a contrast agent. The former can result in patient stress and a lost appointment slot for the radiology department, whilst the latter will result in less accurate CT images. Sometimes contrast may be administered in patients thought to be at a low risk of AKI based on other clinical information. Point-of-care (POC) measurement devices allow rapid blood sampling and measurement of eGFR, enabling PC-AKI risk to be assessed and, if low, for the CT appointment to go ahead as planned.

2.2 Current service provision and care pathway

A 2015 review of the quality of available clinical practice guidance documents on different aspects of PC-AKI, and of their recommendations, found variation in how PC-AKI was defined, how patients at risk should be identified, and found limited consensus on the use of interventions for preventing PC-AKI.[7] In light of the significant number of recent and ongoing studies in these areas of research it is important that any clinical guidance is kept up-to-date.

Recent guidelines on the use of contrast media include the ESUR (European Society of Urogenital Radiology) guideline on post-contrast acute kidney injury (2018),[8] the RANZCR (Royal Australian and New Zealand College of Radiologists) iodinated contrast media guideline (2018),[9] and the ACR (American College of Radiology) manual on contrast media (2018). [6 66] The ESUR guideline recommends measurement of eGFR before intravascular iodinated contrast either in all patients, or in patients who have a history of: renal disease (eGFR < 60 ml/min/1.73 m^2), kidney surgery, proteinuria, hypertension, hyperuricemia or diabetes mellitus. Two guidelines recommend using the CKD-EPI equation to calculate eGFR.[8, 9]

Broadly, there is a consensus across all three guidelines in how to identify patients who may be at risk of PC-AKI, with agreement that there is very little evidence that iodinated contrast material is an independent risk factor for AKI in patients with an eGFR ≥30 ml/min/1.73m^2. An eGFR threshold of

<30 ml/min/1.73m^2 is therefore often used to identify patients at risk of PC-AKI. Nevertheless, the RANZCR guideline notes that intravascular iodinated contrast should be given to any patient regardless of renal function status if the perceived diagnostic benefit to the patient, in the opinion of the radiologist and the referrer, justifies this administration.[9] Similarly, the ACR guideline advises that any threshold put into practice must be weighed on an individual patient level with the benefits of administering contrast material.[6]

In patients identified as being at a higher risk of developing PC-AKI, pre- and post-procedural 0.9% intravenous saline is recommended in the RANZCR guidelines as the first-line preventive strategy to mitigate the risk. The ESUR guideline recommends that in high risk patients (an eGFR <30 ml/min/1.73m^2 or known/suspected acute renal failure) clinicians should:

- Consider an alternative imaging method not using iodine-based contrast media
- Use intravenous saline (3-4 hours before and 4-6 hours after contrast) or sodium bicarbonate (1 hour before contrast).
- Individualize preventive hydration in patients with severe congestive heart failure or patients with end-stage renal failure (eGFR<15 ml/min/1.73 m^2).

The ESUR guideline also recommends measurement of eGFR 48 hours after contrast, patient monitoring for at least 30 days and eGFR measurement at regular intervals if, at 48 hours, PC-AKI is diagnosed.

In terms of clinical practice adopted across NHS radiology departments, two surveys conducted in 2015 identified inconsistent or poor compliance with guidance, with the wide practice variation being thought to reflect inconsistencies in published guidance.[10, 11] One of the surveys reported that most (of the responding) NHS CT departments required renal function to be assessed via a blood test for *all* patients, although in some departments only patients at high risk of PC-AKI were assessed.[10] It is thought that risk-stratifying questionnaires may be a more efficient way to identify patients at high-risk of PC-AKI,[12] with blood test results needed only for high risk patients, although conclusive evidence on this approach is still needed. One of the NHS surveys asked about the eGFR or creatinine threshold levels at which contrast was contraindicated. Although the most frequently used threshold was an eGFR of <30ml/min/1.73m^2 (used in 45% of NHS trusts) overall there was notable variation, with 19 different thresholds identified, each leading to different prophylactic treatment strategies.[10]

Variation across the NHS also exists in the way creatinine is measured in laboratories.[13]The Jaffe (alkaline picrate) method is a colourimetric assay which can be affected by interfering substances (such as ketones and bilirubin) and so is prone to over-estimate creatinine. Alternatively, enzymatic laboratory methods can be used, which are more accurate (because they are less prone to interference)

but also more expensive. In order to reduce error and maximise the comparability of creatinine measurements between laboratories, methods should be calibrated against isotope-dilution mass spectrometry (IDMS). Similarly, there is variation in the way eGFR is calculated across the NHS.[13] Although the CKD-EPI equation is recommended in recent guidelines, the MDRD equation is also commonly used, even though it is more prone to underestimate eGFR in some patients.[14]

Regardless of which particular group of patients has their renal function assessed, previous blood test results are not always available prior to CT appointments, which can result in cancellations and re-bookings. The use of point-of-care devices presents a possible solution to this problem by providing eGFR measurements in timeframes short enough to avoid cancellation of CT appointments. POC testing could be done on all patients with missing results or just on those patients identified as being at high-risk of PC-AKI using a questionnaire. Alternatively, some radiology departments avoid this problem by adopting a "no blood test result – no booking" policy, while others mitigate it by making efforts to chase up missing blood results.[10]

2.3 Description of the technologies under assessment

Several POC devices are being assessed, based on their ability to output results as eGFRs: StatSensor (Nova Biomedical), i-STAT Alinity (Abbott), ABL90 FLEX PLUS and ABL800 FLEX (Radiometer), epoc Blood Analysis System (Siemens Healthineers), Piccolo Xpress (Abaxis), and Dri-chem NX500 (Fujifilm).

POC creatinine devices are either handheld, portable or table-top and require only very small blood samples (usually obtained via finger-prick). Some devices use test cartridges and others test strips. Creatinine is measured using enzymatic methods either as one of several analytes or as a single measurement. Although POC devices provide results quickly, their results may not be as accurate as those derived from laboratory analyses.

Currently only around 10% of NHS CT departments use POC devices to get a blood test result for patients attending without a recent result.[10] For POC devices to be adopted more widely in outpatient settings assurances will be needed about their accuracy in providing reliable estimates of eGFR at the point of care, when compared to estimates derived from laboratory analyses. Another area of concern lies in whether or not POC devices can store and transmit results to hospital databases to ensure patient records are as up-to-date and complete as possible.

3 Aims and objectives

3.1 Overall aims and objectives of assessment

The purpose of this assessment is to assess the clinical and cost-effectiveness of point-of-care creatinine tests to assess kidney function, for people who need contrast-enhanced computed tomography (CT) imaging in a non-emergency situation and who do not have a recent serum creatinine measurement. To achieve this, the following objectives are proposed:

Clinical effectiveness

- To perform a systematic review of studies which compare the results of POC creatinine tests with laboratory-based tests to assess kidney function in a non-emergency setting.
- To perform a systematic review of the clinical impacts and implementation of POC creatinine tests to assess kidney function before CT imaging. This will include assessment of the associated mortality and morbidity, patient-centred outcomes, adverse events, acceptability to clinicians and patients and compliance.

Cost-effectiveness

- To perform a systematic review of published cost-effectiveness studies of the use of POC creatinine tests in a secondary care setting to assess kidney function before contrast-enhanced imaging.
- To develop a decision model to estimate the cost-effectiveness of the use of POC creatinine tests to assess kidney function before contrast-enhanced imaging. The relevant population is people who need contrast-enhanced imaging in a non-emergency situation and who do not have a recent serum creatinine measurement.
- The objective of the decision model will link the diagnostic accuracy of POC creatinine tests to short-term costs and consequences (e.g. the impact on cancelled or delayed appointments, use and volume of contrast media and associated risks such as PC-AKI). We will link the short-term risks of PC-AKI to potential longer-term costs and consequences (e.g. chronic kidney disease, end stage renal disease and death) using the best available evidence. Depending on the robustness of the evidence, we may also undertake additional exploratory analyses using assumptions and expert opinion.
- We will also assess the feasibility of extending the decision model to include other clinical outcomes that could be affected by any changes in the imaging decision based on

the POC tests. These outcomes could include: (i) any anxiety associated with having a delayed or cancelled CT scan and (ii) morbidity and mortality implications of performing unenhanced scans, or using lower doses of contrast agent. However, given that these outcomes will differ depending on the specific population and the underlying reason for imaging, we envisage that any extension of this nature will need to be constrained to a specific population/reason for the scan. The practicalities and value of developing a specific 'exemplar' application (with potentially limited generalisability) will be considered versus using a simpler and more generic approach (e.g. using threshold analysis to determine the magnitude of any impact necessary to result in a different decision based on conventional cost-effectiveness decision rules).

- The cost-effectiveness of the alternative POC tests will be expressed in terms of incremental cost per quality-adjusted life year and/or net health (or monetary) benefits.

4 Assessment of Clinical Effectiveness

4.1.1 Searches

Comprehensive searches of the literature were conducted to identify studies relating to POC devices for measuring creatinine levels in the blood.

The search strategy was developed in MEDLINE (Ovid) by an information specialist with input from the review team. The strategy consisted of a set of terms for point of care tests combined with terms for either creatinine or estimated glomerular filtration rate. Text word searches in the title and abstracts of records and relevant subject headings were included in the strategy. No date or language limits were applied and the searches were not restricted by study design. The MEDLINE strategy was adapted for use in all other resources searched.

The searches were carried out in November 2018. The following databases were searched: MEDLINE (including: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), CINAHL Plus, Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Management Information Consortium (HMIC), Health Technology Assessment (HTA) Database, PubMed and Science Citation Index.

In addition, the following resources were searched for on-going, unpublished or grey literature: ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, Open Access Theses and Dissertations, Proquest Dissertations & Theses, PROSPERO and the WHO International Clinical Trials Registry Platform portal and manufacturer websites. References submitted by the manufacturers to NICE were also checked.

The websites of manufacturers of point of care creatinine devices were checked and the reference lists of relevant reviews and included studies were scanned.

Search results were imported into EndNote x8 and deduplicated. Full search strategies can be found in Appendix 11.1.

Separate searches were also made to identify evidence to inform estimation of the risk of an acute kidney injury following a contrast-enhanced CT scan (see section 4.3).

4.1.2 Selection criteria

Two reviewers independently screened all titles and abstracts. Full papers of any titles and abstracts deemed potentially eligible were obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below. Any disagreements were resolved by

consensus. Conference abstracts were included provided they reported sufficient data to assess eligibility.

The following eligibility criteria were used to identify relevant studies:

Participants

To maximise the amount of data on test accuracy, the eligible population for test accuracy studies was any adult patient group receiving POC creatinine testing compared with laboratory testing in a non-emergency/intensive care setting.

For studies reporting clinical or implementation outcomes only studies of adult patients receiving POC tests before CT imaging in a non-emergency, outpatient setting were included.

Interventions

For test accuracy studies, details of the POC devices eligible for the review are presented in Table 1. This list is broader than those reported in the NICE scope and in the study protocol – which were restricted to devices which reported eGFR. This was done to maximise the available evidence-base because early on during the screening process it became evident that many studies were of devices which did not calculate eGFR i.e. creatinine was measured, with eGFR being calculated manually by the study investigators. These studies were included where it was thought (following clinical and technical advice) that the model in question was sufficiently similar to the most recent version of the device (all the most recent models have the facility to present eGFR results). New versions of a device may sometimes incorporate software improvements (to allow eGFR outputs), a different interface, or improved functionality, rather than changes in the way creatinine is analysed. For example, the recently released i-STAT Alinity was "built on the proven technology of the i-STAT System",[15] hence the inclusion of studies which used an "i-STAT" device.

All the eligible devices measure whole blood creatinine using an enzymatic method. The devices are either handheld, table-top or portable and need very small volumes of blood. Creatinine levels may be analysed either as one component of a panel of parameters, or as a single measurement via a test card or specific cartridge.

Table 1 Point of care devices eligible for inclusion in the systematic review

Manufacturer & Devices	Device format	Parameters measured	Sample volume	Analysis time	eGFR equation used
Nova Biomedical StatSensor	Handheld	Creatinine only	1.2 µl	30 seconds	MDRD, CKD-EPI, Cockcroft-Gault, Schwartz and Counahan-Barratt
Related models: StatSensor-i, StatSensor Xpress-i. All models allow offset adjustment of results to correct for measurement bias; StatSensor and StatSensor-i also allow slope adjustment.					
Abbott i-STAT Alinity	Handheld	Multiple parameters	65 µl	2 minutes	MDRD and CKD-EPI
Related models: i-STAT 1, many studies simply state "i-STAT"					
Radiometer ABL90 FLEX PLUS	Portable	19 parameters	65 µl	35 seconds	CKD-EPI, MDRD and Schwartz
ABL800 FLEX	Table-top	18 parameters	125–250 µl	1 minute	CKD-EPI and MDRD
Related models: ABL827, ABL837. All models allow offset and slope adjustment of results to correct for measurement bias.					
Siemens Healthineers Epoc Blood Analysis System	Handheld	11 parameters on one test card	92 µl	<1 minute	CKD-EPI, MDRD and Schwartz
Abaxis Piccolo Xpress	Table-top	Multiple parameters	100 µl	<14 minutes	MDRD
Fujifilm Dri-chem NX500	Table-top	Multiple parameters	10 µl	5 minutes	Expected

CKD-EPI chronic kidney disease epidemiology; eGFR estimated glomerular filtration rate; MDRD modification of diet in renal disease

For studies reporting clinical or implementation outcomes any POC creatinine device used in a radiology or imaging department setting were eligible.

Reference standard

- Non-urgent (results available after an hour) laboratory-based serum creatinine measurement: (a) Jaffe method; (b) enzymatic method
- Urgent (results available within an hour) laboratory-based serum creatinine measurement: (a) Jaffe method; (b) enzymatic method
- No testing, clinical judgement alone

Outcomes

The eligible intermediate outcome measures were:

- Diagnostic accuracy of POC creatinine devices compared with laboratory-based creatinine devices
- Correlation between POC creatinine devices and laboratory-based creatinine devices

- Test failure rates
- Number of delayed, or cancelled and rescheduled scans
- Volume of intravenous contrast material used
- Number of unenhanced scans
- Number of hospital admissions
- Hospital length of stay

All relevant outcome definitions and cut-offs were extracted.

In addition, the following clinical outcomes were eligible:

- Acute kidney injury (either PC-AKI or CI-AKI)
- Fall in baseline eGFR or rise of baseline creatinine
- Temporary renal replacement therapy
- New onset chronic kidney disease (stage 3 or worse)
- End stage renal disease with the need for permanent renal replacement therapy
- Health related quality of life
- Mortality

Eligible outcomes related to the implementation of the interventions of interest and related practical issues included:

- Acceptability of POC devices (to clinicians and patients)
- Patient satisfaction
- Training requirements
- Uptake and compliance

Study designs

Diagnostic accuracy and correlation studies

Studies in which the POC test and laboratory test were performed independently on the same patients were eligible.

Clinical effectiveness/implementation

Any experimental or observational study which compared POC tests with laboratory testing and which report relevant clinical outcomes as listed above were eligible. Studies with a single group design were also eligible. We also included relevant publications reporting issues related to implementation of, or practical advice relating to, POC creatinine test technologies (experimental or observational studies or reviews).

Case reports and studies focusing only on technical aspects of POC creatinine test technologies (such as technical descriptions of the testing process or specifications of machinery) were excluded.

4.1.3 Data extraction

Data on study characteristics and results were extracted by one reviewer using a standardised data extraction form and independently checked by a second reviewer (M.C. and A.L.). Discrepancies were resolved by discussion, with involvement of a third reviewer (S.D.) where necessary. Data from relevant studies with multiple publications were extracted and reported as a single study, quoting the most recent or most complete publication. Where appropriate, study authors and manufacturers were contacted to seek more detailed or missing diagnostic or clinical data. If data on mean measurement bias were reported without 95% limits of agreement (or confidence intervals) these were estimated if a standard deviation and sample size was reported using the Bland and Altman formula.[16]

The type of diagnostic accuracy data and synthesis required for this assessment are different from the typical diagnostic accuracy study where a device might be tested for its ability to detect a dichotomous (yes/no) risk of PC-AKI. As the definition of PC-AKI risk has changed over time, sensitivity and specificity data at a given threshold are not relevant since both the lab and POC device thresholds for defining risk have changed. Therefore, reported sensitivity and specificity will refer to different diagnoses of risk. In addition, in this assessment, we aimed to describe the accuracy of the POC devices in correctly classifying individuals according to their PC-AKI risk categories determined by different levels of eGFR as given in Table 2. These thresholds were chosen because they reflect both the thresholds used in guidelines – which have varied over time – and the thresholds used in defining CKD.[17, 18]

Therefore, we estimated the probability that individuals are correctly classified into the four risk categories in Table 2 and the probabilities that they are incorrectly classified into one of the other categories.

Table 2 eGFR categories considered in the analysis

Category	eGFR (mL/min/1.73 m^2)
1	0-29
2	30-44
3	45-59
4	≥ 60

We therefore primarily extracted data on the number of individuals in each of the cells in a 4 by 4 table, defined by the categories in Table 2. Table 3 presents a data extraction template. Where data

were reported as a combination of these categories (e.g. number of individuals with eGFR < 60 mL/min/1.73 m^2), these were also extracted.

Table 3 Sample data extraction table for diagnostic accuracy data

		POC device result (eGFR mL/min/1.73 m^2)			
		0-29	30-44	45-59	≥60
Lab reference result (eGFR mL/min/1.73m^2)	0-29				
	30-44				
	45-59				
	≥60				

4.1.4 Critical appraisal

The quality of the diagnostic accuracy studies was assessed using the QUADAS-2 tool (Quality Assessment tool of Diagnostic Accuracy Studies), modified to incorporate review-specific issues. QUADAS-2 evaluates both risk of bias and concerns about study applicability to the review question. The Cochrane risk of bias tool was used to evaluate randomised controlled trials identified in the pragmatic reviews. The quality of other studies included in the review was not assessed formally as these studies did not directly inform the quantitative synthesis or parameters informing the economic analyses. Quality assessments were performed by one reviewer (A.L.) and independently checked by a second reviewer (M.C.). Disagreements were resolved through consensus, and where necessary, by consulting a third reviewer (S.D.).

4.1.5 Methods of data synthesis

4.1.5.1 Synthesis of Diagnostic Accuracy data

For each device, estimates of the probabilities that individuals are classified by the POC device as having eGFR in one of the 4 categories in Table 2 given their true eGFR is in one of those categories were required. These probabilities relate to the sensitivity and specificity of each device, which were used to populate the economic model in Section 6.4.2.1. Individuals are categorised as at risk of PC-AKI if their eGFR is below 30 mL/min/1.73 m^2 (category 1 in Table 2). Therefore, the probability that each POC device correctly classifies individuals in this category will reflect their sensitivity to detecting individuals at risk. To calculate the specificity of each POC device it is necessary to know the underlying distribution of patients across the different eGFR categories (see Section 6.4.2.1 for details).

Separate syntheses were carried out for POC devices for which two or more studies reported data on individuals classified into the different categories by lab and POC device. Devices with sufficient data were: StatSensor (including StatSensor, StatSensor-i and StatSensor Xpress -i), i-STAT (including i-STAT and i-STAT1) and ABL (Radiometer, including ABL827 and ABL800 FLEX); hence three separate analyses were carried out, pooling the data on three devices, StatSensor, i-STAT and ABL (Radiometer), assuming the different specifications of each device do not differ in their diagnostic characteristics.

For each study i reporting data on all cells of Table 3, the number of individuals classified by POC device as belonging to eGFR category $k = 1,...,4$, given true eGFR category (as determined by the lab) $j = 1,...,4$, r_{ijk}, were assumed to follow a multinomial distribution, which is a generalisation of the binomial distribution to more than 2 categories:

$$\left(r_{ij1}, r_{ij2}, r_{ij3}, r_{ij4}\right) \sim \text{Multinomial}\left(\left(p_{j1}, p_{j2}, p_{j3}, p_{j4}\right), n_{ij}\right) \quad (1)$$

with n_{ij} defining the number of individuals with true eGFR in category j in study i, and p_{jk} defining the probabilities of being classified by POC device in eGFR category k, when true category is j $(j,k = 1,...,4)$, which were assumed common to all studies.

The model was estimated in a Bayesian framework using Markov chain Monte Carlo (MCMC) in OpenBUGS (version 3.2.3)[19, 20] where the probabilities were given a non-informative Dirichlet prior distribution

$$\left(p_{j1}, p_{j2}, p_{j3}, p_{j4}\right) \sim \text{Dirichlet}\left(1,1,1,1\right) \quad (2)$$

The Dirichlet distribution is an extension of the Beta distribution to multiple dimensions and ensures the estimated probabilities always add to 1.[19, 21] Setting all the parameters equal to one, as in equation (2), assigns equal density *a priori* to any vector of probabilities that sums to one.

Studies reporting only on collapsed categories were assumed to provide information on a function of the probabilities p_{jk}. This function varied depending on which categories were collapsed, with relationships determined using partitioning properties of conditional probabilities. Estimation of the probability that an individual in an included study (as opposed to the underlying population of interest for this assessment – see Section 6.4.2.1) has true eGFR in category j, $T[j]$, was also required. For details see Appendix 11.2.1.

Results are reported as posterior medians with 95% credible intervals (CrI) and plotted as density strips. Density strips are horizontal rectangles that can represent an entire probability distribution in one dimension: the rectangle is darkest at the point of highest probability density, then shaded with darkness proportional to the density, gradually fading to white at points of zero density.[22] The width of the rectangle itself has no meaning, and is only used to distinguish between distributions arising from different analyses. Standard lines representing point and interval estimates tend to give the impression that the data equally supports all points in the interval, whereas density strips give a better description of the uncertainty in a probability distribution, particularly for non-symmetric distributions.

Each model was run until convergence was satisfactory and then the results were based on a further sample of iterations from two separate chains. Convergence was assessed by inspecting history and Brooks-Gelman-Rubin plots.[23, 24]

Data from different studies were pooled under the assumption that they estimate common probabilities, given a true eGFR category (i.e. using a fixed effect model). Extension to a model allowing for between-study heterogeneity in probabilities was considered, but due to the small number of studies reporting data on all categories and the small number of individuals in some categories (including several zeros), this was not deemed feasible. The OpenBUGS code and data used are given in Appendix 11.3.

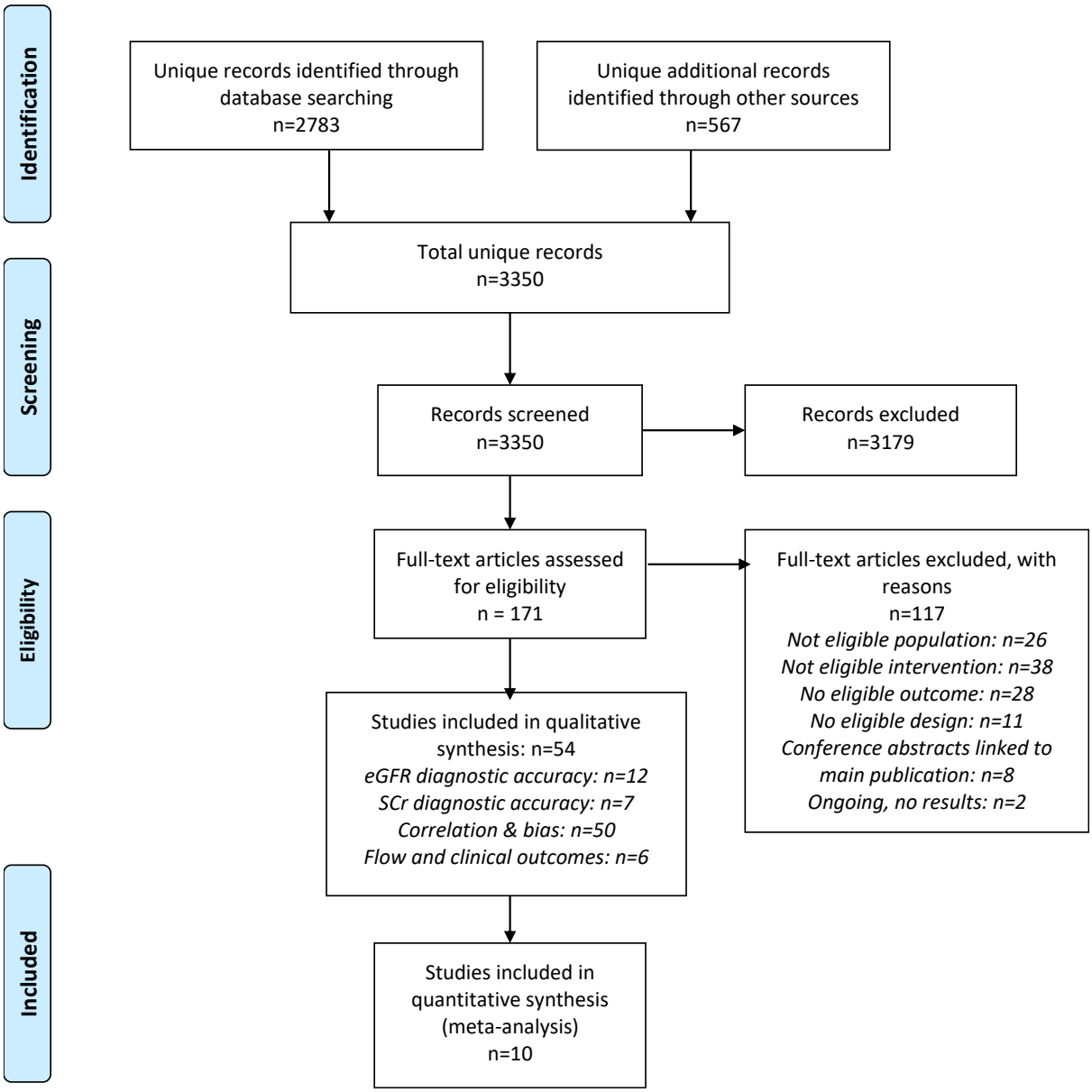
4.2 Clinical Effectiveness Results

4.2.1 Quantity and quality of research available

Figure 1 presents the study selection process. The searches identified a total of 3350 unique records. After title and abstract screening, 171 references were retrieved, and 54 unique studies were included in the review. Of those, 12 studies reported diagnostic accuracy data (expressed as or allowing calculation of sensitivity and specificity) for eGFR,[25-36] seven reported diagnostic accuracy data only for SCr,[37-43] and 50 studies presented data on correlation and/or measurement bias between a POC device and a laboratory reference test.[12, 25, 26, 28-74] Six studies reported data on workflow or clinical outcomes.[27, 57, 60, 75-77]

All studies that reported data on diagnostic accuracy of either eGFR or SCr also reported correlation/ measurement bias results, except one.[27] Three of the studies that reported data on workflow or clinical outcomes also reported data on diagnostic accuracy or correlation/bias.[27, 57, 60]

Figure 1 Study identification process (PRISMA flow diagram)



4.2.2 Risk of bias assessment

Table 4 summarises the results of the QUADAS-2 assessment, split by POC device. Full results, including all signalling questions are reported in Appendix 11.4.

Six studies were at low risk across all risk of bias domains, including two studies of ABL800, [29, 35] three studies of i-STAT[31, 35, 36] and three studies of StatSensor.[26, 28, 35] Among the six studies[25, 27, 32-34] with at least one domain at unclear or high risk of bias, three used correction factors after comparing

initial POC results with laboratory reference results from the same samples, including two studies of i-STAT[32, 33] and one StatSensor study.[34] Correction factors can be entered into StatSensor devices to correct for measurement bias (see Table 1 for further details), However, in these studies the correction was applied to align POC test results with the reference standard results using the same samples. Therefore adjusted analyses reported in these studies may overestimate the accuracy of the POC devices. None of the ABL studies reported using their offset correction functionalities. Four studies (including three conference abstracts)[25, 32, 33] reported insufficient information to assess bias related to patient selection.[25, 32-34] Other risk of bias issues included the use of different MDRD equations between the POC test and laboratory reference test,[29] and the use of a Jaffe method for the laboratory reference test (versus an enzymatic method for the POC test).[30]

Only two studies had low applicability concerns across all domains, including one study of ABL800, i-STAT and StatSensor,[35] and one study of i-STAT.[36] The most common applicability concern was the use of eGFR threshold. Three studies of i-STAT [29, 31, 33] three of StatSensor[26, 29, 34] and one ABL800 study[29] used an eGFR cut-off of 60 or above (see Section 2). Several studies included disease-specific populations, including two StatSensor studies[26, 34] and two i-STAT studies[27, 32] therefore their applicability to a broader population of outpatients referred to CT without a recent eGFR may be limited. One study used a non-standard CKD staging,[32] and one study[28] used a country-specific Japanese equation to calculate eGFR, which limits their applicability to review question.

Overall, two studies were at low risk of bias and had low applicability concerns across all domains assessed, including one that evaluated ABL800, i-STAT and StatSensor,[35] and one of i-STAT only.[36]

Table 4 Risk of bias and applicability assessment of eGFR diagnostic accuracy studies*

	Risk of bias			Concerns about applicability			
	Patient selection	POC & lab reference	Flow & timing	Population	Thresholds	POC	Lab reference
Radiometer studies							
Botz et al 2013[25] Conference abtsract	?	+	+	?	+	+	+
Korpi-Steiner et al 2009[29]	+	+	+	+	-	-	+
Snaith et al 2018[35]	+	+	+	+	+	+	+
Abbott i-STAT studies							
Korpi-Steiner et al 2009[29]	+	-	+	+	-	-	+
Nichols 2007[31]	+	+	+	+	-	+	+
Obrador et al 2012[32] Conference abstract	?	-	+	-	-	-	+
Shephard et al 2008[33] Conference abstract	?	-	?	?	-	-	+
Snaith et al 2018[35]	+	+	+	+	+	+	+
Snaith et al 2019[36]	+	+	+	+	+	+	+
Botz et al 2013[25] Conference abstract	?	+	+	?	+	+	+
Nova StatSensor studies							
Dorward et al 2018[26]	+	+	+	-	-	+	+
Houben et al 2017[27]	+	?	+	-	+	+	+
Korpi-Steiner et al 2009[29]	+	-	+	+	-	-	+
Krige 2017[30]	+	-	+	-	+	+	+
Shephard et al 2010[34]	?	-	+	-	-	+	+
Snaith et al 2018[35]	+	+	+	+	+	+	+
Inoue et al 2017[28]	+	+	+	+	-	-	+

+ low risk of bias or level of applicability concerns; ? unclear risk/concerns; - high risk/concerns.

*Note some studies are presented in several lines as they compare multiple devices (e.g. Snaith et al 2018[35])

4.2.3 Studies reporting bias or correlation outcomes

Fifty studies reported bias or correlation outcomes.[12, 25, 26, 28-74] Eighteen studies were available only as conference abstracts (see Table 5). Where reported, sample sizes ranged from 10 to 3087 patients. Four studies were set in the UK[35, 36, 41, 51] and 11 studies were reported as being conducted in a radiology or CT setting[12, 25, 28, 29, 36, 38, 39, 44, 57, 60, 72]

Studies of StatSensor devices

Twenty-six studies reported measurement bias or correlation results for a StatSensor POC device[12, 26, 28-30, 34, 35, 37-44, 51, 60, 65, 67-74] Eight studies were available only as a conference abstract.[38, 41, 43, 51, 68-70, 72] A large majority of studies were of the StatSensor or StatSensor-i model, with six being of the StatSensor Xpress (or Xpress-I) model.[26, 37, 40, 42, 51, 74] Sample sizes ranged from 15 to 1467 patients. Most studies reported measurement bias results based on levels of creatinine, with only three studies reporting results based on eGFR[28, 60, 68] Of the studies which either exlicitly reported mean measurement bias results, or for which an indication of mean bias could be derived from Bland-Altman plots, there appeared to be no clear trend in terms of the direction of bias with nearly as many studies reporting positive bias (in StatSensor creatinine measurements) as reported a negative bias. Only two studies reported results following offset correction to adjust for bias.[37, 39]

Enzymatic laboratory reference methods are far more specific for measuring creatinine than Jaffe laboratory methods. The latter are prone to over-estimate creatinine (especially at low concentrations) as picric acid reacts with other metabolites or drugs. Results from studies which use enzymatic laboratory methods are therefore preferable to those using Jaffe methods. Of the 10 studies which used an enzymatic laboratory reference five reported a positive measurement bias in creatinine levels when using StatSensor[26, 28, 35, 51, 68] and five reported a negative bias.[29, 34, 60, 71, 74] However, some bias results were reported only as percentage changes. Of those enzymatic reference standard studies which reported mean biases in mg/dL or µmol/L the results (including the often wide limits of agreement) indicated that many StatSensor creatinine measurements are likely to be inaccurate enough to have a clinically significant impact subsequent eGFR calculations. This was evident in studies which reported bias results based on eGFRs, for example, Morita et al reported a mean eGFR bias of 11ml/min/1.73m^2 (95% LOA -22.4 to 44.4).[60] Even studies which did not report significant *mean* bias reported the presence of important bias in measures of variance around the mean, e.g. in the study by Snaith et al the mean bias was very small at 3.56µmol/L (0.04mg/dl) but the 95% limits of agreement were −27.7 µmol/L (-0.31mg/dL) to 34.8µmol/L (0.39mg/dL).[35] Several studies did not report a measure of bias variance. Five studies indicated that bias tended to increase at higher creatinine concentrations.[37, 40, 65, 70, 71]

Most of the studies which reported data on how well StatSensor results correlate with laboratory results (r or r^2) found high levels of correlation. However, these data have limited relevance to this assessment because good correlation of results does not necessarily mean there is good *agreement* between the two methods of measurement.

Studies of i-STAT devices

Eighteen studies reported measurement bias or correlation results for an i-STAT POC device.[25, 29, 31-33, 35, 36, 45-48, 52, 54, 55, 57-59, 62] Seven were available only as conference abstracts.[25, 32, 33, 47, 48, 55, 59] Sample sizes ranged from 15 to 3087 patients. Most studies reported bias results based on levels of creatinine; two reported results based on eGFRs[59, 62] Most studies reported using enzymatic laboratory methods; two used Jaffe methods.[52, 54] One study focused on bias following the addition of serial dilutions of hydroxyurea.[48] Eight studies indicated that there were positive biases in creatinine values derived from i-STAT devices when compared with laboratory results,[29, 31, 33, 54, 58, 59, 62] whereas two studies showed a negative bias[36, 45] In four other studies the bias was very small, being close to zero.[25, 35, 52, 55]. Many of the biases appeared large enough to have a clinically significant impact on subsequent eGFR calculations. The two studies which examined the effect on eGFR reported a mean bias of -2.2ml/min/1.73 m^2[62] and underestimation by 4-12%, depending on gender and absolute creatinine value.[59] Limits of agreement (where available) were mostly narrow, indicating that the biases were quite consistent and predictable.

Studies of ABL series devices

Six studies reported measurement bias or correlation results relating to an ABL device[25, 29, 35, 49, 56, 66] although three were available only as conference abstracts.[25, 49, 56] Four studies were of the ABL800 device,[29, 35, 49, 56] one was of the ABL827[25] and one was of the ABL837.[66] Sample sizes ranged from 70[49] to 2042.[25] All studies used an enzymatic laboratory reference method except one.[56] All bias data related to levels of creatinine. Very small negative mean biases from ABL devices were reported in two studies,[25, 29] with both estimates having narrow 95% limits of agreement. One study reported a mean bias which was close to zero[35] but with 95% limits of agreement which were notably broader than the two aforementioned studies[25, 29] and one study reported a substantial negative bias (of -0.22mg/dL without an accompanying measure of variance.[56]

Studies of Piccolo Xpress devices

Four studies reported measurement bias or correlation data for the Piccolo Xpress device.[53, 61, 63, 64] One was reported in Czech[53] so only minimal data could be extracted and one was available only as a conference abstract.[64] It was unclear whether enzymatic or Jaffe laboratory reference methods were used in all four studies. All the studies were small ($n \leq 60$) though this information could not be extracted for the study published in Czech.[53] Two studies reported bias data only as percentages, with both reporting positive biases (of 8%[53] and 14%[64] respectively), one study did not report an numerical estimate of bias (but did present a Bland-Altman plot),[61] and one study reported a negative bias of -0.2mg/dL (95% LoA estimated as -0.25 to -0.15).[63]

Studies of epoc Blood Analysis System devices

One study reported measurement bias and correlation data for an epoc device.[50] It found that epoc device measurements resulted in a small negative mean bias (of − 0.025mg/dL). The other epoc study

– available only as a conference abstract – investigated whether hydroxyurea caused interference in creatinine measurements using i-STAT and epoc devices and whether the interference resulted in bias.[48] No interference was found for the epoc device.

Studies which compared different types of device

Three of the studies listed in Table 5 directly compared different types of POC device.[25, 29, 35] The Snaith et al[35] and Korpi-Steiner et al[29] studies both compared StatSensor, i-STAT and ABL800 FLEX devices. Both found that the ABL800 FLEX had the strongest agreement with laboratory serum creatinine, followed by the i-STAT and then StatSensor. The study available only as a conference abstract compared an ABL827 device with an i-STAT, concluding that creatinine results from both devices correlated well with laboratory serum creatinine.[25]

Summary

Overall, results from the StatSensor studies illustrate wide variation in the size and direction of measurement bias which can be encountered when using this device. It may be relevant for users to be aware of the availability of the offset functionality to correct for any bias observed with an individual StatSensor device. Only two StatSensor studies reported using an offset adjustment for measurement bias. This raises the possibility that issues such as lack of awareness, or difficulties in implementing the adjustment function to align the POC test to local laboratory methods could be relevant in clinical practice. The tendency for measurement bias to increase at higher creatinine levels (seen in some studies) is also a concern as this has important implications for the care decisions made about sicker patients. Although potentially important measurement bias was identified in some studies of i-STAT and ABL devices, in most of these studies the concordance of results was generally better than was found in most of the StatSensor studies. Few studies were available on the epoc and Piccolo Xpress devices; the limited data and reporting in these studies, coupled with their small sample sizes made it difficult to draw conclusions about creatinine measurement biases.

Although the concordance and measurement bias results reported in these studies suggest there may be important limitations to using POC devices to measure creatinine, it is more important to consider the impact of any measurement bias on results categorised according to clinically-important thresholds which may be used for clinical decision-making. Studies which report such data are presented in section 4.2.5.

Table 5 Studies reporting measurement bias or correlation outcomes

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
Aumatell et al 2010[44]	24 undergoing CT scans Australia	StatSensor	"Vitros version 5" (Ortho Clinical Diagnostics)	R^2 for three different Statsensor devices were 0.9886, 0.9866 and 0.9935 (mean 0.990). B-A plot indicated underestimation of creatinine using StatSensor (a small negative bias) but no further bias results were reported.
Azzouz et al 2014[12]	1467 outpatients with renal dysfunction before MRI or CT Denmark	StatSensor	NR	This study evaluated a structured questionnaire and reported an r=0.9 when comparing lab reference with StatSensor
Bahar et al 2016[45]	244 oncology outpatients split into 3 cohorts corresponding to 3 different periods USA	i-STAT	Jaffe (Beckman Coulter DxC 800)	Cohort 1, n=39 mean bias=-0.48 mg/dL Cohort 2, n=85 mean bias=-0.08mg/dL Cohort 3, n=120 mean bias=0.17 mg/dL
Baier et al 2003[46]	15 organ donors USA	i-STAT	NR	R=0.95
Bender et al 2012[47] *Conference abstract*	54 patients prescribed carboplatin chemotherapy and zoledronic acid, 56% female USA	i-STAT	Enzymatic (Vitros 5600 Ortho Clinical Diagnostics)	The study was designed to determine if whole blood and serum creatinine measurements were interchangeable when calculating dosages for carboplatin and zoledronic acid. For the CG eGFR results i-STAT had an average negative bias of -19.25 mg/dL, while the MDRD eGFR and CKD-EPI eGFR results had positive biases of +115.2mg/dL and +28.0 mg/dL, respectively.
Betman 2015[48] *Conference abstract*	Not reported. USA	i-STAT, "epoc"	Olympus platform (no other details)	Patient serum samples with known creatinine levels were pooled to create three standards - normal, high, and very high range creatinine. Serial dilutions of hydroxyurea were added to aliquots of each standard. i-STAT: a typical dose of hydroxyurea could result in a creatinine level with a positive bias of 6.15 mg/dL. i-STAT SCr measurements showed a dose-response relationship with the concentration of hydroxyurea, but epoc did not.

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
Bobilewicz et al 2008[49] *Conference abstract*	70 potential organ donors, post-extensive surgery Poland	ABL 800	Enzymatic (Integra 800)	R=0.997
Botz et al 2013[25] *Conference abstract*	2042 patients at risk of renal disease prior to radiological examinations, 43% female USA	ABL827, i-STAT1 (sample type NR)	Enzymatic, (Cobas C-501, Roche)	Mean bias for i-STAT was +0.03mg/dL (SD 0.13, 95% LoA estimated by EAG as -0.22 to 0.28) mean bias for ABL827 was -0.06mg/dL (SD 0.13, 95% LoA estimated by EAG as -0.31 to 0.19)
Cao et al 2017[50]	10 USA	epoc Blood Analysis System	Vitros 5600 (Ortho Clinical Diagnostics)	R=0.9313 Mean bias: −0.025mg/dL (−3.4%)
Cory et al 2018[51] *Conference abstract*	15 Pregnant women and non-pregnant controls UK	StatSensor X-press	Enzymatic (Type NR)	R=0.95 R=0.96 (pregnant population subgroup, n=11) The median difference with reference was +12 µmol/L.
Dimeski 2013[52]	40 laboratory staff and renal outpatients Australia	i-STAT	Jaffe (Beckman Coulter DxC 800)	Results presented by method of blood sampling: R^2=0.996 for lithium heparin and R^2=0.995 for blood gas syringe. B-A plots indicated small mean positive biases with i-STAT of between around 3 to 8µmol/L.
Dohnal et al 2008[53] *Reported in Czech*	NR* Czech Republic	Piccolo Xpress	Vitros 950, Konelab 60	Statistically significant bias (+8%, p<0.05)
Dorward et al 2018[26] *Letter to the editor*	187 HIV positive patients from a POC RCT, median age 31 years, 62% female mean creatinine 69.0 µmol/L South Africa	StatSensor Xpress-I (capillary)	Enzymatic (Dimension EXL 200 IDMS, Siemens)	Mean POC bias +10.4 µmol/L (95% LoA: -17.6 to 38.3). r=0.58.

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
Gault et al 2001[54]	149 randomly selected samples, mean creatinine 220µmol/l Canada	i-STAT	Jaffe (Beckman SynchronCX7)	R=0.99. Mean bias +10.9%. Mean difference 20.1µmol/l (SD 30.3) 95% LoA estimated by EAG as -39.3 to 79.5)
Georgievskaya et al 2011[55] *Conference abstract*	33 oncology patients Country NR	i-STAT	Enzymatic (Vista)	R=0.926, mean bias -0.02 mg/dL
Griffin et al 2018[37]	Two studies of field workers: Derivation cohort n=104, Validation cohort n=105. All male. Mean ages 29 and 30 years respectively. Baseline eGFR 117 and 111 respectively. Guatemala	StatSensor Xpress	Jaffe	Creatinine overestimated before adjustment: Derivation cohort unadjusted results mean bias =0.20mg/dl (95% CI 0.17 to 0.24). Adjusted results mean bias = -0.04mg/dl (95% CI -0.01 to -0.07) B-A plot indicated that differences were greater at higher creatinine levels
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haneder et al 2012[39]	401 referred for CT at 2 centres. Mean age 62(14), 63% male. Germany	StatSensor (2 devices: A and B)	Jaffe (Dimension RXL, Siemens; Olympus AU2700)	r=0.93 (A) and 0.92 (B) at centre 1 and 0.85 (A) and 0.82 (B) at centre 2. Creatinine was underestimated by StatSensor before adjustment. For centre 1 (n=201), % bias before offset adjustment: -16% (A) and -15% (B); % bias after offset adjustment: 0.4% (A) and 0.0% (B)
Inoue et al 2017[28]	123 (with unadjusted results), scheduled for CT Mean eGFR 75.3 (SD 21.4)	StatSensor-i (capillary)	Enzymatic, (BioMajesty BM2250, Jeol Ltd)	r for eGFR=0.80, r for creatinine=0.88. Mean bias not reported. B-A plots indicated a positive bias (overestimation) with Statsensor for creatinine and a negative bias for eGFR.

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
	Mean Creatinine 0.8mg/dL (SD 0.29) Japan			
Janetto et al 2006[56] *Conference abstract*	85 heparinised samples USA	ABL800 FLEX	Jaffe (Olympus AU5431)	R=0.996, mean bias -0.22mg/dL
Korpi-Steiner et al 2009[29]	266 excess samples taken before CT procedures. Mean age 68 years, 39% female USA	ABL800 FLEX, i-STAT, StatSensor (with slope and intercept offset option) -hepanirised venous samples	Enzymatic, (Cobas Integra 400 Roche)	Mean bias: StatSensor -0.23 mg/dL (SD 0.18, 95% LoA estimated by EAG -0.58 to 0.12), r2 0.61 (assumed to be without offset option)# i-STAT +0.13mg/dL (SD 0.08, 95% LoA estimated by EAG as -0.03 to 0.29), r2 0.93 ABL800 -0.05mg/dL SD 0.09, 95% LoA estimated by EAG as -0.23 to 0.13) r2 0.89
Kosack et al 2015[40]	60 patients and laboratory workers Netherlands	StatSensor Xpress	Vitros 5,1FS	R=0.97. R's were 0.69, 0.90, and 0.83 for normal SCr levels (<115 µmol/L), low SCr (115 to 270 µmol/L) and high SCr (270 to 600 µmol/L), respectively. B-A plot showed a tendency for StatSensor to underestimate high creatinine values (>600 µmol/L)
Krige 2017[30] *PhD thesis*	103 mixed ancestry South Africans, Mean age 52, 69% female South Africa	StatSensor (capillary)	Jaffe (AU5800 Beckman Coulter)	Mean bias not reported but B-A plot of creatinine showed a negative bias.
Lee Lewandrowski et al[57]	3087 referred for contrast enhanced scan (CT or MRI) without a recent eGFR USA	i-STAT	Jaffe (Roche Cobas C501)	R^2=0.99 for creatinine. B-A plot: i-STAT values were slightly lower for SCr values >2 mg/dl whereas a t-test showed no difference for values less < 2 mg/dl).

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
Lehtonen 2013[58] *PhD thesis, reported in Finnish*	n=63 samples Finland	i-STAT	Modular EVO	Mean bias: +8.8% (NS).
Mahlow et al 2016[59] *Conference abstract*	540 samples, oncology outpatients presenting for chemotherapy infusion USA	i-STAT	Enzymatic (Roche COBAS 8000)	Small but consistent positive bias: i-STAT SCr values were on average higher than the laboratory analyser by 0.11 mg/dL (SD 0.04, 95% LoA estimated by EAG as 0.03 to 0.19) $R^2 = 0.926$. eGFR was underestimated by 4-12% depending on gender and absolute creatinine value
McGough et al 2018[41] *Conference abstract*	33 dialysis patients UK	StatSensor	Jaffe (Cobas 8000, Roche)	Mean bias was -0.15mg/dL (-3.4%)
Minnings et al 2015[42]	100, from health centre or hospital setting. 70% female. Median serum creatinine 0.72mg/dL Nicaragua	StatSensor Xpress	Jaffe (Roche Cobas Integra 400)	Median bias 0.32 mg/dL
Morita et al 2011[60]	113 patients scheduled for CT or MRI without a recent eGFR measurement Japan	StatSensor	Enzymatic (7700 clinical analyser, Hitachi High-Technologies)	For creatinine: mean bias = −0.10 mg/dl (95% LoA −0.43 to 0.22) r=0.74. For eGFR: mean bias = 11ml/min/1.73m^2 (LOA: -22.4 to 44.4), r=0.74
Murata et al 2018[61, 78]	60 ‘residual samples’ USA	Piccolo Xpress	Vitros 5600 (Ortho Clinical Diagnostics)	R=0.93. B-A plot indicted a negative bias.
Naugler at al 2014[62] *Letter to the editor*	Discarded samples Canada	i-STAT	Enzymatic (Cobas 6000)	eGFR: mean bias of −2.18 ml/min. B-A plot indicated better agreement for lower eGFR values than for higher values (>60ml/min).

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
Nichols 2007[31]	50 chemotherapy patients USA	i-STAT (venous)	Jaffe; Enzymatic (Roche)	Positive bias for i-STAT compared with Jaffe (MD 14.1µmol/L, 95% CI 11.5–16.8), r=0.997 and with enzymatic (MD 19.4µmol/L, 95% CI 16.8–22.1), r=0.998
Obrador et al 2012[32] *Conference abstract*	257 diabetic patients Mean age: 57 years, 62% women, mean creatinine 0.8mg/dl (SD 0.4) Mexico	i-STAT (capillary)	NR (Olympus 5400)	r=0.93 (capillary), r=0.90 (venous)
Park et al 2009[63]	60 samples (20 low, 20 medium and 20 high level of SCr) Korea (published in Korean)	Piccolo Xpress	TBA 200-FR (Toshiba Co., Tokyo, Japan)	R=0.9978, mean bias -0.2mg/dL (SD 0.2, 95% LoA estimated by EAG as -0.59 to 0.19)
Rensburg et al 2014[43] *Conference abstract*	Number NR South Africa	StatSensor	Jaffe (Siemens ADVIA 1800)	r=0.987
Schnabl 2008[64] *Conference abstract*	40 samples, broad range of concentrations	Piccolo Xpress	NR (Abbott Architect c8000)	Average positive bias for SCr: +14% "good correlation" (R^2=NR, but ≥0.88)
Schnabl et al 2010[65]	191 which included 97 pre-dialysis and 57 post-dialysis patients Canada	StatSensor	Jaffe (Architect C8000)	R^2=0.9328 overall; R^2=08312 for pre-dialysis patients; R^2=0.9347 for post-dialysis patients. Few bias data reported: a negative bias was seen at high creatinine concentrations, especially in pre-dialysis patients where the bias was -30%.
Shephard et al 2008[33] *Conference abstract*	101 venous blood samples Australia	i-STAT (venous)	Enzymatic (NR)	The i-STAT displayed a positive bias relative to the IDMS-aligned laboratory method (mean % bias of 5.6% overall, 10.4% for samples <150 µmol/L and 4.5% for samples >150 µmol/L). This bias was eliminated by applying a correction formula and IDMS alignment.

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s)</th><th>Laboratory reference</th><th>Results (for creatinine unless stated)</th></tr>
<tr><td>Shephard et al 2010[34]</td><td>100 (63 renal/dialysis patients attending clinic, 37 healthy), 52% female
Australia</td><td>StatSensor (capillary)</td><td>Enzymatic (Creatinine Plus assay, Roche)</td><td>Better concordance in patients with higher SCr for both StatSensor devices pre-post calibration[$]Greater bias for both StatSensor devices pre-calibration.
<table>
<tr><th></th><th>r</th><th>Mean bias µmol/L (95% CI)</th></tr>
<tr><td colspan="3">Pre-recalibration</td></tr>
<tr><td>StatSensor 1 (low sCr, <150µmol/L)</td><td>0.83</td><td>-7.3 (-11.0 to -3.6)</td></tr>
<tr><td>StatSensor 2 (low sCr, <150µmol/L)</td><td>0.84</td><td>-6.7 (-10.3 to -3.1)</td></tr>
<tr><td>StatSensor 1 All</td><td>0.97</td><td>-47.3 (-63.6 to -31.1)</td></tr>
<tr><td>StatSensor 2 All</td><td>0.97</td><td>-46.5 (-63.6 to -29.3)</td></tr>
<tr><td colspan="3">Post-recalibration</td></tr>
<tr><td>StatSensor 1 (low sCr, <150µmol/L)</td><td>0.83</td><td>4.2 (-0.2 to 8.7)</td></tr>
<tr><td>StatSensor 2 (low sCr, <150µmol/L)</td><td>0.84</td><td>5.0 (0.8 to 9.3)</td></tr>
<tr><td>StatSensor 1 All</td><td>0.97</td><td>-4.3 (-14.5 to 5.9)</td></tr>
<tr><td>StatSensor 2 All</td><td>0.97</td><td>-5.5 (-16.4 to 5.3)</td></tr>
</table>
$ Before and after correction of a mean positive bias of 5.6% and alignment to the isotope dilution mass spectrometry (IDMS) reference method</td></tr>
<tr><td>Skurup et al 2008[66]</td><td>104 samples
Denmark</td><td>ABL837</td><td>Enzymatic (Cobas Integra)</td><td>R^2=0.999. B-A plot indicated a very small positive bias which appeared to decrease as creatinine increased.</td></tr>
<tr><td>Snaith et al 2018[35]</td><td>300 attending for routine blood tests (phlebotomy outpatients), mean age 60 years, 47% female, mean creatinine 92µmol/L
UK</td><td>ABL800 FLEX, StatSensor (capillary), i-STAT (venous)</td><td>Enzymatic (Cobas 8000, Roche)</td><td>ABL800 FLEX had the strongest agreement with laboratory measured serum creatinine (r=0.991; mean bias = −0.86 µmol/L, 95% LOA −9.6 to 7.9) followed by i-STAT (r=0.985; mean bias = 3.88µmol/L, 95% LOA −8.8 to 16.6) and StatSensor (r=0.891; mean bias = 3.56µmol/L, 95% LOA −27.7 to 34.8).</td></tr>
<tr><td>Snaith et al 2019[36]</td><td>300 adult outpatients attending for a contrast-enhanced CT scan, mean age</td><td>i-STAT (venous)</td><td>Enzymatic (Cobas 8000, Roche)</td><td>Mean bias -0.21 (units not reported) 95% LoA -13.94 to 13.51. r=0.948.</td></tr>
</table>

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
	65 years, 48% female UK			
Srihong et al 2012[67]	40 random blood samples from the central laboratory Thailand	StatSensor	Jaffe (Beckman Coulter DxC 800)	R^2=0.984
Stojkovic et al 2017[68] *Conference abstract*	56 participants, 48% female, mean age around 53 years Serbia	StatSensor	Enzymatic (Cobas, Roche)	B-A plot showed a mean eGFR bias of -2±10ml/min/1.73m^2 CKD-EPI equation used for eGFR
Straseski et al 2009[69] *Conference abstract*	50 inpatients, median creatinine 1.30 mg/dL USA	StatSensor ('EZ CHEM')	Enzymatic (Roche Hitachi Modular)	Mean bias reported only for subgroups: -0.69 mg/dL for the 14 samples (10 patients) with discordant results (differed by > 0.5 mg/dL between the two methods). A control group (n=10) which was age, gender and race-matched to the patients with discordant results had a mean bias 0.14 mg/dL.
Straseski et al 2010[70] *Conference abstract*	150 inpatients USA	StatSensor ('EZ CHEM')	Enzymatic (Roche Hitachi Modular) and IDMS	R^2=0.791 when compared with IDMS method. Higher discordance in patients with elevated creatinine values (>2.0 mg/dL). Compared with the enzymatic method, 34 (23%) samples differed by more than 0.5 mg/dL. Of these samples, 23 (68%) had enzymatic creatinine results above 2.0 mg/dL. Correlation with enzymatic method was not reported.
Straseski et al 2011[71]	119 intensive care and oncology inpatients, 45% female, mean age 59m years USA	StatSensor	Enzymatic (Roche Hitachi Modular) and IDMS	When compared with the enzymatic method there was increased discordance for results at higher creatinine concentrations. R^2=0.88 B-A plot suggested a negative bias. 22 patients had creatinine results that differed by ≥0.50 mg/dL. 19 of the 22 had eGFR values <30 mL/min/1.73m^2.
Treves et al 2011 [72] *Conference abstract*	NR. Radiology setting. France	StatSensor	LX20, (Beckman-Coulter) and RXL (Siemens)	R^2=0.908

Study	N, Population	POC device(s)	Laboratory reference	Results (for creatinine unless stated)
Too et al 2015[73]	52 'leftover' blood samples Singapore	StatSensor	NR	Positive bias of 11.3% (95% LoA -24.3 to 47.0)
van Lint et al 2016[74]	138 kidney transplant outpatients Netherlands	StatSensor Xpress-i	Enzymatic (Roche Modular P800)	Mean bias = -12.38μmol/L (95% LoA -58.8 to 34.1)

LoA Limits of agreement, *Not reported in English and not extractable using Google translate. [#]eGFR concordance for StatSensor values were calculated with and without application of an offset of 0.28 mg/dL (25 μmol/L) creatinine, which was the offset that maximized overall concordance between StatSensor whole blood and plasma eGFR values for the sample data set. CG Cockcroft-Gault, CKD Chronic kidney disease, B-A Bland-Altman, POC point-of-care, NR Not reported, lab laboratory, IDMS Isotope dilution mass spectrometry, r = correlation coefficient between POC device and laboratory reference, for bias results values <0 indicate a negative bias and values>0 indicate a positive bias, Results in mg/dL can be converted to μmol/L by multiplying by 88.4

4.2.4 Studies reporting diagnostic accuracy results based on creatinine thresholds

Seven studies reported diagnostic accuracy data relating to creatinine thresholds, (Table 6) with four being reported as published papers[37, 39, 40, 42] and three as conference abstracts.[38, 41, 43] Where reported, sample sizes ranged from 33 to 401 patients. Population details were limited with one study (appearing to be) set in the UK[41] and one reported as being of patients due to receive CT scans.[39] All the studies were of StatSensor POC devices. Six studies used a Jaffe method[37-39, 41-43] for the laboratory reference standard and in one study this was unclear.[40]

The creatinine thresholds used in the studies (to calculate sensitivity and specificity) ranged from 1.1mg/dl to 1.5mg/dl (97µmol/l to 133µmol/l). Since eGFR (rather than creatinine alone) is used to estimate kidney function in clinical practice, diagnostic accuracy results based on creatinine thresholds are not as clinically relevant or useful than those based on eGFR thresholds. Moreover, all these (creatinine) studies are of the StatSensor POC device, which allows users to implement offset adjustment of biased results. Two of the seven studies explicitly reported results which incorporated an offset adjustment.[37, 39] The other five studies did not report usingoffset adjustment. Notwithstanding these limitations, most studies reported unadjusted sensitivities which were higher than specificities, indicating that StatSensor tended to overestimate creatinine levels compared to laboratory Jaffe results. The exceptions were the study by Haneder[39] which reported much lower (unadjusted) sensitivities than specificities in the two devices tested, and the small UK study which reported both a sensitivity and specificity of 100%.[41] Although most studies indicated overestimation of creatinine by StatSensor, the Haneder study[39] illustrated that some StatSensor devices may underestimate creatinine. This variation in over- or under-estimation was also seen across the studies which reported results for creatinine level bias (see section 4.2.3).

The results of the Griffin and Haneder studies[37, 39] indicate than even after offset adjustment of creatinine results, StatSensor can produce false-negative and false-positive results. This has the potential to result in unnecessary prophylactic treatment or scans without contrast (false-positives), or unnecessarily exposing high-risk patients to contrast (false-negatives). The laboratory reference standards used in these studies also limits their value as the adjustments may themselves be inaccurate, being based on Jaffe methods rather than more accurate enzymatic methods.

Table 6 Studies reporting diagnostic accuracy outcomes using creatinine thresholds

Study	N, Population	POC device(s)	Laboratory reference	Results and notes
Griffin et al 2018[37]	Two studies of field workers: Derivation cohort n=104, Validation cohort n=105. All male. Mean ages 29 and 30 years respectively. Baseline eGFR 117 and 111 respectively. Guatemala	StatSensor Xpress	Jaffe	Adjusted results with unadjusted results in brackets: 1.1mg/dL cut-off: sensitivity=70% (90%) and specificity=90% (69%) 1.3mg/dL cut-off: sensitivity=73% (91%) and specificity=99% (85%) For the validation cohort: 1.1mg/dL cut-off: sensitivity=80% (96%) and specificity=83% (41%) 1.3mg/dL cut-off: sensitivity=78% (91%) and specificity=95% (65%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haneder et al 2012[39]	401 referred for CT at 2 centres. Mean age 62(14), 37% female. Germany	StatSensor (2 devices: A and B)	Jaffe (Dimension RXL, Siemens; Olympus AU2700)	Centre 1: At a cut-off of 1.2mg/dL sensitivity=35% (A) and 42% (B); specificity=99% (A) and 99% (B). Following offset adjustment the corresponding results were 81% (A) and 71% (B); and 98%(A) and 94% (B). Centre 2; NR.
Kosack et al 2015[40]	60 patients and laboratory workers Netherlands	StatSensor Xpress	Vitros 5,1FS	At a cut-off of ≥115µmol/L (1.3mg/dL): TP 38, FP 2, TN 20, FN 0. i.e. sensitivity =100%, specificity=91%
McGough et al 2018[41]*Conference abstract*	33 dialysis patients UK	StatSensor	Jaffe (Cobas 800 Roche)	At a cut-off of 1.5mg/dL both sensitivity and specificity were 100%
Minnings et al 2015[42]	100, from health centre or hospital setting. 70% female. Median serum creatinine 0.72mg/dL Nicaragua	StatSensor Xpress	Jaffe (Roche Cobas Integra 400)	At a cut-off of 1.1mg/dL sensitivity=92% and specificity=67% At a cut-off of 1.2mg/dL sensitivity=100% and specificity=79% At a cut-off of 1.3mg/dL sensitivity=100% and specificity=84% At a cut-off of 1.4mg/dL sensitivity=100% and specificity=86% At a cut-off of 1.5mg/dL sensitivity=100% and specificity=89%

Study	N, Population	POC device(s)	Laboratory reference	Results and notes
Rensburg et al 2014[43] *Conference abstract*	Number NR South Africa	StatSensor	Jaffe (Siemens ADVIA 1800)	At a cut-off of 130µmol/L (1.5mg/dL): Negative predictive value 100% Positive predictive value 80%.

TP True positive, TN True negative, FP False positive FN false negative, Results in mg/dL can be converted to µmol/L by multiplying by 88.4

4.2.5 Studies reporting diagnostic accuracy results using eGFR thresholds

Table 7 summarises the characteristics of the twelve studies that reported diagnostic accuracy data of eGFR measurements with POC creatinine test devices.

All included studies were observational. The sample size ranged from 50 to 2042 participants. Two studies included outpatients referred for a contrast-enhanced CT scan,[28, 36] two included patients undergoing a radiological examination but did not specify what proportion were outpatients.[25, 29] Four studies included disease-specific populations, including CKD,[34] cancer,[31] diabetes,[32] and HIV.[26] One study focused on women referred for contrast-enhanced spectral mammography.[27] Other studies included phlebotomy outpatients,[35] and mixed ancestry South-African patients.[30]

Three studies were conducted in the USA.[25, 29, 31] Two studies each were from the UK,[35, 36] Australia[33, 34] and South Africa.[26, 30] A single study was conducted in the following countries: Netherlands,[27] Japan,[28] and Mexico.[32] Three studies were only reported as a conference abstract.[25, 32, 33]

Seven studies evaluated i-STAT,[25, 29, 31-33, 35, 36] and seven studies evaluated a StatSensor device.[26-30, 34, 35] Three studies included a Radiometer POC device, including ABL800[29, 35] and ABL827.[25] Two studies evaluated three POC devices (ABL, i-STAT and StatSensor)[29, 35] and one study evaluated two devices (ABL and i-STAT).[25] There were no studies of other eligible POC tests such as ABL90 FLEX PLUS, Dri-chem NX500, epoc Blood Analysis System and Piccolo Xpress.

All sample types used with StatSensor were capillary,[26-28, 30, 34, 35] except in one study (venous sample).[29] Conversely, most i-STAT devices used venous samples[29, 31, 33, 35, 36] except in one study (capillary).[32] Another i-STAT study did not specify the sample type used.[25] None of the studies compared the accuracy of a single device using two different sample types.

Three StatSensor[28, 29, 34] and two i-STAT studies[32, 33] reported using an offset correction to estimates of concordance between the POC test and laboratory reference derived from the study sample. Adjusted and unadjusted results were reported in all three StatSensor studies, but only adjusted results were presented by the two i-STAT studies.

The laboratory reference method was Jaffe in two studies[30, 31] and not reported in one study.[32] All other studies used an enzymatic method. Equations used to calculate eGFR varied across the studies, and only three studies used CKD-EPI.[32, 35, 36]

Individual study results including contingency tables are presented in Table 7. Eight studies reported sufficient data to calculate accuracy at an eGFR threshold of 30mLs/min/1.73 m^2.[25, 27, 28, 30, 31, 34-36] Four studies only reported results using higher eGFR thresholds; two used an eGFR cut-off value of

60mLs/min/1.73 m^2,[29, 33] one study used an eGFR threshold of 90mL/min/1.73 m^2 (although some limited data on an eGFR threshold of 60mL/min/1.73 m^2 was extractable),[26] and one study only reported eGFR results according to a non-standard CKD classification (stages 0 to 4).[32]

Two studies were conference abstracts and did not provide sufficient data to be included in the synthesis.[32, 33] Both studies evaluated i-STAT and reported accuracy results following an offset correction.

Shephard et al 2008[33] compared the accuracy of i-STAT against an enzymatic method using 101 venous blood samples. After correction of a mean positive bias of 5.6% and alignment to the IDMS reference method, i-STAT had 96% sensitivity and 96% specificity for an eGFR threshold of 60 mL/min/1.73 m^2 compared with the laboratory reference test.

Obrador[32] evaluated the accuracy of i-STAT in 257 diabetic patients. Concordance with the laboratory reference was evaluated according to a CKD classification ranging from 0 to 4, with 0 indicating no CKD. No further details were provided on the CKD classification; therefore it is not clear how these results compare to the standard Kidney Disease Improving Global Outcomes (KDIGO) classification, as presented in Table 2. The study used a simple linear regression to estimate a correction factor to align i-STAT SCr to IDMS-SCr. After this correction, the study found that all patients with CKD (stages 1-4) were correctly classified by the POC test (100% sensitivity) and all but one were correctly classified as CKD-free (99.4% specificity).

Table 7 Studies reporting eGFR diagnostic accuracy data

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s) (sample type)</th><th>Laboratory reference</th><th>eGFR equation</th><th>Results</th></tr>
<tr><td>Botz et al 2013[25] Conference abstract</td><td>2042 patients at risk of renal disease prior to radiological examinations, 43% female
USA</td><td>ABL827, i-STAT1 (sample type NR)</td><td>Enzymatic, (Cobas C-501, Roche)</td><td>MDRD</td><td>Contingency table: ABL827 and i-STAT accuracy at eGFR 30 and 60 cut-offs
<table>
<tr><td colspan="2" rowspan="2">Source: publication</td><td colspan="2">ABL827 eGFR</td><td colspan="2">i-STAT eGFR</td></tr>
<tr><td><30</td><td>≥30</td><td><30</td><td>≥30</td></tr>
<tr><td rowspan="2">Lab eGFR</td><td><30</td><td>26</td><td>3</td><td>12</td><td>2</td></tr>
<tr><td>≥30</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td colspan="2" rowspan="2">Stated/implied in paper</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td><60</td><td>≥60</td><td><60</td><td>≥60</td></tr>
<tr><td rowspan="2">Lab eGFR</td><td><60</td><td>520</td><td>183</td><td>NR</td><td>NR</td></tr>
<tr><td>≥60</td><td>24</td><td>2517</td><td>NR</td><td>NR</td></tr>
</table>
Sensitivity and specificity for i-STAT at <60 and ≥60 were both 93%.
n=3244 for ABL827, n=2042 for i-STAT (patients with same-day measurements)</td></tr>
<tr><td>Dorward et al 2018[26] Letter to the editor</td><td>187 HIV positive patients from a POC RCT, median age 31 years [IQR 27-38], 62% female
mean creatinine 69.0 µmol/L
South Africa</td><td>StatSensor Xpress-I (capillary)</td><td>Enzymatic (Dimension EXL 200 IDMS, Siemens)</td><td>Modified MDRD (without race)</td><td>At eGFR<90mL/min threshold, sensitivity was 87.1% (95% CI 76.2 to 94.3), specificity was 52% (95% CI 42.9 to 61.0). One patient had a lab eGFR of <60; this was correctly identified by StatSensor.

At creatinine threshold of >106 µmol/L (1.2 mg/dL) sensitivity was 100% and specificity 95.1% (95% CI 90.9 to 97.7).</td></tr>
</table>

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s) (sample type)</th><th>Laboratory reference</th><th>eGFR equation</th><th>Results</th></tr>
<tr><td>Houben et al 2017[27]</td><td>351 women due for contrast-enhanced spectral mammography
Netherlands</td><td>StatSensor CREAT (capillary)</td><td>Enzymatic (Cobas 8000, Roche)</td><td>MDRD</td><td>Contingency table: StatSensor accuracy at eGFR 30 and 60 cut-offs
<table><tr><td colspan="2" rowspan="2">Source: publication</td><td colspan="4">StatSensor eGFR</td></tr><tr><td><30</td><td>30-44</td><td>45-59</td><td>≥60</td></tr><tr><td rowspan="3">Lab eGFR</td><td><30</td><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>30-44</td><td>0</td><td>0</td><td>1</td><td>2</td></tr><tr><td>≥45-60</td><td>0</td><td>0</td><td colspan="2">348</td></tr></table>
Seven patients had an eGFR <60ml/min/1.73m^2, necessitating additional preparation prior to contrast delivery. The POC device failed to categorize 6 of these 7 patients (86%), leading to unwanted contrast administration. Two patients (including 1 of the 3 patients with eGFR 45) subsequently developed CIN after 2–5 days, which was normalised after 30 days.</td></tr>
<tr><td>Inoue et al 2017[28]</td><td>123 (with unadjusted results), scheduled for CT
Mean eGFR 75.3 (SD 21.4)
Mean Creatinine 0.8mg/dL (SD 0.29)
Japan</td><td>StatSensor-i (capillary)</td><td>Enzymatic, (BioMajesty BM2250, Jeol Ltd)</td><td>Modified MDRD (Japanese CKD patients)</td><td>Contingency table: StatSensor accuracy at eGFR <30, 30-44 and ≥45 cut-offs (unadjusted results)*
<table><tr><td colspan="2" rowspan="2">Source: publication table and plots</td><td></td><td></td><td></td></tr><tr><td><30</td><td>30-44</td><td>≥45</td></tr><tr><td rowspan="3">Lab eGFR</td><td><30</td><td>4</td><td>0</td><td>0</td></tr><tr><td>30-44</td><td>1</td><td>7</td><td>0</td></tr><tr><td>≥45</td><td>1</td><td>11</td><td>99</td></tr></table>
*Adjustment was performed by “applying offset correction on the basis of the slope and intercept of internal sample.” Plots presented after correction suggested that eGFR laboratory measurements were unexpectedly affected by this adjustment, therefore only unadjusted results were extracted.</td></tr>
</table>

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s) (sample type)</th><th>Laboratory reference</th><th>eGFR equation</th><th>Results</th></tr>
<tr>
<td>Korpi-Steiner et al 2009[29]</td>
<td>266 excess samples taken before CT procedures. Mean age 68 years, 39% female
USA</td>
<td>ABL800 FLEX, i-STAT, StatSensor (with slope and intercept offset option)
-hepanirised venous samples</td>
<td>Enzymatic, (Cobas Integra 400 Roche)</td>
<td>Integra 400 and ABL800 used adjusted MDRD (isotope dilution mass spectrometry-IDMS traceable). i-STAT and Statsensor used conventional MDRD</td>
<td>
Contingency table: ABL800 & i-STAT accuracy at eGFR 60 cut-offs
<table>
<tr><td colspan="2" rowspan="2">Source: publication</td><td colspan="2">ABL800 eGFR</td><td colspan="2">i-STAT eGFR</td></tr>
<tr><td><60</td><td>≥60</td><td><60</td><td>≥60</td></tr>
<tr><td rowspan="2">Lab eGFR</td><td><60</td><td>55</td><td>13</td><td>66</td><td>2</td></tr>
<tr><td>≥60</td><td>6</td><td>192</td><td>32</td><td>166</td></tr>
</table>
Contingency table: StatSensor accuracy at eGFR 60 cut-offs, with and without correction offset*
<table>
<tr><td colspan="2" rowspan="2">Source: publication</td><td colspan="2">StatSensor eGFR</td><td colspan="2">StatSensor offset eGFR</td></tr>
<tr><td><60</td><td>≥60</td><td><60</td><td>≥60</td></tr>
<tr><td rowspan="2">Lab eGFR</td><td><60</td><td>11</td><td>57</td><td>40</td><td>28</td></tr>
<tr><td>≥60</td><td>0</td><td>198</td><td>24</td><td>174</td></tr>
</table>
*An offset of 0.28mg/dL was applied that maximised overall concordance between POC and laboratory reference in this dataset.
</td>
</tr>
<tr>
<td>Krige 2017[30]
PhD thesis</td>
<td>103 mixed ancestry South Africans, Mean age 52, 69% female
South Africa</td>
<td>StatSensor-i (capillary)</td>
<td>Jaffe (AU5800 Beckman Coulter)</td>
<td>MDRD (SI units)</td>
<td>
Contingency table: StatSensor-i accuracy at eGFR <30, 30-44, 45-59 and ≥60 cut-offs
<table>
<tr><td colspan="2" rowspan="2">Source: individual patient data in thesis</td><td colspan="4">StatSensor-i eGFR</td></tr>
<tr><td><30</td><td>30-44</td><td>45-59</td><td>≥60</td></tr>
<tr><td rowspan="4">Lab eGFR</td><td><30</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>30-44</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>45-59</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>≥60</td><td>0</td><td>0</td><td>0</td><td>100</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s) (sample type)</th><th>Laboratory reference</th><th>eGFR equation</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>The three low eGFR values were: POC 22, lab 19; POC 48, lab 49 and POC >90, lab 56.</td></tr>
<tr><td>Nichols 2007[31]</td><td>50 chemotherapy patients
USA</td><td>i-STAT (venous)</td><td>Jaffe; Enzymatic (Roche)</td><td>Cockroft-Gault (CG) & MDRD</td><td>Diagnostic accuracy of i-STAT against two laboratory reference methods and two eGFR equations at eGFR <60 cut-off
<table><tr><td>Source: publication</td><td>Sensitivity%</td><td>Specificity%</td></tr><tr><td>MDRD Jaffe</td><td>100</td><td>87.2</td></tr><tr><td>CG Jaffe</td><td>100</td><td>59.2</td></tr><tr><td>MDRD Enzymatic</td><td>100</td><td>85</td></tr><tr><td>CG Enzymatic</td><td>100</td><td>72.5</td></tr></table></td></tr>
<tr><td>Obrador et al 2012[32]
Conference abstract</td><td>257 diabetic patients
Mean age: 57 years, 62% female
Mexico</td><td>i-STAT (capillary)</td><td>NR (Olympus 5400, IDMS aligned)</td><td>CKD-EPI</td><td>Contingency table: i-STAT accuracy by CKD stage (0-4)
<table><tr><td rowspan="2">Source: table in abstract</td><td></td><td colspan="5">IDMS SCr-Laboratory reference</td></tr><tr><td>CKD stage</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td></tr><tr><td rowspan="5">i-STAT SCr CKD</td><td>0</td><td>154</td><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>1</td><td>0</td><td>53</td><td>5</td><td>0</td><td>0</td></tr><tr><td>2</td><td>0</td><td>4</td><td>13</td><td>3</td><td>0</td></tr><tr><td>3</td><td>1</td><td>0</td><td>3</td><td>15</td><td>2</td></tr><tr><td>4</td><td>0</td><td>0</td><td>0</td><td>0</td><td>4</td></tr><tr><td>Total</td><td></td><td>155</td><td>57</td><td>21</td><td>18</td><td>6</td></tr></table>
Simple linear regression was used to estimate a correction factor to align i-STAT SCr to IDMS-SCr. Following this correction, no patient was incorrectly classified as not having CKD by i-STAT (capillary sample) (100% sensitivity) and 1 was incorrectly classified as having CKD (99.4% specificity).</td></tr>
</table>

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s) (sample type)</th><th>Laboratory reference</th><th>eGFR equation</th><th>Results</th></tr>
<tr><td>Shephard et al 2008[33]
Conference abstract</td><td>101 venous blood samples
Australia</td><td>i-STAT (venous)</td><td>Enzymatic (IDMS aligned) (device NR)</td><td>NR</td><td>The i-STAT had a positive measurement bias relative to the IDMS-aligned laboratory method (mean bias of 5.6% overall, 10.4% for samples <150 mmol/L and 4.5% for samples >150 mmol/L). This bias was corrected, and an IDMS alignment performed, using a correction formula based on the regression equation between the i-STAT and laboratory methods: x (corrected i-STAT creatinine) = 0.97 y (IDMS lab creatinine) – 6.5.

Following correction, sensitivity and specificity were both 96% for an eGFR cut-off of 60mLs/min/1.73 $m^{2.}$</td></tr>
<tr><td>Shephard et al 2010[34]</td><td>100 (63 renal/dialysis patients attending clinic, 37 healthy), 52% female
Australia</td><td>StatSensor (capillary)</td><td>Enzymatic (Creatinine Plus assay, Roche)</td><td>MDRD</td><td>Diagnostic accuracy of two StatSensor devices at eGFR 60 cut-off before and after recalibration*
<table>
<tr><td>Source: publication</td><td>Sensitivity%</td><td>Specificity%</td></tr>
<tr><td>StatSensor 1 (pre-lab recalibration)</td><td>86.8</td><td>100</td></tr>
<tr><td>StatSensor 2 (pre-lab recalibration)</td><td>82.4</td><td>100</td></tr>
<tr><td>StatSensor 1 (post-lab recalibration)</td><td>96.2</td><td>78.7</td></tr>
<tr><td>StatSensor 2 (post-lab recalibration)</td><td>92.2</td><td>78.7</td></tr>
</table>
*After correction of a mean positive bias of 5.6% and alignment to the isotope dilution mass spectrometry (IDMS) reference method

Contingency table: StatSensor accuracy at eGFR 60 cut-offs before and after recalibration*
<table>
<tr><td colspan="2">Source: publication in paper</td><td colspan="2">StatSensor 1 eGFR pre-recalibration</td><td colspan="2">StatSensor 1 eGFR post-recalibration*</td></tr>
<tr><td></td><td></td><td><60</td><td>≥60</td><td><60</td><td>≥60</td></tr>
<tr><td rowspan="2">Lab eGFR</td><td><60</td><td>46</td><td>7</td><td>51</td><td>2</td></tr>
<tr><td>≥60</td><td>0</td><td>46</td><td>10</td><td>37</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s) (sample type)</th><th>Laboratory reference</th><th>eGFR equation</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>*After correction of a mean positive bias of 5.6% and alignment to the isotope dilution mass spectrometry (IDMS) reference method

Contingency table: StatSensor accuracy at eGFR <30, 30-59 and ≥60 cut-offs before and after recalibration*
<table>
<tr><td colspan="2" rowspan="2">Source: study figure</td><td colspan="3">StatSensor 1 pre-recalibration</td><td colspan="3">StatSensor 1 post-recalibration</td></tr>
<tr><td><30</td><td>30-59</td><td>≥60</td><td><30</td><td>30-59</td><td>≥60</td></tr>
<tr><td rowspan="3">Lab eGFR</td><td><30</td><td>26</td><td>6</td><td>1</td><td>32</td><td>1</td><td>0</td></tr>
<tr><td>30-59</td><td>0</td><td>14</td><td>6</td><td>1</td><td>17</td><td>2</td></tr>
<tr><td>≥60</td><td>0</td><td>0</td><td>47</td><td>0</td><td>10</td><td>37</td></tr>
</table>
*After correction of a mean positive bias of 5.6% and alignment to the isotope dilution mass spectrometry (IDMS) reference method

No further accuracy results were reported for StatSensor 2.</td></tr>
<tr><td>Snaith et al 2018[35]</td><td>300 attending for routine blood tests (phlebotomy outpatients), mean age 60 years, 47% female, mean creatinine 92µmol/L
UK</td><td>ABL800 FLEX, StatSensor (capillary), i-STAT (venous)</td><td>Enzymatic (Cobas 8000, Roche)</td><td>CKD-EPI (and MDRD for comparison)</td><td>Contingency table: i-STAT accuracy at eGFR <30, 30-44, 45-59 and ≥60 cut-offs
<table>
<tr><td colspan="2" rowspan="2">Source: correspondence with author</td><td colspan="4">i-STAT eGFR result</td></tr>
<tr><td><30</td><td>30-44</td><td>45-59</td><td>≥60</td></tr>
<tr><td rowspan="4">Lab reference eGFR result</td><td><30</td><td>12</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>30-44</td><td>3</td><td>25</td><td>0</td><td>0</td></tr>
<tr><td>45-59</td><td>0</td><td>5</td><td>29</td><td>1</td></tr>
<tr><td>≥60</td><td>0</td><td>1</td><td>14</td><td>210</td></tr>
</table>
Contingency table: ABL800 accuracy at eGFR <30, 30-44, 45-59 and ≥60 cut-offs
<table>
<tr><td></td><td>ABL800 eGFR result</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study</th><th>N, Population</th><th>POC device(s) (sample type)</th><th>Laboratory reference</th><th>eGFR equation</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td colspan="2">Source: correspondence with author</td><td><30</td><td>30-44</td><td>45-59</td><td>≥60</td></tr>
<tr><td rowspan="4">Lab reference eGFR result</td><td><30</td><td>12</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>30-44</td><td>0</td><td>24</td><td>4</td><td>0</td></tr>
<tr><td>45-59</td><td>0</td><td>2</td><td>31</td><td>2</td></tr>
<tr><td>≥60</td><td>0</td><td>0</td><td>1</td><td>224</td></tr>
</table>
Contingency table: StatSensor accuracy at eGFR <30, 30-44, 45-59 and ≥60 cut-offs
<table>
<tr><td colspan="2" rowspan="2">Source: correspondence with author</td><td colspan="4">StatSensor eGFR result</td></tr>
<tr><td><30</td><td>30-44</td><td>45-59</td><td>≥60</td></tr>
<tr><td rowspan="4">Lab reference eGFR result</td><td><30</td><td>8</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>30-44</td><td>3</td><td>17</td><td>8</td><td>0</td></tr>
<tr><td>45-59</td><td>0</td><td>10</td><td>17</td><td>8</td></tr>
<tr><td>≥60</td><td>0</td><td>1</td><td>33</td><td>191</td></tr>
</table>
Test failures occurred 4 times with StatSensor and once with ABL800 FLEX (none for i-STAT). All 5 second tests were successful.
</td></tr>
<tr><td>Snaith et al 2019[36]</td><td>300 adult outpatients attending for a contrast-enhanced CT scan, mean age 65 years, 48% female
UK</td><td>i-STAT (venous)</td><td>Enzymatic (Cobas 8000, Roche)</td><td>CKD-EPI</td><td>
Contingency table: i-STAT accuracy at eGFR <30, 30-44, 45-59 and ≥60 cut-offs
<table>
<tr><td colspan="2" rowspan="2">Source: correspondence with author</td><td colspan="4">i-STAT eGFR result</td></tr>
<tr><td><30</td><td>30-44</td><td>45-59</td><td>≥60</td></tr>
<tr><td rowspan="3">Lab reference eGFR result</td><td><30</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>30-44</td><td>1</td><td>9</td><td>4</td><td>0</td></tr>
<tr><td>45-59</td><td>0</td><td>2</td><td>35</td><td>7</td></tr>
</table>
</td></tr>
</table>

Study	N, Population	POC device(s) (sample type)	Laboratory reference	eGFR equation	Results
					<table><tr><td></td><td>≥60</td><td>0</td><td>1</td><td>7</td><td>234</td></tr></table> Six PoC test failures were recorded.

LoA Limits of agreement, CKD Chronic kidney disease, B-A Bland-Altman, POC point-of-care, NR Not reported, lab laboratory

4.2.6 Available data for quantitative synthesis

Studies of StatSensor devices

Data from the seven studies included in the analysis for StatSensor devices are given in Table 8. One study[26] provided limited data on only one individual with eGFR < 60 mL/min/1.73 m^2 who was correctly classified by StatSensor Xpress-i, but no other data on individuals in other eGFR categories. One study[28] reported data on collapsed categories of eGFR for StatSensor-i. The StatSensor device was compared in five studies, two of which[30, 35] reported data on all eGFR categories in Table 2.

Two studies of StatSensor devices included a user-specified adjustment (Table 1) to correct for systematic measurement bias.[29, 34] A third study[28] reported data using an alternative adjustment which cannot be applied directly to the device. A possible scenario for use of this device in clinical practice is to identify whether there is a systematic bias in device performance and then incorporate an adjustment into the device, to correct subsequent samples. To assess performance of StatSensor under this scenario, an additional "adjusted data" analysis was carried out, where the reported adjusted data from Korpi-Steiner 2009[29] and Shephard 2010[34] were used, but Inoue 2017[28] was removed since bias was identified but the correction was not one that could be implemented in practice.

Studies of i-STAT devices

Data from the five studies included in the analysis for i-STAT devices are given in Table 9. All studies presented results for the i-STAT device, except for Botz 2013[25] which provided limited data on individuals with eGFR < 30 mL/min/1.73 m^2 and their classification using i-STAT1. Two studies[35, 36] reported data on all eGFR categories, although Snaith 2019[36] did not observe any individuals with eGFR < 30 mL/min/1.73 m^2.

Studies of ABL series devices

Data from the three studies included in the analysis for ABL (Radiometer) devices are given in Table 10. Two types of device were compared: ABL800 FLEX[29, 35] and ABL827.[25] Only one study provided data on all eGFR categories.[35].

Studies calculating eGFR using CKD-EPI

All studies used the MDRD equation to calculate eGFR except for two, which used CKD-EPI.[35, 36] The first of these included StatSensor, i-STAT and ABL800 FLEX devices[35] and the second study included only the i-STAT device.[36] In addition, these two studies were also the only ones with low risk of bias and applicability concerns (Table 4). An additional analysis using only the data in these two studies was carried out to check for any differences in classification accuracy. Although only one

study included a StatSensor or ABL device, in order to properly quantify the uncertainty in the probabilities, the model described in Section 4.1.5.1 (equations (1) and (2)) was still used.

Table 8 StatSensor Devices: data used in main analysis of diagnostic accuracy (7 studies).

Lab eGFR	**POC eGFR**	Snaith 2018	Krige 2017	**Lab eGFR**	**POC eGFR**	Houben 2017	**Lab eGFR**	**POC eGFR**	Inoue 2017	**Lab eGFR**	**POC eGFR**	Shephard 2010	**Lab eGFR**	**POC eGFR**	Korpi-Steiner 2009	Dorward 2018
<30	**<30**	8	1	**<30**	**<30**	0	**<30**	**<30**	4	**<30**	**<30**	26	**<60**	**<60**	11	1
	30-44	4	0		**30-44**	0		**30-44**	0		**30-59**	6		**≥60**	57	0
	45-59	0	0		**45-59**	0		**≥45**	0		**>60**	1				
	≥60	0	0		**≥60**	0										
	N	**12**	**1**		**N**	**0**		**N**	**4**		**N**	**33**		**N**	**68**	1
30-44	**<30**	3	0	**30-44**	**<30**	0	**30-44**	**<30**	1	**30-59**	**<30**	0	**≥60**	**<60**	0	NA
	30-44	17	0		**30-44**	0		**30-44**	7		**30-59**	14		**≥60**	198	NA
	45-59	8	0		**45-59**	1		**≥45**	0		**>60**	6				
	≥60	0	0		**≥60**	2										
	N	**28**	**0**		**N**	**3**		**N**	**8**		**N**	**20**		**N**	**198**	**186**
45-59	**<30**	0	0	**≥45**	**<30**	0	**≥45**	**<30**	1	**≥60**	**<30**	0				
	30-44	10	0		**30-44**	0		**30-44**	11		**30-59**	0				
	45-59	17	1		**≥45**	348		**≥45**	99		**>60**	47				
	≥60	8	1													
	N	**35**	**2**		**N**	**348**		**N**	**111**		**N**	**47**				
≥60	**<30**	0	0													
	30-44	1	0													
	45-59	33	0													
	≥60	191	100													
	N	**225**	**100**													

eGFR in mL/min/1.73 m^2.

Table 9 i-STAT Devices: data used in main analysis of diagnostic accuracy (5 studies).

Lab eGFR	POC eGFR	Snaith 2018	Snaith 2019
<30	**<30**	12	0
	30-44	0	0
	45-59	0	0
	≥60	0	0
	N	**12**	**0**
30-44	**<30**	3	1
	30-44	25	9
	45-59	0	4
	≥60	0	0
	N	**28**	**14**
45-59	**<30**	0	0
	30-44	5	2
	45-59	29	35
	≥60	1	7
	N	**35**	**44**
≥60	**<30**	0	0
	30-44	1	1
	45-59	14	7
	≥60	210	234
	N	**225**	**242**

Lab eGFR	POC eGFR	Botz 2013
<30	**<30**	12
	≥30	2
	N	**14**
≥30	**<30**	NA
	≥30	NA
	N	**2028**

Lab eGFR	POC eGFR	Korpi-Steiner 2009	Nichols 2007
<60	**<60**	66	9
	≥60	2	0
	N	**68**	**9**
≥60	**<60**	32	6
	≥60	166	34
	N	**198**	**40**

eGFR in mL/min/1.73 m^2.

Table 10 ABL Devices: data used in main analysis of diagnostic accuracy (3 studies).

Lab eGFR	**POC eGFR**	Snaith 2018
<30	**<30**	12
	30-44	0
	45-59	0
	≥60	0
	N	**12**
30-44	**<30**	0
	30-44	24
	45-59	4
	≥60	0
	N	**28**
45-59	**<30**	0
	30-44	2
	45-59	31
	≥60	2
	N	**35**
≥60	**<30**	0
	30-44	0
	45-59	1
	≥60	224
	N	**225**

Lab eGFR	**POC eGFR**	Botz 2013
<30	**<30**	26
	≥30	3
	N	**29**
30-59	**<30**	NA
	≥30	NA
	N	**674**
≥60	**0-60**	24
	≥60	2517
	N	**2541**

Lab eGFR	**POC eGFR**	Korpi-Steiner 2009
<60	**<60**	55
	≥60	13
	N	**68**
≥60	**<60**	6
	≥60	192
	N	**198**

eGFR in mL/min/1.73 m^2.

4.2.7 Results: assessment of diagnostic accuracy

Convergence was achieved for all synthesis models at (or before) 5,000 iterations. A further 30,000 iterations on two chains were run, therefore all results are based on 60,000 post-convergence iterations.

4.2.7.1 Probability of belonging to each category

The probabilities that an individual belongs to each eGFR category in Table 2 were calculated from the number of individuals in each category reported by all included studies (i.e. regardless of the device being evaluated, one study reporting results on two sets of patients[25]). The probabilities reported in each study are given in Table 11 (raw data in Table 8, Table 9, Table 10). The pooled probabilities of belonging to each of the 4 categories of interest, $T[j]$, $j = 1, 2, 3, 4$, used in the main synthesis model are given in Table 12.

Table 11 Reported probabilities of belonging to lab eGFR categories in each study.

Lab eGFR (mL/min/1.73 m^2)	Snaith 2018[35]	Snaith 2019[36]	Krige 2017[30]
<30	0.040	0.000	0.010
30-44	0.093	0.047	0.000
45-59	0.117	0.147	0.019
≥60	0.750	0.807	0.971
	Inoue 2017[28]	Houben 2017[27]	
<30	0.033	0.000	
30-44	0.065	0.009	
≥45	0.902	0.991	
	Shephard 2010[34]	Botz 2013 (ABL)[25]	
<30	0.330	0.009	
30-59	0.200	0.208	
≥60	0.470	0.783	
	Botz 2013 (i-STAT)[25]		
<30	0.007		
≥30	0.993		
	Korpi-Steiner 2009[29]	Dorward 2018[26]	Nichols 2007[31]
<60	0.256	0.005	0.184

≥60	0.744	0.995	0.816

Most studies included few individuals in category 1 (eGFR < 30 mL/min/1.73 m^2) and more individuals in higher eGFR categories. However, Shephard 2010[34] included a majority of renal patients and therefore individuals had a higher probability of being in category 1, than those in other included studies (33% compared to 0-4%). Excluding this study reduced the pooled probability of being in category 1, $T[1]$, slightly but hardly impacted the other probabilities (Table 12). A sensitivity analysis was conducted to assess how this affected the estimation of the main probabilities of interest (see Section 4.2.7.4).

Table 12 Estimated probabilities of belonging to each eGFR category

	All data		Shephard 2010[34] removed	
	median	95%CrI	median	95%CrI
T[1]	0.014	(0.011, 0.017)	0.009	(0.007, 0.012)
T[2]	0.051	(0.039, 0.064)	0.051	(0.039, 0.064)
T[3]	0.143	(0.127, 0.159)	0.143	(0.127, 0.159)
T[4]	0.792	(0.780, 0.803)	0.797	(0.785, 0.808)

T[j], probability of belonging to eGFR catgory j. Categories are described in Table 2.

4.2.7.2 Probability of classification by POC device, given lab defined category

The pooled probabilities of being classified by POC device in category k, given lab classification in category j, p_{jk} = p[j,k], with $j,k = 1,2,3,4$, are given in Table 13 and plotted as density strips in Figure 2 for the three devices.

Table 13 Pooled probabilities for the three types of device.

	StatSensor		i-STAT		ABL	
	Median	95%CrI	median	95%CrI	median	95%CrI
p[1,1]	0.74	(0.61, 0.85)	0.85	(0.69, 0.94)	0.87	(0.75, 0.95)
p[1,2]	0.18	(0.08, 0.30)	0.04	(0.00, 0.18)	0.03	(0.00, 0.14)
p[1,3]	0.03	(0.00, 0.12)	0.04	(0.00, 0.18)	0.03	(0.00, 0.14)
p[1,4]	0.04	(0.01, 0.11)	0.04	(0.00, 0.16)	0.04	(0.00, 0.15)

p[2,1]	0.09	(0.03, 0.19)	0.10	(0.04, 0.21)	0.02	(0.00, 0.11)
p[2,2]	0.57	(0.42, 0.71)	0.77	(0.64, 0.87)	0.78	(0.61, 0.90)
p[2,3]	0.22	(0.12, 0.36)	0.10	(0.04, 0.21)	0.15	(0.05, 0.29)
p[2,4]	0.10	(0.03, 0.24)	0.01	(0.00, 0.06)	0.03	(0.00, 0.15)
p[3,1]	0.01	(0.00, 0.03)	0.01	(0.00, 0.05)	0.02	(0.00, 0.08)
p[3,2]	0.14	(0.09, 0.20)	0.10	(0.04, 0.17)	0.06	(0.01, 0.16)
p[3,3]	0.25	(0.16, 0.34)	0.81	(0.72, 0.88)	0.74	(0.62, 0.85)
p[3,4]	0.60	(0.51, 0.69)	0.08	(0.04, 0.13)	0.17	(0.09, 0.26)
p[4,1]	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)
p[4,2]	0.00	(0.00, 0.01)	0.01	(0.00, 0.02)	0.00	(0.00, 0.01)
p[4,3]	0.06	(0.04, 0.08)	0.08	(0.06, 0.10)	0.01	(0.00, 0.01)
p[4,4]	0.94	(0.91, 0.95)	0.91	(0.89, 0.93)	0.99	(0.98, 0.99)

p[i,j] probability of being classified in category j by the POC device when lab category is i. Categories are described in Table 2.

The i-STAT and ABL devices have higher median probabilities of correct classification in each of the 3 lowest categories (p[1,1], p[2,2], p[3,3]) than the StatSensor, with the latter appearing particularly poor at correctly classifying individuals in category 3 (eGFR 45-59 mL/min/1.73 m^2). However, there is considerable uncertainty in these probabilities for all devices.

The median probabilities of being correctly classified as being at risk of PC-AKI (defined as eGFR < 30 mL/min/1.73 m^2, sensitivity) using i-STAT or ABL devices are similar (85% and 87% respectively), whereas for StatSensor devices this median probability is lower (74%). The median probabilities of being incorrectly classified as being at risk of PC-AKI by the POC device for individuals with eGFR 30-45 mL/min/1.73 m^2 range from 2% for ABL devices to 9-10% for StatSensor and i-STAT devices, although there is some uncertainty around these values. The probabilities of being incorrectly classified as at risk reduce considerably for individuals with eGFR ≥ 45 mL/min/1.73 m^2.

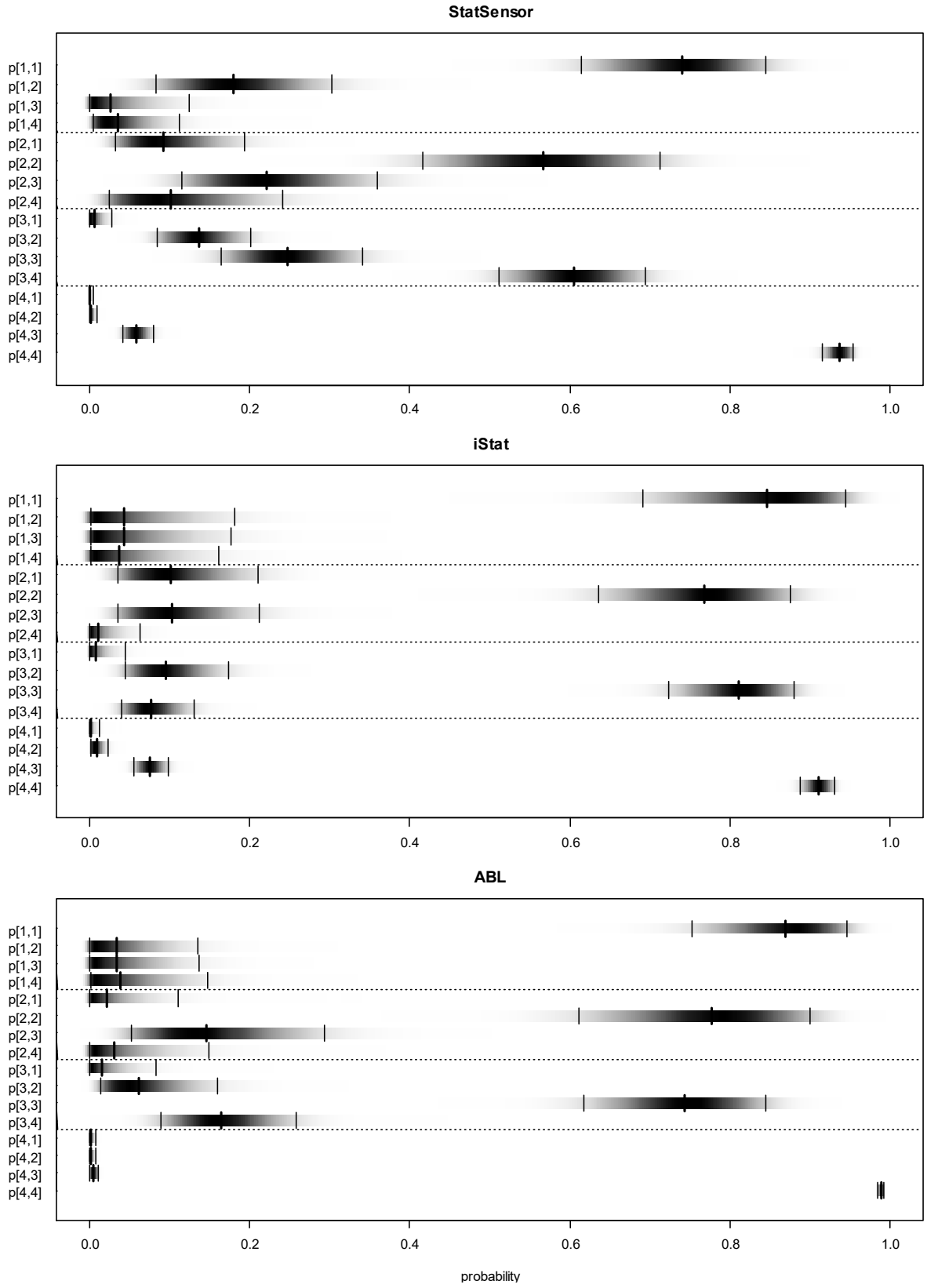


Figure 2 Density strips for classification probabilities for each device with vertical lines defining the median and 95% CrI

4.2.7.3 Additional analyses

Two (non-prespecified) additional analyses were conducted: one using adjusted data for StatSensor devices and a second using only data from studies using the CKD-EPI equation to calculate eGFR (see Section 4.2.6).

StatSensor adjusted data analysis

Adjusted data reported by Korpi-Steiner 2009[29] and Shephard 2010[34] are given in Table 14. The pooled probabilities for StatSensor obtained using these adjusted data and removing Inoue 2017[28] are given in Table 15. Figure 3 presents density strips for the probabilities obtained for StatSensor in the main analysis (black, wide), and using the adjusted data (green, narrow).

Table 14 StatSensor: data used in adjusted analysis of diagnostic accuracy.

true eGFR	**POC eGFR**	Shephard 2010 (StatSensor - adjusted)	**true eGFR**	**POC eGFR**	Korpi-Steiner 2009 (StatSensor – with offset)
<30	**<30**	32	**<60**	**<60**	40
	30-59	1		**≥60**	28
	≥60	0			
	N	**33**		**N**	**68**
30-59	**<30**	1	**≥60**	**<60**	24
	30-59	17		**≥60**	174
	≥60	2			
	N	**20**		**N**	**198**
≥60	**<30**	0			
	30-59	10			
	≥60	37			
	N	**47**			

eGFR in mL/min/1.73 m^2.

Table 15 Pooled probabilities for the StatSensor device under a measurement bias adjustment scenario.

	StatSensor	
	Median	95%CrI
p[1,1]	0.84	(0.73, 0.93)

p[1,2]	0.11	(0.04, 0.22)
p[1,3]	0.02	(0.00, 0.08)
p[1,4]	0.01	(0.00, 0.08)
p[2,1]	0.11	(0.04, 0.22)
p[2,2]	0.51	(0.35, 0.67)
p[2,3]	0.28	(0.15, 0.44)
p[2,4]	0.09	(0.02, 0.22)
p[3,1]	0.01	(0.00, 0.04)
p[3,2]	0.12	(0.06, 0.20)
p[3,3]	0.49	(0.37, 0.60)
p[3,4]	0.38	(0.28, 0.49)
p[4,1]	0.00	(0.00, 0.01)
p[4,2]	0.00	(0.00, 0.01)
p[4,3]	0.12	(0.09, 0.14)
p[4,4]	0.88	(0.85, 0.90)

p[i,j] probability of being classified in category j by the POC device when lab category is i. Categories are described in Table 2. Adjusted data for Korpi-Steiner 2009[29] and Shephard 2010[34] were used and Inoue 2017[28] was removed.

There is good overlap of the 95% CrI for classifications of individuals with true eGFR in the first two categories, although the adjusted analysis gives a higher probability that individuals are correctly classified as being at risk of PC-AKI (sensitivity) (p[1,1] median 84%, Table 15, compared to 74% in the unadjusted analysis, Table 13).

However, there is conflict between results from the adjusted data analysis and the main analysis for categories 3 and 4, particularly for estimated probabilities p[3,3], p[3,4], p[4,3] and p[4,4]. The main analysis suggests a lower probability of correctly classifying individuals in category 3, but a higher probability of correctly classifying individuals in category 4, than the adjusted data analysis. In addition, the main analysis suggests that individuals in category 3 have a lower probability of being classified as belonging to this category than to category 4, whereas this is not the case in the adjusted analysis.

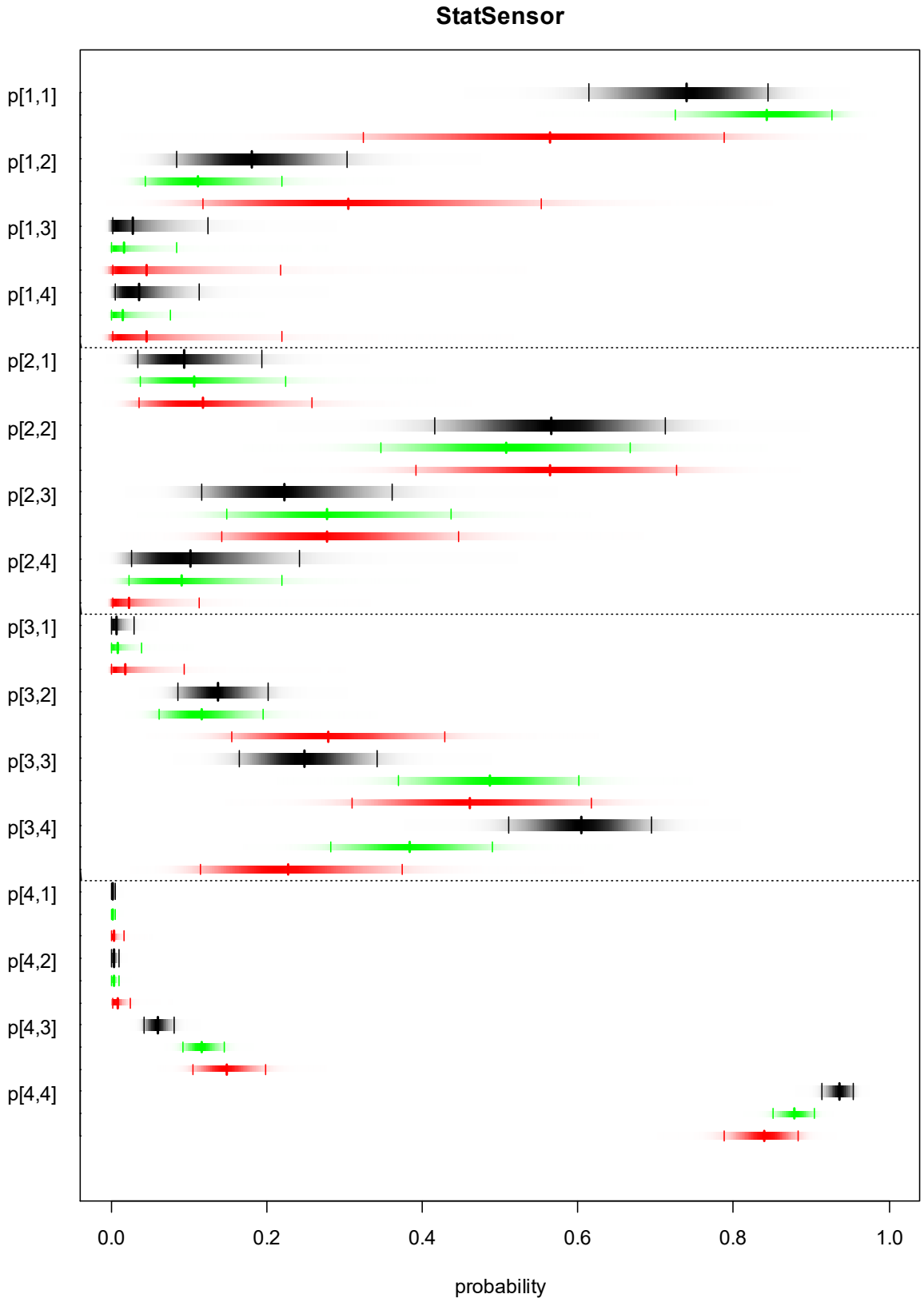


Figure 3 StatSensor: Density strips for classification probabilities for the main analysis (black, wide), the adjusted data analysis (green, narrow) and the analysis including only CKD-EPI data (red, narrow). Vertical lines define the median and 95% CrI.

Including only studies using CKD-EPI equation

The pooled probabilities of being classified by POC device in category k, given lab classification in category j, $p_{jk} = \text{p[j,k]}$, with $j,k = 1,2,3,4$, for StatSensor and ABL800 FLEX estimated from data from the only study which used the CKD-EPI equation[35], and for i-STAT using data from the two studies which used that equation,[35, 36] are presented in Table 16.

Table 16 CKD-EPI data only: Pooled probabilities for the three types of device

	StatSensor		i-STAT		ABL800 FLEX (Radiometer)	
	median	95%CrI	median	95%CrI	median	95%CrI
p[1,1]	0.56	(0.32, 0.79)	0.83	(0.60, 0.96)	0.83	(0.60, 0.96)
p[1,2]	0.31	(0.12, 0.55)	0.05	(0.00, 0.22)	0.05	(0.00, 0.22)
p[1,3]	0.05	(0.00, 0.22)	0.05	(0.00, 0.22)	0.04	(0.00, 0.22)
p[1,4]	0.05	(0.00, 0.22)	0.05	(0.00, 0.22)	0.05	(0.00, 0.22)
p[2,1]	0.12	(0.04, 0.26)	0.10	(0.04, 0.21)	0.02	(0.00, 0.11)
p[2,2]	0.56	(0.39, 0.73)	0.76	(0.63, 0.87)	0.79	(0.63, 0.90)
p[2,3]	0.28	(0.14, 0.45)	0.10	(0.04, 0.21)	0.15	(0.05, 0.30)
p[2,4]	0.02	(0.00, 0.11)	0.02	(0.00, 0.08)	0.02	(0.00, 0.11)
p[3,1]	0.02	(0.00, 0.09)	0.01	(0.00, 0.04)	0.02	(0.00, 0.09)
p[3,2]	0.28	(0.15, 0.43)	0.09	(0.04, 0.17)	0.07	(0.02, 0.18)
p[3,3]	0.46	(0.31, 0.62)	0.79	(0.69, 0.86)	0.83	(0.69, 0.92)
p[3,4]	0.23	(0.11, 0.37)	0.11	(0.05, 0.18)	0.07	(0.02, 0.18)
p[4,1]	0.00	(0.00, 0.02)	0.00	(0.00, 0.01)	0.00	(0.00, 0.02)
p[4,2]	0.01	(0.00, 0.02)	0.01	(0.00, 0.02)	0.00	(0.00, 0.02)
p[4,3]	0.15	(0.11, 0.20)	0.05	(0.03, 0.07)	0.01	(0.00, 0.02)
p[4,4]	0.84	(0.79, 0.88)	0.95	(0.92, 0.96)	0.98	(0.96, 1.00)

p[i,j] probability of being classified in category j by the POC device when lab category is i. Categories are described in Table 2.

StatSensor results

Figure 3 presents density strips for the probabilities obtained for StatSensor using only the CKD-EPI data (narrow, red). These results broadly agree with the adjusted data analysis (narrow, green),

although uncertainty in the probabilities for eGFR < 30 mL/min/1.73 m^2 is larger in the CKD-EPI analysis since only one study is used with only a few individuals in this category.

i-STAT results

Figure 4 presents density strips for the probabilities obtained for i-STAT in the main analysis (wide, black) and the analysis using only the CKD-EPI data[35, 36] (narrow, red). There is good overlap of all density strips, with the main analysis producing slightly more precise results.

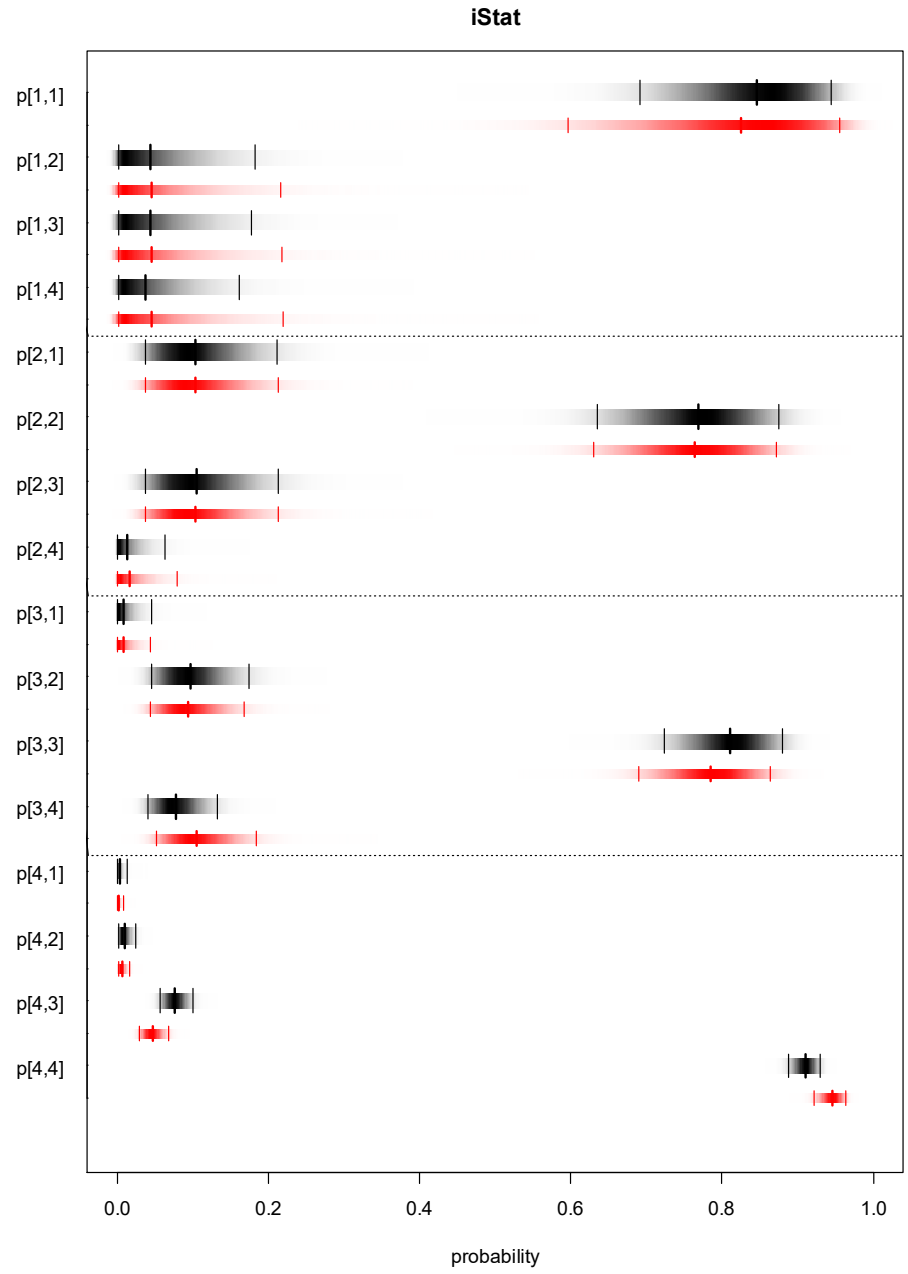


Figure 4 i-STAT: Density strips for classification probabilities for the main analysis (black, wide) and the sensitivity analysis including only CKD-EPI data (red, narrow). Vertical lines define the median and 95% CrI.

ABL (Radiometer) results

Figure 5 presents density strips for the probabilities obtained for ABL (Radiometer) devices in the main analysis (wide, black) and the analysis using only the CKD-EPI data[35] (narrow, red). There is good overlap of all density strips, with the main analysis producing slightly more precise results particularly for the probabilities of being correctly classified as at risk of PC-AKI (eGFR < 30 mL/min/1.73 m^2).

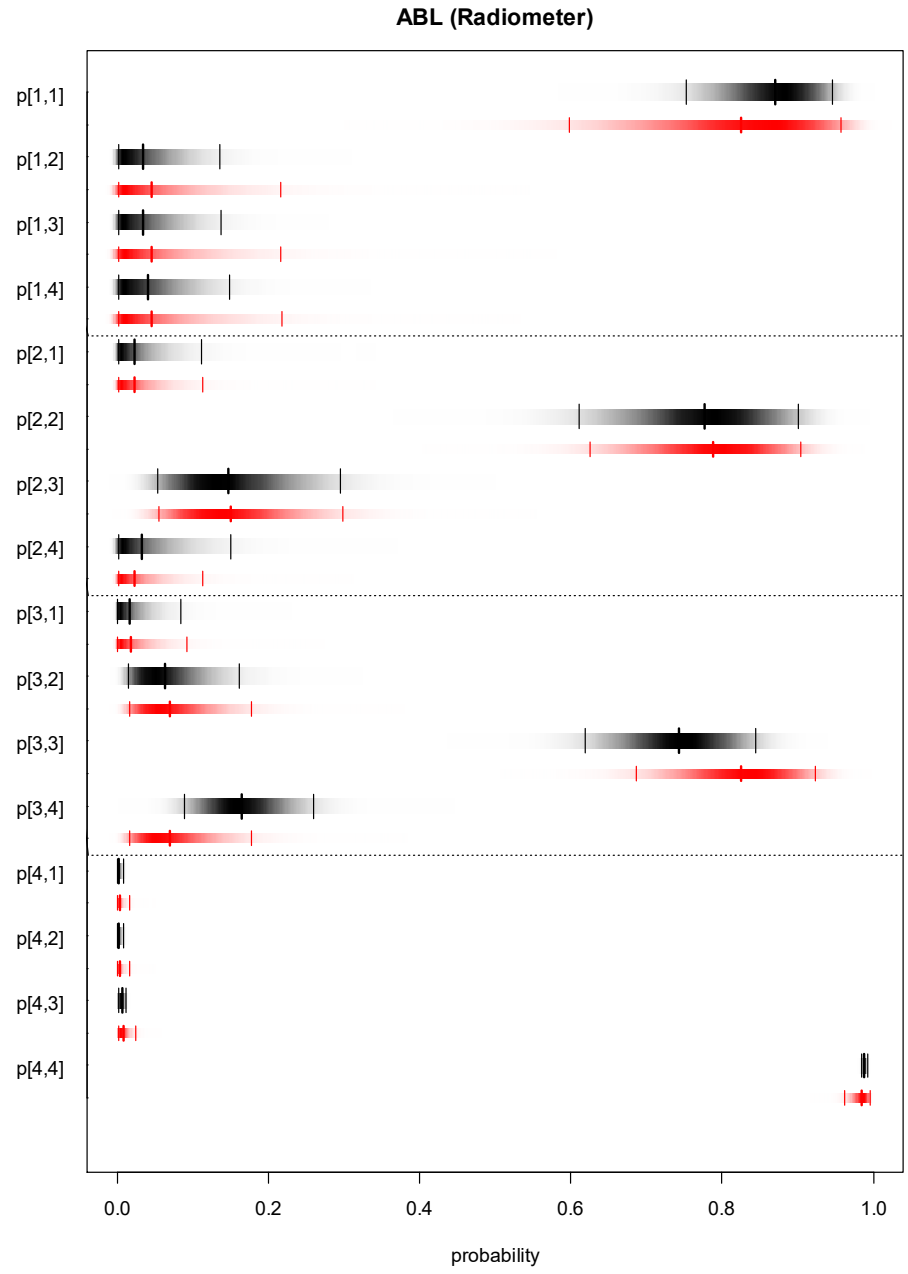


Figure 5 ABL800 FLEX (Radiometer): Density strips for classification probabilities for the main analysis (black, wide) and the sensitivity analysis including only data from Snaith 2018 (red, narrow). Vertical lines define the median and 95% CrI.

4.2.7.4 Sensitivity analysis for true probability calculations

To assess the impact of using different values of $T[j]$ (Table 12) in the model for the probabilities of interest, p_{jk}, a sensitivity analysis was conducted for each device with Shephard 2010[34] removed from the calculation of the $T[j]$ (but retained in the StatSensor synthesis of p_{jk}). The resulting

probabilities are reported in Table 17 and are very close to those reported in the main analysis (Table 13).

Table 17 Sensitivity analysis: Pooled probabilities for the three types of device.

	StatSensor		i-STAT		Radiometer (ABL)	
	Median	95%CrI	median	95%CrI	median	95%CrI
p[1,1]	0.74	(0.61, 0.85)	0.84	(0.69, 0.94)	0.87	(0.75, 0.95)
p[1,2]	0.18	(0.08, 0.30)	0.04	(0.00, 0.18)	0.03	(0.00, 0.14)
p[1,3]	0.03	(0.00, 0.13)	0.04	(0.00, 0.18)	0.03	(0.00, 0.14)
p[1,4]	0.03	(0.00, 0.11)	0.04	(0.00, 0.17)	0.04	(0.00, 0.15)
p[2,1]	0.09	(0.03, 0.19)	0.10	(0.04, 0.21)	0.02	(0.00, 0.11)
p[2,2]	0.57	(0.41, 0.71)	0.77	(0.64, 0.87)	0.78	(0.61, 0.90)
p[2,3]	0.22	(0.12, 0.36)	0.10	(0.04, 0.21)	0.15	(0.05, 0.30)
p[2,4]	0.10	(0.03, 0.24)	0.01	(0.00, 0.06)	0.03	(0.00, 0.15)
p[3,1]	0.01	(0.00, 0.03)	0.01	(0.00, 0.04)	0.02	(0.00, 0.08)
p[3,2]	0.14	(0.09, 0.20)	0.10	(0.05, 0.17)	0.06	(0.02, 0.16)
p[3,3]	0.25	(0.16, 0.34)	0.81	(0.72, 0.88)	0.74	(0.62, 0.84)
p[3,4]	0.60	(0.51, 0.69)	0.08	(0.04, 0.13)	0.16	(0.09, 0.26)
p[4,1]	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)
p[4,2]	0.00	(0.00, 0.01)	0.01	(0.00, 0.02)	0.00	(0.00, 0.01)
p[4,3]	0.06	(0.04, 0.08)	0.08	(0.06, 0.10)	0.01	(0.00, 0.01)
p[4,4]	0.94	(0.91, 0.95)	0.91	(0.89, 0.93)	0.99	(0.98, 0.99)

p[i,j] probability of being classified in category j by the POC device when lab category is i. Categories are described in Table 2. Data from Shephard 2010[34] excluded from calculation of probability of being in each true category.

4.2.7.5 Summary

Data on the classification of individuals according to their PC-AKI risk by POC devices compared to lab reference were pooled to estimate the probabilities that individuals are correctly or incorrectly classified into one of the four eGFR categories used to determine PC-AKI risk. Results suggest that i-STAT and ABL devices are better than StatSensor devices at correctly categorising individuals, particularly for the lower eGFR categories: StatSensor was less accurate at correctly classifying patients with true eGFR below 30 (i.e. lower sensitivity).

The StatSensor device can incorporate an adjustment to better align results with those of the reference lab. An additional analysis using adjusted data improved this device's classification of individuals

with low eGFR, although there were still larger probabilities of misclassification at higher eGFR values than for the other devices.

Analyses that only included studies that measured eGFR with CKD-EPI equation showed that the results were consistent and robust for i-STAT and ABL, whereas results for StatSensor showed some differences.Overall, results suggest that i-STAT and ABL devices show better agreement with the reference laboratory in the classification of individuals' eGFR, particularly for the lower categories, which are of greatest clinical importance.

4.2.8 Studies reporting clinical, workflow or implementation outcomes

Six studies reported clinical, workflow or implementation outcomes relating to POC devices (Table 18).[27, 57, 60, 75-77] One was available only as a conference abstract.[77] Patient sample sizes ranged from 113 to 3087 and one study was a survey of staff at 68 NHS trust sites.[76] Any POC device was eligible to be included in this section of the review: three studies used StatSensor[27, 60, 77]one used an i-STAT device[57] and one used a Reflotron plus POC device (and a screening questionnaire).[75]

In Lee-Lewandrowski et al's[57] U.S. study, an average of 5.3% of patients presented for a CT or MRI study requiring contrast, but without a recent creatinine or eGFR result. A one month audit of these patients (n=384) found that the i-STAT POC device identified 74% of patients as having normal results (defined as eGFR≥60ml/min/1.73m^2) with the CT/MRI study proceeding as planned. Of the patients with an abnormal eGFR (<60ml/min/1.73m^2), 74% of scans were performed with contrast and 26% without contrast. The authors commented that the decision to use contrast in patients with abnormal eGFRs considered the type of study being performed (vascular versus nonvascular) and an assessment of the overall risk/benefit of administering or not administering contrast. Houben et al[27] also used an eGFR threshold of <60ml/min/1.73m^2 for identifying abnormal results, with StatSensor failing to identify six of the seven patients with abnormal results as measured in the laboratory. This resulted in unwanted contrast administration. Two patients subsequently developed PC-AKI after 2–5 days, which was normalised after 30 days.

Ledermann et al studied 1766 patients referred for contrast-enhanced CT at a private Swiss radiology facility.[75] Only 3.5% of patients had external serum creatinine values on their referral forms (as was requested). A Reflotron POC device was used on patients who had risk factors for post-contrast-AKI (identified using a questionnaire). No fixed eGFR threshold on which to base decisions was adopted; although 116 the 796 patients with a risk factor had a POC-measured eGFR of <60ml/min/1.73m^2, the diagnostic procedure was modified in 132 patients. The most frequently adopted changes in management in these 132 patients was a reduction in contrast volume (in 64% of patients) and CT

performed without contrast (30%). Morita et al studied the effect of using a StatSensor device on 113 Japanese patients awaiting CT or MRI examinations who did not have a recent eGFR.[60] Twenty-one patients had an eGFR of <60ml/min/1.73m^2. The seven patients who had an eGFR of 30–50 ml/min/1.73 m^2 underwent IV hydration with 500ml saline.

Snaith et al considered implementation issues in a survey which examined adherence of UK hospitals to guidance on the use of gadolinium-based contrast agents in MRI;[76] the risk of nephrogenic systemic fibrosis is elevated in patients with impaired renal function. Six out of 68 sites indicated that POC creatinine testing would be carried out where recent blood test results were unavailable. Twelve sites had rejected using a POC device as an adjunct, mostly for cost reasons.

Stahr et al's 2010 study reported the proportion of scans involving IV contrast before and after the introduction of a StatSensor device.[77] However, its results are limited by the study design used, the small sample size, and the details reported (it was available only as a conference abstract).

Together, the results of these studies illustrate variation in practice in terms of both the proportions of patients who do not have a recent eGFR result and in the management decisions taken when a POC device indicates an 'abnormal' eGFR. However, many of these studies were undertaken several years ago so the value of their results is somewhat limited because the eGFR thresholds for defining an abnormal result have decreased over time.

Table 18 Studies reporting clinical, workflow or implementation outcomes

Study	N, Population	Device(s)	eGFR equation	Results and notes
Houben et al 2017[27]	351 women due for contrast-enhanced spectral mammography Netherlands	StatSensor	MDRD	Seven patients had an eGFR <60ml/min/1.73m^2, necessitating additional preparation prior to contrast delivery. The POC device failed to categorize 6 of these 7 patients (86%), leading to unwanted contrast administration. Two patients (including 1 of the 3 patients with eGFR 45) subsequently developed CIN after 2–5 days, which was normalised after 30 days.
Ledermann et al 2010[75]	796 of 1766 scheduled for contrast enhanced CT with at least 1 ESUR risk factor for renal insufficiency, 55% female, mean age 61 years. Switzerland	Reflotron plus (Roche) and screening questionnaire	MDRD (Levey modified)	Diagnostic procedure was adapted in 132 patients (16.6%): 85 (10.7%) had contrast dose reduction, 40 (5.0%) had CT without contrast, 3 (0.38%) had MRI and 4 (0.5%) had scintigraphy.
Lee Lewandrowski et al[57]	3087 referred for contrast enhanced scan (CT or MRI) without a recent eGFR USA	i-STAT	MDRD	1 month audit: 285 (74%) of 384 patients referred for CM scan had normal eGFR and could undergo scan with contrast. Of the 99 (26%) with abnormal eGFR (<60ml/min), 73 (74%) received a scan with contrast, and 26 (26.3%) without contrast.
Morita et al 2011[60]	113 patients scheduled for MRI or CT, 43% female, median age 66 years Japan	StatSensor	Modified Japanese Society of Nephrology–Chronic Kidney Disease Initiatives.	Seven patients with an eGFR of 30–50 ml/min/1.73 m^2 underwent IV hydration. No symptoms of PC-AKI observed (the median follow-up period from the examination day was 94 days, range 2–248 days). Test failures = 10 patients (8.8%), of which 6 were due to 'flow errors', though measurements were successfully made at the second attempt.
Snaith 2016[76]	Survey of NHS trusts sites. 68 out of 174 responded (39%). UK	NA	NA	26 sites had considered using POC technology. 6 sites indicated POC tests would be carried out if a result was unavailable. POC was in regular use at a further 2 sites and was currently being evaluated at another 6. The remaining 12 had rejected it as an adjunct, mostly for cost reasons. Other reasons included: a lack of support from pathology, reliability and accuracy of the equipment and incompatibility with pathology measures. Three sites also raised concerns that the immediacy of a POC result could lead to a reduction in imaging capacity (e.g. lost slot).
Stahr et al 2010[77]	360, PET/CT unit Denmark	StatSensor	NR	Before and after (introduction of StatSensor) comparison of scans performed with and without i.v. contrast:

Study	N, Population	Device(s)	eGFR equation	Results and notes
Conference abstract				Before (March 2009): 92 of 114 had i.v. contrast (81%) After (March 2010): 215 of 246 had i.v. contrast (87%) 17 StatSensor measurements were performed in March 2010.

ESUR European Society of Urogenital Radiology, RI renal insufficiency, POC point of care, NA Not applicable

4.3 Pragmatic reviews of further evidence to inform the economic model

4.3.1 Evidence of the risk of acute kidney injury from contrast agents

Patients who need contrast-based imaging sometimes have other risk factors for AKI which makes it difficult to ascribe a causative role to contrast agents. Determining the true incidence of contrast-induced AKI (CI-AKI) from the published literature can be difficult since many studies do not include a control group of patients not receiving contrast. Such studies will likely also include kidney injuries unrelated to contrast. Another important issue when considering the risk of kidney injury following administration of contrast agents is that of the outcomes being evaluated. Acute kidney injury is typically defined as a specific change (relative or absolute) in serum creatinine levels, which makes it a surrogate outcome. The clinical significance of surrogate events can be questionable since they sometimes resolve spontaneously without the patient being aware of their existence. Wherever possible, the identification of the risk of real clinical outcomes – such as mortality or the need for dialysis – is more important and useful to patients, clinicians and researchers alike.

These issues seem particularly important in patients with high serum creatinine levels. In a retrospective study of 32,161 patients who had *not* received iodinated contrast material, researchers analysed serum creatinine levels over five consecutive days. They found that during the five day period, more than two fifths of patients showed a creatinine change (up or down) of at least 0.4 mg/dL, with higher initial creatinine values being associated with a higher frequency of a given absolute change.[79] These results are important given that some commonly used definitions of AKI cover absolute increases in serum creatinine of ≥0.3 to 0.5mg/dL.[6] Similarly, a retrospective study in a more relevant population (11,588 patients undergoing CT investigations either with or without contrast) found that the incidence of AKI increased with increasing baseline creatinine concentration in both contrast and no-contrast groups, concluding that much of the creatinine elevation was attributable to background fluctuation, underlying disease, or treatment.[80] Finally, a prospective study of 716 CT or MRI outpatients found that eGFR values varied independently of whether or not patients received contrast. When comparing pre-imaging values with those three days after, 45% of CT patients had a change greater than ±10 ml/min/1.73 m^2 in the contrast group (n=237) compared with 59% in the smaller control group (n=97).[81]

We anticipated that a large number of studies would report on the risk of kidney injury after contrast agent administration. We therefore initially sought to identify any recent reviews on the subject. A search of Medline was undertaken for reviews reporting data on the risk of AKI in CT patients. The search was run to identify papers published from 2012 to present, the start year was chosen pragmatically to keep the review manageable and to restrict it to the more up-to-date evidence (search

details are presented in Appendix 11.1). From the 291 titles and abstracts retrieved, five potentially relevant reviews were identified. However, the results from three reviews had limited applicability to the outpatient population considered in this assessment, since they were of kidney transplant patients,[82] critically ill patients,[83] and a mixture of emergency, ICU and inpatients.[84] In the two remaining reviews the quality of included studies were limited because they lacked non-contrast control groups.[85, 86].

We therefore focussed on the most recent of the five reviews identified - Aycock 2018[84] – which was also the largest in terms of patient numbers, and broadest in terms of populations. It reported that, compared with non-contrast CT, intravenous contrast enhanced CT was not significantly associated with AKI (OR 0.94, 95% CI 0.83 to 1.07), need for renal replacement therapy (OR 0.83, 95% CI 0.59 to 1.16) or all-cause mortality (OR 1.0, 95% CI 0.73 to 1.36). Although all the studies in the Aycock review had control groups, many studies were small, and most did not attempt to match groups on factors associated with outcomes. We therefore identified the largest studies with matched control groups included in this review: retrospective studies by McDonald et al 2014 (n=21,346)[87] and Davenport et al 2013 (n=20,242).[88] The McDonald study looked at AKI, mortality and the need for renal replacement therapy, reporting similar results to the pooled results reported in the Aycock review (described above). The Davenport study reported results by subgroups based on serum creatinine thresholds, concluding that iodinated contrast material is a nephrotoxic risk factor for AKI, but not in patients with a stable SCr level less than 1.5 mg/dL.

In outpatient clinical practice it is eGFR, not creatinine alone, which is used to estimate kidney function (and make decisions on whether or not to use contrast) so studies which quantify the risk of AKI in populations sub-grouped by baseline eGFR thresholds are more relevant to this assessment. Citation searching using Google Scholar, together with reference lists searches, identified large propensity score-matched studies by the same research groups which reported results risk-stratified by eGFR thresholds.[89, 90] The characteristics and results of these two studies are presented in Table 19.

Propensity score matching attempts to account for the selection bias inherent in non-randomised studies by accounting for patient characteristics which are associated with the development of AKI and other clinical outcomes, and which can affect decisions on whether or not to use contrast. Matched propensity score analyses match patients based on risk factors that predict both whether a contrast enhanced scan is given and the outcome, by calculating a propensity score that reflects the likelihood that a patient is offered a contrast enhanced scan, if the risk factors are present. The choice of covariates used to calculate the propensity score is crucial: all covariates believed to be related both to the decision to use contrast and the outcome, should be measured and included. Propensity score analyses can only adjust for known and measured covariates, as opposed to randomised studies where both known and unknown confounders tend to be balanced across groups, thus the possibility of

residual confounding cannot be completely ruled out. Inclusion of covariates that are related to contrast assignment but not outcome may reduce efficiency of the method, although this is not a serious limitation in large datasets.[91] Additionally the choice of matching method can affect the amount of residual bias.[92]

Although the eGFR thresholds to define subgroups mostly differ, the studies' results are concordant for the risk of AKI in patients with eGFR ≥45 mL/min/1.73 m^2, with contrast not being associated with increased risk. The results differ most notably for the eGFR<30 mL/min/1.73 m^2 subgroups, with the McDonald 2014 study reporting no increased risk[90] and the Davenport study reporting a statistically significant increase in risk in patients receiving contrast[89] (Table 19). Although the Davenport study[89] has the largest overall sample size, it has far fewer patients in the eGFR <30 mL/min/1.73 m^2 subgroup: 116 vs 1486, which is reflected in its very wide confidence intervals for the estimated odds ratios.

Table 19 Comparison of two large propensity score-matched studies of AKI risk stratified by eGFR thresholds in populations undergoing CT examinations

	McDonald et al 2014[90]	**Davenport et al 2013[89]**
Population	Around 90% inpatients, 10% outpatients	All inpatients
Sample size	12,508 (CT examinations between 2000-2010)	17,652 (CT examinations between 2000-2010)
eGFR method	MDRD	Not reported
AKI definition	Increase of ≥0.5mg/dL SCr, 24-72 hours after CT	Increase of ≥0.3mg/dL SCr, or an SCr increase 1.5-fold above baseline within 48 hours (AKIN criteria)
Propensity score matching methods	Generated separately for each eGFR subgroup using logistic regression derived from 13 clinical variables. Nearest neighbour 1:1 matching (with caliper) without replacement.	Generated for the whole group using logistic regression derived from 13 clinical variables.
eGFR thresholds and results: number of AKIs	**eGFR≥90**: 10/821 contrast vs 11/821 no contrast **60-89**: 40/1935 contrast vs 39/1935 no contrast **30-59**: 161/2755 contrast vs 170/2755 no contrast **<30**: 102/743 contrast vs 105/743 no contrast	**≥60**: 379/6971 contrast vs 384/6996 no contrast **45-59**: 134/1273 contrast vs 130/1207 no contrast **30-44**: 90/538 contrast vs 78/551 no contrast **<30**: 16/44 contrast vs 14/72 no contrast
AKI incidence Results as odds ratios (OR) by eGFR threshold	**eGFR ≥90**: OR 0.91 (95% CI 0.38 to 2.15) **60-89**: OR 1.03 (95% CI 0.66 to 1.60) **30-59**: OR 0.94 (95% CI 0.76 to 1.18) **<30**: OR 0.97 (0.72 to 1.30)	**≥60**: OR 1.00 (95% CI 0.86 to 1.12) **45-59**: OR 1.06 (95% CI 0.82 to 1.38) **30-44**: OR 1.40 (95% CI 1.00 to 1.97) **<30**: OR 2.96 (95% CI 1.22 to 7.17) OR was adjusted for two covariates: 'CT performed when patient in the intensive care unit' and 'type I diabetes mellitus' (also included in propensity score calculation).

eGFR in mL/min/1.73 m^2

Another factor which may have contributed to the eGFR<30 mL/min/1.73 m^2 subgroup results being different is the difference in AKI definitions. Davenport et al[89] used a lower absolute SCr increase of 0.3mg/dL compared with the 0.5mg/dL increase used by McDonald et al 2014.[90] Given the

(previously discussed) natural fluctuation in SCr levels, the use of a lower threshold is likely to detect more AKI events in patients with higher baseline SCrs. These events may be less likely to be clinically significant (in terms of their impact on real clinical outcomes) when compared to AKIs defined using larger increases in SCr. This 'noise' of excess events may hamper interpretation of the Davenport results, given the very small denominators in the eGFR<30 mL/min/1.73 m^2 subgroups. The difference in propensity score adjustment methods and matching may also contribute to the differences in results. McDonald et al 2014[90] derived propensity scores separately for each eGFR subgroup which will better account for the different clinical characteristics expected in patients with a lower eGFR score and lead to better matching. In contrast, Davenport et al[89] derived propensity scores for the whole cohort, with mixed eGFR scores, which may explain why differences between two covariates (whether the CT was performed in the intensive care unit and whether the patient had type I diabetes mellitus) remained statistically significant after matching.

The small numbers also mean the Davenport eGFR<30 mL/min/1.73 m^2 results may be prone to chance effects. This can be investigated by calculating the 'fragility index' of the eGFR<30 mL/min/1.73 m^2 subgroup result. The fragility index is the minimum number of patients whose status would have to change from a non-event to an event in order to turn a statistically significant result to a non-significant result; the smaller the fragility index, the more 'fragile' the result.[93] The fragility index is calculated using a Fisher's exact test although other methods, such as a Chi squared test, are often used in studies. The p-value from a Fisher's exact test can be discrepant from a Chi squared test, especially for small studies. In cases where a Fisher's exact test produces a non-significant p-value (without "converting" a patient from a non-event to an event), the fragility index is reported as zero, indicating a lack of robustness of the result. For the Davenport eGFR<30 ml/min/1.73m^2 result based on the published summary patient data, the fragility index is 0, i.e. the result is not statistically significant using Fisher's exact test. However, as mentioned previously, following propensity matching the Davenport odds ratio was adjusted, and the fragility index for the statistically significant odds ratio of 2.96 cannot be calculated from the data available.

If it were assumed that the Davenport eGFR<30 mL/min/1.73 m^2 subgroup result *was* robust, the 'number need to harm' is six. i.e. for every six inpatients with an eGFR<30 mL/min/1.73 m^2 who receive contrast, one inpatient will have an AKI *caused* by contrast. However, it should be remembered that this result is for a surrogate outcome – it is unclear to what extent increases of 0.3mg/dl in the SCr of patients with a baseline eGFR<30 mL/min/1.73 m^2 translate into real clinical outcomes such as mortality, or the need for dialysis. The McDonald et al study identified in the Aycock systematic review reported data on real clinical outcomes – the results suggested no association between the use of contrast agents and need for dialysis, or death, for all eGFR subgroup analyses (eGFR subgroups were based on stages of chronic renal failure).[87] The number of clinical

events in this study were quite small though, particularly for the dialysis outcome. Moreover, if there is a risk of CI-AKI associated with an GFR <30 mL/min/1.73 m^2, it is likely to be lower in the outpatient population of interest in this assessment, given that inpatients are more likely to have other AKI risk factors (including acute illness and exposure to nephrotoxic treatments). Nevertheless, uncertainty about the level of risk remains, primarily because of the unmeasured clinical characteristics, which could not contribute to the propensity scores – most notably the level of prophylactic measures (e.g. IV hydration) used in the contrast groups and the prevalence of potentially nephrotoxic medication use at time of scanning.

The citation and reference searching identified three further publications of interest on the risk of AKI from contrast agents. The first was a review of propensity score matching studies on AKI after contrast[94] which lists several studies by McDonald et al and Davenport et al research groups. This review also cited a large study (n=17,934) by a different research group which reported results by baseline eGFR subgroups.[95] The study setting was an emergency department – different to the inpatients studied by McDonald and Davenport – with comparisons made between contrast-enhanced CT, unenhanced CT and no CT groups. The results were similar to those reported by McDonald et al. 2014[90] with rates of AKI being similar among all groups, including the eGFR 15-30 mL/min/1.73 m^2 subgroups.

The review of propensity score matching studies[94] also cited a further study by McDonald et al which reported the effect of contrast on dialysis and mortality, reported by baseline eGFR subgroups.[96] The study was of 5758 inpatients, emergency patients and outpatients who had a CT scan either with or without contrast. Contrast was not associated with higher rates of dialysis or mortality for any subgroup comparisons, including the CKD stages 4-5 subgroup (i.e. patients with an eGFR<30 mL/min/1.73 m^2) although the latter results are limited by the small number of patients in the contrast group (90, falling to 76 after propensity score matching).

Summary

Although debate about the risk of AKI from contrast agents is ongoing,[2-4] evidence from large propensity matched studies of inpatients is consistent in suggesting that there is no association between the use of contrast agents and the risk of acute kidney injury in patients with an eGFR ≥45 mL/min/1.73 m^2. In patients with an eGFR<45 mL/min/1.73 m^2 there is some uncertainty about whether or not contrast is associated with a small risk, although the most robust evidence available suggests there is no association in inpatients. If a risk does exist, it would be expected to be lower in outpatients than in inpatients.

4.3.2 Evidence on prophylactic interventions for PC-AKI

Pragmatic searches of Medline and recent guidelines were conducted to identify evidence on the effectiveness and safety of standard prophylaxis IV saline hydration for preventing PC-AKI in high risk patients. We included recent systematic reviews (from 2012 onwards) of RCTs comparing IV hydration with oral hydration, placebo or no treatment for preventing PC-AKI in patients with chronic renal failure (defined as eGFR < 60 mL per min/1.73 m^2) undergoing radiological procedures requiring low-osmolality contrast media. Risk of bias was assessed using the Cochrane risk of bias tool.[97]

Review of reviews

Three recent systematic reviews with meta-analysis were identified.[98-100] Characteristics and results of the reviews are summarised in Table 20.

All three reviews included RCTs evaluating prophylactic treatments to prevent PC-AKI in patients undergoing contrast-enhanced procedures. Two meta-analyses evaluated the relative efficacy of IV and oral hydration in head-to-head comparisons and one network meta-analysis evaluated 44 different prophylactic interventions. Most of the evidence focused on patients undergoing cardiac procedures. Overall, all three reviews found no significant difference between IV and oral hydration to prevent PC-AKI. None of the reviews reported data on mortality, dialysis outcomes or complications of IV hydration.

Ahmed et al (2018)[100] conducted a large systematic review and network meta-analysis comparing the efficacy of 44 therapies for the prevention of PC-AKI in patients undergoing a contrast-enhanced procedure. The review included 197 RCTs (42,273 participants). Nearly three-quarters of patients included underwent coronary angiography and 8% underwent a CT procedure. Half of included patients had reduced kidney function, defined as either eGFR<60 ml/min/1.73m^2 or SCr > 1.3 mg/dl (114 mmol/L). Rates of patients with eGFR<45 ml/min/1.73m^2 or lower were not reported. The most common interventions were N-acetylcysteine (68 studies; 6095 participants), IV hydration (41; 5136), NaHCO3 (32; 3393) and statins (14; 3040). Oral hydration was also evaluated (5; 254). The most common comparators were placebo (70; 7044) and control/no treatment (88; 9120). Over half of studies (55.5%) reported using low-osmolar contrast. Most studies were in cardiac patients; coronary angiography was the contrast-dependent procedure in 72.5% of studies. The primary outcome of the review was PC-AKI (referred to as CI-AKI in the review), defined as ≥25% relative increase or ≥ 0.5 mg/dl increase from baseline creatinine one to 5 days post contrast exposure. Overall, the review found that the best-ranked interventions were allopurinol, prostaglandin E1 and oxygen, although these results are based on few and small trials. There was no significant difference in odds of PC-AKI between IV hydration or oral hydration compared with placebo (IV hydration vs. placebo: OR 0.91, 95% CI 0.60-1.34 in all studies, and OR 0.97 95% CI 0.52 to 1.9 in studies with low eGFR/high baseline renal profile; oral hydration vs. placebo: OR 1.09 95% CI 0.41-2.75), and there was no

significant difference between IV and oral hydration (OR 0.83, 95% CI 0.35-1.95). Compared with control/no treatment, there was a statistically significant difference favouring IV hydration (OR 0.71 95% CI 0.52-0.99), but not oral hydration (OR 1.09, 95% CI 0.41-2.75). Overall heterogeneity was 0.55 (95% CrI 0.41-0.69, using a vague prior distribution) and 0.50 (95% CrI 0.37-0.64, informative prior distribution) which is moderate to large on the log-odds ratio scale. Although the authors state that consistency was assessed using an inconsistency plot, reported results are insufficient to conclude whether or not it was present.

Agarwal et al (2015)[99] reported on a meta-analysis of five RCTs (447 participants) comparing oral and IV hydration for the prevention CIN (thereafter PC-AKI) in patients receiving low osmolar contrast media. All 5 RCTs were also included in Ahmed et al (2018)[100] Two-thirds of included participants had chronic kidney disease (not defined), and all except one study only included patients undergoing cardiac procedures. There was no significant difference in the incidence of PC-AKI between IV hydration (7.7%) and oral hydration (8.2%) (RR of 0.97, 95% CI 0.36 to 2.94, I^2=48%). A subgroup analysis of CKD patients (not defined) found no statistically significant difference between treatment arms (RR 1.73, 95% CI 0.69 to 4.33, I^2=0%). The review concluded that oral hydration is at least as effective as IV hydration to prevent PC-AKI.

Hiremath (2013)[98] included six RCTs (513 participants) that compared the relative efficacy of oral and IV hydration. Four of these trials were also included in Agarwal (2015),[99] and all were included in Ahmed et al (2018).[100] All except one study focused exclusively on patients undergoing cardiac procedures. There was no significant difference in the incidence of PC-AKI between IV hydration (8.1%) and oral hydration (9.6%) (OR 1.19, 95% CI 0.46, 3.10, I^2=57%).

Table 20 Summary of recent systematic reviews on PC AKI prophylaxis

Review	**Ahmed (2018)[100]**	**Agarwal (2015)[99]**	**Hiremath (2013)[98]**
N. studies; participants	197; 42,273	5; 447	6; 513
Search date	Up to April 2017	Up to April 2015	Up to November 2011
Population	eGFR<60 ml/min/1.73m2 or SCr > 1.3 mg/dl (114 mmol/L): 50.2% of patients Coronary angiography: 72.5%*; CT imaging: 8%*; peripheral angiography ±angioplasty & stenting 1.5%*	CKD (63.7%) (definition NR) Non emergency cardiac catheterisation: 1 study/11.9% participants Coronary angiography and/or angioplasty: 3/53.9% Various radiological procedures: 1/34.2%	Cardiac catheterisation: 2 studies/17.3% participants Coronary angiography and/or angioplasty: 3 studies/52.8% Various radiological procedures: 1 study/29.8%

Interventions (N. studies; participants)	44 types incl. IV hydration (41; 5136), NAC (68; 6095),control (88; 9120), NaHCO3 (32; 3393); statins (14; 3040), oral hydration (5; 254), placebo (70; 7044), allopurinol (4; 204), PGE1 (4; 304), oxygen (2; 436)	IV hydration (simple saline) or oral hydration	IV hydration (simple saline) or oral hydration
Contrast media type (% studies)	Low osmolar: 55.5%; iso-osmolar: 22%; hyper-osmolar: 1.5%; other/NS: 21%	Low osomolar: 100%	Low osmolar: 4 studies/77.8% NR: 2 studies/22.2%
Synthesis method	Network meta-analysis. 946 pair-wise comparisons, incl. 81 direct comparisons	Pairwise meta-analysis	Pairwise meta-analysis
Outcomes	CI-AKI: ≥25% relative increase or ≥ 0.5 mg/dl increase from baseline creatinine one to 5 days post contrast exposure.	CIN (multiple definitions) >44.2 µmol/L (>0.5 mg/dL) absolute increase, or >25% relative increase in SCr, within 48-72h of contrast exposure.	CIN (multiple definitions) >44.2 µmol/L (0.5 mg/dL) absolute increase, or >26.4 mmol/L (0.3 mg/dl), or >25% relative increase in SCr, within 48-72h of contrast exposure.
Main findings	Top ranked interventions were Allopurinol, Prostaglandin E1 (PGE1) & Oxygen IV hydration vs. oral hydration: OR 0.83 (95% CI 0.35-1.95)# IV hydration vs. placebo: OR 0.91 (95% CI 0.60-1.34)# IV hydration vs. control: OR 0.71 (95% CI 0.52-0.99)# Oral hydration vs. placebo: OR 1.09 (95% CI 0.41-2.75)^ Oral hydration vs. control: OR 0.86 (95% CI 0.86-2.13)^	PC-AKI incidence: IV hydration: 7.7%; oral hydration: 8.2%. RR of 0.97 (95% CI 0.36 to 2.94, I2=48%) Subgroup of 3 studies with CKD patients: RR 1.73 (95% CI 0.69 to 4.33)	PC-AKI incidence: IV hydration 8.1%; oral hydration 9.6%. OR 1.19 (95% CI 0.46, 3.10, I2=57%)
Conclusions	Some options (particularly allopurinol, PGE1 & Oxygen) deserve to be tested in larger RCTs.	Oral hydration is at least as effective as IV hydration with saline to prevent PC-AKI.	Oral hydration may be as effective as IV hydration for the prevention of PC-AKI.

NAC: N-acetylcysteine; SUCRA: surface under the cumulative ranking curve; *Percentage of comparative analyses unless otherwise specified; # OR<1 favours IV hydration; ^ OR<1 favours oral hydration

Randomised trial evidence

As most of the review evidence focused on patients undergoing cardiac procedures, the applicability of the review findings may be limited for the population of outpatients scheduled for contrast-enhanced CT scan without a recent eGFR measurement who may be at higher risk of PC-AKI. Therefore references of studies included in the reviews were checked for RCTs comparing oral or IV hydration versus no treatment for preventing post-contrast AKI in outpatients with chronic renal failure (eGFR below 60 mL per min/1.73 m²) undergoing non-cardiac radiological procedures requiring non-ionic, low-osmolality contrast media.

Two trials met our inclusion criteria: AMACING[101, 102] and Dussol (2006).[103] The characteristics and results of both trials are reported in Table 21**Error! Reference source not found.**. Risk of bias assessment is summarised in Table 22. AMACING[101] was designed as an non-inferiority trial and was therefore not sufficiently powered to detect a significant difference between treatments. Dussol (2006)[103] was significantly smaller (approximately a quarter of the participants were assigned to IV hydration or control) and did not report allocation concealment methods therefore a risk of bias cannot be excluded.[103] Both trials could not blind study participants and study personnel, although this is unlikely to significantly affect assessment of PC-AKI.

AMACING[101] was a single-centre, randomised, parallel-group, open-label, phase 3, non-inferiority trial of no prophylaxis compared with guideline-recommended prophylaxis in preventing what the authors termed CIN (thereafter PC-AKI), and to explore the effect on long-term post-contrast adverse outcomes. A total of 660 adults with eGFR between 30 and 59 mL per min/1.73 m² undergoing an elective procedure requiring iodinated contrast were randomised to standard intravenous prophylactic hydration or no prophylaxis. PC-AKI was measured at 2 to 6 days post-contrast exposure. The trial found no significant difference in the incidence of PC-AKI between IV prophylaxis (2.7%) and no treatment (2.6%) at follow-up (RR 1.04; 95% CI 0.39 to 2.73). No haemodialysis or related deaths occurred within 35 days. Eighteen (5.5%) patients in the IV prophylaxis group experienced IV hydration treatment-related adverse events. At one year following contrast exposure, there was no significant difference in the proportion of patients requiring dialysis between IV prophylaxis and the control group (0.6% incidence in both groups, RR: 1.01, 95% CI 0.14 to 7.14), and no difference in mortality (IV: 9.8% versus control: 10.8%, HR 1.12 95% CI 0.70 to 1.80).

Dussol (2006)[103] was a single-centre, randomised, parallel-group, open-label trial comparing the efficacy of oral saline hydration with intravenous saline hydration, with or without theophylline or furosemide, for preventing PC-AKI. Patients undergoing radiological procedures with a non-ionic, low osmolality contrast agent with eGFR ranging between 15 and 60 ml/min/1.73 m² were randomised to one of four groups: oral hydration, standard IV hydration, IV hydration with theophylline, IV hydration with furosemide. The proportion of patients with eGFR<30 was not

reported. The study found no significant difference in the incidence of PC-AKI between IV prophylaxis (6.6%) and oral hydration (5.2%) (RR 1.27; 95% CI 0.35-4.54) at 48h post-contrast exposure. There were no significant adverse events in either study arm.

Overall both trials found that oral hydration was not inferior to IV hydration for preventing AKI in patients with eGFR<60 ml/min/1.73 m². There was mixed evidence on the safety of IV hydration: one trial (AMACING[101]) suggested that IV hydration was associated with treatment-related complications, and another found no adverse events.[103]

Table 21 Characteristics and results of RCTs of PC-AKI prophylaxis

Study	Design	Selection criteria	Population characteristics	Interventions	Mean contrast volume, mL (SD)[$]	PC-AKI definition	Results
AMACING [101, 102]	Randomised, parallel-group, open-label, non-inferiority trial Netherlands N=660	Adults with eGFR: 30–59 mL per min/1.73 m² undergoing an elective procedure requiring iodinated contrast Exclude: eGFR<30 mL per min/1.73 m², RRT	Age: Male: 62% Inpatient: 8.7% Baseline eGFR: IV: 47.3 (7.95); Ctrl: 47.59 (8.01); Diabetes: 32%; CVD: 75%	IV hydration 0.9% NaCl[£] or no IV hydration	IV: 92(41) Ctrl: 89(41)	Increase in SCr by >25% or 44 µmol/L within 2–6 days post-contrast	<u>PC-AKI incidence (2-6 days f-u):</u> IV hydration: 8/296 (2.7%) Ctrl : 8/307 (2.6%) RR (1.04 ; 95% CI 0.39 to 2.73)[^] <u>Treatment related-AEs (35 days f-u) :</u> No haemodialysis or treatment-related deaths IV hydration: 18/328 (5.5%), incl. 13 leading to premature discontinuation, forced diuresis, or extended hospitalisation; 1 hyponatraemia, 4 arrhythmia during hydration Ctr: NA <u>Mortality (1 year f-u):</u> IV hydration: 32/328 (9.8%) Ctrl: 36/332 (10.8%) HR 1.118 (95% CI 0.695 to 1.801, p=0.65) Absolute risk difference (1.01%; 95% CI −3.55 to 5.72; p = 0.65) <u>Dialysis (1 year f-u):</u> IV hydration: 2/328 (0.6%) Ctrl: 2/332 (0.6%) RR: 1.01 (95% CI 0.14 to 7.14) Absolute risk difference: −0.01%; 95% CI −1.19 to 1.18; p= 0.99 No significant differences between group differences in dialysis and mortality in subgroups with eGFR above and below 45mL min/1.73m².
Dussol (2006)[103]	Randomised, parallel-group, four-arm, open-label France	Chronic renal failure (creatinine clearance 15-60 ml/min/1.73 m²) undergoing scans with a	Age: 64 (11) Male: 84% Inpatient: 0 Baseline eGFR: IV: 38(13) Ctrl: 33(11)	Intravenous 0.9% NaCl[#] or oral hydration[+]	IV: 115 (57) Oral: 120 (40)	Increase in S. Creat. ≥0.5 mg/dL (44 µmol/L) above baseline at	<u>PC-AKI incidence (48h f-u):</u> IV hydration: 5/76 (6.6%) Oral: 4/77 (5.2%) RR (1.27; 95% CI 0.35-4.54)[^]

	N= 330	non-ionic, low osmolality contrast agent Excluded: < 18-years; LVEF<30%; uncontrolled hypertension	Diabetes: 29%; Heart failure: 19%			48 h post-contrast	No significant difference between arms at 24h f-u (results NR in study) <u>Dialysis, fluid overload, significant increase in BP (48h f-u):</u> none in either arm <u>Other adverse events (48h f-u):</u> Oral: vomiting (n=1). No other AEs reported. Further results for theophylline & furosemide arms were reported.

$ 300mg iodine per mL contrast. ^Calculated. £Standard prophylaxis: 3–4 mL/kg per hour for 4 hours before and 4 hours after contrast administration; calculated on a modified ITT basis, including 603 (91%) of 660 patients with a follow-up measurement. “

Table 22 RCTs of PC-AKI prophlyaxis: Risk of bias assessment

	Random sequence allocation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
AMACING [101, 102]	+	+	-	+	+	+
Dussol (2006)[103]	+	?	-	+	+	?

+ low risk of bias; ? unclear risk; - high risk.

Non-randomised evidence

Due to the lack of RCT evidence in patients with eGFR<30 mL/min/1.73 m^2, further pragmatic Medline searches were conducted to identify relevant non-randomised evidence. One retrospective cohort study was found.[104]

Nijssen (2018b) included patients referred for an elective procedure who received intravascular iodinated contrast material administration with an eGFR below 30 mL/min/1.73 m^2 who were excluded from AMACING. Outcomes included CIN (as referred to in the trial, thereafter PC-AKI) (2 to 6 days follow-up), dialysis and mortality within 35 days, post-contrast exposure, and complications of prophylactic intravenous hydration. The characteristic and results of Nijssen (2018b) are reported in Table 23.

Of the 155 patients with eGFR<30 mL/min/1.73 m^2, who received contrast material, 119 (76.8%) received 0.9% intravenous sodium chloride (standard IV hydration), 12 (7.8%) received 1.4% NaHCO3 hydration, and 24 (15.5%) received no prophylaxis. Reasons for deviation from standard prophylaxis are reported in Table 23. Data on 2- to 6-day serum creatinine were only available for 59 (50%) of standard prophylaxis patients. Data on other clinical outcomes were available for 99-100% standard prophylaxis patients. The incidence of clinical outcomes were reported separately for patients with eGFR<30 receiving standard prophylaxis, NaHCO3-hydration and no prophylaxis. PC-AKI occurred in 8/59 (13.6%) of patients with standard prophylaxis, in 1/12 (8.3%) NaHCO3-hydrated patients, and in 1/18 (5.6%) no-prophylaxis patients. Dialysis within 35 days of contrast exposure occurred in 1/118 (0.85%) of standard prophylaxis patients, in 1/12 (8.3%) NaHCO3-hydrated patients, and in none of the 23 patients receiving no prophylaxis. Death within 35 days post-contrast exposure occurred in 11/119 (9.2%) of standard prophylaxis patients. There were no deaths in patients receiving NaHCO3 or no prophylaxis.

Results of patients with eGFR<30 who received standard prophylaxis were analysed against the IV hydration arm of the AMACING trial in unadjusted/unmatched comparisons. Compared with the AMACING trial active arm participants, the incidence of PC-AKI was significantly higher in patients with eGFR <30 mL/min/1.73 m^2 (13.6% versus 2.7%, p=0.0019). Death within 35 days of contrast exposure was also higher in the cohort arm (9.2% versus 0.0%, p<0.0001). There was no difference in the incidence of complications of prophylactic intravenous hydration (5.9% versus 5.5%, p=0.8529) and 35-day dialysis (0.9% versus 0.0%, p=0.2646) between the two groups.

Results from Nijssen (2018b)[104] may not be reliable due to the lack of randomisation, the lack of matching and adjusted comparison and the significant rate of missing PC-AKI data in higher risk patients undergoing standard hydration.

Table 23 Characteristics and results of Nijssen 2018 cohort[104]

Study	Design	Selection criteria	Population characteristics*	Contrast volume	Intervention	PC-AKI definition	Results
Nijssen (2018b)[104]	Retrospective cohort Uncontrolled comparison with patients with eGFR 30-59 mL/min/1.73 m^2 from AMACING trial	eGFR <30 mL/min/1.73 m^2 referred for an elective procedure with intravascular iodinated contrast material administration and excluded from the AMACING trial. Exclude: RRT, emergency procedures, ICU	Age: 74 (10) Male: 54% Inpatient: 40%; Baseline eGFR: 23.70 (4.26); Intra-arterial contrast: 40%; referral for interventional procedure: 25%; CVD: 67%	81 (45)[#]	Intravenous 0.9% NaCl (77%)[£] Intravenous 1.4% NaHCO3 (8%)[^] No IV hydration (16%)[+]	Increase in SCr by >25% or 44 µmol/L within 2–6 days post-contrast	<u>PC-AKI</u> Standard IV hydration: 8/59 (13.6%) NaHCO3 IV hydration: 1/12 (8.3%) No treatment: 1/18 (5.6%) Standard IV hydration (AMACING trial arm): 2.7% (p=0.0019)[#] <u>Dialysis (35 days)</u> Standard IV hydration: 1/118 (0.85%) NaHCO3 IV hydration: 1/12 (8.3%) No treatment: 0/23 Standard IV hydration (AMACING trial arm): 0 (p=0.2646)[#] <u>Mortality (35 days)</u> Standard IV hydration: 11/119 (9.2%) NaHCO3 IV hydration: 0/12 No treatment: 0/24 Standard IV hydration (AMACING trial arm): 0 (p<0.0001)[#] <u>Complications of IV hydration</u> Standard IV hydration: 7/119 (5.9%) Standard IV hydration (AMACING trial arm): 18/328 (5.5%) (p=0.8529)

* Data are presented as n(%) or mean (SD); [#] 3 unknown; [£]Standard prophylaxis: 3–4 mL/kg per hour for 4 hours before and 4 hours after contrast administration; ^3 mL/kg in 60 minutes before and 1 mL/kg per hour during 6 hours after contrast administration. Deviation from standard prophylaxis due to heart failure (42%), logistics (33%), dyspnea (17%), and diabetic renal failure (8%); [+] deviation from standard prophylaxis due to aortic valve stenosis (57%), fluid overload (17%), heart failure (9%), logistics (9%), renal function (4%), and in 1 case no reason was recorded (4%). [#] Standard hydration with eGFR<30 (cohort arm) vs. eGFR 30-59 (AMACING trial arm)

Summary of prophylaxis evidence

We found three recent systematic reviews and meta-analyses evaluating prophylactic treatments to prevent PC-AKI in patients undergoing contrast-enhanced procedures. The reviews were consistent in showing no evidence of a difference in effectiveness between IV and oral hydration to prevent PC-AKI. However, relevant pooled estimates from meta-analyses had wide confidence intervals and there was evidence of heterogeneity, therefore the true effect (or lack of effect) of IV hydration compared with oral hydration to prevent PC-AKI remains uncertain. None of the reviews reported on mortality, dialysis or complications from IV hydration. Most evidence from systematic reviews focused on patients undergoing cardiac procedures, and incidence of PC-AKI was significantly higher than that reported in outpatient populations scheduled for contrast enhanced CT without a recent eGFR measurement, therefore the applicability of much of the evidence to our population of interest is uncertain.

The evidence in patients at higher risk of PC-AKI who are referred for a non-emergency scan with contrast media is more limited. Two RCTs of non-cardiac outpatients with CKD (eGFR<60 mL/min/1.73 m^2) were identified, and both found no evidence that IV prophylaxis reduced the incidence of post-contrast AKI compared to no IV hydration. This is consistent with the broader evidence from the systematic reviews we identified, which primarily included cardiac patients. We only found limited non-RCT evidence for patients with eGFR<30mL/min/1.73 m^2. There was mixed evidence on the safety of IV hydration in non-cardiac outpatients with CKD (eGFR<60 mL/min/1.73 m^2): one trial suggested that IV hydration was associated with treatment-related complications, and another found no adverse events.

Overall, there is no evidence to suggest that IV hydration is more effective than oral hydration or placebo in preventing PC-AKI, RRT, or reducing mortality. Evidence on complications of IV hydration is inconclusive. The certainty of the evidence on the efficacy of IV hydration is limited by the lack of precision in intermediate outcome estimates, lack of hard clinical outcomes, and broader issues surrounding the existence of PC-AKI in patients with CKD.

4.3.3 Evidence of practice variation in renal function assessment

Two quite recent studies which have evaluated how renal function assessment practice varies in the UK were identified by reference list searching and citation searching. A survey undertaken in 2015 by Cope et al[11] assessed compliance with UK 2013 guidelines for the prevention, recognition, and management of CI-AKI. All UK acute NHS providers with a clinical radiology audit lead registered with the RCR were invited to complete a questionnaire. In order to demonstrate guidance compliance in daily practice, audit data on 40 consecutive stable outpatients who had undergone CT with intravenous iodine-based contrast media were also requested from each NHS provider.

Eighty-nine of 172 (52%) health service providers responded to the questionnaire and 91/212 (43%) hospitals provided audit data. In general, the paper noted wide variation in clinical practice and poor compliance with guidelines. Although kidney function test results within 3 months of the scan were available for 86% of outpatients, eGFR results (as recommended in the guidelines) were available for only 66%. Responsibility for checking baseline kidney function was taken by the radiology department in 49% of departments. In 51% the responsibility was either devolved to the referring clinician, or was not clearly defined. Only 30% of radiology departments had a policy for management of patients who developed PC-AKI or had locally agreed arrangements in place for the care of patients when repeat blood tests demonstrate PC-AKI. The requirement for intravenous volume expansion for high-risk patients prior to the scan was met by 64% of departments.

Audit data were available for 3,590 fit outpatients. Analyses were reported for a subgroup of 513 patients with a baseline eGFR<60ml/min/1.73m^2; 288 (56%) had pre- and post-contrast kidney function tests – no change was seen in the median SCr level two days post-contrast. The incidence of clinically significant (requiring treatment or resulting in death) PC-AKI was zero in the 3,590 outpatients.

Harris et al[10] also undertook a UK survey in 2015, requesting data from CT managers in 174 NHS Trusts to identify screening practices prior to outpatient contrast-enhanced CT. The response rate (47%) was similar to the Cope survey.[11] The RCR guideline [105] was most frequently used, although 20% of responders did not cite the use of a specific guideline. Most responding sites (75/82, 92%) required renal function to be assessed via a blood test; most did this for all patients, though 20% of sites assessed only 'high risk' patients. Variation in how blood tests were organized was found, with most radiology departments sharing the responsibility with the referring clinician. Most departments removed or minimised the risk of patients attending radiology without a recent kidney function result by either checking blood results before booking appointments (56%) or when appointments were made (16%), with blood tests booked if needed. Just over a quarter of radiology departments (28%) indicated that results are reviewed on scan day (or the night before).

Variation was also evident in the eGFR or SCr thresholds at which contrast was deemed to be contraindicated; 19 different threshold levels were identified, each leading to different prophylactic strategies. The most frequently used threshold was an eGFR of <30ml/min/1.73m^2, which was used in 35 of 77 (45%) NHS trusts. Blood test results were not checked by (7/82, 8.5%) of sites - they indicated that it was the referrer's responsibility. For patients attending without a recent blood result, 45% send the patient away to have a blood test done and either scan on the same day (if possible) or on a different day and 11% of sites use POC devices to get a quick blood test result. Most of the remaining sites said they would seek advice from a consultant radiologist. Data on practice variation in obtaining follow up (post-contrast) blood tests were also reported. The authors concluded that the

wide variation in practice is a reflection of inconsistencies in published guidance and that an evidence-based consensus on risk thresholds was needed.

5 Assessment of existing economic evidence on POC

This section provides an overview of existing cost effectiveness evidence on the use of POC creatinine tests in an outpatient non-emergency secondary care setting to assess kidney function before contrast-enhanced CT imaging. The relevant population includes adult patients who do not have a recent eGFR measurement. Eligible studies were systematically identified and the main findings narratively summarised and tabulated for comparison. Other sources of evidence with more qualitative consideration of the potential implications of introducing POC testing in the context of the current decision problem were also reviewed. These sources of evidence included i) one existing Medtech innovation briefing on POC devices for creatinine testing, and ii) a report produced by KiteK to support the external assessment group (EAG) report. The findings from the reviews helped inform the development of a new decision analytic model reported in Section 6.

5.1 Methodology of the cost-effectiveness review

5.1.1 Searches

The literature search previously reported in Section 4.1.1 was also used to identify studies reporting on the cost-effectiveness of POC creatinine testing in an outpatient non-emergency setting before contrast-enhanced CT imaging.

5.1.2 Selection process

A broad range of studies were considered in the review including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (i.e. cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses) were included in the review. The inclusion criteria also defined the relevant population as non-emergency outpatients scheduled to receive IV contrast enhanced CT imaging.

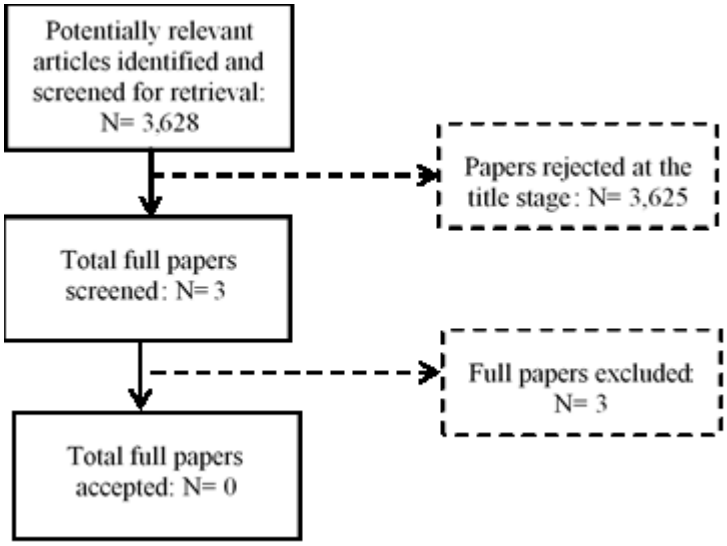
The selection of relevant studies was performed in two stages: i) titles and abstracts identified by the search strategy were examined and screened for possible inclusion, and ii) full texts of the potentially relevant studies were obtained and screened for inclusion. Two researchers (AD and JA) independently screened the titles and abstracts of all reports identified by the bibliographic searches and full-text papers were subsequently obtained for assessment and screened by at least two researchers. Any disagreement was resolved by consensus.

5.1.3 Results

A total of 3,628 records were identified by the initial search of economic databases. Three studies were identified as potentially relevant from their titles and/or abstracts. The full text articles of these records were assessed for eligibility. However, none were found to meet the inclusion criteria. Figure

6 presents a flow diagram of the selection process. Table 65 in Appendix 10.5 lists excluded studies alongside reasons for exclusion.

Figure 6: Assessment of cost effectiveness – Summary of study selection and exclusion



Although no published studies were identified from the systematic review, we identified one unpublished economic study that was considered potentially relevant (Prof. Beverley Snaith, personal communication). Following discussion with the lead author, we were provided with a draft version of the manuscript. This draft was provided by the lead author in academic confidence.

5.1 Review of Shinkins et al (draft unpublished paper).

5.1.4 Overview

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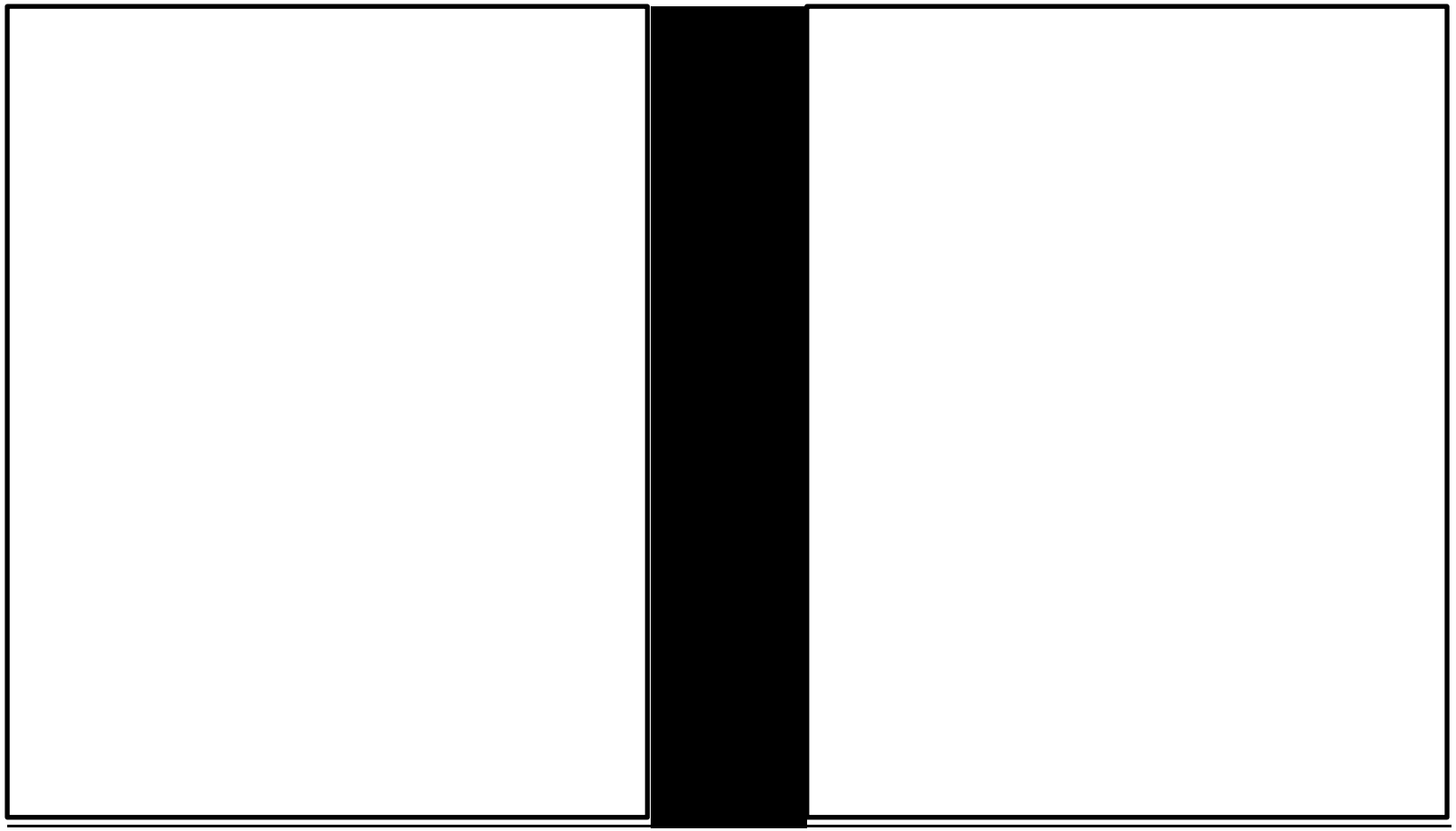

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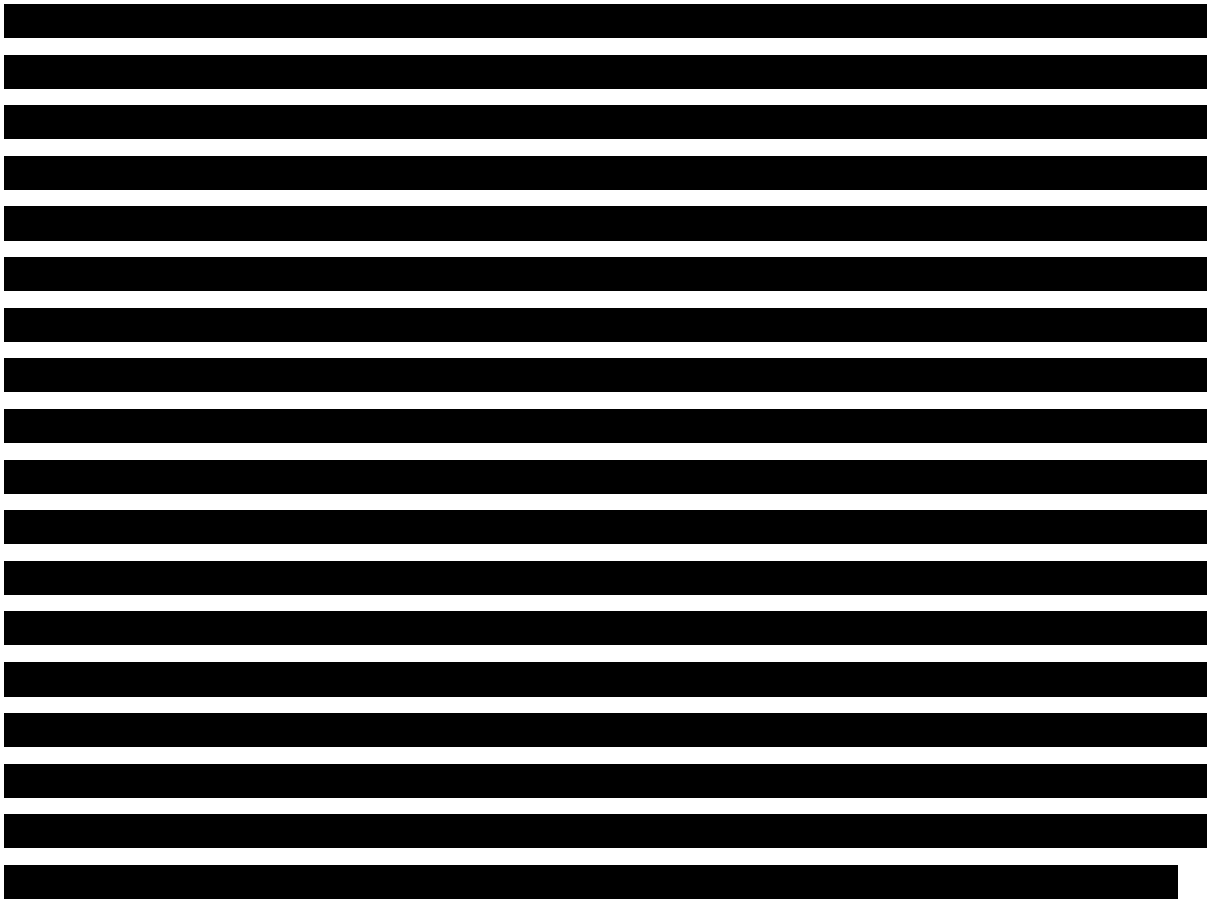


5.2 Overview of other sources of evidence

Although no other studies were identified which met the review inclusion criteria, several additional sources of evidence were identified which provided a more qualitative consideration of the potential implications of introducing POC testing in an outpatient non-emergency secondary care setting to assess kidney function before contrast-enhanced CT imaging. These are briefly summarised below.

5.1.1 Resourcing implications identified in MedTech innovation briefing (MIB136)

The MedTech innovation briefing (MIB)[13] identifies POC testing technologies as an alternative to laboratory based testing in those patients who present for contrast CT scanning without a recent eGFR measurement. In absence of a recent creatinine measurement, these patients may otherwise have their imaging cancelled or rescheduled – given national guidelines for a recent eGFR to be available before imaging [106]. If the scan is not cancelled, MIB authors suggest that the patient would either undergo non-contrast enhanced scanning, or continue with contrast scanning as planned, as such putting the patient at risk of kidney injury.

The authors therefore identify a key benefit of POC devices as reducing the incidence of cancelled CT scans due to the expectation of a reduced patient waiting time for eGFR measurement for those patients who present without a recent eGFR measure. MIB specialist commentators note the administrative cost of cancelling or rescheduling scans, and the impact of cancellations on overall

scanning capacity. The other benefit is more accurately identifying the subset of patients without a recent eGFR measurement who should not proceed with contrast CT scan due to their elevated risk of kidney disease (i.e. patients with an eGFR <30ml/min/1.73m^2). These patients are most likely to suffer adverse effects of contrast induced kidney injury, and thus should not generally proceed to contrast CT scan unless appropriate prophylaxis is provided, have their contrast dose reviewed, or are in urgent need of diagnostic information provided only by contrast enhanced imaging.

The MIB authors note that POC devices are expected to deliver eGFR results from a whole blood sample in 9 minutes or less, compared to laboratory testing which can take between 60 minutes and 24 hours. The specialist clinical group consulted notes this reduction in wait time would reduce the need for additional appointments, delayed appointments and increase patient throughput. The MIB notes that POC devices would be most useful in assessing kidney function in the subgroup of the overall patient population at highest risk of kidney disease, including those with diabetes, people taking metformin and older people.

The authors note that POC testing would increase upfront costs compared to standard laboratory based testing. The unit cost of laboratory test for blood/serum/plasma creatinine of £1.29 at 2015/16 prices (Reference Cost DAPS04[107]). The authors note that the unit cost per POC test for the devices they consider vary between £0.17 and £4.75. The authors also note the significant upfront capital costs of POC devices. On a practical front, the authors note the potential requirement for staff training & compliance and quality assurance policies as well as an increase in storage space for POC consumables, however they also note the latter would be unlikely to be a significant change. The authors also note that additional resources may be required for participation in external quality assurance schemes, with specialist commentators also suggesting potential for cost in integration of recording POC results with the existing hospital reporting system. The specialist group of clinical advisors held divergent opinions on whether POC testing would replace central laboratory testing or supplement it.

The authors note some economic benefits of early diagnosis of chronic kidney disease through use of POC testing as opposed to waiting for GP testing, however they note these savings would be minimal. The authors also cite a US study[108] which showed a reduction in waiting times for eGFR results from an average of 1 hour 54 minutes to 5 minutes following the introduction of radiology POC testing. This study also suggested that the volume of contrast material used was also reduced for 25% of patients (33/125 patients). Although not directly reported in the MIB, this study suggests that rapid testing will enable radiology departments to reduce costs by reducing the number of FTE-equivalent administrative positions needed for checking laboratory results prior to testing, and also reduce technician overtime due to reduced need to accommodate delayed exam times due to waiting for laboratory results.

5.1.2 Implications for the care pathway identified in the KiTEC report

As part of the report produced by KiTEC to support the EAG report [13], clinical experts were also interviewed regarding their views on the implications of introducing POC creatinine testing within the current CT imaging pathway. The KiTEC report noted that all the clinical experts that were interviewed expressed concerns regarding the use of these devices in their departments. The report highlighted two main reasons for these concerns. Firstly, they highlighted that referring clinicians would rely even more on the radiology department to check the patients' eGFR. As a result of this behavioural change, the experts thought this would result in an increase in the number of patients referred for a CT appointment without a recent eGFR measurement. Secondly, the clinicians noted that this would increase the responsibility and resourcing required by radiology to not only action upon a low eGFR but also to explain to the attending patient that their result was abnormal and may require further investigations and changes in management.

5.3 Discussion of existing cost-effectiveness evidence and relevance to current decision problem

[redacted]

To address the issues and uncertainties identified in the review and particularly to inform the cost-effectiveness of POC creatinine testing for the specific decision population under consideration, a new independent decision model was developed.

6 Independent economic assessment

6.1 Overview

Section 5 identified several issues and uncertainties arising from previously published studies. A number of important limitations were also identified in relation to the current decision problem, specifically: (i) only a single cost-consequence analysis was identified and no studies have formally assessed the cost-effectiveness of POC testing in the decision context considered in this appraisal; (ii) the lack of any study which has attempted to formally compare different POC testing devices and (iii) the absence of any study which has attempted to quantify the benefits and risks associated with incorporating POC testing within the current CT imaging pathway. For this reason, it has been necessary to develop a de-novo decision model.

6.2 Contribution of the model

The purpose of the decision model is to assess the cost-effectiveness of POC testing to assess kidney function, for people who need contrast-enhanced CT imaging in a non-emergency situation and who do not have a recent eGFR measurement. The model provides a quantitative framework to link the diagnostic accuracy of POC creatinine tests to short-term costs and consequences (e.g. the impact on cancelled or delayed appointments, use of contrast media with and without IV hydration and associated risks such as PC- AKI) and final health outcomes (e.g. end stage renal disease and death) expressed in terms of QALYs. This linkage is necessary in order to provide decision makers with an indication of the health gain achieved by POC tests, relative to their additional cost, in units which permit comparison with other uses of health service resources.

The purpose of the POC and existing laboratory based tests (urgent and non-urgent) is to inform subsequent scanning decisions, specifically the use of contrast material, prophylactic hydration or the use of alternative imaging modalities. The model characterises the impact of the alternative tests (POC versus laboratory based) based on the person's estimated eGFR and the subsequent decisions according to specific eGFR thresholds. These decisions will affect the use of contrast, prophylaxis and use of alternative imaging modalities. For example, the volume of contrast will depend upon whether a decision is made to proceed with CT imaging using contrast material or to proceed with an unenhanced CT scan or even to an alternative imaging modality. These decisions and the subsequent use of contrast material and prophylactic hydration also need to be linked to any possible impact on the risks of PC-AKI and to final health outcomes including morbidity and mortality.

The use of POC testing within the current CT pathway has implications to the health system that relate to the following main components:

i) System level and resourcing: The use of POC testing may reduce system inefficiencies related to ensuring that a recent laboratory based eGFR measure is available prior to the CT appointment.

Although significant efforts are often made to ensure a recent eGFR measure is available prior to the scheduled CT appointment, a proportion of individuals may present on the day of the scan without a recent eGFR measurement. As a result, these individuals may be sent for blood tests in the hospital laboratory, which means the planned CT scan appointment may need to be delayed or rescheduled.

ii) Diagnostic (in)accuracy: POC tests (used with or without additional risk questionnaires) inevitably introduce some level of misclassification compared to laboratory testing, in that some of the individuals may be misclassified as high-risk of PC-AKI (false positives) and others, that are truly high-risk, may be misclassified as low-risk (false negatives). As a consequence of misclassification, these individuals may not receive the appropriate clinical management strategies leading to potential morbidity and even mortality implications.

iii) Risk of PC-AKI: Equally, POC devices may help to identify individuals at high-risk of PC-AKI; particularly those presenting at their appointment without a recent eGFR measurement and for whom a decision to proceed to contrast enhanced CT scan is made based on clinical judgement alone. By providing a timely eGFR measurement, more individuals at higher risk of PC-AKI may be identified, allowing more appropriate management strategies to be followed. That is, preventative strategies can be put in place including the use oral or IV hydration or identifying individuals where the use of contrast can be avoided without significantly compromising accuracy by performing an unenhanced CT scan or changing diagnostic modality.

The modelling proposed here is designed to address these three components and to be able to determine the overall value of POC testing conferred from each of the possible risks and benefits. The following sections outline the decision problem and the structure of the model and also provide an overview of the key assumptions and data sources used to populate the model.

6.3 Model Structure

6.3.1 Overview

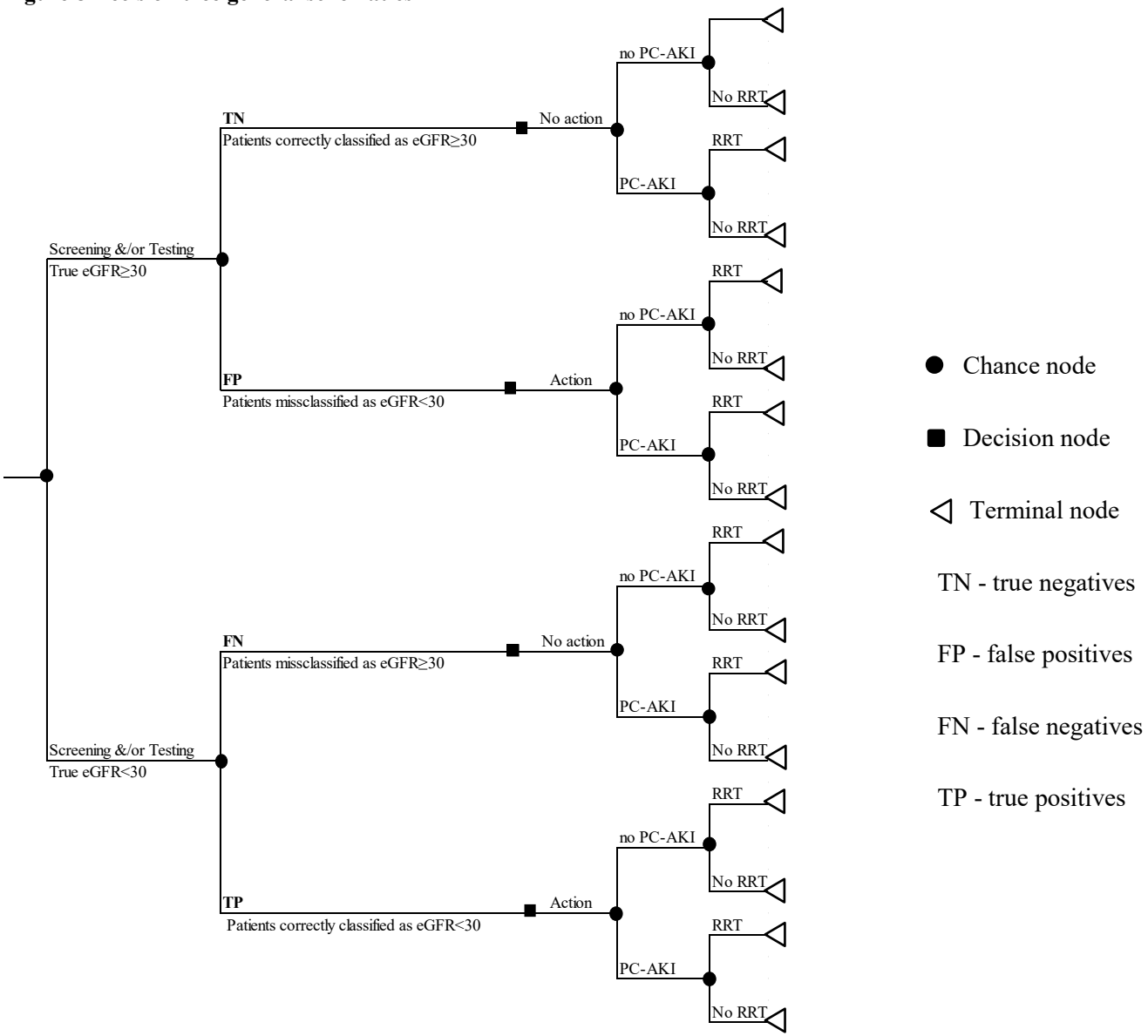
The model evaluates the cost and health outcomes of a cohort of outpatients presenting for a non-emergency contrast enhanced CT scan without a recent eGFR measurement. The model is populated using the results from the quantitative synthesis of the diagnostic accuracy of POC testing as described in Section 4.2.7. Other relevant parameters were informed by a series of additional reviews described throughout this section. These parameters are used to provide a link between the diagnostic accuracy of a given testing strategy, the impact on subsequent treatment decisions and the ultimate effect on health outcomes and costs.

Costs are presented from the perspective of the NHS and Personal Social Services (NHS & PSS) and are reported in UK pounds (£) at a 2018 price base. Outcomes are expressed in terms of QALYs. Outcomes beyond the first year are discounted at a rate of 3.5% per annum.

The model uses a decision tree cohort approach to estimate, based on best available data, the costs and health outcomes of the relevant testing and treatment strategies. The model structure captures: i) individuals' true eGFR status (with the cohort dichotomised based on a cut-off value of 30ml/min/1.73m^2); ii) how these individuals are subsequently classified by different testing strategies (with classification dichotomised on the same eGFR cut-off value of 30ml/min/1.73m^2 and probabilities conditional on true eGFR status); iii) any actions take to mediate PC-AKI risk in patients identified (correctly or incorrectly) as below the eGFR cut-off value; (iv) the subsequent risk of PC-AKI (conditional on eGFR status and any actions taken to mediate PC-AKI risk); and v) the risk of renal replacement therapy (conditional on whether a patient experienced a PC-AKI). Costs and QALYs are linked to the use of screening tests, mediating actions taken and the use of renal replacement therapy (RRT).

A simplified model schematic is shown in Figure 8. Patients are defined as true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) according to their overall classification across each testing strategy and not in relation to individual tests in the sequence. Testing approaches may combine up to three testing elements to identify patients. The elements of testing considered were: i) screening on the basis of a risk factor questionnaire; ii) testing with a POC device; and iii) testing with a laboratory test (urgent or non-urgent). Patients identified as negative by the testing approach will receive no alternative management and undergo a contrast enhanced CT scan. Patients identified as positive will receive mediating action, which in the base case is assumed to be the use of IV hydration prior to undergoing a contrast enhanced CT scan. Following their scan patients may experience a PC-AKI and may subsequently undergo RRT.

Figure 8 Decision tree general schematics



A key assumption in the base-case analysis is that all individuals will eventually proceed to a contrast enhanced CT scan. Hence, the only difference between the alternative testing strategies evaluated concerns the costs and potential health impact of delayed or rescheduled CT scans, whether any mediating action is taken to reduce the risk of PC-AKI (i.e. use of IV hydration) and the consequences of PC-AKI. The base-case analysis does not attempt to include other clinical outcomes that could be affected by changes to the imaging decision itself. These outcomes could include anxiety associated with having a delayed or cancelled scan and morbidity and mortality implications of performing unenhanced scans or using an alternative imaging modality. This simplification was considered necessary given the limited data available and the challenges of characterising the hetereogeneity in the overall population and the underlying reason for imaging and linking this to individualised clinical decision making and associated outcomes.

The challenges of linking different decisions regarding the use of contrast media in imaging to patient outcomes were also highlighted in the KiTEC report[13]. Clinical experts interviewed in the KiTEC report stated that it is difficult to quantify the impact of decisions regarding the use of contrast media on patient outcomes as the benefits of using IV contrast vary depending on the underlying population and scanning indication. The use of IV contrast was considered by the clinical experts to be well-established practice but none was aware of any landmark study that could be used to quantify the benefits compared to alternative imaging decisions.

Although the base-case analysis imposes boundaries around the specific clinical outcomes assessed due to practical considerations and data gaps, a series of additional scenario analysis were undertaken to explore the robustness of the base-case analysis to alternative assumptions concerning the potential impact of alternative imaging decisions on costs and outcomes. These scenarios considered the potential costs as well as any anxiety effects associated with a delayed CT scan or a scan using an alternative imaging modality. The full set of scenarios are discussed in more detail in later sections.

The model evaluates the cost effectiveness of 14 alternative testing strategies to identify and manage patients with eGFR<30ml/min/1.73m^2. The likelihood of an individual being classified as positive (eGFR<30ml/min/1.73m^2) or negative (eGFR≥30ml/min/1.73m^2) is estimated for each strategy based on an individual's true eGFR status and the diagnostic accuracy (sensitivities and specificities) of the different elements of testing that compose the overall testing strategy. Where a strategy involves multiple tests, an individual will progress from one test to the next if the first test classifies them as positive, which in the case of risk factor screening will involve them being classified as at risk or in the case of POC device of having eGFR<30ml/min/1.73m^2. An individual will be identified as positive (either TP or FP) if the final test in the strategy classifies them as being eGFR<30ml/min/1.73m^2.

The risk of PC-AKI is conditioned on an individual's true eGFR value, with higher risk assumed in patients with eGFR lower than 30ml/min/1.73m^2. This risk is assumed to be modifiable by providing either prophylactic measures prior to the provision of contrast or changing the imaging modality. Individuals who test negative are managed with their planned contrast enhanced CT scan, while those who test positive are managed to reduce their risk of PC-AKI. The model assumes that the risk of PC-AKI is modifiable only for patients who have a true eGFR measure lower than 30ml/min/1.73m^2. Therefore, individuals who are misclassified as positive (FP), will incur the costs of the actions taken to reduce their perceived PC-AKI risk, but do not derive any health benefit in terms of a reduction in PC-AKI risk and subsequent clinical events. Individuals who are misclassified as negative (FN) will not incur the cost of these mediating actions, but will fail to realise the health benefits of receiving an action that would reduce their risk of PC-AKI. In the base case, the mediating action is assumed to be IV hydration prior to a full contrast CT scan. In a scenario analysis, individuals were considered to receive a range of possible mediating actions, with a proportion of patients receiving IV hydration prior to a full contrast CT scan, a proportion receiving an unenhanced CT scan and a proportion receiving an MRI scan.

Based on evidence from a series of reviews, all individuals are assumed to be at risk of requiring temporary RRT within 6 months of imaging and this risk is assumed to be conditional solely on experiencing a PC-AKI. Based on this evidence it is also assumed that PC-AKI has no impact on mortality, and that there are no differences between strategies in terms of patients' costs and HRQoL after 6 months post-imaging.

The model considers the costs of testing patients according to the combination of testing components in each strategy. In the base case, undertaking a laboratory test was assumed to always cause a delay and cancellation of the initial CT scan with consequent loss of the imaging time slot and associated costs. Scenario analyses explored the robustness of the results to alternative assumptions including that a proportion of the laboratory tests would be urgent and would not result in a delay unless a positive test result was obtained requiring mediating action. Risk factor screening and POC test would only cause the delay and cancellation of the initial CT scan if they are the final testing component in that strategy and the final result was positive resulting in mediating action being taken. For individuals who undergo mediating actions (IV hydration in the base case), the cost of the action taken and any associated adverse events were captured. PC-AKI events are assumed to impose no costs, although they do alter the risk of a patient requiring RRT which was costed.

Outcomes of patients are captured in quality adjusted life years (QALYs) over their remaining life time. All patients in the model are assumed to have the same life expectancy and HRQoL as the age and sex adjusted general population, with HRQoL decrements applied to those patients who require RRT for a duration of 3 months. No further HRQoL impacts are assumed in the base case analysis. A

scenario analysis considered a HRQoL decrement as a result of anxiety caused by any delay of the CT scan or use of an alternative imaging modality.

Further details of the main structural and input assumptions and the sources of evidence considered for each are discussed in detail in later sections.

6.3.2 Strategies

The strategies included in the model represent the potential pathways that are either part of current clinical practice or represent ways in which POC testing could be integrated into clinical practice. These can be grouped into 6 types of strategy, according to the testing approach followed:

1. Laboratory testing only.
2. Risk factor screening combined with POC testing.
3. Risk factor screening combined with laboratory testing.
4. Risk factor screening combined with POC testing and laboratory testing.
5. POC testing only.
6. POC testing combined with laboratory testing.

A strategy of 'no testing and manage all with contrast enhanced CT' was not included in the base-case analysis. Although this represents a potentially feasible strategy, this strategy was not deemed to be clinically appropriate given the consistent recommendations reported across clinical guidelines recommending the use of some form of screening or testing to identify individuals at risk of PC-AKI. However, for completeness and to aid the overall interpretation of the results, this strategy was included in a separate scenario. Similarly, a strategy of risk factor screening alone was initially considered but then excluded, as this was not deemed to be clinically feasible due to the high-rate of false-positives that would require IV hydration and the limited capacity to provide this.

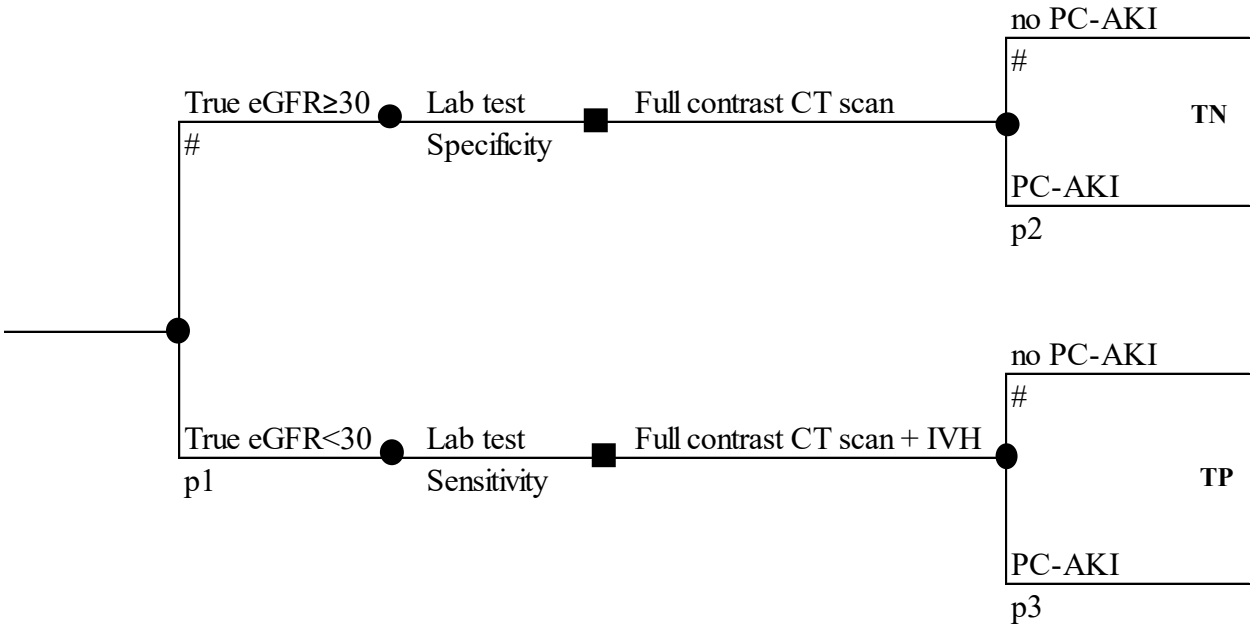
Laboratory testing consists of performing a blood test on all individuals presenting without a recent eGFR measurement prior to imaging. Although the NICE scope distinguished between urgent and non-urgent laboratory tests, no evidence was subsequently identified concerning differences in test performance or unit costs. However, access to urgent laboratory testing has important implications for the timing of clinical decisions and the impact on scanning decisions (i.e. whether the scan can be rescheduled within the same day or requires the scan to be rebooked for a separate day). Inevitably, there exists significant heterogeneity across NHS sites in terms of provision and access to urgent laboratory testing. In the base-case analysis, it was assumed that laboratory testing would require the CT scan to be rescheduled on a separate day (i.e. only non-urgent testing). A series of scenarios were also undertaken which assumed that a proportion of patients (25%, 50%, 75% and 100%) would

receive urgent laboratory testing, allowing their CT scan to be rescheduled for the same day and hence avoiding the full opportunity cost of a lost CT scan appointment.

Individuals who test negative with laboratory testing are assumed to be managed with the planned contrast enhanced CT scan. Those individuals who test positive receive mediating action so as to reduce their PC-AKI risk, with management consisting of IV hydration followed by contrast enhanced CT scan in the base-case analysis.

Figure 9 provides a schematic of the model structure for the laboratory testing strategy.

Figure 9 Model structure – Laboratory testing



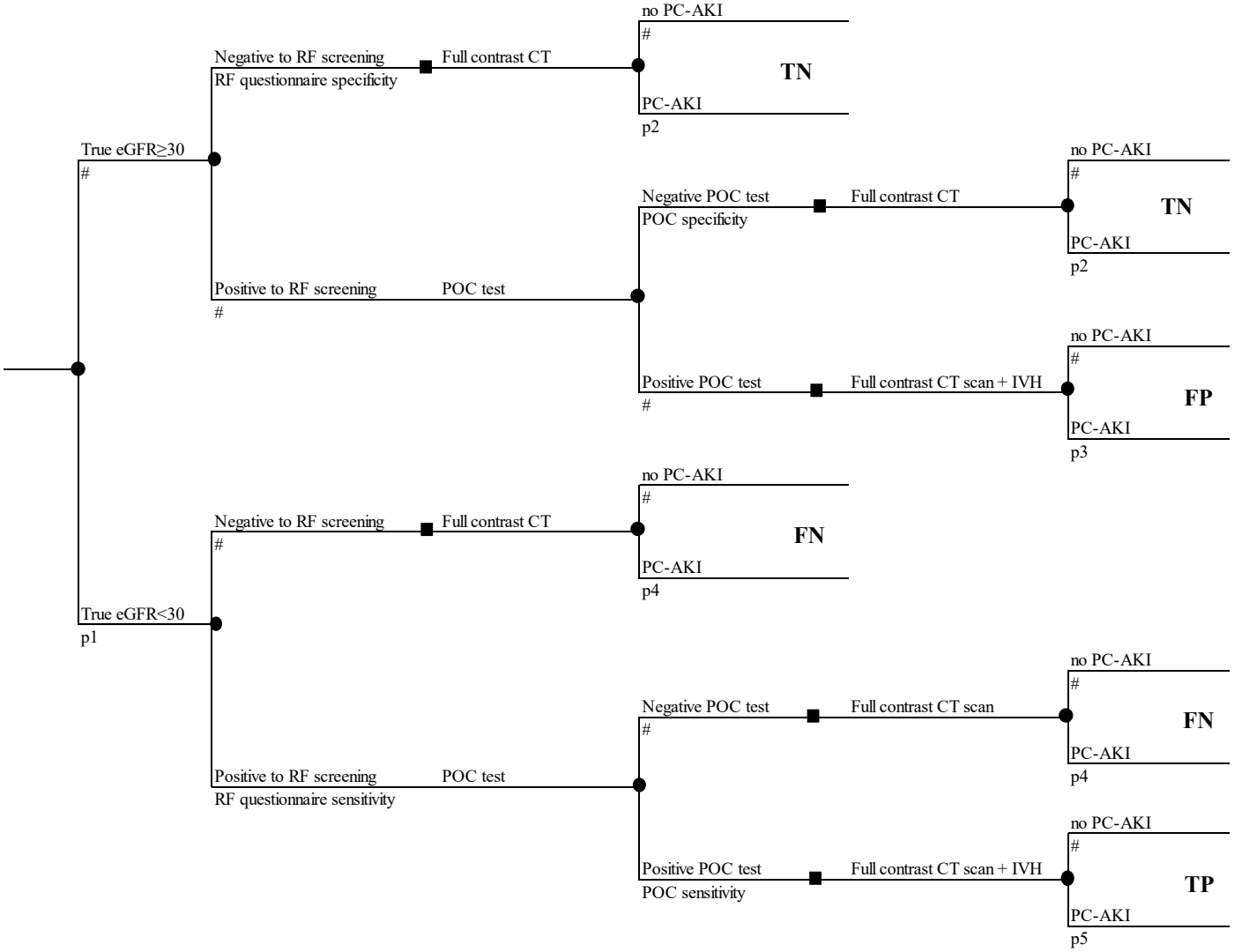
IVH, IV hydration; RR, relative risk; TN, true negatives; TP, true positives.

p1, probability of eGFR<30ml/min/1.73m^2; p2, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan; p3, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration

Risk factor screening combined with POC testing consists of screening individuals with a risk factor questionnaire followed by a POC test for individuals identified with at least one risk factor (risk factor positive). Individuals who screen risk factor negative or test negative with the POC test are assumed to proceed with the planned contrast enhanced CT scan. Individuals who screen positive and have an eGFR measurement of lower than 30ml/min/1.73m^2 with the POC device receive IV hydration to reduce their PC-AKI risk.

Figure 10 provides a schematic of the model structure for the risk factor screening combined with POC testing strategy.

Figure 10 Model structure - Risk factor screening combined with POC testing



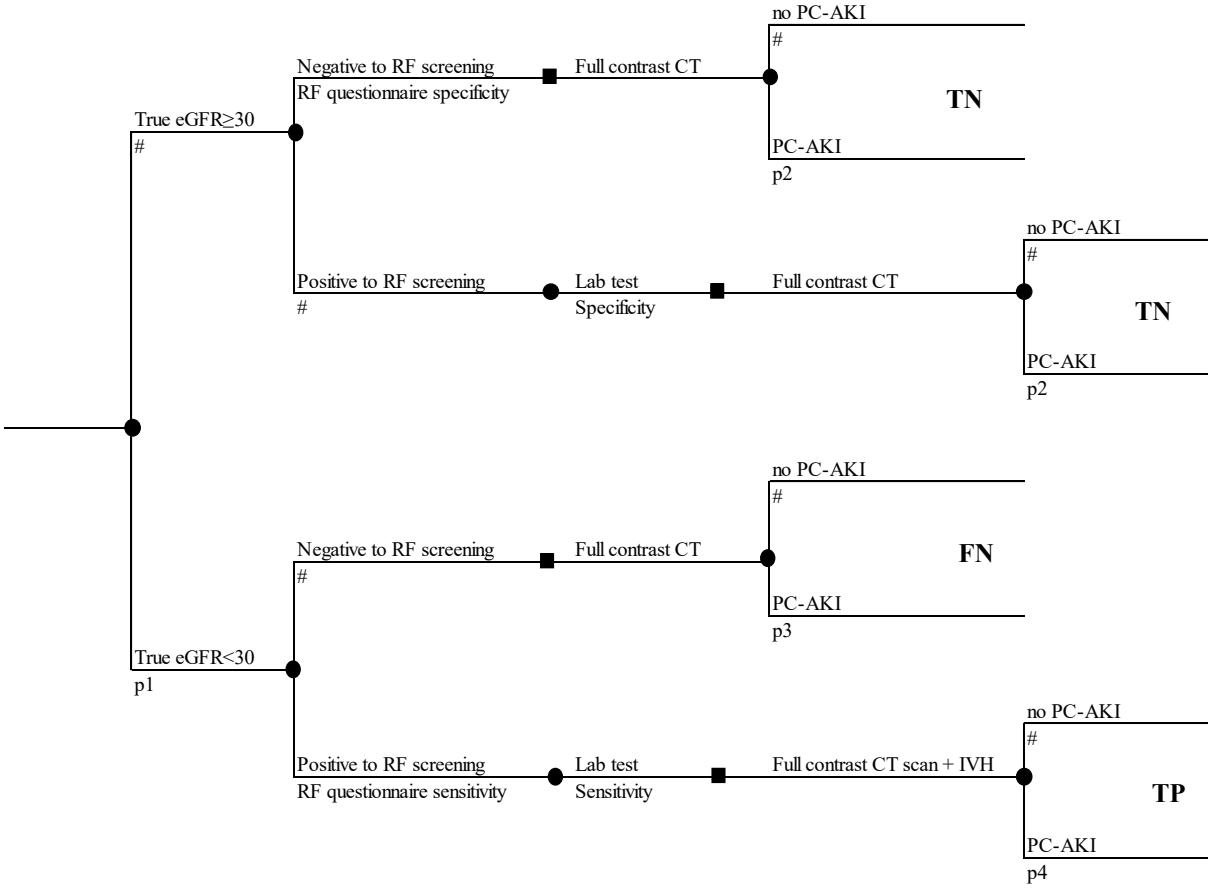
FN, false negatives; FP, false positives; IVH, IV hydration; Risk factor, TN, true negatives; TP, true positives.

p1, probability of eGFR<30ml/min/1.73m^2; p2, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan; p3, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration; p4, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan; p5, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration

Risk factor screening combined with laboratory testing consists of screening individuals with a risk factor questionnaire followed by a laboratory test for those individuals who screen positive for at least one risk factor. Individuals who have no risk factors, and those who test negative on the laboratory test receive contrast enhanced CT scan. Individuals who screen and test positive receive additional management to reduce their risk of PC-AKI.

Figure 11 provides a schematic of the model structure for the risk factor screening combined with laboratory testing strategy.

Figure 11 Model structure - Risk factor screening combined with laboratory testing



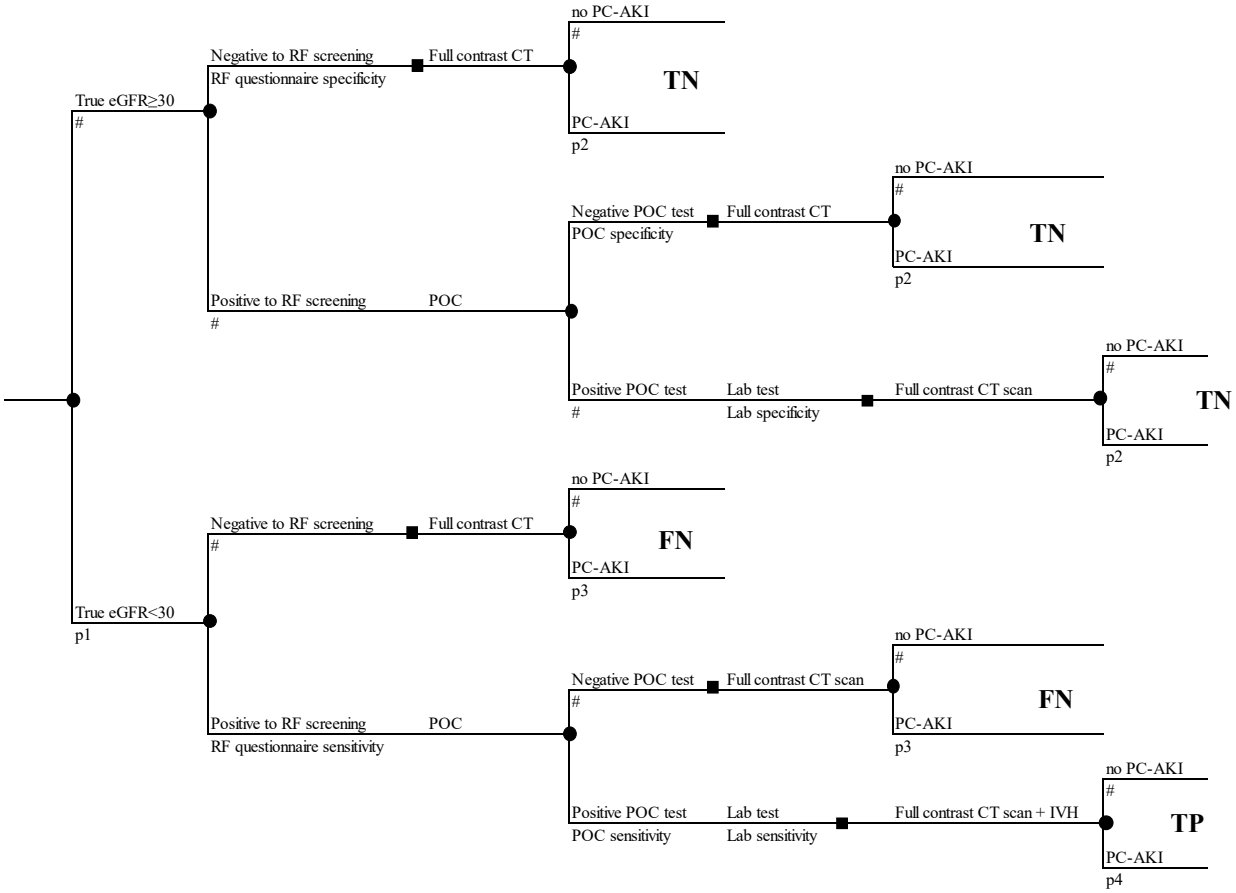
FN, false negatives; IVH, IV hydration; RF, risk factor; TN, true negatives; TP, true positives.

p1, probability of eGFR<30ml/min/1.73m^2; p2, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan; p3, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan; p4, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration

Risk factor screening combined with POC and laboratory testing comprises a three step testing sequence which involves screening all individuals for risk factors, testing with POC devices those with at least one risk factor, and providing individuals who screen and test positive (with POC devices) with a confirmatory laboratory test. All individuals that have a negative result at any point in the testing sequence are managed with a contrast enhanced CT scan. Individuals who test positive at all three steps of the testing sequence receive management to reduce their risk of PC-AKI.

Figure 12 provides a schematic of the model structure for the risk factor screening combined with POC and laboratory testing strategy.

Figure 12 Model structure - Risk factor screening combined with POC and laboratory testing



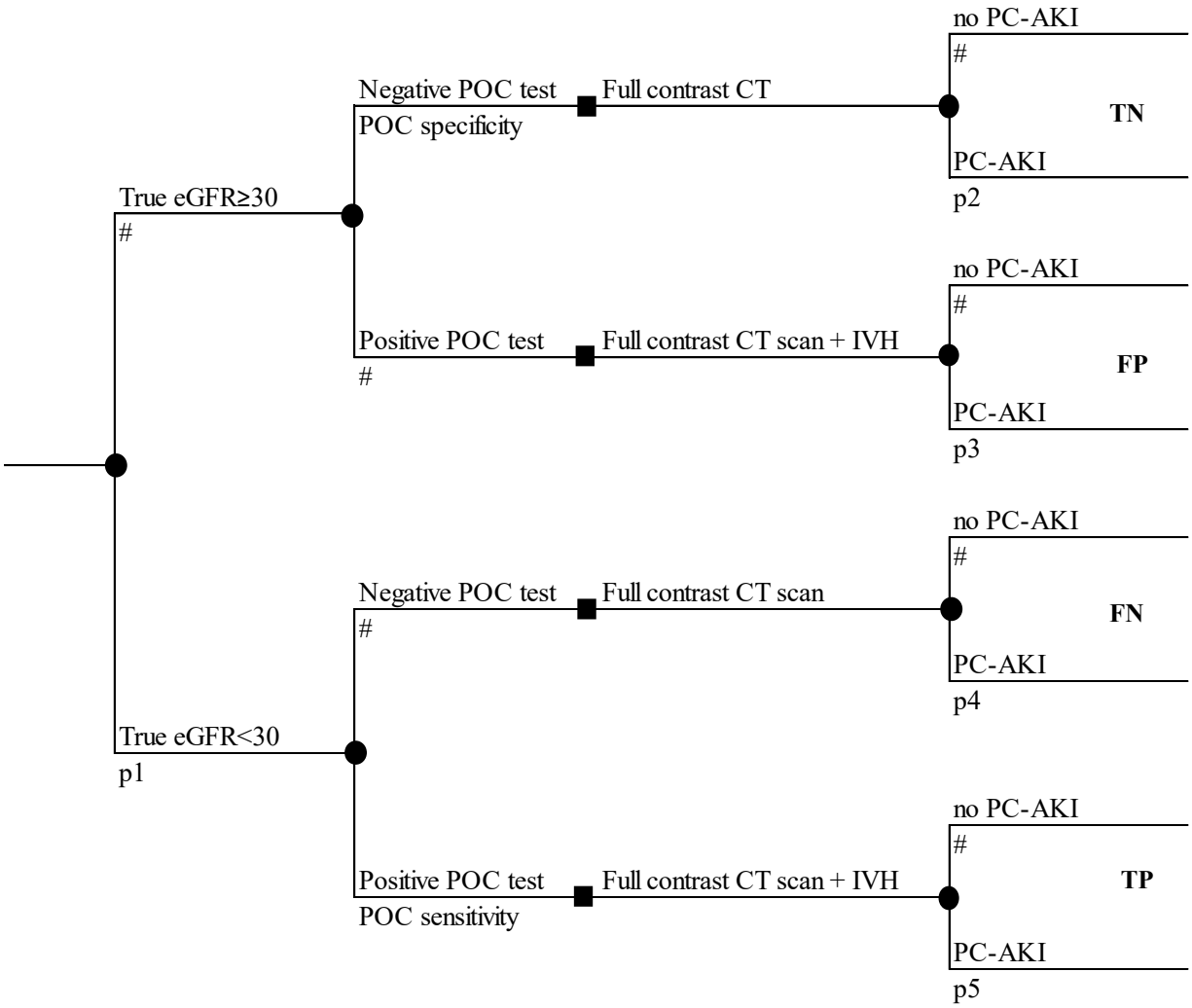
FN, false negatives; FP, false positives; IVH, IV hydration; RF, risk factor; TN, true negatives; TP, true positives.

p1, probability of eGFR<30ml/min/1.73m^2; p2, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan; p3, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan; p4, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration

POC testing consists of testing all individuals with a POC device, with those testing negative managed with a contrast enhanced CT scan and those testing positive sequence receive mediating action to reduce their risk of PC-AKI.

Figure 13 provides a schematic of the model structure for the POC testing strategy.

Figure 13 Model structure - POC testing



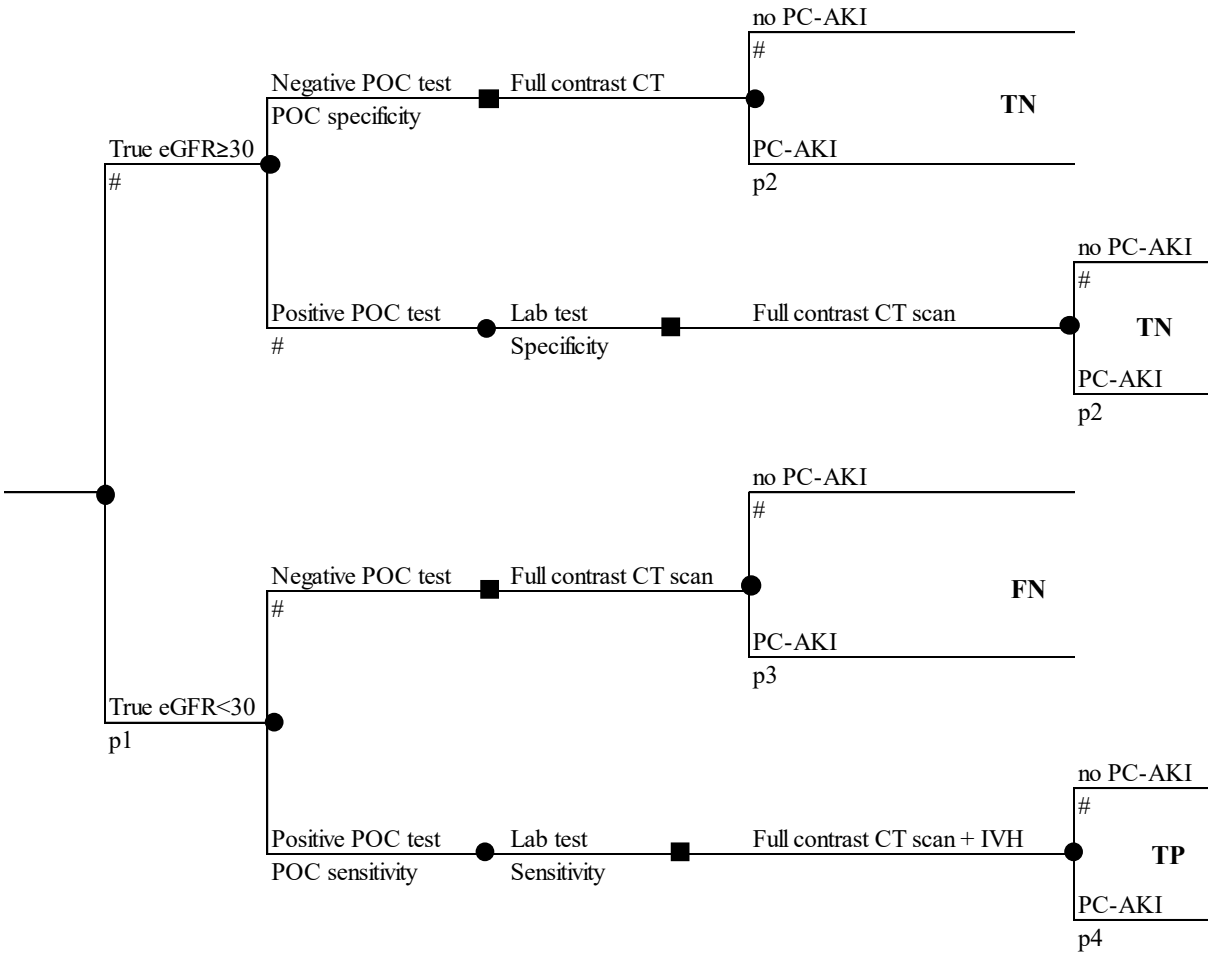
FN, false negatives; FP, false positives; IVH, IV hydration;; TN, true negatives; TP, true positives.

p1, probability of eGFR<30ml/min/1.73m^2; p2, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan; p3, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration; p4, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan; p5, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration

The last strategy type combines POC testing with laboratory testing. Individuals who test positive with the POC test receive a confirmatory laboratory test. Those testing negative to either test receive a contrast enhanced CT, and those testing positive to both sequence receive mediating action so as to reduce their risk of PC-AKI.

Figure 14 provides a schematic of the model structure for the POC testing combined with laboratory testing strategy.

Figure 14 Model structure - POC testing combined with laboratory testing



FN, false negatives; IVH, IV hydration; TN, true negatives; TP, true positives.

p1, probability of eGFR<30ml/min/1.73m^2; p2, probability of AKI conditional on eGFR≥30ml/min/1.73m^2 and contrast enhanced CT scan; p3, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan; p4, probability of AKI conditional on eGFR<30ml/min/1.73m^2 and contrast enhanced CT scan with prophylactic IV hydration

For each type of strategy that includes POC testing, the model considers separate strategies for each of the POC devices. The POC devices considered in the cost effectiveness analysis are restricted to those which reported diagnostic accuracy data using eGFR thresholds reported in the quantitative synthesis (see Section 4.2.7). The three devices considered in the model are i-STAT Alinity, ABL 800 Flex and StatSensor. In line with the clinical effectiveness review, the different models of i-STAT, ABL 800 series and StatSensor are assumed equivalent in terms of diagnostic accuracy data within brand, while the costs are derived for the models that are commercially available in the UK, according to the manufacturer.

Although different types of laboratory-based serum creatinine tests are used in clinical practice to derive eGFR values, it is assumed that these are all equivalent in terms of diagnostic accuracy and

costs. The laboratory test is assumed to have perfect diagnostic accuracy (100% sensitivity and specificity).

Clinical guidelines recommend that only individuals considered at high risk of PC-AKI have their eGFR measured prior to undergoing a contrast enhanced CT scan [9 6 8 10]. However, these guidelines do not recommend the use of any particular screening tool, and there is lack of consistency across this literature regarding the specific criteria that would allow identifying high risk individuals. Therefore, screening in the model was assumed to be conducted with a generic risk factor questionnaire.

Laboratory testing requires time for the test to be processed, which means that some individuals may not be able to undergo their CT scan on the same day. In the base case it was assumed that all individuals undergoing a laboratory test would have their CT scan cancelled. However, a scenario analysis allowed for a proportion of patients to receive a rapid laboratory test, and those who test negative are assumed not to have their CT scan cancelled.

Risk factor screening and POC testing are assumed to be conducted within the original CT scan time slot, and therefore do not introduce any further delays (and associated costs). However, if individuals are identified as requiring alternative management to mitigate the PC-AKI risk, this may also be unfeasible to be conducted within the same day for which their original CT scan was planned. The base-case assumes that all patients who require a laboratory test or test positive at the last step of the testing sequence will incur the costs of delay. The proportions requiring delay are varied in scenario analyses.

The model considers three alternative management options for patients who are identified as having an eGFR<30ml/min/1.73m^2 by any of the testing approaches described above. These management approaches are:

1. IV hydration followed by contrast enhanced CT scan
2. Unenhanced CT scan
3. Unenhanced MRI scan

It is assumed that all approaches are equivalent in terms of diagnostic accuracy of the imaging modality, but differ in terms of cost and effect on the risk of PC-AKI. As previously stated, all patients in the base-case analysis identified as being at high risk of PC-AKI are assumed to be managed with prophylactic IV hydration and proceed with full contrast dose CT scan. It is assumed that adverse events from IV hydration are only associated with costs but not with any health-related quality of life (HRQoL) loss. Separate scenarios are presented assuming alternative management approaches.

Table 28 summarises the 14 strategies evaluated in the base-case cost effectiveness analysis.

Table 28 Strategies evaluated in the base-case analysis

Strategy #	Testing		Management
	Label	**Description**	
1	Lab	Test all with a laboratory test.	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan
2	RF + i-STAT	Screen with RF questionnaire. Patients who screen positive are tested with i-STAT.	
3	RF + ABL800FLEX	Screen with RF questionnaire. Patients who screen positive are tested with ABL800 Flex.	
4	RF + StatSensor	Screen with RF questionnaire. Patients who screen positive are tested with StatSensor.	
5	RF + Lab	Screen with RF questionnaire. Patients who screen positive are also laboratory tested.	
6	RF + i-STAT + Lab	Screen with RF questionnaire. Patients who screen positive are tested with i-STAT. Patients who test positive with POC are also tested with a laboratory test.	
7	RF + ABL800FLEX + Lab	Screen with RF questionnaire. Patients who screen positive are tested with ABL800 Flex. Patients who test positive with POC are tested with a laboratory test.	
8	RF + StatSensor + Lab	Screen with RF questionnaire. Patients who screen positive are tested with StatSensor. Patients who test positive with POC are tested with a laboratory test.	
9	i-STAT	Test with i-STAT. Patients who test positive with POC are tested with a laboratory test.	
10	ABL800FLEX	Test with ABL800 Flex. Patients who test positive with POC are tested with a laboratory test.	
11	StatSensor	Test with StatSensor. Patients who test positive with POC are tested with a laboratory test.	
12	i-STAT+ Lab	Test with i-STAT. Patients who test positive with POC are tested with a laboratory test.	
13	ABL800FLEX+ Lab	Test with ABL800 Flex. Patients who test positive with POC are tested with a laboratory test.	
14	StatSensor + Lab	Test with StatSensor. Patients who test positive with POC are tested with a laboratory test.	

*According to any test in the testing sequence **According to last test in the testing sequence; IVH, intravenous hydration; RF, risk factor questionnaire.

6.4 Model input parameters

6.4.1 Population characteristics

The cost-effectiveness of the alternative strategies will be dependent on the characteristics of the patient population being considered, including the distribution of eGFR and the number of patients who are likely to present without a recent eGFR measurement. The population considered here is non-emergency adult outpatients presenting for intravenous contrast enhanced CT scanning without an available eGFR measurement at attendance to the radiology department.

6.4.1.1 Distribution of eGFR

No published studies were identified in non-emergency adult outpatients presenting for intravenous contrast enhanced CT scanning without an available eGFR measurement which presented sufficient information to determine the underlying distribution of eGFR. Therefore, additional evidence was sought from the clinical adviser to the EAG (Martine Harris) (Dr Martine Harris, personal communication data). Harris provided one month's routine outpatient audit data across three sites from the Mid Yorkshire NHS Trust. Data was grouped by bins of eGFR width of 10 (with eGFR below 30ml/min/1.73m^2 and over 90 ml/min/1.73m^2 treated as individuals bins) was available for 816 outpatients, of which 104 attended radiology without a recent eGFR measure.

Table 29 presents the distribution in the overall sample of 816 outpatients and in the subgroup of patients who attended radiology without a recent eGFR measure. Only one patient in the overall sample ('all outpatients') had an eGFR below 30 ml/min/1.73m^2 (0.12%), whilst no patients in the subgroup who attended without a prior eGFR had a measure below 30 ml/min/1.73m^2. The overall sample and the subgroup without a prior eGFR measurement arppear broadly comparable, with similar proportions falling into each eGFR bin.

Table 29 eGFR for all outpatients and those without a prior eGFR measurement (Harris data)

eGFR (ml/min/1.73m^2)	All outpatients	Patients without a prior eGFR measurement
<30	1 (0.12%)	0 (0%)
30-40	31 (3.8%)	4 (3.85%)
41-50	59 (7.23%)	5 (4.81%)
51-60	91 (11.15%)	14 (13.46%)
61-70	141 (17.28%)	29 (27.88%)
71-80	154 (18.87%)	24 (23.08%)
81-90	150 (18.38%)	16 (15.38%)
>90	189 (23.16%)	12 (11.54%)
Total	816	104

The data provided by Harris was further disaggregated by the reason for referral for CT (suspected cancer, urgent and routine referrals). Table 30 presents the eGFR distribution by reason for referral in the overall sample and in the subgroup of patients who attended radiology without a recent eGFR measure. The reasons for referral appear to differ between the overall sample and the subgroup without a prior eGFR measurement, with the majority of those without a prior eGFR measurement being referred routinely (74%), whilst only a third of the overall sample were referred routinely. Given the additional stratification, and therefore smaller numbers, the percentages within each eGFR bin appear more variable across reason for referral within the subgroup without prior eGFR

measurement. In the overall sample, the percentages across the bins for each reason for referral appear broadly comparable.

Table 30 eGFR by reason for referral for all outpatients and those without a prior eGFR measurement (Mid Yorkshire NHS Trust)

	All outpatients			Patients without a prior eGFR measurement		
	Reason for referral			Reason for referral		
eGFR (ml/min/1.73m^2)	Suspected cancer	Urgent	Routine	Suspected cancer	Urgent	Routine
<30	0 (0%)	0 (0%)	1 (0.37%)	0 (0%)	0 (0%)	0 (0%)
30-40	21 (5.38%)	4 (2.56%)	6 (2.22%)	0 (0%)	1 (6.67%)	3 (3.9%)
41-50	26 (6.67%)	15 (9.62%)	18 (6.67%)	0 (0%)	0 (0%)	5 (6.49%)
51-60	47 (12.05%)	18 (11.54%)	26 (9.63%)	2 (16.67%)	1 (6.67%)	11 (14.29%)
61-70	59 (15.13%)	31 (19.87%)	51 (18.89%)	3 (25%)	6 (40%)	20 (25.97%)
71-80	70 (17.95%)	29 (18.59%)	55 (20.37%)	3 (25%)	4 (26.67%)	17 (22.08%)
81-90	71 (18.21%)	27 (17.31%)	52 (19.26%)	3 (25%)	1 (6.67%)	12 (15.58%)
>90	96 (24.62%)	32 (20.51%)	61 (22.59%)	1 (8.33%)	2 (13.33%)	9 (11.69%)
Total	390 (48%)	156 (19%)	270 (33%)	12 (12%)	15 (14%)	77 (74%)

Evidence at less disaggregated eGFR levels (bands of <30, 30 to 60, and ≥60 ml/min/1.73m^2) was also available from two published studies [109] [36] and a separate report by KiTEC commissioned to support this appraisal[13]. The KiTEC report provided evidence on the eGFR distribution from a two week audit of outpatient radiology patients at Guy's and St Thomas' NHS Foundation Trust.

Table 31 summarises the evidence from these studies compared to the data provided by Harris. Both of the Harris populations (all outpatients and the subgroup without a prior eGFR measurement) appear broadly similar to the populations from the two published studies, although the population in Moos (2014) appears slightly less severe with a higher percentage with eGFR scores above 60 ml/min/1.73m^2. The audit of outpatient radiology patients at Guy's and St Thomas' (GSTT) NHS Foundation Trust reports a more severe population with 15.86% of patients reported to have an eGFR <30 ml/min/1.73m^2. The reason for this marked difference was not clear based on the evidence provided in the KiTEC report but it highlights that the underlying eGFR distribution may vary considerably across different NHS sites.

Table 31 eGFR distribution from different studies

eGFR (ml/min/1.73m^2)	Harris- All outpatients	Harris-Patients without a prior eGFR measurement	Moos 2014	Snaith 2019	KiTEC 2019
<30	0.12%	0.00%	0.32%	0.00%	15.86%

30-60	22.18%	22.12%	9.84%	19.33%	25.17%
>60	77.70%	77.88%	89.84%	80.67%	58.97%
Total	816	104	925	300	580

Given the granularity with regards to narrower eGFR bins of the Harris data and comparability with the two published studies, the Harris data was used to inform the distribution of eGFR of patients in the base-case analysis. In addition, given the similarity in overall eGFR distribution in the overall sample and the subgroup without a prior eGFR measurement, the eGFR distribution in the larger overall sample is used in the base-case analysis. Separate scenario analysis were undertaken using the eGFR distribution from the subgroup with missing eGFR at presentation and the alternative eGFR distribution provided in the KiTEC report from the Guy's and St Thomas' NHS Foundation Trust.

Parametric distributions were fitted to estimate the probability a patient falls into four eGFR categories. These categories represent the eGFR bands reported in the clinical effectiveness review and synthesis (<30, 30 to 45, 45 to 60 and ≥60 ml/min/1.73m^2). Fitting distributions to the full set of data points resulted in a poor visual fit at the lower levels of eGFR, therefore the distribution was fitted only up to eGFR of 60 ml/min/1.73m^2, with the probability of being above or below 60 ml/min/1.73m^2 estimated separately. The log normal distribution was considered to provide the best visual fit. The resulting probabilities are shown in Table 32 below. For the overall sample, the fitted log normal distribution predicted a probability of 0.62% of a patient having an eGFR below 30 ml/min/1.73m^2.

Table 32 Fitted distribution of eGFR values

eGFR category (ml/min/1.73m^2)	**Probability of eGFR in category**	
	All patients N=816	Patients with missing eGFR N=104
<30	0.62%	0.27%
30-45	6.28%	5.1%
45-60	15.45%	16.44%
>60	77.67%	78.18%

6.4.1.2 Number of patients without a recent eGFR measurement

The number of patients who present for a contrast enhanced CT scan without a recent eGFR will determine the size of the population to which POC testing may be offered in the NHS. Based on surveys of NHS services [10, 11] and discussions with clinical advisers, the behaviour of practices regarding the absence of eGFR measurements is likely to be heterogeneous.

The type of practice behaviour most commonly seen in the NHS can be characterised as:

1. CT scans are not allowed to be booked until a recent eGFR measurement can be reported in the referral request; this implies that no individuals arrive to a CT scan without a recent eGFR measurement.
2. CT scans are allowed to booked without a record of a recent eGFR measurement but efforts are made by the radiology department to obtain a recent measurement prior to the scan appointment (i.e. either by checking electronic records, requesting a blood test from the referrer or directly instigating a laboratory test).
3. CT scans are allowed to be booked without a record of a recent eGFR measurement but no further checks are implemented by the radiology department prior to the CT scan appointment.

The first type of practice behaviour means that individuals will not present without a recent eGFR measurement and hence implies no role for POC creatinine testing. Hence, this type of practice behaviour is not explicitly considered in the model.

Practices that allow booking of a contrast enhanced CT scan without a confirmed recent eGFR measure differ in terms of the processes and protocols followed regarding how missing eGFR measurements at the time of booking are obtained prior to the scan appointment. Thus, practice behaviour will determine the proportion of pattients without a recent eGFR at the point of CT scan. This also has implications for patient throughput and the costs of POC tests. It may also impact on the underlying eGFR distribution of patients without a recent eGFR measure.

A formal assessment of the cost-effectiveness of different types of practice behaviour was considered beyond the scope of this appraisal. Instead, a series of assumptions were made concerning the proportion of patients likely to attend wihout a recent eGFR measurement. Scenario analysis was undertaken to explore the impact of using alternative assumptions and throughput estimates.

Table 33 summarises the evidence identified which reported on the proportion of patients in an outpatient setting presenting with and without recent eGFR values at the different stages at which eGFR measurements are checked.

Table 33 Availability of eGFR measurements over time

	Cope 2017 [11]	Snaith 2019 [36]	Harris - All outpatients data	KiTEC report		
				Clinical experts	GSTT audit data 2015	GSTT data January 2019

% eGFR available (n/N) at referral/vetting*	NR	54.0% (162/300)	43.9% (358/816)	NR	53.5% (77/144)	47.7% (580/1215)
% eGFR that were provided after booking by referrer or from other records	NR	NR	43.4% (354/816)	NR	26.4 (38/144)	NR
% eGFR missing (n/N) with test instigated by radiology department**	NR	12.3% (37/300)	12.7% (104/816)	NR	NR	NR
% eGFR missing (n/N) at CT scan	34% (1,220/3,584)	1.33% (4/300)	1.1% (9/816)	Small but non-zero	16.7% (24/144)	NR

*stage at which the justification for the scan is checked; GSTT, Guy's and St Thomas' Trust

Cope et al, 2017[11] reports provides the largest source of UK evidence. However, the results from this audit are aggregated for all responding practices, and thus, the heterogeneity of practice behaviour cannot be characterised. Hence, the percentage of patients with missing eGFR values (34%) will include all types of practice behaviour.

Another source of data on outpatients was the sample of one month CT attendance data retrospectively collected for the three radiology sites of the Mid Yorkshire NHS trust (Dr Martine Harris, personal communication) (also used by Shinkins and colleagues (Dr Bethany Shinkins, personal communication)), which was also used to inform the eGFR distribution in the model. These data may be more reflective of what would be observed in a practice similar to practice type 2, where patients are actively chased for an eGFR measurement up until the scan. When POC testing is not available, the radiology department would try to obtain a laboratory result up until the day of the scan, and 1.1% of patients would still present on the day without a valid eGFR measurement. However, if POC creatinine testing was an option, it was assumed that the radiology department would be unlikely to directly instigate any laboratory tests and the proportion of patients presenting to the CT scan without eGFR would be closer to 12.7%. The results from Snaith et al, 2019[36] appear broadly consistent with this.

The KiTEC report presents results from three sources of data: i) interviews with clinical experts, ii) an internal audit data conducted at the Guy's and St Thomas' NHS trust and iii) a raw data extraction of patients records for outpatients referred to a CT scan at the Guy's and St Thomas' NHS trust over two weeks in January 2019. The clinical experts only provided qualitative data that cannot be used in the

model. According to the audit data, a fairly high proportion of patients will present to CT scan without a recent eGFR measurement (16.7%). The GSTT raw data included only information on patients at the point of referral, so the proportion of patients with missing eGFR values at the point of scan is unknown. The only data available is the proportion of patients with a valid eGFR measure at the point of referral (47.7%) which is lower than in Snaith et al, 2019[36] (54.0%), but higher than in the Mid Yorkshire NHS data (43.4%).

Of the sources identified, estimates from Cope et al, 2017[11] were considered the most representative of the 'average' practice behaviour in a UK setting. Therefore, the base case analysis assumes that 34% of patients have missing eGFR values at the point of CT scan. Scenario analyses were also undertaken to explore the impact of heterogeneity and implications for the throughput assumptions informing the costs of POC testing.

6.4.1.3 Subgroups

The NICE scope identified two subgroups: (i) people with known existing kidney disease and (ii) people at different levels of risk of PC-AKI. In the absence of diagnostic accuracy data specific to these separate subgroups or data reporting the underlying eGFR distributions, a formal assessment of cost-effectiveness in these subgroups was not possible. Although the alternative testing strategies included in the model consider the use of POC testing in different subgroups (i.e. POC testing in all individuals or restricted to only those individuals identified at high risk of PC-AKI), diagnostic accuracy is assumed to be the same for each device regardless of where POC testing is used within the overall patient pathway.

6.4.2 Diagnostic accuracy

6.4.2.1 Diagnostic accuracy of POC creatinine tests

The model is parameterised using the diagnostic accuracy data from the quantitative synthesis presented in Section 4.2.7. The diagnostic accuracy of the POC devices in Section 4.2.7 are presented in terms of the probability a patient is classified in a given eGFR category (<30, 30-45, 45-60 and ≥60 ml/min/1.73m^2) by a POC device conditional on their true eGFR category. However, the economic model only considers a single cut-off of eGFR<30 ml/min/1.73m^2 for informing alternative management decisions. In addition, evidence reported in later sections suggests sufficient similarity in risks of PC-AKI and effects of mediating actions on PC-AKI across the range of eGFR in individuals with eGFR≥30 ml/min/1.73m^2 [110]. Hence, the model structure was further simplified by dichotomising the overall population into two groups, those with eGFR<30 ml/min/1.73m^2 and those with eGFR≥30 ml/min/1.73m^2.

Dichotomising the population into two groups based on a single eGFR threshold (eGFR<30 and eGFR≥30ml/min/1.73m^2) means that the sensitivity and specificity of the POC devices for this

threshold need to be derived from the probabilities reported for each eGFR category (<30, 30-45, 45-60 and ≥60 ml/min/1.73m^2) in Section 4.2.7. The sensitivity of the tests can be taken directly from the results of the quantiative synthesis as the probability that an individual with eGFR<30 ml/min/1.73m^2 is correctly categorised as eGFR<30 ml/min/1.73m^2 (p[1,1]). However, by simplifying the model and combining the patients with true eGFR>30 into one group, it was necessary to combine information on the distribution of population eGFR with the probability of being classified as eGFR<30 ml/min/1.73m^2 for a given true eGFR category (p[i,1] for i [2,3,4]) to estimate the specificity of the POC devices.

The specificity is estimated as the weighted average of the probabilities of being classified as eGFR<30 ml/min/1.73m^2 for the eGFR categories (30-45, 45-60 and >60 ml/min/1.73m^2) with the weights based on the proportions of patients falling into the eGFR categories. Specificity was estimated using the following equation for each device:

$$\sum_{i=2}^{4} (1 - \mathrm{p[i, 1]}) \cdot \mathrm{Weight}_i$$

Where $\mathrm{p[i, 1]}$ is the probability that a patient with true eGFR category i is classified as eGFR<30 ml/min/1.73m^2 and Weight_i represents the proportion of the patient population with eGFR>30 ml/min/1.73m^2 who fall into true eGFR category i.

Given that specificity is based on not only the diagnostic accuracy evidence from Section 4.2.7 but also the distribution of population eGFR, it should be noted that when this distribution is altered, the specificity of the device will also change.

The base-case analysis estimates are informed by the main analysis reported from the quantitative synthesis. Additional scenario analyses were undertaken using results based on the sensitivity analysis reported in Section 4.2.7 and included:

1) StatSensor adjusted data analysis.
2) Analysis with studies using CKD-EPI equation to calculate eGFR.

Table 34 reports POC creatinine diagnostic accuracy estimates applied in the base-case and scenario analyses. Mean p[i,j] estimates were calculated from 1,000 simulated values from the posterior distribution obtained by thinning the 30,000 posterior values generated in each analysis of the evidence synthesis, and used to derive specificity and sensitivity. The model sampled from these p[i,j] simulated values to derive specificity and sensitivity in the probabilistic sensitivity analysis.

Table 34 POC creatinine diagnostic accuracy estimates in the model

	i-STAT		ABL800FLEX		Statsensor		Diagnostic accuracy evidence synthesis
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	
Base-case	84.1%	98.9%	86.1	99.2%	73.9%	99.1%	Base case (main) analysis
Scenario analyses	84.1%	98.9%	86.1	99.2%	84.1%	99.0%	StatSensor adjusted data analysis
	81.7%	98.9%	81.4%	99.1%	56.4%	98.4%	Analysis with CKD-EPI equation studies only

6.4.3 Diagnostic accuracy of risk screening questionnaires

Clinical guidelines recommend risk factor screening for patients without prior eGFR measurements presenting for contrast enhanced CT scans to avoid unnecessary blood testing[9 6 8 60]. However, these guidelines do not recommend the use of any particular screening tool, and there is lack of consistency across this literature regarding the specific criteria to identify high risk patients[10]. Furthermore, survey data of UK radiology departments suggests that different guidelines are followed in clinical practice, resulting in heterogeneity of clinical practice behaviour to prevent PC-AKI.

Another issue relates to the evidence context under which the guidelines and risk factor questionnaires were developed. The eGFR cut-off at which PC-AKI risk is considered to increase to clinically relevant values has also altered over time, and patients are now considered to be at high risk of PC-AKI only at eGFR values below 30 ml/min/1.73m^2. Therefore, it is unclear if existing screening tools would accurately identify patients at risk of PC-AKI under the currently used diagnostic criterion, especially in patient populations where average eGFR is expected to be high, as it is the case for non-emergency CT scan outpatients.

Studies identified through reference list searching and citation searching conducted as part of the pragmatic reviews described in Section 4.3 were examined to identify diagnostic accuracy evidence for risk factor questionnaires. Four studies that examined the diagnostic accuracy of risk factor screening questionnaires in an outpatient setting were identified as potentially relevant [73, 109 12, 111]. In addition, we obtained unpublished risk factor screening diagnostic accuracy data from the Snaith et al., 2019 [36] study (Prof. Beverley Snaith, personal communication).

Table 35 summarises the risk factors included in each of the questionnaires.

Table 35 Risk factor screening questionnaires

Risk factors	Azzouz, 2014	Too, 2015		Snaith, 2019		Schreuder, 2017		Moos, 2014			
		Original	Modified	Original/Modified	RANZCR RF	Model A	Model B	Model 1	Model 2	Model 3	Model 4
Renal disease	x	x	x	x	x	x	x	x	x	x	x
Renal surgery	x	x									
Hypertension	x	x		x		x		x	x	x	
Gout	x	x									
DM and/or metformin	x	x	x	x	x	x	x	x	x	x	x
Proteinuria		x									
Recent/current illness				x							
CV disease						x				x	
Age >75							x				x
Age >60								x	x		
Congestive heart failure				x			x				x
Anaemia								x			
Use of diuretics								x			
Malignancy								x			
Multiple myeloma								x			
WM								x			

CV, cardiovascular; DM, diabetes mellitus; RANZCR RF, Royal Australian and New Zealand College of Radiologists guideline risk factors; WM, Waldenström's macroglobulinemia

The studies examined 12 different questionnaires used to identify individuals at increased risk of PC-AKI. None of the questionnaires included the exact same risk factors, but all questionnaires considered previous renal disease and diabetes mellitus as risk factors.

Three of the studies compared the diagnostic accuracy of risk factor screening questionnaires against POC devices[36 12, 73], while three had a laboratory test as a reference test[36 109, 111]. Only three studies included exclusively outpatients, and, all included patients presenting for a contrast enhanced CT scan. Data for the relevant eGFR cut-off (eGFR<30 mL/min/1.73 m^2) was reported for three of the studies[36 12, 73].

Diagnostic accuracy estimates at different eGFR thresholds arereported, alongside study characteristics, for studies using laboratory and POC test as reference test in Table 36 and Table 37, respectively.

Table 36 Diagnostic accuracy of risk factor screening – reference lab test

Questionnaire	**Reference test**	**eGFR equation**	**Population**	**eGFR<45** mL/min/1.73m^2		**eGFR<60** mL/min/1.73m^2	
				Sen	**Spec**	**Sen**	**Spec**
Schreuder, 2017 model A	Lab	MDRD	Non ICU and non emergency patients scheduled to IV CECT	100.0%	46.3%	88.0%	58.7%
Schreuder, 2017 model B				100.0%	58.7%	76.1%	61.5%
Moos, 2014 model 1	Lab	MDRD	Non ICU and non emergency patients scheduled to IV CECT	100.0%	18.8%	96.4%	20.1%
Moos, 2014 model 2				100.0%	26.1%	96.4%	28.1%
Moos, 2014 model 3				100.0%	38.8%	89.3%	41.1%
Moos, 2014 model 4				100.0%	57.6%	76.8%	60.0%
Snaith, 2019, Original*	Lab	CKD-EPI	Outpatients attending for a contrast-enhanced CT scan	71.4%	48.6%	65.5%	50.8%
Snaith, 2019, Modified*				38.5%	67.6%	35.6%	68.0%
Snaith, 2019, RANZCR RF				35.7%	83.9%	25.9%	85.1%

*, the definition of acute illness differs across these two questionnaires with the modified version considering only patients as acutely ill if they indicated acute admission, diarrhoea and vomiting, or recent commencement of antibiotics, while the original questionnaire considering any acute illness; IV CECT, intravenous contrast enhanced CT scan RANZCR RF, Royal Australian and New Zealand College of Radiologists guideline risk factors; Sen, sensitivity; Spec, specificity; U&E, Urea and Electrolytes

Table 37 Diagnostic accuracy of risk factor screening – reference POC test

Questionnaire	Reference test	eGFR equation	Population	eGFR<30 mL/min/1.73m^2		eGFR<45 mL/min/1.73m^2		eGFR<60 mL/min/1.73m^2	
				Sen	Spec	Sen	Spec	Sen	Spec
Azzouz, 2014	StatSensor	CKD-EPI	Outpatients scheduled for CT scan with and without contrast and MRI	88.2%	45.2%	85.4%	47.1%	-	-
Too, 2015	StatSensor	CKD-EPI	Outpatients without recent measurement scheduled for contrast enhanced CT scan	100.0%	65.2%	92.9%	65.3%	65.9%	65.8%
Too, 2015 modified				-	-	85.7%	86.0%	43.2%	86.3%
Snaith, 2019, Original*	i-STAT	CKD-EPI	Outpatients attending for a contrast-enhanced CT scan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Snaith, 2019, Modified*				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Snaith, 2019, RANZCR RF				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*, the definition of acute illness differs across these two questionnaires with the modified version considering only patients as acutely ill if they indicated acute admission, diarrhoea and vomiting, or recent commencement of antibiotics, while the original questionnaire considering any acute illness; RANZCR RF, Royal Australian and New Zealand College of Radiologists guideline risk factors; Sen, sensitivity; Spec, specificity; U&E, Urea and Electrolytes

Although diagnostic accuracy data comparing risk factor questionnaires to a gold standard reference test would have been preferable to inform the model, no studies reported these data for the diagnostic cut-off of interest (eGFR<30 mL/min/1.73 m^2). However, the data reported for the eGFR <45 and <60 mL/min/1.73 m^2 cut-offs in the studies against a laboratory reference, suggest that sensitivity of the questionnaires is high, and sensitivity becomes 100% for the majority for most questionnaires as we move from a higher to a lower eGFR cut-off. The only questionnaires that do not have a sensitivity of 100% at eGFR<45mL/min/1.73 m^2 are those applied in the Snaith et al (2019) study [36](Prof. Berverley Snaith, personal communication).

The diagnostic accuracy data from studies comparing risk factor questionnaires to POC devices also suggests high sensitivity that tends to 100% at the lower eGFR cut-off (<30mL/min/1.73 m^2). The

questionnaire based on the RANZACR guidelines is the exception with a sensitivity of 0%, but it is also worth noting that only one patient in Snaith et al. (2019) had eGFR<30mL/min/1.73 m^2 and, thus, results are very uncertain. Specificity at eGFR<30mL/min/1.73 m^2 varies between 45.2% and 82.9%. The questionnaire with the lowest overall diagnostic accuracy is that examined by the Azzouz et al (2014) study[12].

In the base-case analysis, the diagnostic accuracy estimates for risk factor screening data were derived from the study by Too et al (2015)[73]. This study reported a sensitivity of 100% which is consistent with the data reported for the studies that used laboratory test as a reference (albeit at higher diagnostic cut-offs). Since uncertainty about the diagnostic performance of screening tools remains, a scenario analysis is conducted with data from the Azzouz et al (2014) questionnaire[12].

Table 38 summarises the risk factor screening diagnostic accuracy estimates applied in the model. Beta distributions were fitted to the sensitivity and specificity data to generate random distributions of these parameters in the probabilistic sensitivity analysis.

Table 38 Risk factor screening diagnostic accuracy estimates in the model

	Sensitivity	**Specificity**	**Source**
Base-case	100.0%	65.2%	Too et al, 2015
Scenario analysis	88.2%	45.2%	Azzouz et al, 2014

6.4.4 Risks of PC-AKI

Clinical guidelines have highlighted that individuals with eGFR less than 30mL/min/1.73 m^2 are potentially at an increased risk of PC-AKI following contrast enhanced CT and that actions should be taken to mitigate that risk such as considering an alternative imaging method not using iodine-based contrast media or by providing IV hydration prophylaxis prior to undertaking contrast enhanced CT [6, 8, 9]. Whether there is an elevated risk in those with an eGFR between 30 and 45 mL/min/1.73 m^2 undergoing contrast enhanced CT remains unclear the[6 9].

For the purposes of modelling, the impact of identifying patients with low eGFR, it is important to establish the risk of PC-AKI conditional on eGFR and any actions taken to mitigate the risk (e.g. providing IV hydration). This section considers the evidence for the risk of PC-AKI conditional on eGFR in individuals receiving contrast enhanced CT, the effect of IV hydration on that risk and the effect of removing IV contrast on that risk.

6.4.4.1 Risk of PC-AKI conditional on eGFR

Most evidence on the risk of PC-AKI following contrast enhanced CT comes from inpatient settings where patients' creatinine levels are routinely monitored following a scan. However, these patients are not considered representative of the outpatient population considered in this appraisal as they are

likely to have greater comorbidities and associated risk factors for PCI-AKI. Therefore, further evidence was sought to estimate the risk of PC-AKI conditional on eGFR in a non-emergency outpatient setting.

Eight studies containing PC-AKI evidence in outpatients were identified through reference list searching and citation searching conducted as part of the pragmatic reviews described in Section 4.3 Three of the 8 studies identified[101, 110, 112] had a high percentage of patients with complete follow-up data for all patients, rather than only for patients considered at risk at baseline. Park et al, 2016, was considered the most relevant study to identify baseline risk in the population, containing data from 8 years of follow-up including patients across eGFR subgroups considered, and using contemporary PC-AKI definitions of an absolute increase in serum creatinine of 0.5 ml/min or 25% from baseline levels. This study also reported data on the consequences of PC-AKI in terms of mortality and need for RRT, which are discussed in later sections.

Park et al, 2016, examined the risk of PC-AKI in 1,666 patients with eGFR<60 mL/min/1.73 m^2 undergoing contrast enhanced CT after receiving prophylactic IV hydration and present the PC-AKI rate for different eGFR categories (<30, 30 to 45 and 45 to 60 mL/min/1.73m^2). These are presented in Table 39 below. Patients with an eGFR below 30 mL/min/1.73m^2 had a PC-AKI rate of 10.80%, and this reduced to 2.39% in patients with an eGFR between 45 and 60 mL/min/1.73m^2.

Table 39 PC-AKI events in patients undergoing contrast enhanced CT angiography- Park et al 2016

eGFR mL/min/1.73m^2	Number of patients	Number of PC-AKI events	PC-AKI rate
<30	250	27	10.80%
30-45	579	14	2.42%
45-60	837	20	2.39%
All patients	1666	61	3.66%

Several other outpatient studies were identified which presented the risks of PC-AKI conditional on eGFR in patients with an eGFR below 60. The results from these other studies are presented in Table 40. The results from these studies are broadly comparable with those from Park et al., with the PC-AKI rate in the 30 to 60 mL/min/1.73m^2 eGFR group ranging from 1.3% to 2.6% and from 10.8% to 12.07% in the below 30 mL/min/1.73m^2 eGFR group.

Table 40 PC-AKI events in patients undergoing contrast enhanced CT angiography in outpatient setting

eGFR mL/min/1.73m^2	Park et al 2016	Nijssen 2017	Nijssen 2018	Kim 2010
<30	10.80%	N/A	11.24%	12.07%

30-60	2.40%	2.65%	N/A	1.30%
Number of patients (<30, 30-60)	1666 (250, 1416)	603 (N/A, 603)	89 (89, N/A)	520 (58, 462)

Given the size of the patient population and its comparability with the other identified outpatient studies, the estimates from Park et al. were used to inform the model. Given the similarity in AKI risk in the eGFR 30 to 45 mL/min/1.73 m^2 and the eGFR 45 to 60 mL/min/1.73 m^2 group, these eGFR categories were pooled resulting in separate PC-AKI risks applied in the model for eGFR<30 and >30 mL/min/1.73m^2.

As all patients in the Park et al, 2016 study received IV hydration, additional evidence was also sought to inform the PC-AKI rate in individuals who would be incorrectly misclassified and hence would not receive IV hydration.

6.4.4.2 Effect of prophylactic IV hydration on PC-AKI risk

To account for the effect of prophylactic IV hydration on the risk of PC-AKI following contrast enhanced CT imaging, evidence from meta-analyses and other randomised and non-randomised were examined. Full detail of study sources considered are provided in section 4.3.2.

Three meta-analyses examined the effectiveness of contrast-associated acute kidney injury prevention methods, the largest and most recent of which was used to parameterise the model [100]. This study considered the impact of prophylactic IV hydration in patients with an eGFR below 60 and found for the comparison against placebo an odds ratio of 0.97 (95% CI 0.52 to 1.9). However, data from the AMACING study, indicated that there was no effect of IV hydration on PC-AKI in patients with eGFR between 30 and 60 mL/min/1.73 m^2. Therefore, for the base case, it was assumed that the prophylactic IV hydration odds ratio of 0.97 (95% CI = 0.52 to 1.9) would be applied to patients with eGFR below 30 mL/min/1.73 m^2, but that there would be no effect on risk in patients with an eGFR above 30 mL/min/1.73 m^2. A scenario analysis was undertaken using the lower bound of the odds ratio (0.52), implying a greater protective effect of IV hydration compared to the base-case analysis.

6.4.4.3 Effect of contrast on PC-AKI risk

A review of propensity matched evidence identified from the recent Aycock meta-analysis was conducted to identify studies providing evidence on the effect of contrast on PC-AKI stratified by eGFR. Three studies [89 90 95] provided evidence on contrast enhanced CT against unenhanced scans by eGFR category. Table 41 summarises the evidence from these three studies, two of which are reported in detail in Section 4.3.1.

Hinson et al. was a large propensity matched study identified through citation searching of the Aycock et al. study. The study by Hinson was excluded from the clinical effectiveness review of evidence of PC-AKI due to being set in an emergency department. However, given the conflicting findings reported by Davenport et al (2013) and McDonald et al (2014), the additional evidence reported by Hinson et al. was considered relevant and the results from all three studies were pooled to inform the model inputs.

A fixed effects meta-analysis of these three studies suggest no effect of contrast on PC-AKI risk (OR = 0.98; 95% CI 0.88 to 1.08). .Hence, it was assumed in the base case that there was no effect of contrast on the risk of PC-AKI.

Table 41 Effect of contrast on PC-AKI risk

Study	Year	Outcome of interest	Type	Odds Ratio (95% CI)
Hinson	2017	AKI, eGFR 15-29 mL/min/1.73m^2	0.3 mg/dL or 50% above baseline	0.96 (0.86 to 1.08)
Davenport	2013	AKI, eGFR <30 mL/min/1.73m^2	0.3 mg/dL or 50% above baseline	2.96 (1.22 to 7.17)
McDonald	2014	AKI, eGFR <30 mL/min/1.73m2	0.5 mg/dL above baseline	0.97 (0.72 to 1.30)

6.4.4.4 Risks of PC-AKI conditional on eGFR, prophylactic IV hydration and use of contrast

For the cost-effectiveness model, the risk of PC-AKI conditional on eGFR and with and without the use of prophylactic IV hydration and/or contrast were required.

The evidence on PC-AKI conditional on eGFR from Park et al. was combined with evidence on the impact of IV hydration from Ahmed et al, 2018[100], to estimate the probability of a PC-AKI in patients with eGFR below 30 mL/min/1.73 m^2 and above 30 mL/min/1.73 m^2 who did not receive IV hydration (with the values for those receiving prophylactic IV hydration taken directly from Park et al, 2016). It was assumed that patients with an eGFR above 60 mL/min/1.73 m^2 had the same risk as those in the eGFR 30 to 60mL/min/1.73m^2 group. Based on the meta-analysis reported in the previous section, it was assumed that there was no impact of contrast on the risk of PC-AKI in the base-case analysis.

Table 42 below summarises the PC-AKI risks used in the cost-effectiveness model.

Table 42 Risks of PC-AKI in the model

eGFR mL/min/1.73m^2	Contrast enhanced CT scan with IV hydration	Contrast enhanced CT scan without IV hydration	Unenhanced CT scan
<30	10.80%	11.1%	11.1%
>30	2.40%	2.40%	2.40%

The parameters in Table 42 were set up probablistically in the model by fitting beta distributions to the probabilities of PC-AKI with IV hydration (for both eGFR≥30 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2) from Park et al, and a lognormal distribution to the odds ratio of PC-AKI for IV hydration vs placebo from Ahmed et al.

6.4.5 AKI consequences and overall mortality

A separate review of published models focusing on the management and consequences of AKI was conducted to further inform the model structure, parameter inputs and assumptions. Further details of the review are reported in Appendix 10.5.

Based on the review findings, the main consequences of PC-AKI include potential mortality risks and the need for RRT. The literature reviewed to inform the risks of PC-AKI in the model was examined for evidence on mortality and risk of RRT conditional on PC-AKI. Park et al, 2016 [110], was considered the most relevant to characterise the consequences of PC-AKI in outpatients presenting to CT scan, as it reports risks of mortality and initiation of RRT over time by PC-AKI status.

Park et al. present Kaplan Meier curves by PC-AKI status (PC-AKI vs no PC-AKI) for time from CT scan until event for i) death and ii) initiation of RRT (renal survival). Two analyses are presented for each outcome; before and after propensity score matching. The study also reports hazard ratios comparing PC-AKI to no PC-AKI for the full study sample and subgroups by eGFR category (<30 vs ≥30 mL/min/1.73m^2) and timing of events (within 6 months vs after 6 months of contrast enhanced CT scan), which are reported in Table 43.

Table 43 Secondary outcomes results from Park et al, 2016

	Before Propensity Matching		After Propensity Matching	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Death	1.05 (0.58–1.91)	0.86	0.90 (0.46–1.76)	0.75
Within 6 months	0.80 (0.31–2.07)	0.64	0.81 (0.29–2.31)	0.70
After 6 months	1.15 (0.53–2.49)	0.72	0.99 (0.41–2.40)	0.98
eGFR ≥30 mL/min/1.73 m^2	1.20 (0.53–2.72)	0.66	0.93 (0.35–2.51)	0.89

eGFR <30 mL/min/1.73 m^2	0.87 (0.35–2.15)	0.76	0.79 (0.29–2.13)	0.64
Initiation of RRT	2.75 (1.52–4.98)	0.001	3.05 (1.43–6.47)	0.003
Within 6 months	4.54 (1.93–10.71)	0.001	8.61 (2.28–32.61)	0.002
After 6 months	1.73 (0.62–4.81)	0.30	1.15 (0.34–3.86)	0.83
eGFR ≥30 mL/min/1.73 m^2	4.47 (1.33–15.07)	0.02	5.23 (0.57–47.64)	0.14
eGFR <30 mL/min/1.73 m^2	2.58 (1.34–4.97)	0.004	2.65 (1.15–6.15)	0.02

HR comparing PC-AKI vs no PC-AKI are adjusted for age, sex, total contrast volume used in CT, serum albumin, baseline eGFR, and history of diabetes mellitus.

The published Kaplan Meier curves suggest no difference in terms of mortality for patients who had PC-AKI compared to those who did not, as the curves are largely overlapping for the two groups of patients. This is further supported by the mortality hazard ratios comparing PC-AKI vs no PC-AKI, which are consistently non-statistically significant across all analyses. Therefore, mortality in the model is assumed to be the same for all patients regardless of PC-AKI status. Mortality was incorporated in the model by applying the costs and QALYs to the PC-AKI pay-offs in the model to the proportion of patients alive at 6 months in Park et al. (94.5%). This proportion is assumed to be the same for patients with and without PC-AKI. Since baseline mortality risks were not reported by eGFR category, mortality was also assumed to be independent of eGFR levels.

A significant effect of PC-AKI was identified on the probability of RRT initiation. Statistically significant hazard ratios for RRT initiation for the full follow-up period and when only events occurring within 6 months of CT scan are considered (Table 43). The effect of PC-AKI on the probability of RRT initiation does not appear statistically significant in the analysis excluding patients with events after the first 6 months, suggesting that any impact of PC-AKI in the rates of RRT initiation occur within 6 months of contrast enhanced CT scan.

The baseline probability of RRT initiation in the model is derived from the probability of not having started RRT at 6 months (0.014) derived from the Kaplan-Meier figure reported for the group who did not experience PC-AKI. The hazard ratio for the within 6 months subgroup (HR = 8.61) is applied to the baseline risk of RRT initiation to estimate the probability of RRT initiation for individuals who experience a PC-AKI event (0.111). The hazard ratio for RRT initiation for PC-AKI vs no PC-AKI was set up probablistically in the model by fitting a log normal distribution to the data reported in Park et al.

6.4.6 Mortality and Health-related Quality of Life

Quality adjusted life years were estimated based on estimated mortality and health related quality of life (HRQoL). QALYs were discounted at an annual rate of 3.5%. Mortality over 6 months was

estimated from a study of post-CT scan patients Park et al, 2010 with mortality post 6 months based on the general population (age and sex adjusted). HRQoL was based on the general population (age and sex adjusted) with utility decrements applied for adverse outcomes, namely undergoing RRT or anxiety resulting from delayed scans. In the base-case, RRT is considered the only source of disutility. A scenario analysis also considers the disutility associated with anxiety from delayed scans.

The proportion of patients expected to be alive 6 months post-CT scan was derived from Park et al, 2016[110], (94.5%), and was estimated as a weighted average of the proportion of patients alive in this study at 6 months post-contrast enhanced by PC-AKI status (PC-AKI and no PC-AKI). A beta distribution was fitted to the proportion of patients alive at 6 months to derive probabilistic estimates for this parameter. UK life time tables were sourced from the Office of National Statistics (2017) [113] for mortality post 6 months.

Age and sex specific general population HRQoL was derived using the equation proposed by Ara and Brazier, 2010 [114] and applied to the proportion of patients expected to be alive each year (from start age in the model until 100 years old).

RRT was assumed to consist of haemodialysis based on a study [112] reporting an earlier data-cut of Park et al, 2016 [110]. The disutility associated with RRT was sourced from a meta-analysis and meta-regression of utilities in CKD patients [115] that was identified on the reference list of one of the studies[116] examined in the context of the AKI models systematic review. The estimate of -0.11 represents the disutility from dialysis. A gamma distribution was fitted to the utility estimate in the model to generate random draws of the parameter for the probabilistic sensitivity analysis. The disutility is applied for 3 months in the model based on the NICE clinical guideline 169[106]. Disutility from anxiety was calculated by assuming that patients would incur the disutility from a EQ-5D-3L score change from level 1 to level 3 (-0.236) in the depression/anxiety domain for two weeks. The two weeks duration of anxiety was assumed to be the maximum time that patients would have to wait before they could have a CT scan after cancellation of the originally planned scan.

Table 44 details the disutility estimates applied in the model alongside the respective sources and assumptions.

Table 44 Utility estimates applied in the model

	Utility value	**95% Confidence interval**	**Source**	**Assumptions**
RRT	-0.11	-0.15; - 0.08	Wyld et al. 2012 [115]	3 months duration
Anxiety	-0.236	NA	EQ-5D-3L score decrement change from level 1 to 3 on the	2 weeks duration

			depression/anxiety domain [117]	

The model does not consider the impact from the delay of the planned CT scan on patient outcomes as a result of any change in their underlying condition during the waiting period. Given the heterogeneity in reasons for referral to CT scan in the relevant population, and the lack of data sources to characterise the potential impact of delay on HRQoL and disease progression across a wide range of conditions, it was considered unfeasible to include this element in the model. No disutility from PC-AKI was considered, as clinical opinion suggests the majority of PC-AKI events are asymptomatic.

The potential disutility from adverse events associated with IV hydration was also not included in the model. The AMACING trial which compared the cost effectiveness of IV hydration to prevent PC-AKI in patients with eGFR between 30 and 60 mL/min/1.73 m^2 compared to no IV hydration found a small difference in excess hospitalisation days due to adverse events from IV hydration between treatment arms (0.06 days)[101]. Therefore, it was considered that any adverse events from IV hydration would have a short duration and have a very limited impact on HRQoL.

6.4.7 Resource use and costs

6.4.7.1 POC device costs

Six manufacturers of a total of seven devices (one manufacturer producing two of the devices) provided evidence on the device costs. These costs included the capital costs per device, consumables per test, quality control consumable costs and annual maintenance costs. Resource use estimates provided included the time to conduct a test, the time to conduct a quality control procedure and the frequency of quality control procedures required. Information was also provided on the expected life span of each device.

Table 45 below details the capital cost per device. For the three devices considered in Section 6, the price per device ranged from £4,995 to £37,945. The higher capital cost of the Radiometer ABL800 flex reflects that this device is a benchtop unit which allows the user to measure a full panel of up to 18 STAT parameters on the same blood sample. This contrasts with the handheld, single-use design provided by i-STAT Alinity and StatSensor devices.

Table 45 Capital cost per device

Device	Capital Cost (per device)	VAT Status
Devices included in the model		
Abbott i-STAT Alinity	£6,500	Excluding
Nova Biomedical StatSensor	£4,995	Uncertain
Radiometer ABL800 flex	£37,495	Excluding

Other devices		
Abaxis Piccolo Express	£11,000	Excluding
Fujifilm Dri-Chem NX500	£8,500	Excluding
Radiometer ABL90 flex plus	£14,995	Excluding
Siemens ePOC	£6,240	Excluding

In terms of the life span of the devices, only two manufacturers provided a life span estimate. Radiometer stated that the maximum life span of devices would be 7 to 10 years, while Fujifilm considered the maximum life span of 6 years. Other manufacturers noted that it is difficult to assess life span as it will be conditional on the way devices are used.

Capital costs were annuitized in the model over the expected lifetime of the devices. Given the difficulties in obtaining robust lifetime estimates across the devices, the model assumed a common lifetime estimate of 7 years for all of the devices considered, to estimate the expected annual capital cost of the device.

Table 46 below details the consumables cost per test for each device as well as the expected time taken for the test to report results. For the 3 devices considered in the model, the cost of consumables per test ranged from £2.88 to £4.75, and the time the devices took to report results varied from 30 seconds to 2 minutes.

Table 46 Consumable costs per test and time to test for each device

Device	**Testing Material Costed**	**Cost per test**	**Time to test (mins)**
Devices included in the model			
Abbott i-STAT Alinity	Creatinine Cartridge	£4.75	2
Nova Biomedical StatSensor	Creatinine Test strip	£3.95	0.5
Radiometer ABL800 flex	Per test proportion of all testing materials	£2.88	1
Other devices			
Abaxis Piccolo Express	Kidney Check Rotor	£12.00	12
Fujifilm Dri-Chem NX500	Dri-chem Creatinine slide; Fujifilm Plasma Filter	£3.73	1
Radiometer ABL90 flex plus	Per test proportion of all testing materials	£2.71	1
Siemens ePOC	Test Cartridge	£5.75	1

Table 47 details the costs of a quality control check required for each device (including multiple levels where necessary) as well as the frequency of quality control checks recommended by the manufacturer. The cost per quality control are presented in two ways, the first includes the total cost of quality control materials for a complete quality control test (this is based on the splitting of quality control materials from larger vials as required) and the second also includes the cost of any test based consumables required for the quality control procedure (see Table 46 above).

For the three POC devices included in the cost-effectiveness model, the cost per quality control check excluding test based consumables ranged from £0.20 to £5.01, and when test based consumables were also included from £4.15 to £6.80. For two of the POC devices considered, quality control needs to be conducted each day, whilst for the other it must be conducted every week, or every 25 tests, whichever is more frequent.

Table 47 Quality control costs for each device

Device	Cost per quality control check (excluding test based consumables)	Cost per quality control check (including test based consumables)	Time to prepare QC materials (mins)	Frequency of quality control
Devices included in model				
Abbott i-STAT Alinity	£2.05	£6.80	45 mins to bring to ambient temperature, 1-2 mins to prepare materials	Every week/every 25 tests
Nova Biomedical StatSensor	£0.20	£4.15	Not known	Every 24 hours
Radiometer ABL800 flex	£5.01	£5.01	Automatic - no time to prepare materials	Every 24 hours
Other devices				
Abaxis Piccolo Express	£19.20	£31.20	30 mins to bring to ambient temperature	Every 30 days/every 10 tests
Fujifilm Dri-Chem NX500	£11.97	£15.70	30 mins to bring to ambient temperature, 30 mins to mix	Every 30 days

Radiometer ABL90 flex plus	£3.76	£3.76	Automatic - no time to prepare materials	Every 24 hours
Siemens ePOC	£28	£33.75	60 mins to bring to ambient temperature	Every 50 tests

Table 48 details the annual maintenance costs for each device. The cost for the devices considered in the model range from £850 per annum to £4,685 per annum.

Table 48 Annual maintenance costs

Device	Annual Maintenance cost	Guarantee Period
Devices included in model		
Abbott i-STAT Alinity	£850 per annum	1 year
Nova Biomedical StatSensor	£850 per annum	1 year
Radiometer ABL800 flex	£4,685 per annum	1 year
Other devices		
Abaxis Piccolo Express	£1675 per annum	1 year
Fujifilm Dri-Chem NX500	£750 per annum	1 year
Radiometer ABL90 flex plus	£1,315 per annum	1 year
Siemens ePOC	£816 per annum	1 year

To estimate the cost per point of care test it is necessary to combine this information on costs with expected throughput. Throughput impacts the amount of capital cost, the annual maintenance cost and the quality control cost attributed per test conducted (with test consumable costs not being impacted by throughput).

Estimates of throughput were based on the data provided by Harris based on one month's routine outpatient audit data across three sites from the Mid Yorkshire NHS Trust. Over a one month period,

816 individuals were scanned across 3 separate sites (272 per site per month). Combining this estimate with the percentage of patients who are assumed to present at their scan appointment without a recent eGFR measurement (34% in the base-case analysis), results in an estimated monthly throughput of 92.6 patients (1,111 per annum) for the POC devices. If a risk factor questionnaire is used to screen individuals prior to a POC test, fewer individuals will undergo a POC test resulting in lower throughput and higher costs per POC test. In such cases, throughput for the POC device will be conditional on the accuracy of the risk factor screening and the distribution of eGFR in the population. In the base case, risk factor screening prior to a POC test results in a POC throughput of 32.6 patients per month. Alternative throughput assumptions were considered in separate scenario analyses.

Table 49 presents the total device cost per point of care test based on the expected monthly throughput of 92.6 patients undergoing a POC test assumed in the base-case analysis. For the three devices incuded in the model the total device cost per test ranged from £6.71 to £14.07. It should be noted that these costs do not include any consumables for collecting or transferring blood to the POC device, nor are any additional costs included for storage of consumables (e.g. additional refrigerator capacity).

Table 49 Total device cost per point of care test

	Capital cost	Annual servicing	Consumables	Quality control materials (including test consumables)	Total device cost per test (based on 92.6 patient per month throughput)
Devices included in model					
Abbot i-STAT alinity	£0.92	£0.77	£4.75	£0.27	£6.71
Nova Biomedical StatSensor	£0.71	£0.77	£3.95	£1.36	£6.79
Radiometer (ABL800 flex)	£5.33	£4.22	£2.88	£1.65	£14.07
Other devices					
Abaxis Picolo Express	£1.56	£1.51	£12.00	£3.12	£18.19
Fujifilm Dri-chem NX500	£1.21	£0.68	£3.73	£0.17	£5.78
Radiometer (ABL90 flex plus)	£2.13	£1.18	£2.71	£1.24	£7.27
Siemens ePOC	£0.89	£0.73	£5.75	£1.58	£8.95

Point of care testing will also involve the use of staff time to conduct the tests, including taking of blood and using the device and to conduct quality control checks. Details of the staff time required for each device for pre testing, time to use the device and for quality controls are provided in Table 50.

Table 50 Staff time and costs for testing and quality control checks

	Pre-testing staff time (mins)	Time to use the device to analyse a sample (mins)	Staff cost per test conducted	Time for QC (mins)	Total QC staff cost	Total staff cost per test conducted (including QC) (based on 92.6 patient per month throughput)
Devices included in model						
Abbot i-STAT alinity	3	2	£2.08	3.5	£1.46	£2.14
Nova Biomedical StatSensor	3	0.5	£1.46	2	£0.83	£1.73
Radiometer (ABL800 flex)	3	1	£1.66	0	£0.00	£1.66
Other devices						
Abaxis Picolo Express	3	12	£6.25	13.5	£5.63	£6.81
Fujifilm Dri-chem NX500	3	1	£1.67	2.5	£1.04	£1.68
Radiometer(ABL90 flex plus)	3	1	£1.49	0	£0.00	£1.49
Siemens ePOC	3	1	£1.67	2.5	£1.04	£1.71

It was assumed that an additional three minutes of staff time would be required for pre testing (i.e. collecting blood), which is assumed to be taken after the patient is cannulated in preparation for the administration of contrast. Time for using the device was based on manufacturer estimates of time it takes the device to report results, with the assumption that the staff member would not conduct any other activities whilst the device was analysing the sample. For quality control testing, it was assumed that preparation of quality control material would take one and a half minutes for each device (based on one manufacturer's reported time) and that conducting the quality control test would take the same time as the device takes to analyse a sample. Where the quality control checking was automatic (two devices), no staff costs were assumed.

Table 50 also reports the estimated total staff cost per test conducted and per quality control procedure conducted (all assumed to be conducted by a Clinical Support Worker band 3). The staff cost for each test for the three devices considered ranged from £1.66 to £2.14 and the staff cost for conducting the quality control check ranged from £0.00 to £1.46. As with the device related quality control costs, quality control staff costs need to be attributed to per test conducted based on expected throughput. The final column shows the estimated total staff cost per test conducted (including the allocated quality control staff cost). For the three devices considered in the model this ranged from £1.66 to £2.14 based on monthly throughput of 92.6 patients (1,111 per annum). It should be noted that no staff time has been considered for training.

6.4.7.2 Other costs

Testing costs

The previous section considered costs associated with the POC devices, including staff costs for conducting tests and quality of control costs. Other costs considered in the model in the testing stage include risk factor screening, laboratory testing and phlebotomist time. Risk factor screening was assumed to take 2 minutes and 40 seconds of a clinical support worker [75], while taking a blood sample was assumed to take [redacted] of a phlebotomist (personal communication, Dr Bethany Shinkins). These were combined with published national unit costs to estimate the cost per test [118]. The cost of laboratory testing was taken from NHS Reference Costs [119].

Table 51 details the unit costs for each of these and the cost per POC test (inclusive of capital, consumable, quality control and staff costs) based on the base-case throughput assumptions of 92.6 patients receiving a POC test without risk factor screening and 32.6 patients with risk factor screening.

Table 51 Unit costs of the identification stage of the model

Cost category	Resource use	Units	Source	Unit cost	Source/Assumptions	Cost
RF screening	Clinical support worker	2.67 minutes	Ledermann, 2010	£25.00/hour	PSSRU 2017, Assumed the equivalent to hospital nurse (Band 3)	£1.11
Lab test	Lab work	1 test	-	£1.11/test	NHS reference costs 2017/18, DAPS04, directly accessed Clinical Biochemistry	
	Phlebotomist	[redacted]	Shinkins	£22.00/hour	PSSRU 2017. Assumed the equivalent to hospital nurse (Band 2)	
	Total cost of Lab Test					£3.31
POC tests	i-STAT without RF screening	1 test	See section 6.4.7.1	£ 8.85/test	See section 6.4.7.1	£ 8.85
	ABL800FLEX without RF screening	1 test		£15.73/test		£15.73
	StatSensor without RF screening	1 test		£8.52/test		£8.52
	i-STAT with RF screening	1 test		£ 11.96/test		£11.96
	ABL800FLEX with RF screening	1 test		£36.36/test		£36.36
	StatSensor with RF screening	1 test		£14.25/test		£14.25

RF, risk factor

Table 52 reports the testing costs for each stage of all of the strategies as well as the total identification costs if a patient undergoes all of the screening and test steps for that strategy. Risk factor screening costs £1.11, whilst POC test costs vary from £8.52 to £15.73 when used without risk

factor screening and from £11.96 to £36.36 when used with risk factor screening, and a laboratory test costs £3.31.

For POC test costs, there is an additional £2.50 cost of setting up the cannula if the contrast enhanced CT scan is cancelled as a result. This was based on the assumption that 6 minutes of a Clinical Support Workers time is needed to set up the cannula for the admission of intravenous contrast for the CT scan, which is done prior to the taking of blood for the POC test (which as previously stated was assumed to take an additional 3 minutes of the clinical support worker's time). This cost is captured in the contrast enhanced CT HRG and so is already reflected in the cost applied if the patient goes on to receive a contrast enhanced CT scan (described in the next section). However, if the CT scan is cancelled the cost of an unenhanced CT scan HRG is used to reflect the cost of a cancelled test, which would not include the cost of the initial cannulisation. Therefore, the additional cost of 6 minutes of clinical support worker time is added. For laboratory testing, whether this is done subsequently to a POC test or not, it is assumed that an additional 6 minutes of a phlebotomist time is required, and the cost of £3.31 for the phlebotomist (£2.20) and laboratory work (£1.11) is always applied.

Table 52 Testing costs for each strategy

Strategy	**Risk Factor screening cost**	**POC test cost***	**Lab test cost**	**Total testing costs** (excluding additional phlebotomist cost for a positive POC test)
1. Lab	1. Lab	-	-	£3.31
2. RF + i-STAT	2. RF + i-STAT	£1.11	£ 11.96	-
3. RF + ABL800FLEX	3. RF + ABL800FLEX	£1.11	£36.36	-
4. RF + StatSensor	4. RF + StatSensor	£1.11	£14.25	-
5. RF + Lab	5. RF + Lab	£1.11	-	£3.31
6. RF + i-STAT + Lab	6. RF + i-STAT + Lab	£1.11	£ 11.96	£3.31
7. RF + ABL800FLEX + Lab	7. RF + ABL800FLEX + Lab	£1.11	£36.36	£3.31
8. RF + StatSensor + Lab	8. RF + StatSensor + Lab	£1.11	£14.25	£3.31
9. i-STAT	9. i-STAT	-	£ 8.85	-
10. ABL800FLEX	10. ABL800FLEX	-	£15.74	-
11. StatSensor	11. StatSensor	-	£8.52	-
12. i-STAT+ Lab	12. i-STAT+ Lab	-	£ 8.85	£3.31
13. ABL800FLEX+ Lab	13. ABL800FLEX+ Lab	-	£15.74	£3.31

14. StatSensor + Lab	14. StatSensor + Lab	-	£8.52	£3.31

*An additional cost for blood collection (6 minutes of Clinical Support Workers time; £2.50 per test) for POC test was assumed whenever the patient did not proceed to contrast enhanced CT scan

Management and imaging costs

In addition to the identification costs there are also the costs associated with patient management and the imaging conducted. Management costs include cancellation and rebooking of appointments, follow up appointments with nephrologists for those patients categorised as eGFR<30, IV hydration for patients before undergoing full contrast CT scans and costs associated with adverse events from IV hydration. Imaging considered includes the contrast enhanced CT scan, unenhanced CT scan and use of MRI.

Table 53 summarises the costs used for patient management and imaging. Costs were estimated based on resource use estimates and assumptions and combined with national reference costs [118, 119]. If a scan is cancelled, the cost of an unenhanced CT scan (£87.92) is applied to reflect the cost of the cancelled scan. It is assumed that it takes [redacted] of a staff member's time to rebook a CT scan and/or book IV hydration, costing [redacted] (Dr Bethany Shinkins , personal communication,). If a patient is identified as having eGFR<30 ml/min/1.73 m^2, it is assumed that they will have a follow-up appointment with a nephrologist to discuss their chronic kidney disease, costing £186.49.

Patients who required IV hydration are assumed to be admitted as a day-case at a cost of £340.89. IV hydration is also associated with adverse events including hospitalisation, specialist inpatient consultation and in hospital diagnostics. The probability of these occurring was taken from Nijssen 2017 and the costs of each from NHS reference costs, resulting in an expected cost of adverse events per patient undergoing IV hydration of £32.76. To reflect the variation in the number of areas being scanned and whether the scans were costed as outpatients or direct access, weighted averages of HRG codes were used to estimate the cost of each type of scan (unenhanced CT scan, contrast enhanced CT scan and MRI), with the weight reflecting the total number of each type of HRG in the NHS. The costs of imaging were £87.92 for an unenhanced CT scan, £111.65 for a contrast enhanced CT scan and £151.98 for an MRI.

Table 53 Unit costs related to the management and imaging of patients

Cost category	Resource use	Units	Source	Unit cost	Source/ Assumptions	Cost
Imaging	CT scan - contrast enhanced	1 scan	-	£111.65/scan	NHS reference costs 2017/18, activity weighted averaged of HRG currency codes RD21A, RD24Z, RD25Z for outpatients and direct access undergoing CT scan with contrast	£111.65
	CT scan - unenhanced	1 scan	-	£87.92/scan	NHS reference costs 2017/18, activity weighted averaged of HRG currency codes RD20A, RD23Z, RD25Z for outpatients and direct access undergoing CT scan without contrast	£87.92
	MRI	1 scan	-	£ 151.98/scan	NHS reference costs 2017/18, activity weighted averaged of HRG currency code RD04Z for outpatients and direct access undergoing MRI without contrast	£170.53
Cancellations	Rebooking CT scan and/or hydration	[redacted]	Shinkins	£22.00/hour	PSSRU 2017, clerical support (Band 2 hospital nurse)	[redacted]
	Cancelation	1 scan	Assumption	£87.92/scan	Same as a unenhanced CT scan	£87.92
Follow-up	Nephrologist	1 visit	Assumption	£186.49	NHS, reference costs 2017/18, all outpatient, consultant led, Nephrology	£186.49
IV hydration	Admission	1 day	-	£340.89/day	NHS reference costs 2017/18, weighted average KC05K-N, Fluid or Electrolyte Disorders, without Interventions	£340.89
AEs from IV hydration	Hospitalisation	0.06	Nijssen, 2017	£431.00/night	NHS reference costs 2017/18, Elective Inpatients Excess Bed Days (across all codes)	
	Specialist inpatient consultation	0.04	Nijssen, 2017	£143.44/visit	NHS reference costs 2017/18, average across HRGs of outpatient consultant led appointments	
	In hospital diagnostics	0.02	Nijssen, 2017	£58.36/test	NHS reference costs 2017/18, activity weighted averaged of HRG currency codes AA33C, Total HRG activity excluding excess bed days	
	Total cost of AEs from IV hydration per patient					£32.76

Costs associated with outcomes (RRT)

The cost of RRT is applied to patients who underwent RRT in the model. Table 54 summarises the costs of RRT. As highlighted in Section 6.4.6, RRT was assumed to consist of haemodialisys and have a duration of three months. The number of haemodialysis sessions of per week was sourced from NICE clinical guideline 169[106], and unit costs taken from NHS reference costs [119]. The total cost of RRT applied in the model was £9,758.

Table 54 Unit costs related to RRT

Cost category	Resource use	Units	Source	Unit cost	Source/Assumptions	Cost
RRT	Haemodialysis sessions	3 weekly for 3 months	NICE CG169	£271.06 per session	NHS, reference costs 2017/18, HRG currency code LE01A, Haemodialysis for Acute Kidney Injury, 19 years and over	£9,758

6.5 Analytic Methods

6.5.1 Overview

The decision-analytic model is evaluated deterministically and probablistically for the base-case analysis using 1,000 Monte Carlo simulations to reflect the joint uncertainty across all of the inputs according to the probability distributions assigned to each. The parameters set up probabilistically in the model are: POC devices diagnostic accuracy data; risk factor questionnaire diagnostic accuracy data; risks of PC-AKI; hazard ratio for the initiation of RRT; proportion of patients alive at 6 month post-contrast; and disutility from RRT.

Following conventional decision rules for cost-effectiveness, the mean costs and QALYs for the various strategies are presented and cost-effectiveness compared by estimating the incremental cost-effectiveness ratios (ICERs), as appropriate.

A limitation of conventional ICER decision rules is that the interpretation of negative and positive ICERs is ambiguous without reference to the cost-effectiveness plane. In contrast to conventional ICER decision rules, the net-benefit approach provides an unambiguous decision rule. Net-benefits can be expressed on the effect scale (Net Health Benefits; NHB) or the cost scale (Net Monetary Benefits; NMB) and are estimated by re-arranging the elements of the conventional ICER equation, where:

$$Net\ Health\ Benefit\ (NHB) = QALYs - \frac{Costs}{Cost{-}effectiveness\ threshold}$$

$$Net\ Monetary\ Benefit\ (NMB) = Costs - \frac{QALYs}{Cost{-}effectiveness\ threshold}$$

In contrast to conventional ICER decision rules, the net-benefit approach provides an unambiguous decision rule. For a given cost-effectiveness threshold, the strategy with the highest net benefit is the same strategy that would be considered cost-effective when comparing ICERs against the threshold. A further advantage of using the net-benefit framework in the current appraisal is that they are useful to summarise results when there are small effect differences between strategies. In these circumstances ICERs can be very volatile and sensitive to small changes in the denominator.

Uncertainty regarding the appropriate source of data, the appropriate assumptions or model structure and other scenarios are explored using a series of deterministic scenario analysis, as described further in Section 6.5.3.

6.5.2 Base-case analysis

The parameters and main assumptions used within the base-case economic model, and their characteristics, are summarised in Table 55.

Table 55 Model parameters (base-case analysis)

	Value	Source
Population characteristics		
Probability of eGFR	<30*: 0.006 30-45*: 0.063 45-60*: 0.154 ≥60*: 0.777	Gamma distribution fitted to Mid Yorkshire NHS trust data
Age and male proportion	65 years, 51.7%	Snaith et al (2019)
% missing eGFR	34%	Cope et al. (2017)
Patients per site	272 monthly	Harris all outpatient data
Diagnostic accuracy		
Lab test	Sensitivity: 100% Specificity: 100%	Assumption
i-STAT	Sensitivity: 84.1% Specificity: 98.9%	Evidence synthesis of POC diagnostic accuracy - main analysis
ABL	Sensitivity: 86.1% Specificity: 99.2%	
StatSensor	Sensitivity: 73.9% Specificity: 99.1%	
Risk factor questionnaire	Sensitivity: 100% Specificity: 65.2%	Too et al. (2015)
Probability of AKI with contrast conditional on		
eGFR<30* and no IV hydration	11.1%	Park et al. (2010), Ahmed et al. (2018)
eGFR<30* and IV hydration	10.8%	Park et al. (2016)
eGFR≥30* with no IV hydration	2.4%	Assumption
eGFR≥30* with IV hydration	2.4%	Park et al. (2016)
Probability of RRT (no PC-AKI)	0.014	Park et al. (2016)
Probability of RRT (PC-AKI)	0.111	Park et al. (2016)
Proportion of patients alive at 6 months post imaging	94.5%	Park et al. (2016)
HRQoL adjusted life expectancy	9.80 QALYs	Calculated from ONS mortality data and Ara and Brazier, 2010 general population utility equation
QALY loss from RRT	-0.0275	Wyld et al 2012, and assuming 3 months of RRT
QALY loss from anxiety due to delays	0	Assumption
Cost		
Lab test	£3.31	NHS reference costs 2017/18
Risk factor screening	£1.11	Lederman et al. (2010), NHS reference costs 2017/18
i-STAT without RF screening	£ 8.85	See section 6.4.7.1
ABL800FLEX without RF screening	£15.73	See section 6.4..7.1
StatSensor without RF screening	£8.52	See section 6.4..7.1

i-STAT with RF screening	£11.96	See section 6.4.7.1
ABL800FLEX with RF screening	£36.36	See section 6.4..7.1
StatSensor with RF screening	£14.25	See section 6.4..7.1
Contrast enhanced CT scan	£111.65	NHS reference costs 2017/18
CT scan rebooking	[redacted]	Shinkins et al (in submission)
CT scan cancellation	£87.92	NHS reference costs 2017/18, assumed to be the cost of an unenhanced CT scan
IV hydration	£340.89	NHS reference costs 2017/18
Adverse events from	£32.76	Nijssen et al. (2017), NHS reference costs 2017/18
Follow-up if test positive**	£186.49	NHS reference costs 2017/18
RRT	£9,758	NHS reference costs 2017/18 and assuming 3 weekly sessions over 3 months
Mediating action if positive**		
IV hydration and constrast enhanced CT scan	100% of patients	Assumption
Unenhanced CT scan	0% of patients	Assumption
MRI	0% of patients	Assumption
Proportion of rebooked and cancelled scans if test positive**	100%	Assumption

*mL/min/1.73 m^2; **, According to last test in the testing sequence

6.5.3 Scenario analyses

To investigate the impact of several key parameter and structural assumptions, a series of deterministic scenario analyses were undertaken. These scenarios are summarised in Table 56.

Table 56 Summary of scenario analyses

Number	Scenario name	Element of uncertainty	Description
1.	StatsSensor adjusted analysis	Diagnostic accuracy – additional analyses	Data for StatSensor based on adjusted data analysis (see section 4.2.8.2)
2.	CKD-EPI equation studies	Diagnostic accuracy – additional analyses	Quantitive synthesis based only on studies calculating eGFR using CKD-EPI equation (see section 4.2.8.1).
3.	Alternative risk factor questionnaire	Diagnostic accuracy – quantitative synthesis	Diagnostic accuracy of risk factor screening questionnaires informed by data on an alternative questionnaire (Azzouz et al 2014).
4.	eGFR distribution – Harris subgroup	eGFR distribution	Distribution of eGFR based on the subgroup of individuals without a prior eGFR measurement at referral (Mid Yorkshire Trust).
5	eGFR distribution – GSST audit	eGFR distribution	Distribution of eGFR based on a raw data extraction of patient records for outpatients referred to a CT scan at the Guy's and St Thomas' NHS trust over two weeks in January 2019.
6.1	Throughput	Throughput estimates	Throughput estimates adjusted for alternative assumption concerning the proportion of individuals attending a scan appointment without a recent eGFR measurement. 12.7% (compared to 34% in base-case analysis) based on data from Mid Yorkshire NHS trust.
6.2	Throughput	Throughput estimates	Throughput estimates 50% lower than base-case
6.3.	Throughput	Throughput estimates	Throughput estimates 50% higher than base-case
7.1	Proportion of cancelled CT scans (0%)	Opportunity cost of delayed/rescheduled CT scan	0% of CT scans are cancelled as a result of requiring a laboratory test (i.e. all laboratory testing assumed to be urgent).
7.2	Proportion of cancelled CT scans (25%)	Opportunity cost of delayed/rescheduled CT scan	25%.of CT scans are cancelled as a result of requiring a laboratory rest (i.e. 75% of laboratory testing assumed to be urgent and 25% non-urgent)
7.3	Proportion of cancelled CT scans (50%)	Opportunity cost of delayed/rescheduled CT scan	50% of CT scans are cancelled as a result of requiring a laboratory rest (i.e. 50% of laboratory testing assumed to be urgent and 50% non-urgent)
7.4	Proportion of cancelled CT scans (75%)	Opportunity cost of delayed/rescheduled CT scan	75% of CT scans are cancelled as a result of requiring a laboratory rest (i.e. 25% of laboratory testing assumed to be urgent and 75% non-urgent)
8.	Anxiety from delay	HRQoL impact of scan delay	Disutility from anxiety is included for patients who have their CT scan delayed.
9.	Effect of IV hydration (PC-AKI risk)	Effect of IV hydration on PC-AKI risk (eGFR<30)	The effect of IV hydration in reducing the risk of PC-AKI was increased using the lower bound of the treatment effect reported by Ahmed et al (Odds ratio = 0.52 vs 0.97 applied in the base-case analysis) .
10.1	Management approach for test positives	Management approach assumed for patients who test positive to POC/lab	50% receive IV hydration followed by contrast enhanced CT scan 50% receive unenhanced CT scan

Number	Scenario name	Element of uncertainty	Description
10.2.	Management approach for test positives	Management approach assumed for patients who test positive to POC/lab	1/3rd receive IV hydration followed by contrast enhanced CT scan 1/3rd receive unenhanced CT scan 1/3rd receive MRI
11.1	No testing – IV contrast media for all	Exclusion of no testing strategy in base-case	All patients assumed to be given IV contrast with no additional testing.
11.2	No testing – IV contrast media for all	Exclusion of no testing strategy in base-case and more optimistic assumption concerning the effect of IV hydration is reducing PC-AKI risk (eGFR<30)	Combination of scenario 9 and 11.1

6.5.4 Model validation

The model was developed by one researcher (AD) and the programming was checked by a second researcher (MS). A separate version of the model was independently programmed by a 3rd researcher (SW) who successfully replicated the base-case results.

6.6 Results of the independent economic assessment

6.6.1 Base-case

Deterministic and probabilistic results expressed in NMB and NHB at a cost-effectiveness threshold of £20,000 per QALY are presented in Table 57 and Table 58, respectively. Strategy ranking from highest (1) to lowest (14) average net benefit are presented in both tables. Incremental net benefit was calculated for each strategy compared to laboratory testing ('Lab'). Results for the upper bound of the cost effectiveness threshold recommended by NICE, £30,000 per additional QALY are not presented with the exception of probabilities, which are presented for the range of cost effectiveness thresholds. Results were consistent across the range of cost effectiveness thresholds considered, and for both deterministic and probabilistic analyses.

The strategy with highest incremental net benefit is strategy 6, 'RF+i-STAT+Lab', with an incremental NMB of £87.42 (Table 57) compared to 'Lab'. This is also the strategy with the highest probability of being the most cost-effective (Table 58, 79.3% for cost effectiveness thresholds of £20,000 and £30,000 per additional QALY). 'RF+i-STAT+Lab' is also the least costly of all strategies under comparison with expected total costs of £275.84, but generates fewer QALYs than the majority of other strategies.

Table 59 shows the results of the fully incremental ICER analysis. The ICER of strategy 5, RF+Lab, compared to strategy 6, 'RF+i-STAT+Lab' is £3.61 million per additional QALY, and, therefore, suggests that strategy 6 is the most cost effective strategy at conventional cost effectiveness threshold ranges. As highlighted in Section 6.5.1, the fully incremental ICERs appear particularly sensitive to the small effect differences between strategies, limiting their interpretability. Given the small effect differences and challenges of interpreting the ICER results, fully incremental ICER results are only presented for the base-case, with all other results expressed in terms of net benefits.

In general, strategies that combine risk factor screening with POC testing and lab testing result in higher net benefit than other types of strategies involving a POC testing component, as they have a high positive predictictive value (PPV) (Table 60) at a lower average total cost (Table 61). Strategies combining risk factor screening with POC testing and laboratory testing all have a PPV of 1 meaning that all patients identified as positive are true positives. This allows avoiding unnecessary

management of false positves with IV hydration, which imposes costs associated with cancelling and rebooking CT scans (for those patients identified as true negative only at the laboratory testing stage), delivery of IV hydration, treatment of IV hydration adverse events and patient follow-up. The appropriate management of patients with true eGFR>30ml/min/1.73m2 appears to be a key driver of cost-effectiveness, with the appropriate management of patients with true eGFR<30ml/min/1.73m2 being less important given their low prevalence.The next highest ranking strategies are those that combine risk factor screening with POC testing, but which do not use confirmatory laboratory testing. These strategies have lower overall specificity and result in more false positives compared to risk factor screening combined with POC and confirmatory laboratory testing, with increased costs from unnecessary management of patients misclassified as positive (cancelling and rebooking CT scans, delivery of IV hydration, treatment of IV hydration adverse events and patient follow-up).

Strategies with POC testing and laboratory testing have lower average net benefit than risk factor screening combined with POC testing strategies despite not misclassifying patients as false positives (with associated costs of management), due to the higher costs of testing arising when all patients receive POC testing.

The strategies where POC is used in isolation are the lowest ranking amongst strategies involving POC, because they misclassify more patients as false positives than any other strategies and all patients incur the cost of POC testing.

Although the highest ranking strategy at £20,000 per additional QALY is strategy 6, 'RF+i-STAT+Lab', it is worth noting that the corresponding strategy with StatSensor, strategy 8, has only a marginally smaller average incremental net benefit (£87.11 compared to £87.42 for stategy 6). i-STAT and StatSensor are both handheld devices with similar diagnostic accuracy, with StatSensor having a slightly higher specificity (99.1% vs 98.9%) and lower sensitivity (81.7% vs 84.1%). The cost per test appears higher for StatSensor (£14.25) than for i-STAT (£11.96) when these tests are preceeded by risk factor screening, but similar when POC testing is the first step of the testing sequence (£8.52 and £8.85 for StatSensor and i-STAT, respectively) due to the impact of different throughput assumptions. In all other types of strategies involving POC testing (risk factor screening combined with POC testing, POC testing with laboratory testing, and POC testing only), the strategies with StatSensor have higher net benefit than corresponding ones with i-STAT. This highlights the importance of specificity in the model given the high costs associated with false positives.

Strategies including testing with ABL800FLEX (strategy 3, 7, 10 and 13) have consistently lower net benefit compared to corresponding strategies with i-STAT and StatSensor due to higher costs of testing with this device. The ABL800FLEX is a benchtop device with much higher capital costs than the handheld devices (see section 6.4.7.1). The cost per ABL800FLEX test is, therefore, considerably

higher than that of i-STAT and StatSensor, especially at lower patient throughputs (e.g. when strategies including risk factor screening determine that fewer patients receive POC tests). Although ABL800FLEX is the best performing device in terms of diagnostic accuracy, any net benefit gains from avoided misclassification are offset by the higher cost of the device.

The strategies that yield the higher QALY gains, strategy 1, 'Lab', and 5, 'RF+Lab', are those that avoid misclassification of patients resulting in no false positives or false negatives. These are also the strategies with the lowest average net benefit because the small QALY benefits from the appropriate management of patients are offset by the highest costs of cancellation and rebooking (especially for strategy 1) and of managing patients who test positive.

The base-case cost effectiveness results appear to be largely driven by the balance between the costs of testing and the costs associated with mismanagement of false positives. The reduction of PC-AKI risk and, thus the probability of RRT (Table 60), do not appear to be major drivers in the model. Due to the low prevalence of patients who have a true eGFR<30ml/min/1.73m^2, the low risk of PC-AKI in the model population and lack of evidence of impact of IV hydration in reducing this risk, the expected risk of PC-AKI is similar across strategies. Consequently, the QALY gains (Table 57) and the costs resulting from RRT (Table 61), are also similar across all strategies. The QALY gains of appropriately managing patients who have a true eGFR<30ml/min/1.73m^2 are small (QALY difference between true positive and false negative is only 0.0000079237), while costs of managing patients who test positive are high. The low prevalence of patients who have a true eGFR<30ml/min/1.73m^2 combined with other factors, means that specificity appears a more important cost-effectiveness driver than sensitivity, as avoiding false positives translates into considerably higher net benefit gains than mismanaging false negatives.

Table 57 Base-case deterministic cost effectiveness results – Net benefit

	Identification	Management	Total costs	Total QALYs	NHB *** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	14
2	RF + i-STAT		£278.02	9.991371002	9.97747	£199,549.40	0.00426	£85.25	4
3	RF + ABL800FLEX		£285.87	9.991371003	9.97708	£199,541.55	0.00387	£77.39	9
4	RF + StatSensor		£277.84	9.991370997	9.97748	£199,549.58	0.00427	£85.42	3
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	13
6	RF + i-STAT + Lab		£275.84	9.991371002	9.97758	£199,551.58	0.00437	£87.42	1
7	RF + ABL800FLEX + Lab		£284.39	9.991371003	9.97715	£199,543.03	0.00394	£78.87	8
8	RF + StatSensor + Lab		£276.15	9.991370997	9.97756	£199,551.27	0.00436	£87.11	2
9	i-STAT		£286.35	9.991371002	9.97705	£199,541.07	0.00385	£76.91	10
10	ABL800FLEX		£290.99	9.991371003	9.97682	£199,536.43	0.00361	£72.28	12
11	StatSensor		£283.96	9.991370997	9.97717	£199,543.46	0.00396	£79.30	7
12	i-STAT+ Lab		£280.08	9.991371002	9.97737	£199,547.34	0.00416	£83.18	6
13	ABL800FLEX+ Lab		£286.70	9.991371003	9.97704	£199,540.72	0.00383	£76.56	11
14	StatSensor + Lab		£279.09	9.991370997	9.97742	£199,548.33	0.00421	£84.17	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 58 Base-case probabilistic cost effectiveness results – Net benefit

	Identification	Management	Total costs	Total QALYs	NHB *** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank	Probability CE	
										£20,000/ QALY	£30,000/ QALY
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£367.12	9.993255191	9.97490	£199,497.99	0.00000	£0.00	14	0.0%	0.0%
2	RF + i-STAT		£281.87	9.993255167	9.97916	£199,583.23	0.00426	£85.24	4	0.0%	0.0%
3	RF + ABL800FLEX		£289.72	9.993255171	9.97877	£199,575.39	0.00387	£77.40	9	0.0%	0.0%
4	RF + StatSensor		£281.70	9.993255154	9.97917	£199,583.40	0.00427	£85.42	3	0.0%	0.0%
5	RF + Lab		£307.94	9.993255191	9.97786	£199,557.17	0.00296	£59.18	13	0.0%	0.0%
6	RF + i-STAT + Lab		£279.70	9.993255167	9.97927	£199,585.40	0.00437	£87.42	1	79.3%	79.3%
7	RF + ABL800FLEX + Lab		£288.24	9.993255171	9.97884	£199,576.87	0.00394	£78.88	8	0.0%	0.0%
8	RF + StatSensor + Lab		£280.01	9.993255154	9.97925	£199,585.09	0.00436	£87.10	2	20.7%	20.7%
9	i-STAT		£290.20	9.993255167	9.97875	£199,574.90	0.00385	£76.91	10	0.0%	0.0%
10	ABL800FLEX		£294.83	9.993255171	9.97851	£199,570.27	0.00361	£72.28	12	0.0%	0.0%
11	StatSensor		£287.82	9.993255154	9.97886	£199,577.29	0.00396	£79.30	7	0.0%	0.0%
12	i-STAT+ Lab		£283.93	9.993255167	9.97906	£199,581.17	0.00416	£83.19	6	0.0%	0.0%
13	ABL800FLEX+ Lab		£290.55	9.993255171	9.97873	£199,574.55	0.00383	£76.57	11	0.0%	0.0%
14	StatSensor + Lab		£282.95	9.993255154	9.97911	£199,582.15	0.00421	£84.17	5	0.1%	0.1%

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 59 Base-case cost effectiveness deterministic results – full incremental analysis

	Identification	Management	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY)
6	RF + i-STAT + Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£275.84	9.99137100231	-	-	-
8	RF + StatSensor + Lab		£276.15	9.99137099733	£0.31	-0.000000005	Dominated
4	RF + StatSensor		£277.84	9.99137099733	£1.99	-0.000000005	Dominated
2	RF+ i-STAT		£278.02	9.99137100231	£2.17	0.00000000000	Dominated
14	StatSensor+ Lab		£279.09	9.99137099733	£3.25	-0.000000005	Dominated
12	i-STAT+ Lab		£280.08	9.99137100231	£4.23	0.00000000000	Dominated
11	StatSensor		£283.96	9.99137099733	£8.12	-0.00000000499	Dominated
7	RF+ABL800FLEX+Lab		£284.39	9.99137100330	£8.55	0.00000000099	Extendedly dominated
3	RF+ABL800FLEX		£285.87	9.99137100330	£10.03	0.00000000099	Dominated
9	i-STAT		£286.35	9.99137100231	£10.51	0.00000000000	Dominated
13	ABL800FLEX+ Lab		£286.70	9.99137100330	£10.86	0.00000000099	Dominated
10	ABL800FLEX		£290.99	9.99137100330	£15.14	0.00000000099	Dominated
5	RF + Lab		£304.06	9.99137101011	£28.22	0.00000000779	£3,620,669,780
1	Lab		£363.26	9.99137101011	£87.42	0.00000000779	Dominated

*According to any test in the testing sequence **According to last test in the testing sequence

Table 60 Base-case– overall diagnostic accuracy by strategy and probability of PC-AKI and RRT

	Identification	Management	Diagnostic accuracy				Probability of	
			FP*	FN*	Test positive*	PPV	PC-AKI	RRT
1	Lab	Test negative* - Contrast enhanced CT scan Test positive* - IVH + Contrast enhanced CT scan	0.0000	0.0000	0.0062	1.000	0.024529	0.0158936
2	RF+ i-STAT		0.0039	0.0010	0.0091	0.569	0.024532	0.0158939
3	RF + ABL800FLEX		0.0027	0.0009	0.0080	0.664	0.024532	0.0158938
4	RF + StatSensor		0.0031	0.0016	0.0076	0.599	0.024534	0.0158941
5	RF + Lab		0.0000	0.0000	0.0062	1.000	0.024529	0.0158936
6	RF + i-STAT + Lab		0.0000	0.0010	0.0052	1.000	0.024532	0.0158939
7	RF + ABL800FLEX + Lab		0.0000	0.0009	0.0053	1.000	0.024532	0.0158938
8	RF + StatSensor + Lab		0.0000	0.0016	0.0046	1.000	0.024534	0.0158941
9	i-STAT		0.0113	0.0010	0.0165	0.315	0.024532	0.0158939
10	ABL800FLEX		0.0077	0.0009	0.0130	0.407	0.024532	0.0158938
11	StatSensor		0.0088	0.0016	0.0133	0.342	0.024534	0.0158941
12	i-STAT+ Lab		0.0000	0.0010	0.0052	1.000	0.024532	0.0158939
13	ABL800FLEX+ Lab		0.0000	0.0009	0.0053	1.000	0.024532	0.0158938
14	StatSensor+ Lab		0.0000	0.0016	0.0046	1.000	0.024534	0.0158941

*According to last test in the testing sequence: FN, false negatives; FP, false positives; PPV, positive predictive value.

Table 61 Base-case cost effectiveness deterministic results – disaggregated costs

	Identification	Management	Probability of		Costs						Total
			Incurring a delay	Unnecessary IVH	Testing	Cancellation and rebooking	Follow-up	IVH & AEs	CT scan	Post Contrast	
1	Lab	Test negative* - Contrast enhanced CT scan Test positive* - IVH + Contrast enhanced CT scan	1.0000	0.0000	£3.31	£89.75	£1.15	£2.30	£111.65	£155.09	£363.26
2	RF + i-STAT		0.0091	0.0039	£5.34	£0.82	£1.70	£3.41	£111.65	£155.10	£278.02
3	RF + ABL800FLEX		0.0080	0.0027	£13.92	£0.72	£1.49	£2.99	£111.65	£155.10	£285.87
4	RF + StatSensor		0.0076	0.0031	£6.14	£0.68	£1.42	£2.84	£111.65	£155.10	£277.84
5	RF + Lab		0.3519	0.0000	£2.28	£31.58	£1.15	£2.30	£111.65	£155.09	£304.06
6	RF + i-STAT + Lab		0.0091	0.0000	£5.37	£0.82	£0.97	£1.94	£111.65	£155.10	£275.84
7	RF + ABL800FLEX + Lab		0.0080	0.0000	£13.95	£0.72	£0.99	£1.98	£111.65	£155.10	£284.39
8	RF + StatSensor + Lab		0.0076	0.0000	£6.17	£0.68	£0.85	£1.70	£111.65	£155.10	£276.15
9	i-STAT		0.0165	0.0113	£8.89	£1.48	£3.07	£6.16	£111.65	£155.10	£286.35
10	ABL800FLEX		0.0130	0.0077	£15.77	£1.17	£2.43	£4.87	£111.65	£155.10	£290.99
11	StatSensor		0.0133	0.0088	£8.55	£1.20	£2.49	£4.98	£111.65	£155.10	£283.96
12	i-STAT+ Lab		0.0165	0.0000	£8.94	£1.48	£0.97	£1.94	£111.65	£155.10	£280.08
13	ABL800FLEX+ Lab		0.0130	0.0000	£15.81	£1.17	£0.99	£1.98	£111.65	£155.10	£286.70
14	StatSensor+ Lab		0.0046	0.0000	£8.59	£1.20	£0.85	£1.70	£111.65	£155.10	£279.09

*According to any test in the testing sequence **According to last test in the testing; IVH, intravenous hydration

6.6.2 Scenario analyses

The deterministic results for the scenario analyses are presented in Appendix 10.6 (**Table 76** to Table 91). Table 62 summarises the ranking of each strategy in terms of net benefit at £20,000 per additional QALY for the base-case and scenario analyses. Figure 15 shows strategy ranks from highest (top line) to lowest (bottom line) net benefit across scenario analyses. The strategies are labelled with their corresponding number within the circles.

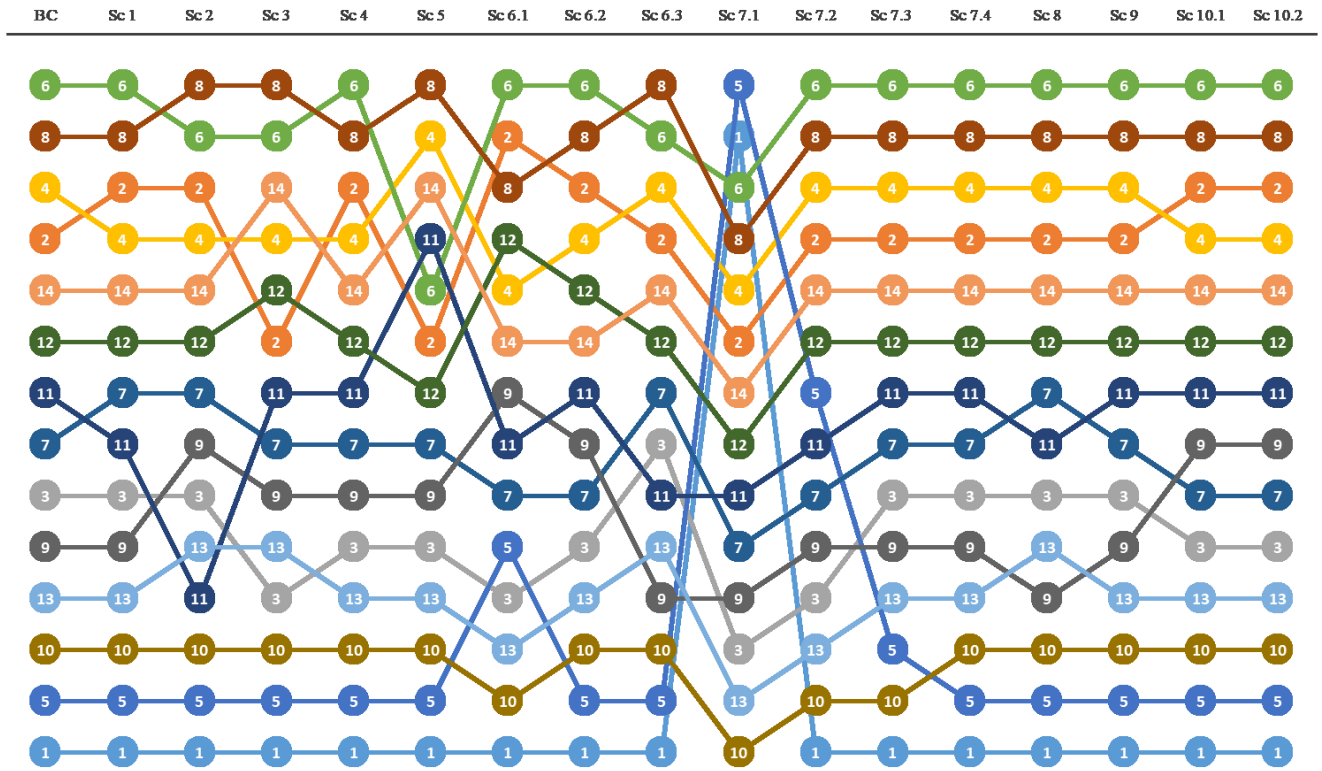
The results suggest that strategy 6, 'RF+i-STAT+Lab', has the highest net benefit across the majority of scenarios. However, this finding appears sensitive to alternative assumptions in terms of diagnostic accuracy (scenario 2 and 3), eGFR distribution (scenario 5), throughput estimates (scenario 6.3) and opportunity costs of delayed/rescheduled scan (scenario 7.1). Despite some changes in rankings, differences in net benefits between strategies, and particularly between i-STAT and StatSensor, appear extremely small. The clinical and economic importance of the differences between individual devices and different types of strategies may be limited.

Table 62 Net benefit ranking of strategies for base-case and scenario analyses

Strategy number	BC	Scenario															
		1	2	3	4	5	6.1	6.2	6.3	7.1	7.2	7.3	7.4	8	9	10.1	10.2
6	1	1	2	2	1	5	1	1	2	3	1	1	1	1	1	1	1
8	2	2	1	1	2	1	3	2	1	4	2	2	2	2	2	2	2
4	3	4	4	4	4	2	5	4	3	5	3	3	3	3	3	4	4
2	4	3	3	6	3	6	2	3	4	6	4	4	4	4	4	3	3
14	5	5	5	3	5	3	6	6	5	7	5	5	5	5	5	5	5
12	6	6	6	5	6	7	4	5	6	8	6	6	6	6	6	6	6
11	7	8	11	7	7	4	8	7	9	9	8	7	7	8	7	7	7
7	8	7	7	8	8	8	9	9	7	10	9	8	8	7	8	9	9
3	9	9	9	11	10	10	11	10	8	12	11	9	9	9	9	10	10
9	10	10	8	9	9	9	7	8	11	11	10	10	10	11	10	8	8
13	11	11	10	10	11	11	12	11	10	13	12	11	11	10	11	11	11
10	12	12	12	12	12	12	13	12	12	14	13	13	12	12	12	12	12
5	13	13	13	13	13	13	10	13	13	1	7	12	13	13	13	13	13
1	14	14	14	14	14	14	14	14	14	2	14	14	14	14	14	14	14

Scenarios: 1, StatSensor Adjusted analysis; 2, CKD-EPI equation studies; 3, Alternative risk factor questionnaire; 4, eGFR distribution - Harris subgroup without prior eGFR; 5, eGFR distribution - GSTT audit data population; 6.1, Throughput – 12.7% without a prior eGFR; 6.2, Throughput - 50% lower than base-case; 6.3; Throughput - 50% higher than base-case; 7.1, Proportion of cancelled CT scans (0%); 7.2, Proportion of cancelled CT scans (25%); 7.3, Proportion of cancelled CT scans (50%); 7.4, Proportion of cancelled CT scans (75%); 8, Anxiety from delay; 9, Effect of IV hydration (PC-AKI risk); 10.1, Management approach for test positives (50% IV hydration + contrast CT scan, 50% no contrast CT scan); 10.2, Management approach for test positives (1/3rd IV hydration + contrast CT scan, 1/3rd no contrast CT scan+1/3rd MRI).

Figure 15 Summary of net benefit ranking across scenario analysis



BC, base-case; Sc, Scenario; Scenarios: 1, StatSensor Adjusted analysis; 2, CKD-EPI equation studies; 3, Alternative risk factor questionnaire; 4, eGFR distribution - Harris subgroup without prior eGFR; 5, eGFR distribution - GSTT audit data population; 6.1, Throughput – 12.7% without a prior eGFR; 6.2, Throughput - 50% lower than base-case; 6.3; Throughput - 50% higher than base-case; 7.1, Proportion of cancelled CT scans (0%); 7.2, Proportion of cancelled CT scans (25%); 7.3, Proportion of cancelled CT scans (50%); 7.4, Proportion of cancelled CT scans (75%); 8, Anxiety from delay; 9, Effect of IV hydration (PC-AKI risk); 10.1, Management approach for test positives (50% IV hydration + contrast CT scan, 50% no contrast CT scan); 10.2, Management approach for test positives (1/3rd IV hydration + contrast CT scan, 1/3rd no contrast CT scan+1/3rd MRI).

When the diagnostic accuracy of POC devices is sourced solely from studies using the CKD-EPI equation to calculate eGFR (scenario 2), there is a switch in the net benefit rank between strategy 6 ('RF+i-STAT+Lab') and 8 ('RF+StatSensor+Lab'). When this source of data is used the sensitivities of all POC devices decreases compared to base-case, with StatSensor having the greatest decrease in sensitivity compared to base-case (56.4% vs 73.9%). This results in an increase of the proportion of false negatives for strategy 8, 'RF+StatSensor+Lab', with consequent decrease in costs from managing positive patients. The decrease in costs is sufficient to offset the higher costs of testing for strategy 8, 'RF+StatSensor+Lab', compared to strategy 6, 'RF+i-STAT+Lab', and under this scenario the strategy becomes the cost effective alternative.

In scenario 3, it is assumed that risk factor screening is performed with a questionnaire with worse diagnostic accuracy. Compared to the base case analysis, the sensitivity of the questionnaire is reduced from 100% to 88.2% while specificity is reduced from 65.2% to 45.2%. The lower specificity of the questionnaire results in an increase in throughput for POC testing for strategies where POC testing is preceeded by risk factor screening, with consequent reduction in the costs of POC testing. The cost per test of StatSensor (with risk factor screening) reduces proportionately more compared to i-STAT, and despite remaining the more costly of the two tests (£11.06 vs £10.23, respectively), this small difference in the cost of testing is now offset by the lower costs of managing patients identified as positive by StatSensor. Therefore, strategy 8, 'RF+StatSensor+Lab', switches with strategy 6, 'RF+i-STAT+Lab', as the cost effective alternative for scenario 3. Strategy 14, 'StatSensor+Lab' also has higher net benefit than both strategy 2, 'RF+i-STAT', and strategy 4, 'RF+StatSensor'. This is due to an increase in the costs of testing in the strategies including risk factor screening, given that the lower specificity of the questionnaire result in more patients being tested with POC (even if the cost per POC test reduces).

Scenario 5 assumes that the underlying distribution of eGFR values in the relevant population matches that of GSTT audit population. This population is characterised by a higher proportion of patients with eGFR<30 ml/min/1.73 m^2 compared to base-case (15.9% vs 0.6%). When the proportion of patients with patients with true eGFR<30 ml/min/1.73 m^2 is higher, there will be more patients testing positive and thus receiving more intensive patient management. There will also be more patients who can benefit from management to reduce PC-AKI (as risk will be overall higher), but the benefit of being managed with IV hydration remains small. The proportion of patients who test positive (and incur more costs for a small benefit) will be higher for strategies with lower specificity and higher sensitivity. In this scenario, the strategy with highest net benefit is strategy 8, 'RF+StatSensor+Lab', followed by strategy 4, 'RF+StatSensor', and strategy 14 'StatSensor+Lab'. Since StatSensor is the POC device with lowest sensitivity, strategies including this device will result in proportionally fewer positive POC tests with lower costs from delays and, where POC is not

followed by laboratory testing, lower costs from managing patients who test positive across the testing strategy. The increase of the proportion of patients with patients with true eGFR<30 ml/min/1.73 m^2 also results in reduction of the cost per test for all POC devices when combined with risk factor screening, but proportionally more for StatSensor than for i-STAT. The cost effectiveness of strategies including POC testing with StatSensor is more favourable over that of strategies with other devices when the the proportion of patients with true eGFR<30 ml/min/1.73 m^2 increases to 15.9% despite its lower sensitivity.

Higher levels of throughput (Scenario 6.3) result in a switch in the net benefit rank between strategy 6 and 8, with strategy 8, 'RF+StatSensor+Lab' generating higher net benefit. Higher throughput reduces the cost per POC test for all devices. The cost of per test of StatSensor is more sensitive (due to the costs of quality control) to changes in throughput than i-STAT, and reduces proportionately more compared to base-case than the cost per i-STAT test. Therefore, strategy 6, 'RF+StatSensor+Lab', becomes less costly than strategy 8, 'RF+i-STAT+Lab', and becomes the cost-effective strategy in scenario 6.3.

Scenarios 7.1 to 7.4 explore uncertainty in the proportion of patients who can have their laboratory test and/or IV hydration performed urgently and, therefore, without incurring the opportunity costs of a delayed CT scan. The results of the base-case analysis are robust to all alternative assumptions tested under this scenario except when it is assumed that all patients are urgent cases and none incurs the opportunity costs of a delayed CT scan (Scenario 7.1). If there were no delays to CT scanning from laboratory testing and/or IV hydration, strategy 5, 'RF+Lab' would become the strategy with the highest net benefit followed by strategy 1, 'Lab'. The two strategies are equivalent in terms of QALY gains (as risk factor screening is assumed to 100% sensitive), but risk factor screening allows reducing the overall costs of testing as only patients who are risk factor positive receive the lab test. Under scenario 7.1, these strategies become the least costly across all other strategies, because all other costs of managing test positive patients are only incurred by true positives (the strategies do not allow for misclassification) and the costs of testing are lower than for the other strategies.

Scenarios 8 to 10.2 explored alternative assumptions concerning the impact of anxiety due to delay (scenario 8), the effect of IV hydration (scenario 9) and the costs of alternative imaging decisions (scenarios 10.1 and 10.2). Although there were some minor changes in rankings across these scenarios, strategies 6 (RF+i-STAT+Lab) and 8 (REF+StatSensor+Lab) remained the highest ranked strategies across all these scenarios.

As stated previousy, a strategy of 'no testing and manage all with contrast enhanced CT' was not included in the base-case analysis, as this strategy was not deemed to be clinically appropriate given the consistent recommendations reported across clinical guidelines recommending the use of some

form of screening or testing to identify individuals at risk of PC-AKI. However, for completeness and to aid the overall interpretation of the results, 2 additional scenarios were included (scenarios 11.1 and 11.2). Scenario 11.1 (Table 63**Error! Reference source not found.**) replicated the base-case analysis but including an additional 'no testing' strategy. Scenario 11.2 (Table 64) included the additional 'no testing' strategy and also altered the assumptions concerning the effectiveness of IV hydration in reducing the risk of PC-AKI.

In both scenarios 11.1 and 11.2, the 'no testing and manage all with contrast enhanced CT' was associated with the highest net benefit.

Table 63 Cost effectiveness results – Scenario 11.1: No testing – IV contrast media for all

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive* - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	15
2	RF+ i-STAT		£278.02	9.991371002	9.97747	£199,549.40	0.00426	£85.25	5
3	RF + ABL800FLEX		£285.87	9.991371003	9.97708	£199,541.55	0.00387	£77.39	10
4	RF + StatSensor		£277.84	9.991370997	9.97748	£199,549.58	0.00427	£85.42	4
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	14
6	RF + i-STAT + Lab		£275.84	9.991371002	9.97758	£199,551.58	0.00437	£87.42	2
7	RF + ABL800FLEX + Lab		£284.39	9.991371003	9.97715	£199,543.03	0.00394	£78.87	9
8	RF + StatSensor + Lab		£276.15	9.991370997	9.97756	£199,551.27	0.00436	£87.11	3
9	i-STAT		£286.35	9.991371002	9.97705	£199,541.07	0.00385	£76.91	11
10	ABL800FLEX		£290.99	9.991371003	9.97682	£199,536.43	0.00361	£72.28	13
11	StatSensor		£283.96	9.991370997	9.97717	£199,543.46	0.00396	£79.30	8
12	i-STAT+ Lab		£280.08	9.991371002	9.97737	£199,547.34	0.00416	£83.18	7
13	ABL800FLEX+ Lab		£286.70	9.991371003	9.97704	£199,540.72	0.00383	£76.56	12
14	StatSensor + Lab		£279.09	9.991370997	9.97742	£199,548.33	0.00421	£84.17	6
15	No testing	Contrast enhanced CT	£266.77	9.991370961	9.97803	£199,560.65	0.00482	£96.50	1

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 64 Cost effectiveness results – Scenario 11.2: 'No testing – IV contrast media for all' combined with Scenario 9 (Effect of IV hydration)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive* - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	15
2	RF+ i-STAT		£278.09	9.991370798	9.97747	£199,549.33	0.00426	£85.17	5
3	RF + ABL800FLEX		£285.93	9.991370825	9.97707	£199,541.48	0.00387	£77.33	10
4	RF + StatSensor		£277.96	9.991370662	9.97747	£199,549.46	0.00426	£85.30	4
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	14
6	RF + i-STAT + Lab		£275.92	9.991370798	9.97757	£199,551.50	0.00437	£87.34	2
7	RF + ABL800FLEX + Lab		£284.46	9.991370825	9.97715	£199,542.96	0.00394	£78.80	9
8	RF + StatSensor + Lab		£276.27	9.991370662	9.97756	£199,551.14	0.00435	£86.98	3
9	i-STAT		£286.43	9.991370798	9.97705	£199,540.99	0.00384	£76.83	11
10	ABL800FLEX		£291.05	9.991370825	9.97682	£199,536.37	0.00361	£72.21	13
11	StatSensor		£284.08	9.991370662	9.97717	£199,543.33	0.00396	£79.17	8
12	i-STAT+ Lab		£280.15	9.991370798	9.97736	£199,547.26	0.00416	£83.11	7
13	ABL800FLEX+ Lab		£286.77	9.991370825	9.97703	£199,540.65	0.00382	£76.49	12
14	StatSensor + Lab		£279.21	9.991370662	9.97741	£199,548.20	0.00420	£84.04	6
15	No testing	Contrast enhanced CT	£267.22	9.991369679	9.97801	£199,560.17	0.00480	£96.02	1

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

6.7 Discussion of the independent economic assessment

The purpose of the decision model was to assess the cost-effectiveness of POC testing to assess kidney function, for people who need contrast-enhanced CT imaging in a non-emergency situation and who do not have a recent eGFR measurement. The decision model considered the potential benefits and possible risks of using of a range of alternative POC testing approaches within the current CT pathway.

A potential limitation of the model is the assumption made in the base-case analsysis that all individuals will eventually proceed to a contrast enhanced CT scan. This simplification was considered necessary given the limited data available and the challenges of characterising the hetereogeneity in the overall population and the underlying reason for imaging and linking this to individualised clinical decision making and associated outcomes. However, an extensive series of scenario analyses were undertaken to explore the potential impact of alternative assumptions.

The finding that a scenario including a 'no testing and manage all with contrast enhanced CT'strategy had the highest net benefit of all the strategies suggests that additional testing costs required to obtain either a laboratory assessment or a POC test result may not provide sufficient improvements in patient outcomes to warrant routine testing. However, these findings also need to be considered alongside the limitations of the model assumptions and the uncertainties that clearly remain regarding the risks of contrast media and the benefits of appropriate prophylactic management to reduce the risk of PC-AKI.

6.8 Conclusions of the cost effectiveness section

The base case cost-effectiveness results showed that the testing strategy with highest net benefit (i.e. most cost-effective) was a a three step testing sequence which involves initially screening all individuals for risk factors, testing with a POC device those individuals identified with at least one risk factor, and including a final confirmatory laboratory test for individuals who also test positive with a POC device. Within this testing approach type, the specific POC device with the highest net benefit was i-STAT. However, differences in the net benefit between the i-STAT and StatSensor devices were very small. These findings appeared robust to a wide range of scenario analyses. Despite some changes in rankings, differences in net benefits between many of the individual strategies remained extremely small.

Differences in the cost and diagnostic specificity of the individual testing strategies appeared more important drivers than diagnostic sensitivity. The reduction of PC-AKI risk and associated consequences were not major drivers in the model due to the low risk of PC-AKI estimated for this population, the lack of evidence suggesting an increased risk of PC-AKI associated with the use of contrast media and the lack of evidence of impact of IV hydration in reducing the risk of PC-AKI.

7 Discussion

7.1 Statement of principal findings

Most of the 54 studies which were eligible for inclusion in the systematic review reported only measurement bias or correlation outcomes and so were of limited relevance to the economic modelling part of the assessment. Correlation results data are limited because results which might appear impressive (i.e. correlation coefficients close to 1) can sometimes hide imperfect agreement between methods. Of the studies reporting data on creatinine/eGFR measurement bias, results from the StatSensor studies demonstrated wide variation in both the size and direction of bias. It is therefore important that StatSensor users are aware of the availability of the offset facility to correct for any measurement bias observed, as this did not appear to have been done in most StatSensor studies. It is also preferable that any bias corrections should be informed by data from enzymatic laboratory reference methods, rather than Jaffe methods, which are well known to be less accurate than enzymatic methods for measuring creatinine. Although potentially important measurement bias was also identified in some studies of the i-STAT and ABL devices, in most of these studies the concordance of results was generally better than was found in most of the StatSensor studies. No eligible studies were available on the Dri-chem NX500 device and few studies were available on the epoc and Piccolo Xpress devices; the limited data and reporting in these studies, coupled with their small sample sizes made it difficult to draw conclusions about creatinine measurement biases.

All seven studies which reported diagnostic accuracy results based on creatinine thresholds were of the StatSensor device. However, these were of limited value to this assessment because only two of the seven studies explicitly reported results which incorporated an offset adjustment (both of which were based on Jaffe laboratory methods) and diagnostic accuracy results based on creatinine thresholds are not as clinically relevant as results based on eGFR thresholds.

Twelve studies reported eGFR diagnostic accuracy data but these covered only three types of device: StatSensor, i-STAT and ABL devices. Although half of these studies were assessed as having results with a low risk of bias, there were some concerns about the applicability of results to the outpatient CT setting in all but two studies. Results of the eGFR data synthesis show better sensitivity to detect risk of PC-AKI for i-STAT and ABL devices than for StatSensor devices. In addition, i-STAT and ABL devices also have higher probabilities of correctly classifying individuals in the same eGFR categories as the reference laboratory, than StatSensor devices. This is particularly marked for the lower categories, which are of greatest clinical importance. Additional analyses carried out using adjusted StatSensor data and including only studies which used the CKD-EPI equation confirmed these findings.

A three step testing sequence that involves combining a risk factor questionnaire, POC testing and confirmatory laboratory testing would potentially reduce unnecessary delays or rescheduling of CT scans. This testing approach appears more cost-effective than the current approach which involves obtaining a recent laboratory based measurement prior to administering contrast media.

7.2 Strengths and limitations of the assessment

The systematic review was performed using transparent, reproducible and robust methods. Our comprehensive literature searches sought to identify all relevant published and unpublished studies, which minimised the possibility of publication or language biases affecting the review results. Similarly, key review processes were performed in duplicate which minimised the possibility of any reviewer errors and biases. We also successfully obtained previously unpublished data from two important studies of diagnostic accuracy based on eGFR thresholds. Study quality was evaluated in studies reporting eGFR diagnostic accuracy data using a modified version of the QUADAS-2 tool. Appropriate synthesis methods were used to evaluate the accuracy of the devices and provide the inputs needed to the economic evaluation in the form probabilities of correct classification by the POC device into the same eGFR range as the reference laboratory. Uncertainty in the data was taken into account although it was not possible to fully account for between-study differences in results.

A further strength of our review was the broadness of its scope: in addition to studies reporting diagnostic accuracy data we sought studies reporting measurement bias and clinical or workflow outcomes.

The de novo decision model is the first formal evaluation of the potential clinical benefits, risks and costs of incorporating POC testing to assess kidney function, for people who need contrast-enhanced CT imaging in a non-emergency outpatient setting and who present without a recent eGFR measurement. The main strength of the decision model is the linkage between the diagnostic accuracy of a given strategy, the impact on subsequent treatment decisions and the ultimate effect on health outcomes and costs.

Some studies were limited by small sample sizes and most studies had few patients with eGFR values of <30 ml/min/1.73m^2. Although this is reflective of outpatient populations it limits the data available for analyses based on the most important eGFR threshold of <30 ml/min/1.73m^2. Few studies directly compared different POC creatinine devices and eGFR diagnostic accuracy data were not available for the ABL90 FLEX PLUS, Dri-chem NX500, epoc Blood Analysis System and Piccolo Xpress POC devices.

Another potential limitation of our assessment is the assumption made in the base-case analsysis is that all individuals will eventually proceed to a contrast enhanced CT scan. This simplification was

considered necessary given the limited data available and the challenges of characterising the hetereogeneity in the overall population and the underlying reason for imaging and linking this to individualised clinical decision making and associated outcomes. However, an extensive series of scenario analyses were undertaken to explore the potential impact of alternative assumptions.

7.3 Uncertainties

There were few studies which reported data on the impact of POC devices in CT departments on the use (or rates of non-use) of contrast agents for diagnostic procedures nor were there many data on the use of prophylactic treatments or workflow outcomes such as cancelled appointments. No data were available on clinical outcomes such as need for renal replacement therapy or hospital admissions. The impact of POC devices on these important outcomes is therefore uncertain.

The finding that a 'no testing and use of IV contrast for all' strategy had the highest net benefit suggests that that additional testing costs required to obtain either a laboratory assessment or a POC test result may not provide sufficient improvements in patient outcomes to warrant routine testing. However, these findings also need to be considered alongside the limitations of the model assumptions and the uncertainties that clearly remain regarding the risks of contrast media and the benefits of appropriate prophylactic management to reduce the risk of PC-AKI.

8 Conclusions

8.1 Implications for healthcare

Our findings suggest that the use of POC devices may reduce costs to the health system arising from unecessary delays in CT scanning appointments for the majority of individuals. Any savings also need to be considered against the potential risks arising from misclassification. However, while the use of POC devices results in a marginal reduction in outcomes compared to a strategy of obtaining a laboratory measurement for all individuals, the loss in outcomes appears more than offset by the estimated cost savings.

8.2 Suggested research priorities

Debate exists about how best to resolve the issue of the risks of contrast media with some suggesting a need for a randomised study to fully determine the contribution of intravenous contrast media to the development of acute kidney injury.[95] Others though have documented that prospective studies in patients with eGFRs of <30 ml/min/1.73m^2 have been attempted but had to be terminated early; further clarification on the risk from contrast could be gained from studies of specific patient subgroups which did not receive IV. prophylaxis (e.g. CT angiography), irrespective of renal function.[94]

Evidence on the diagnostic accuracy of the Piccolo, ABL90 FLEX PLUS, Dri-chem NX500, and epoc Blood Analysis System devices is needed. A study which evaluates the impact of risk stratifying questionnaires on workflow outcomes in CT patients attending without a recent eGFR results may also be worthwhile. Studies comparing the accuracy of POC devices using different types of samples (e.g. capillary samples vs. whole blood) may be relevant for devices that offer that functionality.

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Data sharing

The data used in the analyses in this report are predominantly drawn from published and publically available sources, as cited throughout the report. Summaries of the non-confidential data and of the models used are available on request from the corresponding author.

Contributions of authors

Mark Corbett contributed to writing the protocol, conducted study selection, data extraction, validity assessment, interpretation of evidence, and co-wrote the clinical sections of the report.

Ana Duarte contributed to the writing of the protocol and the cost-effectiveness section, developed the economic model, and performed the economic analysis.

Alexis Llewellyn conducted study selection, data extraction, validity assessment and co-wrote the clinical sections of the report.

James Altunkaya contributed to the writing of the cost-effectiveness section.

Melissa Harden devised the search strategy, carried out the literature searches and wrote the search sections of the report.

Martine Harris provided clinical advice during the project and previously unpublished data, and commented on drafts of the report.

Simon Walker contributed to the writing of the cost-effectiveness section, assisted with the economic analysis and validated the economic model.

Stephen Palmer contributed to the writing of the protocol and the cost-effectiveness section, commented on drafts of the report and contributed to all aspects of the project.

Sofia Dias contributed to writing the protocol, developed the data synthesis model, contributed to data extraction, interpretation of evidence and co-wrote the clinical sections of the report.

Marta Soares contributed to the writing of the cost-effectiveness section and development of the economic model, contributed to model validation, and had overall responsibility for the cost-effectiveness section of the report.

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11 Appendices

11.1 Literature search strategies

Database search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to November 5th 2018

Searched on: 6th November 2018

Records retrieved: 935

1 Point-of-Care Systems/ (11059)

2 Point-of-Care Testing/ (999)

3 point-of-care.ti,ab,kf. (15874)

4 (POC or POCT).ti,ab,kf. (4593)

5 (rapid$ adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (72301)

6 ((bedside$ or bed-side$) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (3654)

7 ((on-site or onsite) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (2472)

8 (near adj4 patient$ adj4 test$).ti,ab. (429)

9 (near adj4 patient$ adj4 determin$).ti,ab. (18)

10 (near adj4 patient$ adj4 assess$).ti,ab. (40)

11 (near adj4 patient$ adj4 analys$).ti,ab. (52)

12 (near adj4 patient$ adj4 analyz$).ti,ab. (21)

13 (near adj4 patient$ adj4 identif$).ti,ab. (38)

14 (near adj4 patient$ adj4 measur$).ti,ab. (88)

15 (near adj4 patient$ adj4 screen$).ti,ab. (15)

16 or/1-15 (98921)

17 Creatinine/ (53591)

18 creatinin$.ti,ab,kf. (103420)

19 serumcreatinin$.ti,ab,kf. (4)

20 SCr.ti,ab,kf. (6111)

21 or/17-20 (127272)

22 16 and 21 (584)

23 Kidney Function Tests/ (24304)

24 Glomerular Filtration Rate/ (40393)

25 ((kidney$ or renal) adj3 (function$ or dysfunction$)).ti,ab. (122372)

26 glomerul$ filtration rate$.ti,ab,kf. (39656)

27 glomerulofiltration rate$.ti,ab,kf. (6)

28 GFR.ti,ab,kf. (17926)

29 eGFR.ti,ab,kf. (49812)

30 or/23-29 (208018)

31 16 and 30 (531)

32 22 or 31 (933)

33 Computers, Handheld/ (3272)

34 ((handheld or hand held) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (1598)

35 ((desktop or desk top) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (74)

36 ((table top or tabletop or bench top or benchtop) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (145)

37 ((portab$ or transportab$) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (3217)

38 (near patient$ adj2 (device$ or analyser$ or analyzer$)).ti,ab. (28)

39 or/33-38 (8033)

40 21 or 30 (290065)

41 39 and 40 (50)

42 32 or 41 (966)

43 (i-STAT or iSTAT).ti,ab,kf. (486)

44 40 and 43 (23)

45 (StatSensor or Stat Sensor).ti,ab,kf. (16)

46 ABL90 FLEX PLUS.ti,ab,kf. (0)

47 (ABL800 FLEX or ABL800FLEX or ABL 800 FLEX).ti,ab,kf. (25)

48 Dri-chem NX500.ti,ab,kf. (0)

49 epoc Blood Analysis.ti,ab,kf. (3)

50 Piccolo Xpress.ti,ab,kf. (7)

51 or/44-50 (69)

52 42 or 51 (1003)

53 exp animals/ not humans/ (4511292)

54 52 not 53 (935)

Key:

/ = indexing term (MeSH heading)
exp = exploded indexing term (MeSH heading)
$ = truncation
ti,ab = terms in either title or abstract fields
kf = author keywords field
adj3 = terms within three words of each other (any order)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 10 of 12, October 2018

Searched on: 6th November 2018

Records retrieved: 107

The strategy below was used to search both CENTRAL and CDSR.

#1 MeSH descriptor: [Point-of-Care Systems] this term only 387

#2 MeSH descriptor: [Point-of-Care Testing] this term only 46

#3 point-of-care:ti,ab,kw 1465

#4 (POC or POCT):ti,ab,kw 1329

#5 (rapid* near/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)):ti,ab,kw 2811

#6 ((bedside* or bed-side*) near/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)):ti,ab,kw 330

#7 ((on-site or onsite) near/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)):ti,ab,kw 179

#8 ("near" near/4 patient* near/4 test*):ti,ab,kw 46

#9 ("near" near/4 patient* near/4 determin*):ti,ab,kw 3

#10 ("near" near/4 patient* near/4 assess*):ti,ab,kw 9

#11 ("near" near/4 patient* near/4 analys*):ti,ab,kw 1

#12 ("near" near/4 patient* near/4 analyz*):ti,ab,kw 1

#13 ("near" near/4 patient* near/4 identif*):ti,ab,kw 4

#14 ("near" near/4 patient* near/4 measur*):ti,ab,kw 8

#15 ("near" near/4 patient* near/4 screen*):ti,ab,kw 1

#16 {OR #1-#15} 5677

#17 MeSH descriptor: [Creatinine] this term only 3779

#18 creatinin*:ti,ab,kw 17537

#19 serumcreatinin*:ti,ab,kw 34

#20 SCr:ti,ab,kw 890

#21 120-#20-#20 17896

#22 #16 AND #21 61

#23 MeSH descriptor: [Kidney Function Tests] this term only 1162

#24 MeSH descriptor: [Glomerular Filtration Rate] this term only 2488

#25 ((kidney* or renal) near/3 (function* or dysfunction*)):ti,ab,kw 14814

#26 glomerul* next filtration next rate*:ti,ab,kw 7103

#27 glomerulofiltration next rate*:ti,ab,kw 0

#28 GFR:ti,ab,kw 4858

#29 eGFR:ti,ab,kw 4823

#30 {OR #23-#29} 21219

#31 #16 AND #30 65

#32 #22 OR #31 103

#33 MeSH descriptor: [Computers, Handheld] this term only 230

#34 ((handheld or "hand held") near/2 (device* or analyser* or analyzer*)):ti,ab,kw 227

#35 ((desktop or "desk top") near/2 (device* or analyser* or analyzer*)):ti,ab,kw 6

#36 (("table top" or tabletop or "bench top" or benchtop) near/2 (device* or analyser* or analyzer*)):ti,ab,kw 5

#37 ((portab* or transportab*) near/2 (device* or analyser* or analyzer*)):ti,ab,kw 330

#38 (("near patient" or "near patients") near/2 (device* or analyser* or analyzer*)):ti,ab,kw 1

#39 {OR #33-#38} 775

#40 #21 OR #30 32349

#41 #39 AND #40 9

#42 #32 OR #41 112

#43 (i-STAT or iSTAT):ti,ab,kw 20

#44 (StatSensor or Stat-Sensor):ti,ab,kw 0

#45 "ABL90 FLEX PLUS":ti,ab,kw 0

#46 (ABL800 FLEX or ABL800FLEX or ABL 800 FLEX):ti,ab,kw 4

#47 Dri-chem NX500:ti,ab,kw 0

#48 "epoc Blood Analysis":ti,ab,kw 0

#49 Piccolo Xpress:ti,ab,kw 0

#50 121-#49-#49 22

#51 #42 OR #50 133

#52 #42 or #50 in Cochrane Reviews 26

#53 #42 or #50 in Trials 107

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 11 of 12, November 2018

Searched on: 6th November 2018

Records retrieved: 26

See above under CENTRAL for search strategy used.

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 5th November 2018

Searched on: 6th November 2018

Records retrieved: 398

S1	MH "Point-of-Care Testing" OR MH "Clinical Information Systems"	8,790
S2	TI point-of-care OR AB point-of-care	5,832
S3	TI (POC or POCT) OR AB (POC or POCT)	1,220
S4	TI (rapid* N3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) OR AB (rapid* N3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))	8,379
S5	TI ((bedside* or bed-side*) N3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) OR AB ((bedside* or bed-side*) N3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))	1,641
S6	TI ((on-site or onsite) N3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) OR AB ((on-site or onsite) N3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))	10,344
S7	TI (near N4 patient* N4 test*) OR AB (near N4 patient* N4 test*)	152
S8	TI (near N4 patient* N4 determin*) OR AB (near N4 patient* N4 determin*)	11
S9	TI (near N4 patient* N4 assess*) OR AB (near N4 patient* N4 assess*)	23
S10	TI (near N4 patient* N4 analys*) OR AB (near N4 patient* N4 analys*)	23
S11	TI (near N4 patient* N4 analyz*) OR AB (near N4 patient* N4 analyz*)	5
S12	TI (near N4 patient* N4 identif*) OR AB (near N4 patient* N4 identif*)	24
S13	TI (near N4 patient* N4 measur*) OR AB (near N4 patient* N4 measur*)	36

S14	TI (near N4 patient* N4 screen*) OR AB (near N4 patient* N4 screen*)	4
S15	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	31,354
S16	MH "Creatinine"	8,128
S17	TI creatinin* OR AB creatinin*	13,520
S18	TI serumcreatinin* OR AB serumcreatinin*	2
S19	TI SCr OR AB SCr	737
S20	S16 OR S17 OR S18 OR S19	17,758
S21	S15 AND S20	186
S22	MH "Kidney Function Tests"	2,679
S23	MH "Glomerular Filtration Rate"	8,043
S24	TI ((kidney* or renal) N3 (function* or dysfunction*)) OR AB ((kidney* or renal) N3 (function* or dysfunction*))	16,250
S25	TI glomerul* N1 filtration N1 rate* OR AB glomerul* N1 filtration N1 rate*	6,789
S26	TI glomerulofiltration N1 rate* OR AB glomerulofiltration N1 rate*	2
S27	TI GFR OR AB GFR	2,398
S28	TI eGFR OR AB eGFR	8,593
S29	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	30,731
S30	S15 AND S29	160
S31	S21 OR S30	289
S32	MH "Computers, Hand-Held"	3,826
S33	MH "Portable Equipment"	1,004
S34	TI ((handheld or "hand held") N2 (device* or analyser* or analyzer*)) OR AB ((handheld or "hand held") N2 (device* or analyser* or analyzer*))	629

S35 TI ((desktop or "desk top") N2 (device* or analyser* or analyzer*)) OR AB ((desktop or "desk top") N2 (device* or analyser* or analyzer*)) 36

S36 TI (("table top" or tabletop or "bench top" or benchtop) N2 (device* or analyser* or analyzer*)) OR AB (("table top" or tabletop or "bench top" or benchtop) N2 (device* or analyser* or analyzer*)) 36

S37 TI ((portab* or transportab*) N2 (device* or analyser* or analyzer*)) OR AB ((portab* or transportab*) N2 (device* or analyser* or analyzer*)) 870

S38 TI ((("near patient" or "near patients") N2 (device* or analyser* or analyzer*))) OR AB ((("near patient" or "near patients") N2 (device* or analyser* or analyzer*))) 6

S39 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 6,102

S40 S20 OR S29 41,597

S41 S39 AND S40 11

S42 S31 OR S41 296

S43 TI (i-STAT or iSTAT) OR AB (i-STAT or iSTAT) 92

S44 TI (StatSensor or Stat-Sensor) OR AB (StatSensor or Stat-Sensor) 3

S45 TI ABL90 FLEX PLUS OR AB ABL90 FLEX PLUS 0

S46 TI ((ABL800 FLEX or ABL800FLEX or ABL 800 FLEX)) OR AB ((ABL800 FLEX or ABL800FLEX or ABL 800 FLEX)) 7

S47 TI Dri-chem NX500 OR AB Dri-chem NX500 0

S48 TI epoc Blood Analysis OR AB epoc Blood Analysis 6

S49 TI Piccolo Xpress OR AB Piccolo Xpress 2

S50 S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 108

S51 S42 OR S50 398

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

N3 = terms within three words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 6th November 2018

Records retrieved: 4

The strategy below was used to search all 3 of the CRD databases - DARE, the HTA database and NHS EED. As the term near is a stopword in the CRD databases it cannot be used as a search term. Therefore lines 8-15 and line 38 of the MEDLINE strategy were omitted from the search of the CRD databases.

1 MeSH DESCRIPTOR Point-of-Care Systems 157

2 MeSH DESCRIPTOR Point-of-Care Testing 1

3 (point-of-care) 224

4 (POC or POCT)23

5 (rapid* NEAR3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) 370

6 ((test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*) NEAR3 rapid*) 128

7 ((bedside* or bed-side*) NEAR3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) 27

8 ((test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*) NEAR3 (bedside* or bed-side*)) 14

9 ((on-site or onsite) NEAR3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) 11

10 ((test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*) NEAR3 (on-site or onsite)) 6

11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 645

12 MeSH DESCRIPTOR Creatinine 114

13 (creatinin*) 499

14 (serumcreatinin*) 0

15 (SCr) 17

16 #12 OR #13 OR #14 OR #15 503

17 #11 AND #16 7

18 MeSH DESCRIPTOR Kidney Function Tests 53

19 MeSH DESCRIPTOR Glomerular Filtration Rate 92

20 ((kidney* or renal) NEAR3 (function* or dysfunction*)) OR ((function* or dysfunction*) NEAR3 (kidney* or renal)) 541

21 (glomerul* filtration rate*) 176

22 (glomerulofiltration rate*) 0

23 (GFR) OR (eGFR) 194

24 #18 OR #19 OR #20 OR #21 OR #22 OR #23 784

25 #11 AND #24 2

26 #17 OR #25 9

27 MeSH DESCRIPTOR Computers, Handheld 13

28 ((handheld or hand held) NEAR2 (device* or analyser* or analyzer*)) OR ((device* or analyser* or analyzer*) NEAR2 (handheld or hand held)) 19

29 ((desktop or desk top) NEAR2 (device* or analyser* or analyzer*)) OR ((device* or analyser* or analyzer*) NEAR2 (desktop or desk top)) 2

30 ((table top or tabletop or bench top or benchtop) NEAR2 (device* or analyser* or analyzer*)) OR ((device* or analyser* or analyzer*) NEAR2 (table top or tabletop or bench top or benchtop)) 0

31 ((portab* or transportab*) NEAR2 (device* or analyser* or analyzer*)) OR ((device* or analyser* or analyzer*) NEAR2 (portab* or transportab*)) 29

32 #27 OR #28 OR #29 OR #30 OR #31 59

33 #16 OR #24 1095

34 #32 AND #33 1

35 #26 OR #34 10

36 (i-STAT) OR (iSTAT) 3

37 (StatSensor) OR (Stat Sensor) 0

38 (ABL90 FLEX PLUS) 0

39 (ABL800 FLEX or ABL800FLEX or ABL 800 FLEX) 0

40 (Dri-chem NX500) 0

41 (epoc Blood Analysis) 0

42 (Piccolo Xpress) 0

43 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 13

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

NEAR3 = terms within three words of each other (order specified)

EconLit

via Ovid http://ovidsp.ovid.com/

1886 to November 1st 2018

Searched on: 6th November 2018

Records retrieved: 0

1 point-of-care.mp. (9)

2 (POC or POCT).mp. (14)

3 (rapid$ adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).mp. (319)

4 ((bedside$ or bed-side$) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).mp. (1)

5 ((on-site or onsite) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).mp. (28)

6 (near adj4 patient$ adj4 test$).mp. (2)

7 (near adj4 patient$ adj4 determin$).mp. (0)

8 (near adj4 patient$ adj4 assess$).mp. (0)

9 (near adj4 patient$ adj4 analys$).mp. (0)

10 (near adj4 patient$ adj4 analyz$).mp. (0)

11 (near adj4 patient$ adj4 identif$).mp. (0)

12 (near adj4 patient$ adj4 measur$).mp. (0)

13 (near adj4 patient$ adj4 screen$).mp. (0)

14 or/1-13 (369)

15 creatinin$.mp. (8)

16 serumcreatinin$.mp. (0)

17 SCr.mp. (53)

18 or/15-17 (61)

19 14 and 18 (0)

20 ((kidney$ or renal) adj3 (function$ or dysfunction$)).mp. (7)

21 glomerul$ filtration rate$.mp. (1)

22 glomerulofiltration rate$.mp. (0)

23 GFR.mp. (6)

24 eGFR.mp. (1)

25 or/20-24 (15)

26 14 and 25 (0)

27 19 or 26 (0)

28 ((handheld or hand held) adj2 (device$ or analyser$ or analyzer$)).mp. (16)

29 ((desktop or desk top) adj2 (device$ or analyser$ or analyzer$)).mp. (2)

30 ((table top or tabletop or bench top or benchtop) adj2 (device$ or analyser$ or analyzer$)).mp. (0)

31 ((portab$ or transportab$) adj2 (device$ or analyser$ or analyzer$)).mp. (8)

32 (near patient$ adj2 (device$ or analyser$ or analyzer$)).mp. (1)

33 or/28-32 (25)

34 18 or 25 (74)

35 33 and 34 (0)

36 27 or 35 (0)

37 (i-STAT or iSTAT).mp. (180)

38 34 and 37 (0)

39 (StatSensor or Stat Sensor).mp. (0)

40 ABL90 FLEX PLUS.mp. (0)

41 (ABL800 FLEX or ABL800FLEX or ABL 800 FLEX).mp. (0)

42 Dri-chem NX500.mp. (0)

43 epoc Blood Analysis.mp. (0)

44 Piccolo Xpress.mp. (0)

45 38 or 39 or 40 or 41 or 42 or 43 or 44 (0)

46 36 or 45 (0)

Key:

$ = truncation
mp = terms in either title, abstract, or heading word fields
adj3 = terms within three words of each other (any order)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2018 November 05

Searched on: 6th November 2018

Records retrieved: 1967

1 "point of care testing"/ (10679)

2 rapid test/ (3395)

3 point-of-care.ti,ab,kw. (22688)

4 (POC or POCT).ti,ab,kw. (7243)

5 (rapid$ adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (88530)

6 ((bedside$ or bed-side$) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (5676)

7 ((on-site or onsite) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).ti,ab. (3323)

8 (near adj4 patient adj4 test$).ti,ab. (596)

9 (near adj4 patient$ adj4 determin$).ti,ab. (33)

10 (near adj4 patient$ adj4 assess$).ti,ab. (68)

11 (near adj4 patient$ adj4 analys$).ti,ab. (74)

12 (near adj4 patient$ adj4 analyz$).ti,ab. (27)

13 (near adj4 patient$ adj4 identif$).ti,ab. (70)

14 (near adj4 patient$ adj4 measur$).ti,ab. (125)

15 (near adj4 patient$ adj4 screen$).ti,ab. (22)

16 or/1-15 (124452)

17 creatinine/ (156366)

18 creatinine blood level/ (97275)

19 creatinin$.ti,ab,kw. (164758)

20 serumcreatinin$.ti,ab,kw. (161)

21 SCr.ti,ab,kw. (10539)

22 or/17-21 (240268)

23 16 and 22 (1184)

24 kidney function test/ (10451)

25 exp glomerulus filtration rate/ (84857)

26 ((kidney$ or renal) adj3 (function$ or dysfunction$)).ti,ab. (179335)

27 glomerul$ filtration rate$.ti,ab,kw. (55656)

28 glomerulofiltration rate$.ti,ab,kw. (10)

29 GFR.ti,ab,kw. (33036)

30 eGFR.ti,ab,kw. (93375)

31 or/24-30 (315007)

32 16 and 31 (988)

33 23 or 32 (1837)

34 portable equipment/ (2209)

35 ((handheld or hand held) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (2365)

36 ((desktop or desk top) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (98)

37 ((table top or tabletop or bench top or benchtop) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (220)

38 ((portab$ or transportab$) adj2 (device$ or analyser$ or analyzer$)).ti,ab. (4155)

39 (near patient$ adj2 (device$ or analyser$ or analyzer$)).ti,ab. (45)

40 or/34-39 (8570)

41 22 or 31 (476117)

42 40 and 41 (98)

43 33 or 42 (1905)

44 (i-STAT or iSTAT).ti,ab,kw,dv. (923)

45 44 and 41 (79)

46 (StatSensor or Stat Sensor).ti,ab,kw,dv. (37)

47 ABL90 FLEX PLUS.ti,ab,kw,dv. (3)

48 (ABL800 FLEX or ABL800FLEX or ABL 800 FLEX).ti,ab,kw,dv. (106)

49 Dri-chem NX500.ti,ab,kw,dv. (0)

50 epoc Blood Analysis.ti,ab,kw,dv. (8)

51 Piccolo Xpress.ti,ab,kw,dv. (34)

52 or/45-51 (256)

53 43 or 52 (2077)

54 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5588968)

55 53 not 54 (1967)

Key:

/ = indexing term (Emtree heading)
exp = exploded indexing term (Emtree heading)
$ = truncation
ti,ab = terms in either title or abstract fields
kw = terms in the author keywords field
dv = terms in the device trade name field
adj3 = terms within three words of each other (any order)

Health Management Information Consortium (HMIC)
via Ovid http://ovidsp.ovid.com/

1979 to July 2018

Searched on: 6th November 2018

Records retrieved: 5

1 near patient tests/ (26)

2 point-of-care.mp. (225)

3 (POC or POCT).mp. (45)

4 (rapid$ adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).mp. (280)

5 ((bedside$ or bed-side$) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).mp. (23)

6 ((on-site or onsite) adj3 (test$ or determin$ or assess$ or analys$ or analyz$ or identif$ or measur$ or screen$)).mp. (32)

7 (near adj4 patient$ adj4 test$).mp. (63)

8 (near adj4 patient$ adj4 determin$).mp. (0)

9 (near adj4 patient$ adj4 assess$).mp. (3)

10 (near adj4 patient$ adj4 analys$).mp. (3)

11 (near adj4 patient$ adj4 analyz$).mp. (0)

12 (near adj4 patient$ adj4 identif$).mp. (2)

13 (near adj4 patient$ adj4 measur$).mp. (0)

14 (near adj4 patient$ adj4 screen$).mp. (1)

15 or/1-14 (605)

16 creatinine/ (3)

17 creatinin$.mp. (116)

18 serumcreatinin$.mp. (0)

19 SCr.mp. (22)

20 16 or 17 or 18 or 19 (138)

21 15 and 20 (3)

22 ((kidney$ or renal) adj3 (function$ or dysfunction$)).mp. (139)

23 glomerul$ filtration rate$.mp. (60)

24 glomerulofiltration rate$.mp. (0)

25 GFR.mp. (17)

26 eGFR.mp. (37)

27 22 or 23 or 24 or 25 or 26 (187)

28 15 and 27 (0)

29 portable equipment/ (74)

30 exp Portability/ (16)

31 ((handheld or hand held) adj2 (device$ or analyser$ or analyzer$)).mp. (16)

32 ((desktop or desk top) adj2 (device$ or analyser$ or analyzer$)).mp. (5)

33 ((table top or tabletop or bench top or benchtop) adj2 (device$ or analyser$ or analyzer$)).mp. (0)

34 ((portab$ or transportab$) adj2 (device$ or analyser$ or analyzer$)).mp. (19)

35 (near patient$ adj2 (device$ or analyser$ or analyzer$)).mp. (0)

36 29 or 30 or 31 or 32 or 33 or 34 or 35 (123)

37 20 or 27 (286)

38 36 and 37 (0)

39 21 or 28 or 38 (3)

40 (i-STAT or iSTAT).mp. (2)

41 (StatSensor or Stat Sensor).mp. (0)

42 ABL90 FLEX PLUS.mp. (0)

43 (ABL800 FLEX or ABL800FLEX or ABL 800 FLEX).mp. (0)

44 Dri-chem NX500.mp. (0)

45 epoc Blood Analysis.mp. (0)

46 Piccolo Xpress.mp. (0)

47 40 or 41 or 42 or 43 or 44 or 45 or 46 (2)

48 39 or 47 (5)

Key:

/ = subject heading search
$ = truncation
mp = terms in either title, abstract, heading word or other title fields
adj3 = terms within three words of each other (any order)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2018

Searched on: 6th November 2018

Records retrieved: 5

See above under DARE for search strategy used.

NHS Economic Evaluations Database (NHS EED)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 6th November 2018

Records retrieved: 4

See above under DARE for search strategy used.

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 5th November 2018

Records retrieved: 499

Search ((((((((((((("Creatinine"[Mesh:NoExp]) OR creatinin*[Title/Abstract]) OR serumcreatinin*[Title/Abstract]) OR SCr[Title/Abstract])) OR (((((((("Kidney Function Tests"[Mesh:NoExp]) OR "Glomerular Filtration Rate"[Mesh:NoExp]) OR (((kidney*[Title/Abstract] OR renal[Title/Abstract])) AND (function*[Title/Abstract] OR dysfunction*[Title/Abstract]))) OR glomerul* filtration rate*[Title/Abstract]) OR glomerulofiltration rate*[Title/Abstract]) OR GFR[Title/Abstract]) OR eGFR[Title/Abstract]))) AND ((((((((("Point-of-Care Systems"[Mesh]) OR "Point-of-Care Testing"[Mesh:NoExp]) OR point-of-care[Title/Abstract]) OR ((POC[Title/Abstract] OR POCT[Title/Abstract]))) OR ((rapid*[Title/Abstract]) AND (test[Title/Abstract] OR tests[Title/Abstract] OR testing[Title/Abstract] OR testings[Title/Abstract] OR tested[Title/Abstract] OR determin*[Title/Abstract] OR assess*[Title/Abstract] OR analys*[Title/Abstract] OR analyz*[Title/Abstract] OR identif*[Title/Abstract] OR measur*[Title/Abstract] OR screen*[Title/Abstract]))) OR (((bedside*[Title/Abstract] OR bed-side*[Title/Abstract])) AND (test[Title/Abstract] OR tests[Title/Abstract] OR testing[Title/Abstract] OR testings[Title/Abstract] OR tested[Title/Abstract] OR determin*[Title/Abstract] OR assess*[Title/Abstract] OR analys*[Title/Abstract] OR analyz*[Title/Abstract] OR identif*[Title/Abstract] OR measur*[Title/Abstract] OR screen*[Title/Abstract]))) OR (((on-site[Title/Abstract] OR onsite[Title/Abstract])) AND (test[Title/Abstract] OR tests[Title/Abstract] OR testing[Title/Abstract] OR testings[Title/Abstract] OR tested[Title/Abstract] OR determin*[Title/Abstract] OR assess*[Title/Abstract] OR analys*[Title/Abstract] OR analyz*[Title/Abstract] OR identif*[Title/Abstract] OR measur*[Title/Abstract] OR screen*[Title/Abstract]))) OR near patient*[Title/Abstract]))) OR ((((((((("Creatinine"[Mesh:NoExp]) OR creatinin*[Title/Abstract]) OR serumcreatinin*[Title/Abstract]) OR SCr[Title/Abstract])) OR (((((((("Kidney Function Tests"[Mesh:NoExp]) OR "Glomerular Filtration Rate"[Mesh:NoExp]) OR (((kidney*[Title/Abstract] OR renal[Title/Abstract])) AND (function*[Title/Abstract] OR dysfunction*[Title/Abstract]))) OR

glomerul* filtration rate*[Title/Abstract]) OR glomerulofiltration rate*[Title/Abstract]) OR GFR[Title/Abstract]) OR eGFR[Title/Abstract]))) AND (((((("Computers, Handheld"[Mesh:NoExp]) OR (((handheld[Title/Abstract] OR hand-held[Title/Abstract])) AND (device*[Title/Abstract] OR analyser*[Title/Abstract] OR analyzer*[Title/Abstract]))) OR (((desktop[Title/Abstract] OR desk-top[Title/Abstract])) AND (device*[Title/Abstract] OR analyser*[Title/Abstract] OR analyzer*[Title/Abstract]))) OR (((table-top[Title/Abstract] OR tabletop[Title/Abstract] OR bench-top[Title/Abstract] OR benchtop[Title/Abstract])) AND (device*[Title/Abstract] OR analyser*[Title/Abstract] OR analyzer*[Title/Abstract]))) OR (((portab*[Title/Abstract] OR transportab*[Title/Abstract])) AND (device*[Title/Abstract] OR analyser*[Title/Abstract] OR analyzer*[Title/Abstract])))))) OR ((((((((((i-STAT[Title/Abstract] OR iSTAT[Title/Abstract]))) AND ((((((("Creatinine"[Mesh:NoExp]) OR creatinin*[Title/Abstract]) OR serumcreatinin*[Title/Abstract]) OR SCr[Title/Abstract])) OR (((((((("Kidney Function Tests"[Mesh:NoExp]) OR "Glomerular Filtration Rate"[Mesh:NoExp]) OR (((kidney*[Title/Abstract] OR renal[Title/Abstract])) AND (function*[Title/Abstract] OR dysfunction*[Title/Abstract]))) OR glomerul* filtration rate*[Title/Abstract]) OR glomerulofiltration rate*[Title/Abstract]) OR GFR[Title/Abstract]) OR eGFR[Title/Abstract])))) OR ((StatSensor[Title/Abstract] OR Stat-Sensor))) OR ABL90 FLEX PLUS[Title/Abstract]) OR ((ABL800 FLEX[Title/Abstract] OR ABL800FLEX[Title/Abstract] OR ABL 800 FLEX[Title/Abstract]))) OR Dri-chem NX500[Title/Abstract]) OR epoc Blood Analysis[Title/Abstract]) OR Piccolo Xpress[Title/Abstract]))) NOT ((animals[mh] NOT humans[mh])))) AND ((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))

The above search strategy incorporates the following search line to limit to studies found in PubMed but not available in Ovid MEDLINE: (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) Reference: Duffy S, de Kock S, Misso K, Noake C, Ross J, Stirk L. Supplementary searches of PubMed to improve currency of MEDLINE and MEDLINE In-Process searches via Ovid. *J Med Libr Assoc* 2016;104:309-312.

Key:

[Mesh] = exploded indexing term (MeSH heading)
[Mesh:noexp] = indexing term (MeSH heading) not exploded
* = truncation

[Title/Abstract]) = terms in either title or abstract fields

Science Citation Index

via Web of Science, Clarivate Analytics https://clarivate.com/

1900 – 5th November 2018

Searched on: 6th November 2018

Records retrieved: 1011

34 1,011 #32 not #33

Indexes=SCI-EXPANDED Timespan=1900-2018

33 2,864,727 TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or cat or cats or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)

32 1,053 #31 OR #30 OR #28 OR #20 OR #16

31 75 TS=(StatSensor or Stat-Sensor or ABL90 FLEX PLUS or ABL800 FLEX or ABL800FLEX or ABL 800 FLEX or Dri-chem NX500 or epoc Blood Analysis or Piccolo Xpress)

30 26 #29 AND #27

29 455 TS=(i-STAT or iSTAT)

28 56 #27 AND #26

27 255,088#19 OR #15

26 10,534 #25 OR #24 OR #23 OR #22 OR #21

25 38 TS=(near-patient* NEAR/2 (device* or analyser* or analyzer*))

24 7,004 TS=((portab* or transportab*) NEAR/2 (device* or analyser* or analyzer*))

23 281 TS=((table-top or tabletop or bench-top or benchtop) NEAR/2 (device* or analyser* or analyzer*))

22 201 TS=((desktop or desk-top) NEAR/2 (device* or analyser* or analyzer*))

21 3,280 TS=((handheld or hand-held) NEAR/2 (device* or analyser* or analyzer*))

20 562 #19 AND #14

19 190,586#18 OR #17

18 93,612 TS=((glomerul* NEAR/1 filtration NEAR/1 rate*) OR (glomerulofiltration NEAR/1 rate*) OR GFR OR eGFR)

17 118,800TS=((kidney* or renal) NEAR/3 (function* or dysfunction*))

16 550 #15 AND #14

15 99,211 TS=(creatinin* or serumcreatinin* or SCr)

14 137,790#13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

13 22 TS=("near" NEAR/4 patient* NEAR/4 screen*)

12 110 TS=("near" NEAR/4 patient* NEAR/4 measur*)

11 53 TS=("near" NEAR/4 patient* NEAR/4 identif*)

10 20 TS=("near" NEAR/4 patient* NEAR/4 analyz*)

9 65 TS=("near" NEAR/4 patient* NEAR/4 analys*)

8 67 TS=("near" NEAR/4 patient* NEAR/4 assess*)

7 32 TS=("near" NEAR/4 patient* NEAR/4 determin*)

6 500 TS=("near" NEAR/4 patient* NEAR/4 test*)

5 5,961 TS=(("on-site" or "onsite") NEAR/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))

4 3,668 TS=((bedside* or bed-side*) NEAR/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))

3 109,855TS=(rapid* NEAR/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))

2 7,275 TS=(POC or POCT)

1 16,121 TS=(point-of-care)

Key:

TS = topic tag; searches terms in title, abstract, author keywords and keywords plus fields
TI = search in title field
* = truncation
" " = phrase search
NEAR/3 = terms within 3 words of each other (any order)

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 8th November 2018

Records retrieved: 103

1. 26 Studies found for: (creatinine OR serumcreatinine OR SCr) AND (point-of-care OR near patient)

2. 26 Studies found for: (kidney function OR renal function OR kidney dysfunction OR renal dysfunction) AND (point-of-care OR near patient)

3. 8 Studies found for: (glomerular filtration rate OR GFR OR eGFR) AND (point-of-care OR near patient)

4. 43 Studies found for: istat OR i-stat OR StatSensor OR Stat-Sensor OR ABL90 FLEX PLUS OR ABL800 FLEX OR ABL800FLEX OR ABL 800 FLEX OR Dri-chem NX500 OR epoc Blood Analysis OR Piccolo Xpress

Conference Proceedings Citation Index: Science

via Web of Science, Clarivate Analytics https://clarivate.com/

1990 – 5th November 2018

Searched on: 6th November 2018

Records retrieved: 78

34 78 #32 not #33

Indexes=CPCI-S Timespan=1900-2018

33 258,819TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or cat or cats or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)

32 80 #31 OR #30 OR #28 OR #20 OR #16

31 6 TS=(StatSensor or Stat-Sensor or ABL90 FLEX PLUS or ABL800 FLEX or ABL800FLEX or ABL 800 FLEX or Dri-chem NX500 or epoc Blood Analysis or Piccolo Xpress)

30 3 #29 AND #27

29 73 TS=(i-STAT or iSTAT)

28 4 #27 AND #26

27 28,719 #19 OR #15

26 8,738 #25 OR #24 OR #23 OR #22 OR #21

25 3 TS=(near-patient* NEAR/2 (device* or analyser* or analyzer*))

24 5,017 TS=((portab* or transportab*) NEAR/2 (device* or analyser* or analyzer*))

23 114 TS=((table-top or tabletop or bench-top or benchtop) NEAR/2 (device* or analyser* or analyzer*))

22 308 TS=((desktop or desk-top) NEAR/2 (device* or analyser* or analyzer*))

21 3,501 TS=((handheld or hand-held) NEAR/2 (device* or analyser* or analyzer*))

20 32 #19 AND #14

19 21,751 #18 OR #17

18 9,710 TS=((glomerul* NEAR/1 filtration NEAR/1 rate*) OR (glomerulofiltration NEAR/1 rate*) OR GFR OR eGFR)

17 13,364 TS=((kidney* or renal) NEAR/3 (function* or dysfunction*))

16 53 #15 AND #14

15 9,631 TS=(creatinin* or serumcreatinin* or SCr)

14 20,101 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

13 5 TS=("near" NEAR/4 patient* NEAR/4 screen*)

12 16 TS=("near" NEAR/4 patient* NEAR/4 measur*)

11 8 TS=("near" NEAR/4 patient* NEAR/4 identif*)

10 5 TS=("near" NEAR/4 patient* NEAR/4 analyz*)

9 6 TS=("near" NEAR/4 patient* NEAR/4 analys*)

8 8 TS=("near" NEAR/4 patient* NEAR/4 assess*)

7 3 TS=("near" NEAR/4 patient* NEAR/4 determin*)

6 42 TS=("near" NEAR/4 patient* NEAR/4 test*)

5 2,391 TS=(("on-site" or "onsite") NEAR/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))

4 356 TS=((bedside* or bed-side*) NEAR/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))

3 13,933 TS=(rapid* NEAR/3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*))

2 1,280 TS=(POC or POCT)

1 2,689 TS=(point-of-care)

Key:

TS = topic tag; searches terms in title, abstract, author keywords and keywords plus fields
TI = search in title field
* = truncation
" " = phrase search
NEAR/3 = terms within 3 words of each other (any order)

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 7th November 2018

Records retrieved: 15

1. 4 result(s) found for: (creatinine OR serumcreatinine) AND ("point of care" OR point-of-care OR "near patient")

2. 2 result(s) found for: ("kidney function" OR "renal function" OR "kidney dysfunction" OR "renal dysfunction") AND ("point of care" OR point-of-care OR "near patient")

3. 3 result(s) found for: ("glomerular filtration rate" OR "glomerulofiltration rate" OR GFR OR eGFR) AND ("point of care" OR point-of-care OR "near patient")

4. 6 result(s) found for: istat OR i-stat OR "i stat" OR StatSensor OR Stat-Sensor OR "Stat Sensor" OR "ABL90 FLEX PLUS"

5. 0 results found for "ABL800 FLEX" OR ABL800FLEX OR "ABL 800 FLEX" OR "Dri-chem NX500"

6. 0 results found for "epoc Blood Analysis" OR "Piccolo Xpress"

Open Access Theses and Dissertations

https://oatd.org/

Searched on: 8th November 2018

Records retrieved: 36

1. (creatinine OR serumcreatinine OR SCr) AND ("point of care") = 15 hits

2. (creatinine OR serumcreatinine OR SCr) AND ("near patient") = 0 hits

3. ("kidney function" OR "renal function" OR "kidney dysfunction" OR "renal dysfunction") AND ("point of care" OR "near patient") = 11 hits

4. ("glomerular filtration rate" OR GFR OR eGFR) AND ("point of care" OR "near patient") = 2 hits

5. (istat OR "i-stat") AND (creatinine OR serumcreatinine OR SCr OR "glomerular filtration rate" OR GFR OR eGFR) = 2 hits

6. StatSensor OR "Stat-Sensor" OR "ABL90 Flex Plus" OR "ABL800 FLEX" OR "ABL800FLEX" OR "ABL 800 FLEX" OR "Dri-chem NX500" OR "epoc Blood analysis" OR "Piccolo Xpress" = 6 hits

Proquest Dissertations & Theses A&I

via Proquest https://www.proquest.com/

Searched on: 6th November 2018

Records retrieved: 68

1. (TI,AB,IF(point-of-care) OR TI,AB,IF(POC OR POCT)) AND (TI,AB,IF(creatinin* OR serumcreatinin* OR SCr) OR TI,AB,IF((kidney* OR renal) NEAR/3 (function* OR dysfunction*)) OR TI,AB,IF(glomerul* filtration rate*) OR TI,AB,IF(glomerulofiltration rate*) OR TI,AB,IF(GFR OR eGFR))

15 results

2. (TI,AB,IF(rapid* NEAR/3 (test* OR determin* OR assess* OR analys* OR analyz* OR identif* OR measur* OR screen*)) OR TI,AB,IF((bedside* OR bed-side*) NEAR/3 (test* OR determin* OR assess* OR analys* OR analyz* OR identif* OR measur* OR screen*))) AND (TI,AB,IF(creatinin* OR serumcreatinin* OR SCr) OR TI,AB,IF((kidney* OR renal) NEAR/3 (function* OR dysfunction*)) OR TI,AB,IF(glomerul* filtration rate*) OR TI,AB,IF(glomerulofiltration rate*) OR TI,AB,IF(GFR OR eGFR))

29 results

3. TI,AB,IF((on-site OR onsite) NEAR/3 (test* OR determin* OR assess* OR analys* OR analyz* OR identif* OR measur* OR screen*)) AND (TI,AB,IF(creatinin* OR serumcreatinin* OR SCr) OR TI,AB,IF((kidney* OR renal) NEAR/3 (function* OR dysfunction*)) OR TI,AB,IF(glomerul* filtration rate*) OR TI,AB,IF(glomerulofiltration rate*) OR TI,AB,IF(GFR OR eGFR))

3 results

4. (TI,AB,IF("near" NEAR/4 patient* NEAR/4 test*) OR TI,AB,IF("near" NEAR/4 patient* NEAR/4 determin*) OR TI,AB,IF("near" NEAR/4 patient* NEAR/4 assess*) OR TI,AB,IF("near" NEAR/4 patient* NEAR/4 analys*) OR TI,AB,IF("near" NEAR/4 patient* NEAR/4 analyz*) OR TI,AB,IF("near" NEAR/4 patient* NEAR/4 identif*) OR TI,AB,IF("near" NEAR/4 patient* NEAR/4 measur*) OR TI,AB,IF("near" NEAR/4 patient* NEAR/4 screen*)) AND (TI,AB,IF(creatinin* OR serumcreatinin* OR SCr) OR TI,AB,IF((kidney* OR renal) NEAR/3 (function* OR dysfunction*)) OR TI,AB,IF(glomerul* filtration rate*) OR TI,AB,IF(glomerulofiltration rate*) OR TI,AB,IF(GFR OR eGFR))

3 results

5. ((TI,AB,IF(creatinin* OR serumcreatinin* OR SCr) OR TI,AB,IF((kidney* OR renal) NEAR/3 (function* OR dysfunction*)) OR TI,AB,IF(glomerul* filtration rate*) OR TI,AB,IF(glomerulofiltration rate*) OR TI,AB,IF(GFR OR eGFR)) AND (TI,AB,IF((handheld OR hand-held) NEAR/2 (device* OR analyser* OR analyzer*)) OR TI,AB,IF((desktop OR desk-top) NEAR/2 (device* OR analyser* OR analyzer*)) OR TI,AB,IF((table-top OR tabletop OR bench-top OR benchtop) NEAR/2 (device* OR analyser* OR analyzer*)) OR TI,AB,IF((portab* OR transportab*) NEAR/2 (device* OR analyser* OR analyzer*)) OR TI,AB,IF(("near patient" OR "near patients") NEAR/2 (device* OR analyser* OR analyzer*)))) OR TI,AB,IF(i-STAT OR iSTAT OR StatSensor OR Stat-Sensor OR ABL90 FLEX PLUS OR ABL800 FLEX OR ABL800FLEX OR ABL 800 FLEX OR Dri-chem NX500 OR epoc Blood Analysis OR Piccolo Xpress)

18 results

PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

Searched on: 6th November 2018

Records retrieved: 13

#1 MeSH DESCRIPTOR Point-of-Care Systems 41

#2 MeSH DESCRIPTOR Point-of-Care Testing 14

#3 point-of-care 171

#4 POC or POCT 51

#5 rapid* adj3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*) 210

#6 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*) adj3 rapid* 88

#7 ((bedside* or bed-side*) adj3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) 32

#8 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*) adj3 ((bedside* or bed-side*)) 15

#9 ((on-site or onsite) adj3 (test* or determin* or assess* or analys* or analyz* or identif* or measur* or screen*)) 8

#10 "near" adj4 patient* adj4 test* 5

#11 "near" adj4 patient* adj4 determin* 0

#12 "near" adj4 patient* adj4 assess* 0

#13 "near" adj4 patient* adj4 analys* 0

#14 "near" adj4 patient* adj4 analyz* 0

#15 "near" adj4 patient* adj4 identif* 0

#16 "near" adj4 patient* adj4 measur* 0

#17 "near" adj4 patient* adj4 screen* 0

#18 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 432

#19 MeSH DESCRIPTOR Creatinine 12

#20 creatinin* 452

#21 serumcreatinin* 0

#22 SCr 54

#23 #19 OR #20 OR #21 OR #22 480

#24 #18 AND #23 5

#25 MeSH DESCRIPTOR Kidney Function Tests 4

#26 MeSH DESCRIPTOR Glomerular Filtration Rate 10

#27 ((kidney* or renal) adj3 (function* or dysfunction*)) 536

#28 glomerul* filtration rate* 192

#29 glomerulofiltration rate* 0

#30 GFR 167

#31 eGFR 246

#32 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 786

#33 #32 AND #18 7

#34 #24 OR #33 12

#35 MeSH DESCRIPTOR Computers, Handheld 8

#36 ((handheld or hand held) NEAR2 (device* or analyser* or analyzer*)) 40

#37 ((device* or analyser* or analyzer*) NEAR2 (handheld or hand held)) 3

#38 ((handheld or hand held) adj2 (device* or analyser* or analyzer*)) 40

#39 ((device* or analyser* or analyzer*) adj2 (handheld or hand held)) 3

#40 ((desktop or desk top) adj2 (device* or analyser* or analyzer*)) 0

#41 ((device* or analyser* or analyzer*) adj2 (desktop or desk top)) 2

#42 ((table top or tabletop or bench top or benchtop) adj2 (device* or analyser* or analyzer*))1

#43 ((device* or analyser* or analyzer*) adj2 (table top or tabletop or bench top or benchtop))0

#44 ((portab* or transportab*) adj2 (device* or analyser* or analyzer*)) 40

#45 ((device* or analyser* or analyzer*) adj2 (portab* or transportab*)) 3

#46 ((device* or analyser* or analyzer*) adj2 ("near" patient*)) 0

#47 (("near" patient*) adj2 (device* or analyser* or analyzer*)) 0

#48 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 82

#49 ((function* or dysfunction*) adj3 (kidney* or renal)) 107

#50 #32 OR #49 808

#51 #18 AND #50 7

#52 #50 OR #23 1002

#53 #52 AND #48 1

#54 #24 OR #51 OR #53 13

#55 i-STAT or iSTAT 1

#56 StatSensor or Stat Sensor 0

#57 ABL90 FLEX PLUS 0

#58 ABL800 FLEX or ABL800FLEX or ABL 800 FLEX 0

#59	Dri-chem NX500	0
#60	epoc Blood Analysis	0
#61	Piccolo Xpress	0
#62	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61	13

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)
* = truncation
adj3 = terms within 3 words of each other (order specified)

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 8th November 2018

Records retrieved: 28

1. 6 records for 6 trials found for: creatinine AND point of care

2. No results were found for: creatinine AND near patient

3. No results were found for: serumcreatinine AND point of care

4. No results were found for: serumcreatinine AND near patient

5. No results were found for: SCr AND point of care

6. No results were found for: SCr AND near patient

7. 2 records for 2 trials found for: kidney function AND point of care

8. 1 trial found for: kidney function AND near patient

9. 2 records for 2 trials found for: renal function AND point of care

10. 1 trial found for: renal function AND near patient

11. No results were found for: kidney dysfunction AND point of care

12. No results were found for: kidney dysfunction AND near patient

13. No results were found for: glomerular filtration rate AND point of care

14. No results were found for: glomerular filtration rate AND near patient

15. No results were found for: glomerulofiltration rate AND point of care

16. No results were found for: glomerulofiltration rate AND near patient

17. No results were found for: GFR AND point of care

18. No results were found for: GFR AND near patient

19. No results were found for: eGFR AND point of care

20. No results were found for: eGFR AND near patient

21. 17 records for 16 trials found for: istat OR i-stat OR StatSensor OR Stat-Sensor OR ABL90 FLEX PLUS OR ABL800 FLEX OR ABL800FLEX OR ABL 800 FLEX OR Dri-chem NX500 OR epoc Blood Analysis OR Piccolo Xpress

Search for review evidence on the risk of AKI from contrast agents following CT scans

Database: Ovid MEDLINE(R) ALL <1946 to November 27, 2018>

28/11/2018

1 exp Acute Kidney Injury/ (42013)

2 (acute adj2 (renal or kidney) adj2 (fail$ or injur$ or insufficien$)).ti,ab. (41624)

3 ((acute or renal or kidney) adj2 tubular necrosis).ti,ab. (3611)

4 or/1-3 (60170)

5 tomography, x-ray computed/ or colonography, computed tomographic/ or four-dimensional computed tomography/ or positron emission tomography computed tomography/ or single photon emission computed tomography computed tomography/ or tomography, spiral computed/ or multidetector computed tomography/ (374663)

6 ((compute$ adj2 tomograph$) or tomodensitometry or cine-CT).ti,ab. (268668)

7 ((CT or CAT) adj2 (scan$ or imag$)).ti,ab. (118123)

8 ((CT or CAT) adj2 contrast).ti,ab. (8124)

9 (cross-sectional adj2 (scan$ or imag$)).ti,ab. (6368)

10 ((emission or positron or proton) adj2 tomograph$).ti,ab. (68380)

11 (PET or PET-CT$ or PET?CT$ or CT-PET$ or CT?PET$).ti,ab. (85352)

12 (SPECT or SPECT-CT$ or SPECT?CT$ or CT-SPECT$ or CT?SPECT$).ti,ab. (26355)

13 (SPET or SPET-CT$ or SPET?CT$ or CT-SPET$ or CT?SPET$).ti,ab. (1327)

14 or/5-13 (624723)

15 exp Administration, Intravenous/ (137931)

16 (intravenous or IV).ti,ab. (609985)

17 15 or 16 (670695)

18 4 and 14 and 17 (223)

19 (contrast induced adj (AKI or acute kidney injury or nephropathy or tubular necrosis)).ti,ab. (2295)

20 (radiocontrast induced adj (AKI or acute kidney injury or nephropathy or tubular necrosis)).ti,ab. (115)

21 ((postcontrast or post-contrast) adj (AKI or acute kidney injury or nephropathy or tubular necrosis)).ti,ab. (22)

22 ((contrast or radiocontrast) adj nephropathy).ti,ab. (376)

23 (CI-AKI or CIAKI or PC-AKI).ti,ab. (403)

24 or/19-23 (2730)

25 14 and 24 (326)

26 18 or 25 (488)

27 exp animals/ not humans/ (4519266)

28 26 not 27 (480)

29 limit 28 to yr="2012 -Current" (291)

11.2 Modelling collapsed category data

Studies reporting only on collapsed categories were assumed to provide information on a function of the probabilities of interest. This function varied depending on which categories were collapsed, with relationships were determined using conditional partitioning of probabilities:

$$\Pr(B \mid C) = \Pr(A_1 \mid C)\Pr(B \mid A_1, C) + \Pr(A_2 \mid C)\Pr(B \mid A_2, C) \quad (3)$$

where C is the true reported category, which is collapsed over (i.e. contains) categories A_1 and A_2 from Table 2, and B is the category estimated by the POC device. Note also that since A_1 and A_2 are contained in C, we can simplify equation (3) to

$$\Pr(B \mid C) = \Pr(A_1 \mid C)\Pr(B \mid A_1) + \Pr(A_2 \mid C)\Pr(B \mid A_2) \quad (4)$$

For each value of B, A_1 and A_2, $\Pr(B \mid A_1)$ and $\Pr(B \mid A_2)$ can be expressed in terms of the probabilities of interest, p_{jk}.

We also needed to calculate $\Pr(A_1 \mid C)$ and $\Pr(A_2 \mid C)$, that is the conditional probabilities of an individual belonging to true eGFR categories A_1 and A_2, given that they belong to the joint category C. We separately estimated T_j, the probability that an individual included in a study in the synthesis, has true eGFR in category j, and these were used to calculate the conditional true probabilities as

$$\Pr(A_j \mid C) = \frac{T_j}{T_1 + T_2} \quad , \quad j = 1, 2 \quad (5)$$

The number of individuals classified by POC device as belonging to the collapsed eGFR category, given their true collapsed eGFR category (determined by the lab), were also assumed to follow a multinomial distribution with dimensions depending on the number of categories reported and probabilities written in terms of p_{jk}, using equation (4). For an example see Section 11.2.2.

Equations (4) and (5) can also be extended to collapsing over more than 2 consecutive categories, when necessary.

11.2.1 Model for the probability that an individual has true eGFR in each category

All included studies were used to estimate the probability that an individual has true eGFR (as measured by the lab) in each of the 4 categories of interest (Table 2).

Let y_{ij} be the number of individuals in study i with true eGFR in category j, assumed to follow a multinomial distribution

$$\left(y_{i1}, y_{i2}, y_{i3}, y_{i4}\right) \sim \text{Multinomial}\left(\left(T_1, T_2, T_3, T_4\right), N_i\right) \tag{6}$$

with N_i defining the total number of individuals in study i, and T_j the probabilities that an individual has true eGFR in category j.

The model was estimated in a Bayesian framework using Markov chain Monte Carlo in OpenBUGS (version 3.2.3)[19, 20] where the probabilities were given a non-informative Dirichlet prior distribution with equal probabilities in each category:

$$\left(T_1, T_2, T_3, T_4\right) \sim \text{Dirichlet}\left(1,1,1,1\right) \tag{7}$$

Studies reporting on collapsed categories contributed to the corresponding sum of probabilities T_j. The number of individuals in the collapsed categories were assumed to follow a multinomial distribution with an appropriate number of dimensions and probabilities written as functions of T_j.

11.2.2 Example likelihood and probability calculations for collapsed data

Shephard 2010[34] reported the number of patients in classified as having eGFR < 30, eGFR 30-59 and eGFR ≥ 60 30mLs/min/1.73 m^2 by the lab and StatSensor POC device (Table 8).

The number of individuals classified by the POC device as belonging to each eGFR category, given true eGFR category $j = 1, 2, 3$, $r^*_{j1}, r^*_{j2}, r^*_{j3}$, were assumed to follow a multinomial distribution:

$$\left(r^*_{j1}, r^*_{j2}, r^*_{j3}\right) \sim \text{Multinomial}\left(\left(p^*_{j1}, p^*_{j2}, p^*_{j3}\right), n_j\right) \tag{8}$$

with n_j defining the number of individuals with true eGFR in category j in this study. The probabilities p^*_{jk} were written as function of the probabilities of interest p_{jk}, according to equation (4) by writing

$$\begin{aligned} C &= \text{true eGFR 30-59} \\ A_1 &= \text{true eGFR 30-44} \\ A_2 &= \text{true eGFR 45-59} \end{aligned} \tag{9}$$

Thus letting $B = \text{POC eGFR} < 30$ we can write

$$
\begin{aligned}
p^{*}_{11} &= \Pr(\text{POC eGFR} < 30 \mid \text{true eGFR} < 30) &&= p_{11} \\
p^{*}_{12} &= \Pr(\text{POC eGFR 30-59} \mid \text{true eGFR} < 30) &&= p_{12} + p_{13} \\
p^{*}_{13} &= \Pr(\text{POC eGFR} \geq 60 \mid \text{true eGFR} < 30) &&= p_{14}
\end{aligned}
\tag{10}
$$

letting $B = \text{POC eGFR } 30-59$ and noting that

$$
\begin{aligned}
\Pr(\text{true eGFR 30-44} \mid \text{true eGFR 30-59}) &= \frac{\Pr(\text{true eGFR 30-44})}{\Pr(\text{true eGFR 30-59})} = \frac{T_2}{T_2 + T_3} \\
\Pr(\text{true eGFR 45-59} \mid \text{true eGFR 30-59}) &= \frac{\Pr(\text{true eGFR 30-44})}{\Pr(\text{true eGFR 30-59})} = \frac{T_3}{T_2 + T_3}
\end{aligned}
\tag{11}
$$

we can write

$$
\begin{aligned}
p^{*}_{21} &= \Pr(\text{POC eGFR} < 30 \mid \text{true eGFR 30-59}) &&= p_{21}\frac{T_2}{T_2 + T_3} + p_{31}\frac{T_3}{T_2 + T_3} \\
p^{*}_{22} &= \Pr(\text{POC eGFR 30-59} \mid \text{true eGFR 30-59}) &&= (p_{22} + p_{23})\frac{T_2}{T_2 + T_3} + (p_{32} + p_{33})\frac{T_3}{T_2 + T_3} \\
p^{*}_{23} &= \Pr(\text{POC eGFR} \geq 60 \mid \text{true eGFR 30-59}) &&= p_{24}\frac{T_2}{T_2 + T_3} + p_{34}\frac{T_3}{T_2 + T_3}
\end{aligned}
$$

(12)

and letting $B = \text{POC eGFR } \geq 60$ we can write

$$
\begin{aligned}
p^{*}_{31} &= \Pr(\text{POC eGFR} < 30 \mid \text{true eGFR} \geq 60) &&= p_{41} \\
p^{*}_{32} &= \Pr(\text{POC eGFR 30-59} \mid \text{true eGFR} \geq 60) &&= p_{42} + p_{43} \\
p^{*}_{33} &= \Pr(\text{POC eGFR} \geq 60 \mid \text{true eGFR} \geq 60) &&= p_{44}
\end{aligned}
\tag{13}
$$

Thus linking all the probabilities with data available with the probabilities of interest.

11.3 OpenBUGS code for analyses

11.3.1 StatSensor main analysis (includes calculation of probability of true eGFR in each category)

```
model{
# T = probability of true eGFR belonging to each category
#
# All categories
for (i in 1:ny){                    # loop through studies with all categories
  y[i,1:4] ~ dmulti(T[], N[i])
  # calculate residual deviance
  for (m in 1:4){                   # loop through all reported thresholds
    yhat[i,m] <-  T[m] * N[i]       # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)     # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
```

```
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,])       # summed residual deviance contribution for this
study
 }
totresdevT <- sum(yresdev[])       # Total Residual Deviance
T[1:4] ~ ddirch(omega[])           # prior distribution for T (WinBUGS compatible)
for (j in 1:4){                    # loop through all categories
  omega[j] <- 1                    # Dirichlet parameter (non-inf)
 }
# type A data: 0-30; 30-60; >60
for (i in (ny+1):(ny+nyA)){        # loop through studies with type A data
  y[i,1:3] ~ dmulti(TA[], N[i])
  # calculate residual deviance
  for (m in 1:3){                  # loop through all reported thresholds
    yhat[i,m] <-  TA[m] * N[i]     # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)    # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,1:3])    # summed residual deviance contribution for this
study
 }
# link probabilities
TA[1] <- T[1]                      # type A: true < 30
TA[2] <- T[2] + T[3]               # type A: 30 < true < 60
TA[3] <- T[4]                      # type A: true > 60
#
# type C data: 0-30; 30-45; >45
for (i in (ny+nyA+1):(ny+nyA+nyC)){ # loop through studies with type C data
  y[i,1:3] ~ dmulti(TC[], N[i])
  # calculate residual deviance
  for (m in 1:3){                  # loop through all reported thresholds
    yhat[i,m] <-  TC[m] * N[i]     # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)    # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,1:3])    # summed residual deviance contribution for this
study
 }
# link probabilities
TC[1] <- T[1]                      # type C: true < 30
TC[2] <- T[2]                      # type C: 30 < true < 45
TC[3] <- T[3] + T[4]               # type C: true > 45
#
# type E data: 0-60; >60
for (i in (ny+nyA+nyC+1):(ny+nyA+nyC+nyE)){  # loop through studies with type E
data
  y[i,1] ~ dbin(TE[1], N[i])
  # Deviance contribution
  yhat[i,1] <- TE[1] * N[i]        # expected value of the numerators
  y1[i,1] <- max(y[i,1], 0.1)      # correction for zero cell
  yhat1[i,1] <- max(yhat[i,1], 0.1) # correction for p=0
  # Deviance contribution when non-zero cell (allows p=0)
  ydev1[i,1] <- 2 * (y1[i,1]*(log(y1[i,1])-log(yhat1[i,1]))
             +(N[i]-y1[i,1])*(log(N[i]-y1[i,1])
               - log(N[i]-yhat1[i,1])))
  # Deviance contribution when zero cell (allows p=0)
  ydev0[i,1] <- 2*N[i]*log(N[i]/(N[i]-yhat[i,1]))
  # Calculate deviance contribution
  yresdev[i] <- ydev1[i,1]*(1-equals(y[i,1],0)) + ydev0[i,1]*equals(y[i,1],0)
```

```
 }
# link probabilities
TE[1] <- T[1] + T[2] + T[3]          # type E: true < 60
TE[2] <- T[4]                        # type E:  true > 60
#
# type F data: 0-30; >30
for (i in (ny+nyA+nyC+nyE+1):(ny+nyA+nyC+nyE+nyF)){ # loop through studies with
type F data
  y[i,1] ~ dbin(TF[1], N[i])
  # Deviance contribution
  yhat[i,1] <- TF[1] * N[i]          # expected value of the numerators
  y1[i,1] <- max(y[i,1], 0.1)        # correction for zero cell
  yhat1[i,1] <- max(yhat[i,1], 0.1) # correction for p=0
  # Deviance contribution when non-zero cell (allows p=0)
  ydev1[i,1] <- 2 * (y1[i,1]*(log(y1[i,1])-log(yhat1[i,1]))
             +(N[i]-y1[i,1])*(log(N[i]-y1[i,1])
               - log(N[i]-yhat1[i,1])))
  # Deviance contribution when zero cell (allows p=0)
  ydev0[i,1] <- 2*N[i]*log(N[i]/(N[i]-yhat[i,1]))
  # Calculate deviance contribution
  yresdev[i] <- ydev1[i,1]*(1-equals(y[i,1],0)) + ydev0[i,1]*equals(y[i,1],0)
 }
# link probabilities
TF[1] <- T[1]                        # type F: true < 30
TF[2] <- T[2] + T[3] + T[4]          # type F:  true > 30
#
# p[j,m]: probability of being in true category j and POC category m
#
# All categories
for (i in 1:ns){                     # loop through studies with all categories
  for (j in 1:4){                   # loop through all categories
    r[i,j,1:4] ~ dmulti(p[j,], n[i,j])
    # calculate residual deviance
    for (m in 1:4){                 # loop through all reported thresholds
      # predicted number events
      rhat[i,j,m] <-  p[j,m] * n[i,j]
      r1[i,j,m] <- max(r[i,j,m], 0.1) # correction for zero cell
      rhat1[i,j,m] <- max(rhat[i,j,m], 0.1) # correction for p=0
      # Deviance contribution when non-zero cell (allows p=0)
      dv1[i,j,m] <- 2*r1[i,j,m]*(log(r1[i,j,m])-log(rhat1[i,j,m]))
      # Calculate deviance contribution, when zero cell=zero
      dv[i,j,m] <- dv1[i,j,m]*(1-equals(r[i,j,m],0))
#      dv[i,j,m] <- 2*r[i,j,m]*(log(r[i,j,m])-log(rhat[i,j,m]))
     }
    dev[i,j] <- sum(dv[i,j,])
   }
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:4])
 }
totresdev <- sum(resdev[])           # Total Residual Deviance
for (j in 1:4){                      # loop through all categories
  p[j,1:4] ~ ddirch(alpha[])         # prior distribution for p (WinBUGS compatible)
  alpha[j] <- 1                      # Dirichlet parameter (non-inf)
 }
#
# type A data: 0-30; 30-60; >60
for (i in (ns+1):(ns+nsA)){          # loop through studies with type A data
  for (j in 1:3){                   # loop through all categories
    r[i,j,1:3] ~ dmulti(pA[j,], n[i,j])
    # calculate residual deviance
    for (m in 1:3){                 # loop through all reported thresholds
      # predicted number events
      rhat[i,j,m] <-  pA[j,m] * n[i,j]
      r1[i,j,m] <- max(r[i,j,m], 0.1) # correction for zero cell
      rhat1[i,j,m] <- max(rhat[i,j,m], 0.1) # correction for p=0
      # Deviance contribution when non-zero cell (allows p=0)
      dv1[i,j,m] <- 2*r1[i,j,m]*(log(r1[i,j,m])-log(rhat1[i,j,m]))
      # Calculate deviance contribution, when zero cell=zero
```

```
      dv[i,j,m] <- dv1[i,j,m]*(1-equals(r[i,j,m],0))
#       dv[i,j,m] <- 2*r[i,j,m]*(log(r[i,j,m])-log(rhat[i,j,m]))
      }
    dev[i,j] <- sum(dv[i,j,1:3])
   }
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:3])
 }
# link probabilities
# type A: true < 30
pA[1,1] <- p[1,1]                  # POC <30
pA[1,2] <- p[1,2] + p[1,3]         # 30 < POC < 60
pA[1,3] <- p[1,4]                  # POC >60
# type A: 30 < true < 60
sumA <- T[2]+T[3]
pA[2,1] <- p[2,1]*T[2]/sumA + p[3,1]*T[3]/sumA  # POC <30
pA[2,2] <- (p[2,2]+p[2,3])*T[2]/sumA + (p[3,2]+p[3,3])*T[3]/sumA # 30 < POC < 60
pA[2,3] <- p[2,4]*T[2]/sumA + p[3,4]*T[3]/sumA  # POC >60
# type A: true > 60
pA[3,1] <- p[4,1]                  # POC <30
pA[3,2] <- p[4,2] + p[4,3]         # 30 < POC < 60
pA[3,3] <- p[4,4]                  # POC >60
#
# type C data: 0-30; 30-45; >45
for (i in (ns+nsA+1):(ns+nsA+nsC)){ # loop through studies with type C data
  for (j in 1:3){                  # loop through all categories
    r[i,j,1:3] ~ dmulti(pC[j,], n[i,j])
    # calculate residual deviance
    for (m in 1:3){                # loop through all reported thresholds
      # predicted number events
      rhat[i,j,m] <-  pC[j,m] * n[i,j]
      r1[i,j,m] <- max(r[i,j,m], 0.1) # correction for zero cell
      rhat1[i,j,m] <- max(rhat[i,j,m], 0.1) # correction for p=0
      # Deviance contribution when non-zero cell (allows p=0)
      dv1[i,j,m] <- 2*r1[i,j,m]*(log(r1[i,j,m])-log(rhat1[i,j,m]))
      # Calculate deviance contribution, when zero cell=zero
      dv[i,j,m] <- dv1[i,j,m]*(1-equals(r[i,j,m],0))
#       dv[i,j,m] <- 2*r[i,j,m]*(log(r[i,j,m])-log(rhat[i,j,m]))
      }
    dev[i,j] <- sum(dv[i,j,1:3])
   }
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:3])
 }
# link probabilities
# type C: true < 30
pC[1,1] <- p[1,1]                  # POC <30
pC[1,2] <- p[1,2]                  # 30 < POC < 45
pC[1,3] <- p[1,3] + p[1,4]         # POC >45
# type C: 30 < true < 45
pC[2,1] <- p[2,1]                  # POC <30
pC[2,2] <- p[2,2]                  # 30 < POC < 45
pC[2,3] <- p[2,3] + p[2,4]         # POC >45
# type C: true > 45
sumC <- T[3]+T[4]
pC[3,1] <- p[3,1]*T[3]/sumC + p[4,1]*T[4]/sumC  # POC <30
pC[3,2] <- p[3,2]*T[3]/sumC + p[4,2]*T[4]/sumC  # 30 < POC < 45
pC[3,3] <- (p[3,3]+p[3,4])*T[3]/sumC + (p[4,3]+p[4,4])*T[4]/sumC # POC >45
#
# type E data: 0-60; >60
for (i in (ns+nsA+nsC+1):(ns+nsA+nsC+nsE)){ # loop through studies with type E data
  for (j in 1:2){                  # loop through all categories
    r[i,j,1] ~ dbin(pE[j,1], n[i,j])
    # Deviance contribution
    rhat[i,j,1] <- pE[j,1] * n[i,j] # expected value of the numerators
    r1[i,j,1] <- max(r[i,j,1], 0.1) # correction for zero cell
    rhat1[i,j,1] <- max(rhat[i,j,1], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
```

```
    dev1[i,j,1] <- 2 * (r1[i,j,1]*(log(r1[i,j,1])-log(rhat1[i,j,1]))
             +(n[i,j]-r1[i,j,1])*(log(n[i,j]-r1[i,j,1])
               - log(n[i,j]-rhat1[i,j,1])))
    # Deviance contribution when zero cell (allows p=0)
    dev0[i,j,1] <- 2*n[i,j]*log(n[i,j]/(n[i,j]-rhat[i,j,1]))
    # Calculate deviance contribution
    dev[i,j] <- dev1[i,j,1]*(1-equals(r[i,j,1],0)) + dev0[i,j,1]*equals(r[i,j,1],0)
   }
  # summed residual deviance contribution for this study
  resdev[i] <- sum(dev[i,1:2])
 }
for (j in 1:2){                    # loop through all categories
  pE[j,2] <- 1-pE[j,1]
 }
# link probabilities
# type E: true < 60
sumE <- T[1]+T[2]+T[3]
pE[1,1] <- (p[1,1]+p[1,2]+p[1,3])*T[1]/sumE + (p[2,1]+p[2,2]+p[2,3])*T[2]/sumE
+ (p[3,1]+p[3,2]+p[3,3])*T[3]/sumE # POC <60
# type E: true > 60
pE[2,1] <- p[4,1]+p[4,2]+p[4,3]    # POC <60
#
#
# type C2 data: TRUE 0-30; 30-45; >45 (extra info of POC categories)
for (i in (ns+nsA+nsC+nsE+1):(ns+nsA+nsC+nsE+nsC2)){# loop through studies w/ type
C2 data
  for (j in 1:2){                  # loop through true eGFR categories 1 and 2
    r[i,j,1:4] ~ dmulti(p[j,], n[i,j]) # all POC categories reported
    # calculate residual deviance
    for (m in 1:4){                # loop through all reported thresholds
      # predicted number events
      rhat[i,j,m] <-  p[j,m] * n[i,j]
      r1[i,j,m] <- max(r[i,j,m], 0.1) # correction for zero cell
      rhat1[i,j,m] <- max(rhat[i,j,m], 0.1) # correction for p=0
      # Deviance contribution when non-zero cell (allows p=0)
      dv1[i,j,m] <- 2*r1[i,j,m]*(log(r1[i,j,m])-log(rhat1[i,j,m]))
      # Calculate deviance contribution, when zero cell=zero
      dv[i,j,m] <- dv1[i,j,m]*(1-equals(r[i,j,m],0))
#      dv[i,j,m] <- 2*r[i,j,m]*(log(r[i,j,m])-log(rhat[i,j,m]))
     }
    dev[i,j] <- sum(dv[i,j,1:4])
   }
  # true eGFR category 3
  r[i,3,1:3] ~ dmulti(pC2[3,], n[i,3]) # 3 POC categories reported
  # calculate residual deviance
  for (m in 1:3){                  # loop through all reported thresholds
    # predicted number events
    rhat[i,3,m] <-  pC2[3,m] * n[i,3]
    r1[i,3,m] <- max(r[i,3,m], 0.1) # correction for zero cell
    rhat1[i,3,m] <- max(rhat[i,3,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    dv1[i,3,m] <- 2*r1[i,3,m]*(log(r1[i,3,m])-log(rhat1[i,3,m]))
    # Calculate deviance contribution, when zero cell=zero
    dv[i,3,m] <- dv1[i,3,m]*(1-equals(r[i,3,m],0))
#    dv[i,3,m] <- 2*r[i,3,m]*(log(r[i,3,m])-log(rhat[i,3,m]))
   }
  dev[i,3] <- sum(dv[i,3,1:3])
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:3])
 }
# link probabilities
# type C: true > 45
pC2[3,1] <- pC[3,1]                # POC <30
pC2[3,2] <- pC[3,2]                # 30 < POC < 45
pC2[3,3] <- pC[3,3]                # POC >45
}
```

11.3.1.1 OpenBUGS Data

```
# ns = number of studies reporting all categories; nsA = number of studies reporting data of type A; etc
# nsA = number of studies of type A; etc

list(ns=2, nsA=1, nsC=1,nsE=2, nsC2=1, ny=3, nyA=2, nyC=2, nyE=3, nyF=1)

y[,1]   y[,2]   y[,3]   y[,4]   N[]
12      28      35      225     300     #       Snaith 2018         ALL
0       14      44      242     300     #       Snaith 2019         ALL
1       0       2       100     103     #       Krige 2017          ALL
33      20      47      NA      100     #       Shephard 2010       TYPE A
29      674     2541    NA      3244    #       Botz 2013 (ABL)     TYPE A
4       8       111     NA      123     #       Inoue 2017          TYPE C
0       3       348     NA      351     #       Houben 2017         TYPE C
68      198     NA      NA      266     #       Korpi-Steiner 2009  TYPE E
1       186     NA      NA      187     #       Dorward 2018        TYPE E
9       40      NA      NA      49      #       Nichols 2007        TYPE E
14      2028    NA      NA      2042    #       Botz 2013 (iSTAT)   TYPE F
END

r[,1,1]   r[,1,2]   r[,1,3]   r[,1,4]   n[,1]   r[,2,1]   r[,2,2]   r[,2,3]   r[,2,4]   n[,2]   r[,3,1]   r[,3,2]
          r[,3,3]   r[,3,4]   n[,3]     r[,4,1]   r[,4,2]   r[,4,3]   r[,4,4]   n[,4]   #       Study ID
8         4         0         0         12        3         17        8         0         28      0         10        17
          8         35        0         1         33        191       225       #         Snaith 2018         FULL DATA
1         0         0         0         1         0         0         0         0         0       0         0         1
          1         2         0         0         0         100       100       #         Krige 2017          FULL DATA
26        6         1         NA        33        0         14        6         NA        20      0         0         47
          NA        47        NA        NA        NA        NA        NA        #         Shephard 2010 (data from plot)
          TYPE A
4         0         0         NA        4         1         7         0         NA        8       1         11        99
          NA        111       NA        NA        NA        NA        NA        #         Inoue 2017 (pre adjustment)
          TYPE C
11        57        NA        NA        68        0         198       NA        NA        198     NA        NA        NA
          NA        NA        NA        NA        NA        NA        NA        #         Korpi-Steiner 2009 (no offset)
          TYPE E
1         0         NA        NA        1         NA        NA        NA        NA        186     NA        NA        NA
          NA        NA        NA        NA        NA        NA        NA        #         Dorward 2018        TYPE E
0         0         0         0         0         0         0         1         2         3       0         0         348
          NA        348       NA        NA        NA        NA        NA        #         Houben 2017         TYPE C2
END
```

11.3.2 i-STAT main analysis (includes calculation of probability of true eGFR in each category)

```
model{
# T = probability of true eGFR belonging to each category
#
# All categories
for (i in 1:ny){                    # loop through studies with all categories
  y[i,1:4] ~ dmulti(T[], N[i])
  # calculate residual deviance
  for (m in 1:4){                   # loop through all reported thresholds
    yhat[i,m] <-  T[m] * N[i]       # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)     # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,])        # summed residual deviance contribution for this
study
 }
totresdevT <- sum(yresdev[])        # Total Residual Deviance
T[1:4] ~ ddirch(omega[])            # prior distribution for T (WinBUGS compatible)
for (j in 1:4){                     # loop through all categories
  omega[j] <- 1                     # Dirichlet parameter (non-inf)
 }
# type A data: 0-30; 30-60; >60
for (i in (ny+1):(ny+nyA)){         # loop through studies with type A data
```

```
  y[i,1:3] ~ dmulti(TA[], N[i])
  # calculate residual deviance
  for (m in 1:3){                  # loop through all reported thresholds
    yhat[i,m] <-  TA[m] * N[i]     # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)    # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,1:3])    # summed residual deviance contribution for this
study
 }
# link probabilities
TA[1] <- T[1]                      # type A: true < 30
TA[2] <- T[2] + T[3]               # type A: 30 < true < 60
TA[3] <- T[4]                      # type A: true > 60
#
# type C data: 0-30; 30-45; >45
for (i in (ny+nyA+1):(ny+nyA+nyC)){ # loop through studies with type C data
  y[i,1:3] ~ dmulti(TC[], N[i])
  # calculate residual deviance
  for (m in 1:3){                  # loop through all reported thresholds
    yhat[i,m] <-  TC[m] * N[i]     # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)    # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,1:3])    # summed residual deviance contribution for this
study
 }
# link probabilities
TC[1] <- T[1]                      # type C: true < 30
TC[2] <- T[2]                      # type C: 30 < true < 45
TC[3] <- T[3] + T[4]               # type C: true > 45
#
# type E data: 0-60; >60
for (i in (ny+nyA+nyC+1):(ny+nyA+nyC+nyE)){  # loop through studies with type E
data
  y[i,1] ~ dbin(TE[1], N[i])
  # Deviance contribution
  yhat[i,1] <- TE[1] * N[i]        # expected value of the numerators
  y1[i,1] <- max(y[i,1], 0.1)      # correction for zero cell
  yhat1[i,1] <- max(yhat[i,1], 0.1) # correction for p=0
  # Deviance contribution when non-zero cell (allows p=0)
  ydev1[i,1] <- 2 * (y1[i,1]*(log(y1[i,1])-log(yhat1[i,1]))
             +(N[i]-y1[i,1])*(log(N[i]-y1[i,1])
               - log(N[i]-yhat1[i,1])))
  # Deviance contribution when zero cell (allows p=0)
  ydev0[i,1] <- 2*N[i]*log(N[i]/(N[i]-yhat[i,1]))
  # Calculate deviance contribution
  yresdev[i] <- ydev1[i,1]*(1-equals(y[i,1],0)) + ydev0[i,1]*equals(y[i,1],0)
 }
# link probabilities
TE[1] <- T[1] + T[2] + T[3]        # type E: true < 60
TE[2] <- T[4]                      # type E:  true > 60
#
# type F data: 0-30; >30
for (i in (ny+nyA+nyC+nyE+1):(ny+nyA+nyC+nyE+nyF)){ # loop through studies with
type F data
  y[i,1] ~ dbin(TF[1], N[i])
  # Deviance contribution
  yhat[i,1] <- TF[1] * N[i]        # expected value of the numerators
  y1[i,1] <- max(y[i,1], 0.1)      # correction for zero cell
```

```
  yhat1[i,1] <- max(yhat[i,1], 0.1) # correction for p=0
  # Deviance contribution when non-zero cell (allows p=0)
  ydev1[i,1] <- 2 * (y1[i,1]*(log(y1[i,1])-log(yhat1[i,1]))
             +(N[i]-y1[i,1])*(log(N[i]-y1[i,1])
               - log(N[i]-yhat1[i,1])))
  # Deviance contribution when zero cell (allows p=0)
  ydev0[i,1] <- 2*N[i]*log(N[i]/(N[i]-yhat[i,1]))
  # Calculate deviance contribution
  yresdev[i] <- ydev1[i,1]*(1-equals(y[i,1],0)) + ydev0[i,1]*equals(y[i,1],0)
 }
# link probabilities
TF[1] <- T[1]                       # type F: true < 30
TF[2] <- T[2] + T[3] + T[4]         # type F:  true > 30
#
# p[j,m]: probability of being in true category j and POC category m
#
# All categories
for (i in 1:ns){                    # loop through studies with all categories
  for (j in 1:4){                   # loop through all categories
    r[i,j,1:4] ~ dmulti(p[j,], n[i,j])
    # calculate residual deviance
    for (m in 1:4){                 # loop through all reported thresholds
      # predicted number events
      rhat[i,j,m] <-  p[j,m] * n[i,j]
      r1[i,j,m] <- max(r[i,j,m], 0.1) # correction for zero cell
      rhat1[i,j,m] <- max(rhat[i,j,m], 0.1) # correction for p=0
      # Deviance contribution when non-zero cell (allows p=0)
      dv1[i,j,m] <- 2*r1[i,j,m]*(log(r1[i,j,m])-log(rhat1[i,j,m]))
      # Calculate deviance contribution, when zero cell=zero
      dv[i,j,m] <- dv1[i,j,m]*(1-equals(r[i,j,m],0))
#      dv[i,j,m] <- 2*r[i,j,m]*(log(r[i,j,m])-log(rhat[i,j,m]))
     }
    dev[i,j] <- sum(dv[i,j,])
   }
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:4])
 }
totresdev <- sum(resdev[])          # Total Residual Deviance
for (j in 1:4){                     # loop through all categories
  p[j,1:4] ~ ddirch(alpha[])        # prior distribution for p (WinBUGS compatible)
  alpha[j] <- 1                     # Dirichlet parameter (non-inf)
 }
#
# type E data: 0-60; >60
for (i in (ns+1):(ns+nsE)){         # loop through studies with type E data
  for (j in 1:2){                   # loop through all categories
    r[i,j,1] ~ dbin(pE[j,1], n[i,j])
    # Deviance contribution
    rhat[i,j,1] <- pE[j,1] * n[i,j] # expected value of the numerators
    r1[i,j,1] <- max(r[i,j,1], 0.1) # correction for zero cell
    rhat1[i,j,1] <- max(rhat[i,j,1], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    dev1[i,j,1] <- 2 * (r1[i,j,1]*(log(r1[i,j,1])-log(rhat1[i,j,1]))
             +(n[i,j]-r1[i,j,1])*(log(n[i,j]-r1[i,j,1])
               - log(n[i,j]-rhat1[i,j,1])))
    # Deviance contribution when zero cell (allows p=0)
    dev0[i,j,1] <- 2*n[i,j]*log(n[i,j]/(n[i,j]-rhat[i,j,1]))
    # Calculate deviance contribution
    dev[i,j] <- dev1[i,j,1]*(1-equals(r[i,j,1],0)) + dev0[i,j,1]*equals(r[i,j,1],0)
#    dev[i,j] <- 2 * (r[i,j,1] * (log(r[i,j,1])-log(rhat[i,j,1]))
#             +  (n[i,j]-r[i,j,1]) * (log(n[i,j]-r[i,j,1]) - log(n[i,j]-
rhat[i,j,1])))
   }
  # summed residual deviance contribution for this study
  resdev[i] <- sum(dev[i,1:2])
 }
for (j in 1:2){                     # loop through all categories
  pE[j,2] <- 1-pE[j,1]
```

```
 }
# link probabilities
# type E: true < 60
sumE <- T[1]+T[2]+T[3]
pE[1,1] <- (p[1,1]+p[1,2]+p[1,3])*T[1]/sumE + (p[2,1]+p[2,2]+p[2,3])*T[2]/sumE
+ (p[3,1]+p[3,2]+p[3,3])*T[3]/sumE # POC <60
# type E: true > 60
pE[2,1] <- p[4,1]+p[4,2]+p[4,3]    # POC <60
#
# type F data: 0-30; >30
for (i in (ns+nsE+1):(ns+nsE+nsF)){ # loop through studies with all categories
  for (j in 1:2){                   # loop through all categories
    r[i,j,1] ~ dbin(pF[j,1], n[i,j])
    # Deviance contribution
    rhat[i,j,1] <- pF[j,1] * n[i,j] # expected value of the numerators
    r1[i,j,1] <- max(r[i,j,1], 0.1) # correction for zero cell
    rhat1[i,j,1] <- max(rhat[i,j,1], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    dev1[i,j,1] <- 2 * (r1[i,j,1]*(log(r1[i,j,1])-log(rhat1[i,j,1]))
             +(n[i,j]-r1[i,j,1])*(log(n[i,j]-r1[i,j,1])
               - log(n[i,j]-rhat1[i,j,1])))
    # Deviance contribution when zero cell (allows p=0)
    dev0[i,j,1] <- 2*n[i,j]*log(n[i,j]/(n[i,j]-rhat[i,j,1]))
    # Calculate deviance contribution
    dev[i,j] <- dev1[i,j,1]*(1-equals(r[i,j,1],0)) + dev0[i,j,1]*equals(r[i,j,1],0)
#    dev[i,j] <- 2 * (r[i,j,1] * (log(r[i,j,1])-log(rhat[i,j,1]))
#             +  (n[i,j]-r[i,j,1]) * (log(n[i,j]-r[i,j,1]) - log(n[i,j]-
rhat[i,j,1])))
   }
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:2])
 }
for (j in 1:2){                     # loop through all categories
  pF[j,2] <- 1-pF[j,1]
 }
# link probabilities
# type F: true < 30
pF[1,1] <- p[1,1]                   # POC <30
# type F: true > 30
sumF <- T[2]+T[3]+T[4]
pF[2,1] <- p[2,1]*T[2]/sumF + p[3,1]*T[3]/sumF + p[4,1]*T[4]/sumF # POC <30
}
```

11.3.2.1 OpenBUGS data

ns = number of studies reporting all categories; nsA = number of studies reporting data of type A; etc
nsA = number of studies of type A; etc

list(ns=2, nsE=2, nsF=1, ny=3, nyA=2, nyC=2, nyE=3, nyF=1)

y[,1]	y[,2]	y[,3]	y[,4]	N[]			
12	28	35	225	300	#	Snaith 2018	ALL
0	14	44	242	300	#	Snaith 2019	ALL
1	0	2	100	103	#	Krige 2017	ALL
33	20	47	NA	100	#	Shephard 2010	TYPE A
29	674	2541	NA	3244	#	Botz 2013 (ABL)	TYPE A
4	8	111	NA	123	#	Inoue 2017	TYPE C
0	3	348	NA	351	#	Houben 2017	TYPE C
68	198	NA	NA	266	#	Korpi-Steiner 2009	TYPE E
1	186	NA	NA	187	#	Dorward 2018	TYPE E
9	40	NA	NA	49	#	Nichols 2007	TYPE E
14	2028	NA	NA	2042	#	Botz 2013 (iSTAT)	TYPE F

END

r[,1,1]	r[,1,2]	r[,1,3]	r[,1,4]	n[,1]	r[,2,1]	r[,2,2]	r[,2,3]	r[,2,4]	n[,2]	r[,3,1]	r[,3,2]
	r[,3,3]	r[,3,4]	n[,3]	r[,4,1]	r[,4,2]	r[,4,3]	r[,4,4]	n[,4]	#	Study ID	
12	0	0	0	12	3	25	0	0	28	0	5	29
	1	35	0	1	14	210	225	#	Snaith 2018		FULL DATA	

```
0       0       0       0       0       1       9       4       0       14      0       2       35
        7       44      0       1       7       234     242     #       Snaith 2019             FULL DATA
66      2       NA      NA      68      32      166     NA      NA      198     NA      NA      NA
        NA      NA      NA      NA      NA      NA      NA      #       Korpi-Steiner 2009      TYPE E
9       0       NA      NA      9       6       34      NA      NA      40      NA      NA      NA
        NA      NA      NA      NA      NA      NA      NA      #       Nichols 2007            TYPE E
12      2       NA      NA      14      NA      NA      NA      NA      2028    NA      NA      NA
        NA      NA      NA      NA      NA      NA      NA      #       Botz 2013               TYPE F
END
```

11.3.3 ABL (Radiometer) main analysis (includes calculation of probability of true eGFR in each category)

```
model{
# T = probability of true eGFR belonging to each category
#
# All categories
for (i in 1:ny){                    # loop through studies with all categories
  y[i,1:4] ~ dmulti(T[], N[i])
  # calculate residual deviance
  for (m in 1:4){                   # loop through all reported thresholds
    yhat[i,m] <-  T[m] * N[i]       # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)     # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,])        # summed residual deviance contribution for this
study
 }
totresdevT <- sum(yresdev[])        # Total Residual Deviance
T[1:4] ~ ddirch(omega[])            # prior distribution for T (WinBUGS compatible)
for (j in 1:4){                     # loop through all categories
  omega[j] <- 1                     # Dirichlet parameter (non-inf)
 }
# type A data: 0-30; 30-60; >60
for (i in (ny+1):(ny+nyA)){         # loop through studies with type A data
  y[i,1:3] ~ dmulti(TA[], N[i])
  # calculate residual deviance
  for (m in 1:3){                   # loop through all reported thresholds
    yhat[i,m] <-  TA[m] * N[i]      # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)     # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,1:3])     # summed residual deviance contribution for this
study
 }
# link probabilities
TA[1] <- T[1]                       # type A: true < 30
TA[2] <- T[2] + T[3]                # type A: 30 < true < 60
TA[3] <- T[4]                       # type A: true > 60
#
# type C data: 0-30; 30-45; >45
for (i in (ny+nyA+1):(ny+nyA+nyC)){ # loop through studies with type C data
  y[i,1:3] ~ dmulti(TC[], N[i])
  # calculate residual deviance
  for (m in 1:3){                   # loop through all reported thresholds
    yhat[i,m] <-  TC[m] * N[i]      # predicted number events
    y1[i,m] <- max(y[i,m], 0.1)     # correction for zero cell
    yhat1[i,m] <- max(yhat[i,m], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
```

```
    ydv1[i,m] <- 2*y1[i,m]*(log(y1[i,m])-log(yhat1[i,m]))
    # Calculate deviance contribution, when zero cell=zero
    ydv[i,m] <- ydv1[i,m]*(1-equals(y[i,m],0))
   }
  yresdev[i] <- sum(ydv[i,1:3])     # summed residual deviance contribution for this
study
 }
# link probabilities
TC[1] <- T[1]                       # type C: true < 30
TC[2] <- T[2]                       # type C: 30 < true < 45
TC[3] <- T[3] + T[4]                # type C: true > 45
#
# type E data: 0-60; >60
for (i in (ny+nyA+nyC+1):(ny+nyA+nyC+nyE)){  # loop through studies with type E
data
  y[i,1] ~ dbin(TE[1], N[i])
  # Deviance contribution
  yhat[i,1] <- TE[1] * N[i]         # expected value of the numerators
  y1[i,1] <- max(y[i,1], 0.1)       # correction for zero cell
  yhat1[i,1] <- max(yhat[i,1], 0.1) # correction for p=0
  # Deviance contribution when non-zero cell (allows p=0)
  ydev1[i,1] <- 2 * (y1[i,1]*(log(y1[i,1])-log(yhat1[i,1]))
             +(N[i]-y1[i,1])*(log(N[i]-y1[i,1])
               - log(N[i]-yhat1[i,1])))
  # Deviance contribution when zero cell (allows p=0)
  ydev0[i,1] <- 2*N[i]*log(N[i]/(N[i]-yhat[i,1]))
  # Calculate deviance contribution
  yresdev[i] <- ydev1[i,1]*(1-equals(y[i,1],0)) + ydev0[i,1]*equals(y[i,1],0)
 }
# link probabilities
TE[1] <- T[1] + T[2] + T[3]         # type E: true < 60
TE[2] <- T[4]                       # type E:  true > 60
#
# type F data: 0-30; >30
for (i in (ny+nyA+nyC+nyE+1):(ny+nyA+nyC+nyE+nyF)){ # loop through studies with
type F data
  y[i,1] ~ dbin(TF[1], N[i])
  # Deviance contribution
  yhat[i,1] <- TF[1] * N[i]         # expected value of the numerators
  y1[i,1] <- max(y[i,1], 0.1)       # correction for zero cell
  yhat1[i,1] <- max(yhat[i,1], 0.1) # correction for p=0
  # Deviance contribution when non-zero cell (allows p=0)
  ydev1[i,1] <- 2 * (y1[i,1]*(log(y1[i,1])-log(yhat1[i,1]))
             +(N[i]-y1[i,1])*(log(N[i]-y1[i,1])
               - log(N[i]-yhat1[i,1])))
  # Deviance contribution when zero cell (allows p=0)
  ydev0[i,1] <- 2*N[i]*log(N[i]/(N[i]-yhat[i,1]))
  # Calculate deviance contribution
  yresdev[i] <- ydev1[i,1]*(1-equals(y[i,1],0)) + ydev0[i,1]*equals(y[i,1],0)
 }
# link probabilities
TF[1] <- T[1]                       # type F: true < 30
TF[2] <- T[2] + T[3] + T[4]         # type F:  true > 30
#
# p[j,m]: probability of being in true category j and POC category m
#
# All categories
for (i in 1:ns){                    # loop through studies with all categories
  for (j in 1:4){                  # loop through all categories
    r[i,j,1:4] ~ dmulti(p[j,], n[i,j])
    # calculate residual deviance
    for (m in 1:4){                # loop through all reported thresholds
      # predicted number events
      rhat[i,j,m] <-  p[j,m] * n[i,j]
      r1[i,j,m] <- max(r[i,j,m], 0.1) # correction for zero cell
      rhat1[i,j,m] <- max(rhat[i,j,m], 0.1) # correction for p=0
      # Deviance contribution when non-zero cell (allows p=0)
      dv1[i,j,m] <- 2*r1[i,j,m]*(log(r1[i,j,m])-log(rhat1[i,j,m]))
```

```
      # Calculate deviance contribution, when zero cell=zero
      dv[i,j,m] <- dv1[i,j,m]*(1-equals(r[i,j,m],0))
#      dv[i,j,m] <- 2*r[i,j,m]*(log(r[i,j,m])-log(rhat[i,j,m]))
     }
    dev[i,j] <- sum(dv[i,j,])
   }
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:4])
 }
totresdev <- sum(resdev[])          # Total Residual Deviance
for (j in 1:4){                     # loop through all categories
  p[j,1:4] ~ ddirch(alpha[])        # prior distribution for p (WinBUGS compatible)
  alpha[j] <- 1                     # Dirichlet parameter (non-inf)
 }
#
# type E data: 0-60; >60
for (i in (ns+1):(ns+nsE)){         # loop through studies with type E data
  for (j in 1:2){                   # loop through all categories
    r[i,j,1] ~ dbin(pE[j,1], n[i,j])
    # Deviance contribution
    rhat[i,j,1] <- pE[j,1] * n[i,j] # expected value of the numerators
    r1[i,j,1] <- max(r[i,j,1], 0.1) # correction for zero cell
    rhat1[i,j,1] <- max(rhat[i,j,1], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    dev1[i,j,1] <- 2 * (r1[i,j,1]*(log(r1[i,j,1])-log(rhat1[i,j,1]))
             +(n[i,j]-r1[i,j,1])*(log(n[i,j]-r1[i,j,1])
               - log(n[i,j]-rhat1[i,j,1])))
    # Deviance contribution when zero cell (allows p=0)
    dev0[i,j,1] <- 2*n[i,j]*log(n[i,j]/(n[i,j]-rhat[i,j,1]))
    # Calculate deviance contribution
    dev[i,j] <- dev1[i,j,1]*(1-equals(r[i,j,1],0)) + dev0[i,j,1]*equals(r[i,j,1],0)
   }
  # summed residual deviance contribution for this study
  resdev[i] <- sum(dev[i,1:2])
 }
for (j in 1:2){                     # loop through all categories
  pE[j,2] <- 1-pE[j,1]
 }
# link probabilities
# type E: true < 60
sumE <- T[1]+T[2]+T[3]
pE[1,1] <- (p[1,1]+p[1,2]+p[1,3])*T[1]/sumE + (p[2,1]+p[2,2]+p[2,3])*T[2]/sumE
+ (p[3,1]+p[3,2]+p[3,3])*T[3]/sumE # POC <60
# type E: true > 60
pE[2,1] <- p[4,1]+p[4,2]+p[4,3]     # POC <60
#
# type A2 data: 0-30; 30-60; >60
for (i in (ns+nsE+1):(ns+nsE+nsA2)){ # loop through studies with type A2 data
  for (j in 1:3){                   # loop through all categories
    r[i,j,1] ~ dbin(pA2[j,1], n[i,j])
    # Deviance contribution
    rhat[i,j,1] <- pA2[j,1] * n[i,j] # expected value of the numerators
    r1[i,j,1] <- max(r[i,j,1], 0.1) # correction for zero cell
    rhat1[i,j,1] <- max(rhat[i,j,1], 0.1) # correction for p=0
    # Deviance contribution when non-zero cell (allows p=0)
    dev1[i,j,1] <- 2 * (r1[i,j,1]*(log(r1[i,j,1])-log(rhat1[i,j,1]))
             +(n[i,j]-r1[i,j,1])*(log(n[i,j]-r1[i,j,1])
               - log(n[i,j]-rhat1[i,j,1])))
    # Deviance contribution when zero cell (allows p=0)
    dev0[i,j,1] <- 2*n[i,j]*log(n[i,j]/(n[i,j]-rhat[i,j,1]))
    # Calculate deviance contribution
    dev[i,j] <- dev1[i,j,1]*(1-equals(r[i,j,1],0)) + dev0[i,j,1]*equals(r[i,j,1],0)
   }
  # summed residual deviance contribution for this study
  resdev[i] <- sum(dev[i,1:3])
 }
for (j in 1:3){                     # loop through all categories
  pA2[j,2] <- 1-pA2[j,1]
```

```
 }
# link probabilities
# type A2: true < 30
pA2[1,1] <- p[1,1]                  # POC <30
# type A2: true 30-60
pA2[2,1] <- pA[2,1]                 # POC >30
# probability for type A data
sumA <- T[2]+T[3]
pA[2,1] <- p[2,1]*T[2]/sumA + p[3,1]*T[3]/sumA  # POC <30
# type A2: true > 60
pA2[3,1] <- p[4,1] + p[4,2] + p[4,3] # POC >60
}
```

11.3.3.1 OpenBUGS data

ns = number of studies reporting all categories; nsA = number of studies reporting data of type A; etc
nsA = number of studies of type A; etc

list(ns=1, nsE=1, nsA2=1, ny=3, nyA=2, nyC=2, nyE=3, nyF=1)

y[,1]	y[,2]	y[,3]	y[,4]	N[]			
12	28	35	225	300	#	Snaith 2018	ALL
0	14	44	242	300	#	Snaith 2019	ALL
1	0	2	100	103	#	Krige 2017	ALL
33	20	47	NA	100	#	Shephard 2010	TYPE A
29	674	2541	NA	3244	#	Botz 2013 (ABL)	TYPE A
4	8	111	NA	123	#	Inoue 2017	TYPE C
0	3	348	NA	351	#	Houben 2017	TYPE C
68	198	NA	NA	266	#	Korpi-Steiner 2009	TYPE E
1	186	NA	NA	187	#	Dorward 2018	TYPE E
9	40	NA	NA	49	#	Nichols 2007	TYPE E
14	2028	NA	NA	2042	#	Botz 2013 (iSTAT)	TYPE F

END

r[,1,1]	r[,1,2]	r[,1,3]	r[,1,4]	n[,1]	r[,2,1]	r[,2,2]	r[,2,3]	r[,2,4]	n[,2]	r[,3,1]	r[,3,2]	
	r[,3,3]	r[,3,4]	n[,3]	r[,4,1]	r[,4,2]	r[,4,3]	r[,4,4]	n[,4]	#	Study ID		
12	0	0	0	12	0	24	4	0	28	0	2	31
	2	35	0	0	1	224	225	#	Snaith 2018		FULL DATA	
55	13	NA	NA	68	6	192	NA	NA	198	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA	#	Korpi-Steiner 2009		TYPE E	
26	3	NA	NA	29	NA	NA	NA	NA	674	24	2517	NA
	NA	2541	NA	NA	NA	NA	NA	#	Botz 2013		TYPE A2	

END

11.4 Quality assessment of diagnostic accuracy studies

11.4.1 Risk of bias: patient selection

SQ1: Was a consecutive or random sample of patients enrolled?

SQ2: Did the study avoid inappropriate exclusions?

RoB: Could the selection of patients have introduced bias?

Study	Description	SQ1	SQ2	RoB	Notes
Botz et al 2013[25]	2042 patients at risk of renal disease prior to radiological examinations, 43% female, USA. "We retrospectively obtained all i-STAT1 and Radiometer 827 whole blood creatinine results performed on the same day of service as a serum creatinine for the period January 1- December 31, 2011"	UC	UC	UC	Retrospective selection of patients with both POC and ref std. It is not clear how they were classified as at risk of renal disease. Conference abstract only.
Dorward et al 2018[26]	187 HIV positive patients who recently initiated 1st-line ART, median age 31 years [IQR 27-38], 62% female, South Africa. Prospectively recruited trial arm population.	yes	no	low	Excluded 1 patient with eGFR<30 who was clinically unstable. Unlikely to introduce significant bias
Houben et al 2017[27]	351 women due for contrast-enhanced spectral mammography. Netherlands. Women eligible for Contrast enhanced spectral mammography between December 2014 & June 2016 "were asked to voluntarily participate in this observational study".	UC	yes	low	Not explicitly stated if consecutively recruited but appears likely. No inappropriate exclusions

Inoue et al 2017[28]	233 consecutive outpatients scheduled for contrast-enhanced CT studies. Of the 233 patients, 123 patient samples were evaluated prior to adjustment and the other 110 following adjustment.	yes	yes	low	Consecutive, no inappropriate exclusions
Korpi-Steiner et al 2009[29]	"266 excess lithium heparin whole blood samples submitted for stat evaluation of creatinine/eGFR before contrast administration for CT procedures were used." "Institutional protocol requires creatinine/eGFR measurement for patients older than 70 years, patients with a history of diabetes, and patients with a history of renal disease or renal transplantation. For patients meeting these criteria without a current (within 30 days) creatinine/eGFR value available and patients with a pending creatinine/ eGFR value at the time of CT, samples are sent to the stat laboratory for creatinine/eGFR measurement. Sample selection was not consecutive because staff was available only during selected hours to perform the whole blood creatinine testing. The study was conducted between November 1 and December 31, 2008."	no	UC	low	Reasons provided for non-consecutive recruitment are acceptable and unlikely to introduce bias. There was no evidence of inappropriate exclusion.
Krige 2017[30]	103 mixed ancestry healthy South Africans, Mean age 52, 69% female	yes	UC	low	Random sampling
Nichols 2007[31]	50 consecutive patients requiring creatinine levels prior to chemotherapy administration. 52% male, 6% Black African	yes	yes	low	Consecutive, no inappropriate exclusions reported
Obrador et al 2012[32]	257 diabetic patients Mean age: 56.9 (12.5), 62% women	UC	UC	UC	Insufficient information (conference abstract)
Shephard et al 2008[33]	101 venous blood samples. No other information (conference abstract)	UC	UC	UC	Insufficient information (conference abstract)
Shephard et al 2010[34]	100 (63 renal/dialysis patients attending clinic, 37 healthy), 52% female	UC	UC	UC	No information suggesting recruitment

					was consecutive or random. 67% dialysis patients, 33% healthy volunteers.
Snaith et al 2018[35]	"Over a 6-week period in September and October 2016, consecutive adult outpatients (≥18 years) attending a UK hospital phlebotomy department for routine Urea and Electrolytes (U&E) blood tests were approached. No upper age limit was adopted, but pregnant individuals and those unable to consent were excluded." 300 attending for routine blood tests (phlebotomy outpatients), mean age 60 years, 47% female, mean creatinine 92µmol/L	yes	yes	low	Consecutive, no inappropriate exclusions reported though 61 consenting patients excluded because target sample size of 300 had been reached.
Snaith et al 2019[36]	CT outpatients without recent (within 3 months) eGFR. "Over an eight-week period between February and April 2017 consecutive adult outpatients (≥18 years) attending for a contrast-enhanced CT scan were approached."	yes	yes	low	Consecutive, no inappropriate exclusions reported

11.4.2 Risk of bias: index test and reference standard

SQ1: Is the reference standard likely to measure eGFR/creatinine accurately enough?

SQ2: Was the same method used to calculate eGFR/creatinine for both index test and reference standard?

RoB: Could the conduct or interpretation of the index test or reference standard have introduced bias?

Study	Description	SQ1	SQ2	RoB	Notes

Botz et al 2013[25]	i-STAT1 and Radiometer 827 whole blood creatinine. Roche Cobas Enzymatic C-501analyzer. MDRD formula.	yes	UC	low	Conference abstract. No information suggesting the method used to calculate eGFR/creatinine for both index test and reference standard were different.
Dorward et al 2018[26]	Calibrated Statsensor Xpress-I using finger-prick capillary wholeblood. Dimension EXL 200 Enzymatic. StatSensor Xpress-i, "factory calibrated" setting were used, so (it appears) the authors did not add an offset to the device, even though the device has that functionality. Only non-offset results are reported.	yes	UC	low	No information suggesting the method used to calculate eGFR/creatinine for both index test and reference standard were different.
Houben et al 2017[27]	Statsensor used according to manual instructions. Enzymatic reference standard. StatSensor CREAT, no mention of offset or adjustments and only raw results are reported.	yes	UC	UC	Unclear if MDRD equation used for POC and the laboratory reference are the same (factor 186 for POC vs. 175 for laboratory reference?)
Inoue et al 2017[28]	"All blood samples were taken in the radiology suite(...) Cubital vein blood samples obtained with a 20- or a 22-gauge needle (Supercath; Medikit Co., Ltd., Tokyo, Japan) were collected into a blood-collecting vessel containing a blood coagulation accelerant, thrombin (Neotube; Nipro Corporation, Osaka, Japan). The venous samples were analyzed in the laboratory with a creatinine kit (…) that applies the enzymatic method in	yes	yes	low	Low as assessment only applies to unadjusted accuracy estimates.

	an automatic analyzer (BioMajesty™ JCA-BM2250; JEOL Ltd., Tokyo, Japan). The eGFR was calculated using a converting equation, as follows: eGFR=194x(sCr)-1.094x(age)-0.287x(-0.739 for females) published by the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives." Uses StatSensor-i and included an adjustment ("adjustment by applying offset correction on the basis of the slope and intercept of internal sample"). Adjusted and unadjusted plots and table of results show the lab eGFR measurements also change, which is not supposed to happen (it should only adjust the device values). So the reported adjusted results from this study may not represent NHS practice. Therefore only the unadjusted results were used for the synthesis.				
Korpi-Steiner et al 2009[29]	Different MDRD equations used for lab reference and i-STAT and StatSensor. For lab reference and ABL800: standard MDRD calibrated to IDMS traceability (eGFR (mL/min) = 175 × Cr–1.154 × Age–0.203 (× 0.742 if female) (× 1.212 if African American). For i-STAT and StatSensor: MDRD equation originally validated with conventional creatinine calibrations: eGFR (mL/min) = 186 × Cr–1.154 × Age–0.203 (× 0.742 if female) (× 1.212 if African American). Results with offset (0.28mg/dL) and no offset were reported. "The StatSensor device offers users the ability to enter a slope and an intercept offset to match whole blood to plasma creatinine values. The manufacturer of the device recommends a simple fixed offset to match whole blood to plasma values within a narrow range of values. For this reason, we calculated eGFR concordance for StatSensor values with and without application of a fixed offset of 0.28 mg/ dL (25 µmol/L) creatinine, which was the offset that maximized overall concordance between StatSensor whole blood and plasma eGFR values for the 266 sample data set."	yes	no	low (ABL800); high (i-STAT and StatSensor)	Different MDRD equations used for lab reference and i-STAT and StatSensor.

Krige 2017[30]	Capillary sample for POC. Siemens ADVIA® 1800, which used an IDMS standardised kinetic Jaffe assay method. Statsensor: no offset used.	yes	no	high	Jaffe method for ref lab (vs. enzymatic for POC test).
Nichols 2007[31]	"Whole blood, green-top, lithium heparin specimens were collected by venipuncture" MDRD formula. Jaffe and enzymatic used. Note this assessment only focuses on MDRD enzymatic lab reference, which was used for the pooled analyses.	yes	yes	low	No significant concerns. MDRD used for both POC and lab reference
Obrador et al 2012[32]	Simple linear regression was used to estimate a correction factor to align i-STAT SCr to IDMS-SCr. CKD staging was not standard (0-4). It is unclear what eGFR values correspond to each CKD stage. Diagnostic accuracy results were only reported post-correction.	yes	UC	high	Simple linear regression was used to estimate a correction factor to align i-STAT SCr to IDMS-SCr. Diagnostic accuracy results were only reported post-correction.
Shephard et al 2008[33]	The i-STAT had a positive bias relative to the IDMS-aligned laboratory method (mean %bias of 5.6% overall, 10.4% for samples <150 mmol/L and 4.5% for samples >150 mmol/L). This bias was eliminated, and an IDMS alignment performed, by applying a correction formula. Accuracy estimates were only reported post-correction and alignment. Reference standard used was enzymatic, with no further details reported.	UC	UC	high	The i-STAT had a positive bias relative to the laboratory method. Mean %bias of 5.6% overall, 10.4% for samples <150 mmol/L and 4.5% for samples >150 mmol/L. Correction and alignment were performed. Accuracy estimates were only

					reported post-correction & alignment. Reference lab test used was enzymatic, with no further details reported.
Shephard et al 2010[34]	MDRD. eGFR60 cut-off. Two devices were tested: Nova 1 and Nova 2. 2x2 table only available for Nova 1. Tests were performed before and after calibration. Two MDRD equations were used: factory factor was 186, and factor used post-calibration was 175 (standard). For POC, 186 and 175 factors were both used to calculate sens/spec estimates before calibration; post calibration, only 175 was used. Lab ref MDRD equation used factor 175 before and after calibration. Plasma samples only were used for the lab reference. "eGFR on the Nova StatSensor, calculated automatically from the MDRD equation (factor 186), was also plotted against eGRF from the laboratory method, calculated by the laboratory information system (LIS) from the measured creatinine using the standardised MDRD equation (factor 175). After alignment of the Nova StatSensor results to the laboratory creatinine method, this process was repeated, now using an eGFR factor of 175 for the Nova StatSensor." On calibration: "Using the Passing-Bablok slope and intercept factors, the significant overall negative bias observed across the full creatinine concentration range with the factory-calibrated Nova 1 device was corrected using a reciprocal recalibration equation: Nova (recalibrated) = Nova (factory calibration)X 1.3333 – 13.53 mmol/L." Results pre and post-correction are reported..	yes	no (pre-adjustment)	high	High risk after calibration and adjustment as the offset adjustment was performed against the laboratory reference using the same samples. For pre-calibration results it appears that eGFR MDRD equation was used with factor 186 (vs. factor 175 for laboratory test). Plasma was used for lab ref test.
Snaith et al 2018[35]	CKD-EPI used for POC tests and lab reference for the main analysis. No offset adjustments done for any of the devices. "The standard U&E blood sample was collected	yes	yes	low	CKD-EPI used for POC tests and lab reference for

	by an experienced phlebotomist and processed following local operating procedures. To ensure minimal patient intervention, an additional sample of blood was immediately collected from the same venous puncture site. The whole blood research sample (S-Monovette Lithium Heparin 2.7 mL tube, Ref 05.1553; Sarstedt, Numbrecht, Germany) was labelled with a unique study identifier and transferred to the on-site laboratory for analysis." Lab ref method: Enzymatic (Cobas 8000, Roche). "the between-run imprecision was determined using independent commercially available QC materials, the standard practice in the laboratory." Clarification from M. Harris: "Both the ABL800 and i-STAT were used with venous samples only, the StatSensor was the only device where we used a capillary sample." "In an ideal world it would have been great if we could have tested the StatSensor and i-STAT using both venous and capillary samples as both are possibilities, however, for the purposes of ethical approval through a Research Ethics Committee we had to minimise patient interventions as so we used them as we know that they are being used in clinical practice."				the main analysis. Enzymatic reference standard.
Snaith et al 2019[36]	I-STAT & Enzymatic (Cobas 8000, Roche). CKD-EPI used for both.	yes	yes	low	No significant concerns.

11.4.3 Risk of bias: flow and timing

SQ1: Did all patients receive both the index test and reference standard?

SQ2: Were all patients included in the analysis?

SQ3: Did all patients receive the same reference standard?

SQ4: Was there an acceptable time gap between taking the index test blood and the reference standard blood samples?

RoB: Could the patient flow have introduced bias?

Study	Description	SQ1	SQ2	SQ3	SQ4	RoB	Notes
Botz et al 2013[25]	Retrospective. Analysed all i-STAT1 whole blood creatinine results performed on the same day (not clear how long in between) of service as a serum creatinine within 1 year. Radiometer 827 results did not appear to be all on the same day.	yes	yes	yes	UC	low	See description
Dorward et al 2018[26]	8 reference samples were excluded due to a laboratory strike or because they were processed 48h after sampling.	no	no	yes	yes	low	Exclusions are unlikely to have significantly biased the results
Houben et al 2017[27]	14 excluded "due to the inability to withdraw venous blood through the vacuum system used". Blood drawn for lab measurement within 15min of POC test.	no	no	yes	yes	low	Exclusions are unlikely to have introduced bias.
Inoue et al 2017[28]	Reported as consecutive though retrospective. All blood samples taken in the radiology suite prior to CT. Time gap unknown but unlikely to be significant.	yes	yes	yes	UC	low	Unlikely
Korpi-Steiner et al 2009[29]	Excess samples of lithium heparin whole blood was removed after sample mixing torun on the i-STAT, StatSensor, and Radiometer methods (inthat order) followed by centrifugation of the sample for 2 minutes at 4,500g for analysis of plasma creatinine on the Integra 400.	yes	yes	yes	yes	low	Retrospective, but no significant concerns about flow
Krige 2017[30]	Both capillary and venous blood samples were collected at the same time. Time gap between analysis of sample types was not reported.	yes	yes	yes	yes	low	Considered low, though gap between

							analysis of sample types was not reported.
Nichols 2007[31]	"Whole blood analyses were completed immediately after specimen collection, and the remainder of the specimen was centrifuged and plasma collected for analysis by the core laboratory methods. All testing was completed within 2 h of specimen collection. One specimen had too little sample to allow duplicate testing by all methods, and was excluded from the analysis." All samples were collected over 3 days.	yes	yes	yes	yes	low	See description
Obrador et al 2012[32]	No description (conference abstract)	yes	yes	yes	UC	low	Insufficient information (conference abstract)
Shephard et al 2008[33]	No description (conference abstract)	UC	UC	UC	UC	UC	Insufficient information (conference abstract)
Shephard et al 2010[34]	"63 were patients attending either the renal clinic or dialysis clinic at the Renal Unit, Flinders Medical Centre (FMC), and 37 subjects were healthy volunteers. Capillary whole blood specimens were obtained from each subject and immediately analyzed in singlicate with two Nova StatSensor creatinine devices	yes	no	yes	yes	low	See description

	using the same reagent strip lot number.A venous whole blood specimen anticoagulated with lithium heparin (…) was obtained from each subject at the same time and sent to the pathology laboratory at FMC." Predialysis results from one patient were omitted from graphs and statistical calculations because of very inconsistent results. Collection of POC and lab ref samples at the same time, but time gap between POC and lab reference analysis is unclear.						
Snaith et al 2018[35]	"Where there was incomplete data, i.e. results not available across all methods, the participants were excluded from the sample." After venous blood was collected, "capillary blood sampling was subsequently performed from the fingertip of each participant by two research radiographers (BS and MAH), as would be the case in routine practice. The skin was pierced with a spring-loaded lancet and the sample collected directly onto the analysis strip avoiding squeezing of the finger or milking of blood." Contacted author - time gap between samples was within 10 mins.	yes	yes	yes	Yes	low	See description
Snaith et al 2019[36]	"All patients were cannulated by a CT radiographer or clinical support worker (CSW) following local standard operating procedures and two whole blood samples were collected. One sample (SMonovette Lithium Heparin 2.7ml tube, Ref 05.1553, Sarstedt) was transported to the hospital laboratory for routine analysis. The other sample (1ml BD Plastipak syringe, Ref 303172, Becton Dickinson, San Agustin del Guadalix) was immediately tested on the PoC device within the CT scan suite." If PoC test result identified a decline in kidney function from their baseline result, this prompted a requirement to wait for laboratory confirmation before CT. Contacted author - time gap between samples was within 10 mins. Only	yes	yes	yes	yes	low	See description

	four samples excluded: 1 unable to get blood, 1 lab sample haemolysed, 2 missing samples						

11.4.4 Applicability concerns

AC1: Are there concerns that the included patients do not match the review question?

AC2: Are there concerns that the eGFR/creatinine thresholds used do not match the review question?

AC3: Are there concerns that the index test, its conduct, or interpretation differ from the review question?

AC4: Are there concerns that the reference standard, its conduct, or interpretation differ from the review question?

Study	Description	AC1	AC2	AC3	AC4
Botz et al 2013[25]	Not clear how participants were classified as at risk of renal disease. Not clear if they were outpatients. Conference abstract only. eGFR threshold: 30 & 60. Whole blood samples used for POC.	UC	low	low	low
Dorward et al 2018[26]	HIV positive population, younger & higher proportion of women than average outpatient population. Only 1 patient had eGFR<60. eGFR threshold: 90. Finger prick whole blood used for POC.	high	high	low	low
Houben et al 2017[27]	Only women referred for CE spectral mammography were recruited. Data on all relevant thresholds were extractable.	high	low	low	low
Inoue et al 2017[28]	Pre-adjustment study included 123 consecutive outpatients (74 males, 49 females,mean age 66.7±12.5 years) who underwent CE-CT between September 2011 and February 2012. SCr level of the patients had not been assessed in the month preceding hospital admittance. In the post-adjustment study, 110 consecutive outpatients (62 males, 48 females, mean age 70.1±12.7 years) who underwent CE-CT at Kohka Public Hospital between June and November 2012, were included. <30, 30-45 and >45 thresholds extractable, but equation used to calculate eGFR is not standard (Japanese Society of Nephrology-Chronic Kidney	low	high	high	low

	Disease Initiatives). Uses StatSensor-i and included an adjustment ("adjustment by applying offset correction on the basis of the slope and intercept of internal sample"). Adjusted and unadjusted plots and table of results show the lab eGFR measurements also change, which is not supposed to happen (it should only adjust the device values). So the reported adjusted results from this study may not represent NHS practice. Therefore only unadjusted results were assessed and used in the meta-analysis.				
Korpi-Steiner et al 2009[29]	Patients referred for CT without a recent eGFR/SCr measurement considered at risk. <60 threshold only. Excess lithium hepanirised whole blood samples used.	low	high	high	low
Krige 2017[30]	103 mixed ancestry healthy outpatients attending nephrology clinic. South Africans, Mean age 52, 69% female. Jaffe method used. IPD reported allowed derivation of <30 cut-off data.	high	low	low	low
Nichols 2007[31]	Only chemotherapy patients but no significant reasons to believe they depart from the main population of interest. Only eGFR<60 cut-off assessed.	low	high	low	low
Obrador et al 2012[32]	Only diabetics, 62% women. Simple linear regression was used to estimate a correction factor to align i-STAT SCr to IDMS-SCr. Diagnostic accuracy results were only reported post-correction. CKD staging was not standard (0-4). It is unclear what eGFR values correspond to each CKD stage.	high	high	high	low
Shephard et al 2008[33]	Insufficient information (conference abstract). Results only reported for eGFR=60mLs/min/1.73 m2. Accuracy estimates were only calculated post-correction and alignment.	UC	high	high	low
Shephard et al 2010[34]	67% were dialysis patients, 33% were healthy volunteers. Only eGFR<60 cut-off assessed. Low applicability concerns for post-calibration method (uses standard MDRD factor, as per lab reference). Mentions StatSensor (not clear which model), but used an adjustment to correct for bias. Results pre and post-correction are reported. A similar adjustment could in theory be implemented in the StatSensor Xpress-i so potentially used on the NHS.	high	high	low	low
Snaith et al 2018[35]	Phlebotomy outpatients. Characteristics may differ from outpatients scheduled for CT without recent SCr measurement, but deemed unlikely to significantly affect applicability. All relevant eGFR cut-offs reported.	low	low	low	low

	States device only as StatSensor (unclear which model) and did not use any offset. Only the raw results only are available.				
Snaith et al 2019[36]	CT outpatients without recent (within 3 months) eGFR. No significant concerns. Venous samples were used for POC.	low	low	low	low

11.5 Systematic review of cost-effectiveness studies

Table 65 lists the studies excluded from the review alongside reasons for exclusion.

Table 65 Summary of excluded studies

Study	Reason for rejection
Adams et al,1998 [122]	Study does not include any comparators, and no health outcomes were considered.
CADTH, 2013 [123]	Not a cost-effectiveness analysis.
Lee-Lewandrowski, et al, 2012 [57]	Cost analysis, no health outcomes were considered

11.6 Supplementary cost-effectiveness review

Given that initial scoping searches conducted while drafting the study protocol indicate that the existing cost-effectiveness literature addressing the relevant decision problem is likely to be limited, one targeted search was also conducted to identify further evidence. The aim of this search was to identify cost-effectiveness studies evaluating the treatment and management of AKI. The additional review should mitigate some of the potential limitations of the existing cost-effectiveness literature, as one of the key conceptual issues concerns the nature of the linked evidence modelling required to estimate the occurrence of PC-AKI and their associated consequences (e.g. CKD, end stage renal disease and death).

11.6.1 Methods

11.6.1.1 Searches

Searches were undertaken to identify cost-effectiveness studies evaluating the treatment and management of AKI. A search strategy was developed in MEDLINE (Ovid) consisting of terms for AKI combined with a search strategy developed by Canadian Agency for Drugs and Technologies in Health (CADTH) to limit retrieval to cost-effectiveness studies[124]. The search was limited to studies published from 2012 onwards in any language. The MEDLINE strategy was adapted for use in all other databases searched.

The following databases were searched in January 2019: MEDLINE ALL (includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE),

EconLit, EMBASE, NHS Economic Evaluation Database (NHS EED), Research Papers in Economics (RePEc) and the Science Citation Index.

Search strategy

Database: Ovid MEDLINE(R) ALL <1946 to January 11, 2019>

14/01/2019

Search Strategy:

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1 exp Acute Kidney Injury/ (42239)

2 (acute adj2 (renal or kidney$ or nephr$) adj2 (fail$ or injur$ or insufficien$)).ti,ab. (42016)

3 ((acute or renal or kidney$ or nephr$) adj2 tubular necrosis).ti,ab. (3660)

4 or/1-3 (60629)

5 (contrast adj3 (kidney$ or renal or nephr$) adj3 (injur$ or fail$ or insufficien$ or tubular necrosis)).ti,ab. (1049)

6 (contrast adj3 (AKI or nephropath$ or nephrotoxic$)).ti,ab. (2895)

7 ((radiocontrast or radio-contrast) adj3 (kidney$ or renal or nephr$) adj3 (injur$ or fail$ or insufficien$ or tubular necrosis)).ti,ab. (69)

8 ((radiocontrast or radio-contrast) adj3 (AKI or nephropath$ or nephrotoxic$)).ti,ab. (299)

9 ((postcontrast or post-contrast) adj3 (kidney$ or renal or nephr$) adj3 (injur$ or fail$ or insufficien$ or tubular necrosis)).ti,ab. (19)

10 ((postcontrast or post-contrast) adj3 (AKI or nephropath$ or nephrotoxic$)).ti,ab. (13)

11 (CI-AKI or CIAKI or PC-AKI or PCAKI).ti,ab. (406)

12 or/5-11 (3991)

13 4 or 12 (62842)

14 economics/ (26988)

15 exp "costs and cost analysis"/ (221067)

16 economics, dental/ (1901)

17 exp "economics, hospital"/ (23279)

18 economics, medical/ (8991)

19 economics, nursing/ (3986)

20 economics, pharmaceutical/ (2833)

21 exp "Fees and Charges"/ (29548)

22 exp Budgets/ (13436)

23 budget*.ti,ab,kf. (26878)

24 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (207844)

25 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (255303)

26 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (142936)

27 (value adj2 (money or monetary)).ti,ab,kf. (2107)

28 exp models, economic/ (13754)

29 economic model*.ab,kf. (2928)

30 markov chains/ (13149)

31 markov.ti,ab,kf. (19884)

32 monte carlo method/ (26253)

33 monte carlo.ti,ab,kf. (44643)

34 exp Decision Theory/ (11296)

35 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (20435)

36 or/14-35 (664050)

37 13 and 36 (769)

38 exp animals/ not humans/ (4535562)

39 37 not 38 (763)

40 limit 39 to yr="2012 -Current" (425)

11.6.1.2 Study selection

Studies using decision models to evaluate the cost-effectiveness of AKI management and published from 2012 until 2019 were considered for inclusion. Only full economic evaluations that compared two or more options and considered both costs and consequences (i.e. cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses).

Two researchers (AD and JA) independently screened the titles and abstracts of all reports identified by the bibliographic searches and full-text papers were subsequently obtained for assessment and screened by at least two researchers. Disagreements were resolved by consensus.

11.6.2 Results

The initial search of economic databases identified a total of 2,972 records of which 2,157 remained after deduplication. Eight titles were identified as potentially relevant based on their titles and/or abstracts. The full text articles of these records were assessed for eligibility. Four studies were found to meet the selection criteria [116] [106, 125, 126] and included in the review. These studies were not subject to a formal assessment but used to assist in the overall development of the new analytical model. Table 66 shows the results of the searches, while Table 67 lists excluded studies alongside reasons for exclusion. The studies identified in the review are summarised in Table 68.

Table 66 Results of the AKI models search

Database	Number of records retrieved before deduplication	Number of records after deduplication
MEDLINE **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)**	425	420
EMBASE Ovid	1649	1242
EconLit Ovid	3	2
NHS EED CRD databases	6	0

Science Citation Index Clarivate	877	486
RePeC	12	7
Total in EndNote	**2972**	**2157**

Table 67 Summary of excluded studies

Study	Reason for rejection
De Smedt et al, 2012[127]	Area under the curve model
Ethgen et al, 2015[128]	Does not compare patients with and without AKI
Kerr et al, 2014 [129]	Not a comparison of alternative interventions
Petrovic et al, 2015 [91]	Uses RIFLE definition of AKI and was on paediatric population

Table 68 Studies identified in the review of AKI models

Study, country	Interventions	Patient population	Time horizon	Model type	Health states	Key results
Chicaíza-Becerrra et al, 2012, Colombia	Iso- and low-osmolality contrast media	Outpatients at high risk of CI-AKI	Lifetime	Decision tree	Treatment + no AKI + death/ no death; treatment + AKI + dialysis/no dialysis + death/ no death	Other alternatives dominated by lopamidol and iodixanol Iodixanol vs. iopamidol = US$14,660/LYG
CG 169, UK	Prophylactic hydration to prevent CI-AKI	Patients at high-risk of CI-AKI	Lifetime	Markov model	CKD stage 3-4, CKD stage 5, CI-AKI, death	NAC + sodium chloride 0.9% NMB = £47,957 Sodium bicarbonate NMB = £47,585 At a threshold of £20,000 per additional QALY
Hall et al, 2018 UK	Nephrocheck, cystatin C in urine, plasma and serum and NGAL in urine, plasma and serum	ICU patients	Lifetime	Decision tree + two-period decision model	Decision tree: no AKI, test + FP, test +FN, Test + TP, test +TN, pre-admission AKI Hospitalisation period: Normal kidney function in ICU, 5 ICU AKI stages, hospital ward,	Cystatin C (urine and plasma), NGAL (urine and plasma) dominated by cystatin C (serum). ICERs for cystatin C

					hospital ward + RRT, discharge, discharge + RRT Follow-up period: outpatient follow-up, CKD stage 1-4, ESRD no dialysis, ESRD+dialysis, ESRD transplant, death	(serum), NGAL (serum) and Nephrocheck were £11,476, £25,492 and £12,855,101 per additional QALY, respectively.
Iannazzo et al, 2014, Italy	Iodixanol vs. low-osmolar contrast media	Patients with intravenous contrast media CT	Lifetime	Markov model	AKI free, AKI, myocardial infarction, death	Iodixanol dominated low-osmolar contrast media

LYG, life years gained; NGAL, neutrophil gelatinase-associated lipocalin

Two studies quantify the impact of the interventions under comparison on costs and outcomes by modelling CKD progression after AKI[116] [106] with a Markov model structure. One study [126] also uses a model Markov structure to compare cost-effectiveness between alternative contrast media, but does not characterise CKD progression and considers only progression to myocardial infarction. One study[125] follows a more simplified structure, whereby a decision tree structure is used to quantify the pay-offs in terms of costs and outcomes of dialysis and death.

The CG169 and Chicaíza-Becerra et al 2012 models[106, 125] were considered the most relevant examples of how costs and outcomes associated with AKI can be quantified, as they represent the two extremes of model structure complexity in the context of CI-AKI. The studies were examined with the aim of identifying important structural assumptions, parameter estimates and highlighting key areas of uncertainty. We summarise these studies and highlight the elements potentially relevant to inform the conceptualisation and development of the new decision model.

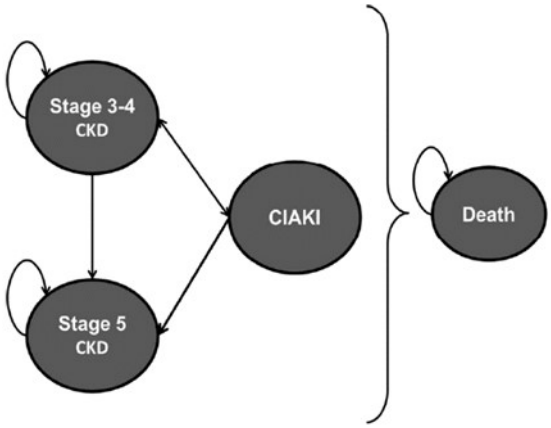
11.6.2.1 Review CG169

The National Clinical Guideline Centre developed a Markov model to assess the cost effectiveness of prophylactic hydration strategies for the prevention of CI- AKI in patients at with stage 3–4 CKD (with and without diabetes) who need a CT scan. The analysis followed the perspective of the NHS and PSS. Costs were expressed as pound sterling (2011/12) and health outcomes as QALYs. Costs and outcomes discounted at an annual rate of 3.5%.

Model structure

The model considers a lifetime horizon and 3 months cycles. The structure of the model is depicted below.

Figure 16 CG169 Model structure



The model is composed of four mutually exclusive health states: Stage 3-4 CKD, Stage 5 CKD, PC-AKI (CI-AKI in the original text), and death. Patients enter the model through the stage 3–4 CKD state and undergo a CT scan, and can then transition to PC-AKI, remain on the initial state or transition to stage 5 CKD. Patients who transition to PC-AKI will remain on that state for one cycle only (3 months), and either return to Stage 3-4 CKD or progress to Stage 5 CKD. After the first cycle, a continuous risk of PC-AKI from repeated scans is assumed for patients in stage 3–4 CKD state. Patients in stage 5 CKD can only remain on the state or die. The model assumes no regression from stage 5 CKD to less severe CKD states, and no further PC-AKI after transition to stage 5 CKD. Patients can transition to death from any other state in the model.

Baseline transition probabilities and treatment effects

The population consists of patients with known stage 3-4 CKD (average age 70 years old) presenting for a CT scan in an unspecified setting. The data sources used to inform baseline transition probabilities to the PC-AKI state, treatment effects from prophylactic hydration, and PC-AKI mortality were drawn mostly from studies in cardiovascular patients receiving contrast. The severity of AKI was assumed to impact only on mortality rates for the PC-AKI state. AKI stage specific mortality rates were obtained from a large observational study[130]in coronary angiography patients and weighted by the relative proportion of patients at each AKI severity stage following the cardiovascular intervention in the same study to estimate the overall probability of death following PC-AKI. The baseline risk of PC-AKI was informed by the incidence of AKI in the renal insufficiency subgroup prophylactically IV hydrated with the sodium chloride 0.9% treatment from a trial comparing two hydration strategies in patients undergoing coronary angiography[131]. The probability of a repeat scan was derived from the probability of repeat PCI in a trial of patients with coronary artery disease [132], and applied to the baseline risk of PC-AKI to calculate the risk of PC-AKI from the second cycle in the model onwards.

The age-dependent probability of disease progression from stage 3–4 to stage 5 CKD was derived from a retrospective longitudinal study of stage 3 CKD patients[133].The probability of death on stage 3-4 CKD was estimated by applying age and sex- dependent standardised mortality rates (SMRs) to UK general population life-tables, and converting the annual rates to 3 months probabilities. The model implicitly assumed the same rate of progression to stage 5 CKD and mortality for both stage 3 and 4 CKD patients, despite the latter having more severe renal function impairment.

Mortality on stage 5 CKD was estimated by applying age and sex- dependent SMRs from prospective cohort study in an ESRD population to UK general population life-tables.

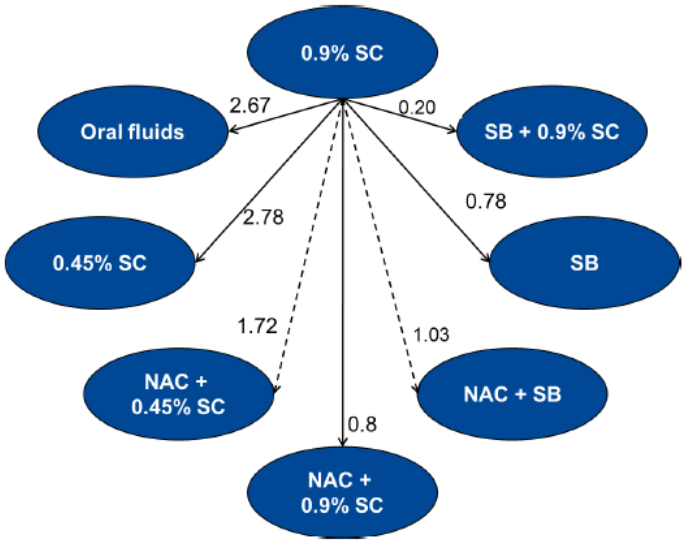
Baseline treatment properties in the model are summarise in Table 69, alongside sources of evidence.

Table 69 Baseline transition probabilities and treatment effects in the model

Transition	Probability	Source
Stage 3-4 to PC-AKI (1st cycle)	0.0217	Mueller et al. 2002 [131]
Stage 3-4 (2nd cycle and subsequent cycles)	0.0007	Mueller et al. 2002[131] Serruys et al 2009[132]
PC-AKI stage 1 to stage 5 CKD	0.015	James et al, 2011[130] Applied to 83% of PC-AKI patients
PC-AKI stage 2-3 to stage 5 CKD	0.109	James et al, 2011[130] Applied to 17% of PC-AKI patients
PC-AKI to stage 5 CKD	0.031	Calculated
CKD stage 3–4 to CKD stage 5 (mean–age dependant)	0.001	Eriksen and Ingebretsen, 2006[133]
PC-AKI stage 1 to death	0.136	James et al, 2011[130] Applied to 83% of PC-AKI patients
PC-AKI stage 2-3 to death	0.378	James et al, 2011[130] Applied to 17% of PC-AKI patients
PC-AKI to death	0.182	Calculated

The treatment effect of each alternative prophylactic IV hydration strategy was estimated as a relative risks of PC-AKI using a mix of direct and indirect comparisons, and applied to the baseline risk of PC-AKI for the reference hydration strategy (Sodium chloride 0.9%). Figure 17 illustrates the treatment effects (RRs) estimated in comparison to sodium chloride 0.9%. Adverse events from prophylaxis were not considered in the model.

Figure 17 Comparisons of relative treatment effects available from meta-analysis of trials (CG169)



NAC, N-acetilcysteine; SB, sodium bicarbonate; SC, sodium chloride.

Health-related quality of life

Health state utility was informed by a literature review conducted by the authors. Estimates from a Japanese[134] study reporting EQ-5D utility scores by CKD stage (1 to 5) was applied to the UK general population utility estimate for the 65-74 age bracket[135]to yield health state utility estimates. For the PC-AKI health state was estimated by multiplying the utility estimate for renal failure from a UK-based catalogue of EQ-5D index scores[136]by the same general UK population utility estimate used to adjust the CKD states' estimates.

Resource use and costs

The resource use and costs included in the model were the ones associated with the acquisition and administration of the hydration strategies, and health state costs.

The acquisition unit costs for the hydration strategies were sourced from published national sources, manufacturers' price lists, and personal communications with Commercial Medicines Unit of the UK Department of Health. The resource use associated with infusion (and dose) was based on the hydration regimes that constituted each strategy, rather than the regimes on the trials informing treatment effectiveness. It was assumed that only infusions during more than 8 hours would require hospitalisation. No administration costs were included for hydration strategies administered over a shorter period. The unit cost for infusions requiring hospitalisation was that of a coronary angiography excess bed day from NHS reference costs [137].

Health state unit costs were sourced from national published sources: NHS reference costs 2011/12 [137], Personal Social Services Research Unit 2012 [138] British National Formulary (BNF) 62[139] and other

NICE guidance. Resource use was based on assumptions informed by expert opinion. Table 70 to Table 73 summarise health states resource use and costs.

Table 70 PC-AKI state costs and resource use

Category	Resource use	Source/details	Unit Cost	Source	Cost per cycle
PC-AKI	1	Event in the model	£2,013	Weighted average of AKI related HRG codes (LA07C-G) from NHS reference costs, 2011[137]	£2,013

The PC-AKI health state costs were estimated by pooling the average costs of all AKI related HRG codes in the NHS reference costs weighted by their respective activity. The cost per cycle was £2,013.

Costs in stage 3-4 CKD include specialist appointments, eGFR measurements, anaemia management with epoetin α and diuretics. The cost per cycle on this state was £176.

Table 71 Stage 3-4 CKD state costs and resource use

Category	Resource use	Source/details	Unit Cost	Source	Cost per cycle
Nephrologist appointment	1	Per cycle, assumption	£157	NHS reference costs, 2011[137]	£157
eGFR measurement					
Biochemistry	1	Per cycle , assumption	£1.26	NHS reference costs, 2011[137]	£1.26
Phlebotomist	5 minutes	Per cycle, assumption	£3.42	PSSRU,2012[138]	£3.42
Drugs					
Diuretics	40mg/day	Assumed that 26% patients were in stage 4 and of these patients around 60% would be treated with furosemide.	£0.26	BNF62[139]	£4
Epoetin α	1,788 units/week	Applied to 9% of who are patients assumed to require treatment for anaemia. Dose and proportion of patients informed by previous NICE guidance	£0.0051	BNF62[139]	£11

Patients in stage 5 CKD will incur costs associated with either RRT or conservative management (management without RRT). It was assumed that 90% of patients received RRT and 10% conservative managements. For patients on RRT the costs in stage 5 CKD differed for cycle 1 (£7,252) and for cycle 2 onwards (£6,284 per cycle), with higher resource use intensity in cycle 1 due to the need to perform access procedures for RRT before starting treatment. Access procedures are then assumed to be required once every 1 to 5 years. Patients on conservative management for CKD stage 5 patients also incur the costs of diuretic drugs and additional check-ups. The cost per cycle of conservative management was £642. Considering all patients (RRT and conservative management) the cost on the first cycle was £6,585, and the £5,512 per subsequent cycle.

Table 72 Stage 5 CKD state costs and resource use for RRT patients

	Category	Resource use	Source/details	Unit Cost	Source	Cost per cycle
1st cycle	Nephrologist appointment	2	Per cycle , assumption	£157	NHS reference costs, 2011[137]	£374
	eGFR measurement	12	See Table 71	£4.67	See Table 71	£56
	Epoetin α	1.788 units/week	Applied to 33% of patients who are assumed to require treatment for anaemia. Dose and proportion of patients informed by previous NICE guidance	£0.01	BNF62[139]	£39
	Access procedure	1	Assumption	£1,323	Pooled average of HRG codes for RRT access procedures from NHS reference costs, 2011[137]	£1,323
	RRT	3 haemodialysis sessions/week 7 peritoneal dialysis sessions/week	Assumption. Distribution of patients on peritoneal dialysis and haemodialysis (21% and 79% of patients on RRT, respectively) and frequency of sessions was informed by the Renal Registry report.	£ 157.76 haemodialysis £54.70 peritoneal dialysis	Activity weighted average of HRG codes for RRT procedures from NHS reference costs, 2011[137]	£5,460
After cycle 1st	Nephrologist appointment	2	Per cycle , assumption	£157	NHS reference costs, 2011[137]	£314
	eGFR measurement	12	See Table 71	£4.67	See Table 71	£56
	Epoetin α	1.788 units/week	Applied to 33% of patients who are assumed to require treatment for anaemia. Dose and proportion of patients informed by NICE CG114	£0.01	BNF62	£39
	Access procedure	0.15	Assumption	£1,323	Pooled average of HRG codes for RRT access procedures from NHS reference costs, 2011[137]	£199
	RRT	3 weekly haemodialysis sessions or 7 weekly peritoneal dialysis sessions	Assumption. Distribution of patients on peritoneal dialysis and haemodialysis (21% and 79% of patients on RRT, respectively)	£ 157.76 for haemodialysis £54.70 for peritoneal dialysis	Activity weighted average of HRG codes for RRT procedures from NHS reference costs, 2011[137]	£5,460

			and frequency of sessions was informed by the Renal Registry report.			

Table 73 Stage 5 CKD state costs and resource use for conservative management patients

Category	Resource use	Source/details	Unit Cost	Source	Cost per cycle
Nephrologist appointment	2	Per cycle , assumption	£157	NHS reference costs, 2011[137]	£374
Specialist nurse					
Phone call	12	Per cycle, assumption	£5.30	PSSRU, 2012[138]	£64
Home visit	3	Per cycle, assumption	£22.08	PSSRU, 2012 [138]	£66
eGFR measurement	12	See Table 71	£4.67	See Table 71	£56
Drugs					
Epoetin α	1.788 units/week	Applied to 33% of patients who are assumed to require treatment for anaemia. Dose and proportion of patients informed by NICE CG114	£0.01	BNF62[139]	£39
Diuretics	80mg/day	Assumed that 90% patients would be treated with furosemide.	£0.26	BNF62[139]	£43

Uncertainty

Joint parameter uncertainty was considered in the model by performing probabilistic sensitivity analysis. Probabilistic distributions were attributed to most parameters in the model and random draws of these distributions were sampled over 1,000 model simulations to yield probabilistic cost effectiveness estimates.

The authors conducted an extensive number of scenario analyses testing assumptions around resource use associated with IV hydration, costs of PC-AKI, age in the model, baseline risk of PC-AKI, probability of repeat scans, treatment effect of hydration, health state utilities, and discount rates.

Findings

Under base-case assumptions, the cost effective strategy to prevent PC-AKI in patients with stage 3-4 CKD undergoing CT scans was considered to be IV hydration with sodium chloride 0.9% in addition to NAC with a NMB of £47,957 at a threshold £20,000 per additional QALY. This strategy also had the highest probability of cost effectiveness, 43%, at the same cost effectiveness threshold. Sodium bicarbonate with sodium chloride 0.9% was the most effective strategy, generating 0.006 additional QALYs on average compared to sodium chloride in addition to NAC. However, the additional QALYs did not offset the incremental costs when comparing these two strategies (£370).

The results were robust to the majority of the scenario analysis undertaken. The key drivers of the model were identified as the cost of admission for the IV hydration regimens requiring it and the treatment effectiveness estimates.

When it was assumed that all patients were inpatients and no additional costs of hospital admission were considered for IV hydration strategies administered over periods longer than 8 hours, the cost effective strategy became sodium bicarbonate with sodium chloride 0.9% with a NMB of £47,738 and 90% probability of cost effectiveness at £20,000 per QALY gained. When it was assumed that strategies containing either sodium chloride 0.9% or sodium bicarbonate patients required a hospital admission sodium bicarbonate with sodium chloride 0.9% was also the cost effective strategy with a NMB of £47,304 and 70% probability of cost effectiveness at £20,000 per QALY gained.

Applying the treatment effect for NAC plus sodium bicarbonate vs. sodium chloride 0.9% estimated from an alternative indirect link in the treatment effectiveness meta-analysis (RR=0.63 instead of 1.03), the cost effective strategy was NAC plus sodium bicarbonate with a NMB of £47,670 and 48% probability of cost effectiveness at £20,000 per QALY gained.

Limitations of the model in the context of our study

The model structure does not consider patients with normal kidney function and at earlier stages of renal disease (CKD stage1-2), as these were not part of the study population. Therefore, the model would require substantial structural adaptations to include those patients.

The parameter estimates informed by evidence generated in the context of PCI and coronary angiography are unlikely to be directly generalisable to our study population, as the underlying risk of CI- AKI, severity of AKI and associated mortality is likely to be much higher for patients who i) undergo intra-arterial contrast administration, and ii) have more cardiovascular related comorbidities that are also risk factors for AKI (e.g. diabetes) than we expect to observe in an outpatient population referred for IV contrast enhanced CT scanning.

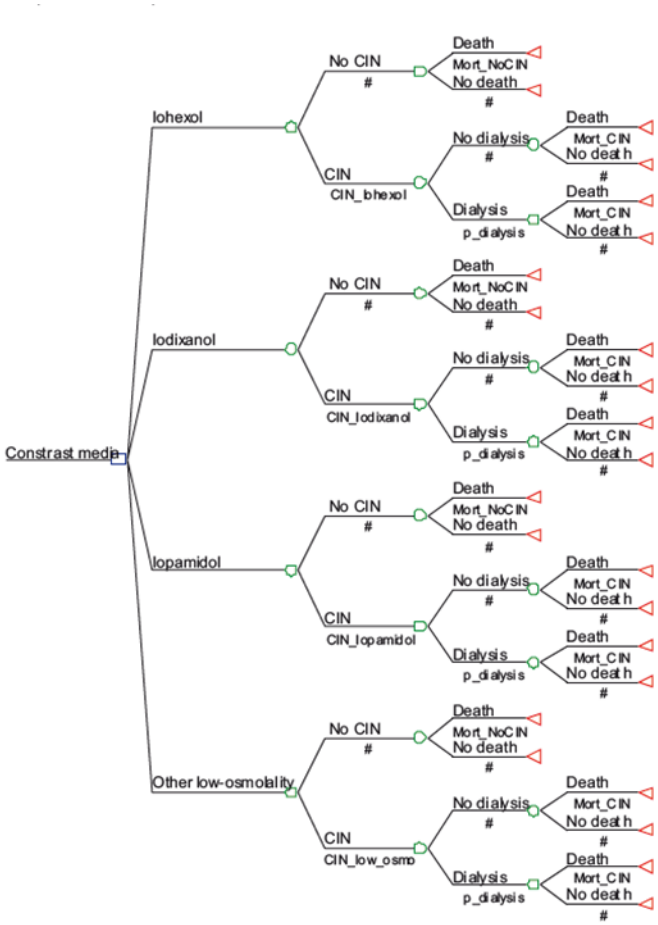
11.6.2.2 Review Chicaíza-Becerra et al, 2012

The authors used a decision tree model to evaluate the cost effectiveness of iso and low-osmolality contrast media for outpatients at high risk of PC-AKI from the perspective of the Colombian NHS. Costs were expressed as US dollars, 2009 price year, and health outcomes as life years gained (LYG). Base-case results are presented for undiscounted costs and outcomes, as well as applying a 3% annual rate on both.

Model structure

The decision tree considers a lifetime horizon and is illustrated in Figure 18Table 1.

Figure 18 Decision tree structure (Chicaíza-Becerra et al. 2012)



All patients undergo a procedure (not described) that requires administration of one of 4 possible contrast media alternatives: Iohexol, iodixanol, iopamidol or other low-osmolality contrast media. The structure of the decision tree is the same for each of the 4 contrast options. The first chance node divides patients according to their probability of having PC-AKI (CIN in the original paper) after contrast administration. Patient who do not have PC-AKI, can die or survive. Patients without PC-AKI, may have to undergo dialysis or not. All patients who suffer a PC-AKI event have a PC-AKI specific mortality risk at the last chance node. Surviving patients have the full life expectancy of the Colombian general population (74 years).

Probabilities and treatment effects

The study population is described as outpatients at high risk of PC-AKI, however, the authors do not define what consists high risk in this context. The patients' average age in the model is 63 years old. Table 74 summarises the probability estimates in the model and sources of evidence.

Table 74 Probabilities and treatment effects in the model

Probability	Point estimate	Source
Probability of PC-AKI		

Iohexol	0.21	Solomon et al, 2005[140] Nguyen et al, 2008{#5818 Solomon and Dumouchel, 2006{#5819}
Iodixanol	0.09	
iodixanol	0.1	
Other low osmolality media	0.18	
Mortality PC-AKI	0.16	From et al, 2008[141]
Mortality no AKI	0.05	
Probability of Dialysis (if PC-AKI)	0.36	Klarenbach et al. 2006[142] Aguirre Caicedo et al 2007[143]
Probability of hospitalisation on CCU	0.29	

CCU – critical care unit

The authors do not state if dialysis is transient or permanent, and what was the period of time considered to estimate the probability of dialysis. Since the risk of death is not conditional on dialysis, dialysis is likely to be transient. Furthermore, only 6 days of hospitalisation were considered for patients who initiate dialysis (see resource use and costs). It is also not described what time period was considered for the estimation of the probabilities of death.

Health-related quality of life

Health-related quality of life was not considered in the model due to the lack of health utility estimates specific to Colombia at the time of the study. Effectiveness was measured in life years gained, and the average life expectancy of the Colombian population was assumed for patients who survived in the model.

Resource use and costs

The study included the following elements of resource use and costs: direct costs related to contrast media, and the treatment of associated renal complications. The cost of prophylactic IV hydration was not included, as the same costs would apply to every strategy under comparison. The unit costs for contrast media were market prices, and the unit cost of healthcare use for handling complications was taken from the Colombian national tariff set for medicines and health procedures. Table 75 summarises the resource use in the model. Unit costs were not extracted as it was not clear whether the costs reported in the study were unit costs.

Table 75 Summary of resource use in Chicaíza-Becerra et al 2012

Category	Resource use	Source/details
Contrast media		
Iopamidol	17.5mL	Assumes 5 mL of contrast for each kilogram of patient's body weight divided by serum creatinine level. The average weight in the model is assumed to be 70Kg and average serum creatinine 2mg/dL.
Iohexol		
Other low-osmolality		
Iodixanol		

Days of hospitalisation without nephropathy	2	Klarenbach et al. 2006[142] Aguirre Caicedo et al 2007[143]
Days of hospitalisation with nephropathy and no dialysis	4	
Days of hospitalisation with nephropathy and dialysis	6	
Dialysis	1	
Placement temporary venous catheter	1	Not clear to whom these costs apply in the model
Creatinine, BUN, electrolites and blood gas analysis	1	

BUN, Blood urea nitrogen; CCU, critical care unit

Uncertainty

The model considered joint parameter uncertainty by performing probabilistic sensitivity analysis. Probabilistic distributions were attributed to most parameters in the model, but no further details are provided on the probabilistic sensitivity analysis. The authors conducted univariate deterministic sensitivity analysis by varying most parameters within a range of values. The rational for each range of values was not presented.

Findings

The iohexol and other low osmolality contrast media were dominated by iopamidol and iodixanol in the base-case analysis. At a cost-effectiveness threshold of US $5,356 per additional QALY (the Colombian threshold value) iopamidol was identified as the cost effective option for the analyses applying a 0% and 3% annual discount rate on both costs and outcomes. Iopamidol was also the strategy most likely to be cost effective at a willingness to pay ranging between US $0 to $11,740.

The results were sensitive to variation in the risk of PC-AKI for iopamidol (if it became higher than 0.11, iodixanol would dominate all strategies), and to the costs of contrast media. Iopamidol became less cost-effective when the price per 50 ml vial was higher than US $51 (base case US $26.6), while iodixanol became cost-effective when the price for 50 ml vial was lower than $28 (base case US $52.7).

Limitations of the model in the context of our study

While the model structure is flexible enough to consider the full population of non-emergency outpatients presenting for a CT scan, the evidence sources informing the model are mostly informed by studies in patients at a higher risk of PC-AKI (and subsequent events). Furthermore, the assumptions on time frame for the occurrence of short term events (death and dialysis) and for duration of adverse outcomes (dialysis) are not explicitly stated. Finally, the model does not consider HRQoL.

11.6.3 Conclusion

The structure of the model described in Chicaíza-Becerra et al. 2012 [125] links PC-AKI to the relevant outcomes in terms of costs and HRQoL, and can be easily be adapted to address the decision problem in our study. Although the model developed for CG169 [106] also allows to establish this link, the additional evidence that is required to parameterise this more complex model is not available for the population of interest. The increased complexity of the CG169 model was necessary to capture the impact of PC-AKI in a specific population with pre-existing Grade 3-4 CKD disease, but is less relevant in the context of our study. Furthermore, the model structure in CG169 does not consider patients with normal kidney function and at earlier stages of renal disease (CKD stage1-2), and would, therefore, require substantial structural adaptation to reflect the population in our decision problem.

11.7 Scenario analyses results

Table 76 Cost effectiveness results – Scenario 1: StatSensor adjusted analysis

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	14
2	RF + i-STAT		£278.02	9.991371002	9.97747	£199,549.40	0.00426	£85.25	3
3	RF + ABL800FLEX		£285.87	9.991371003	9.97708	£199,541.55	0.00387	£77.39	9
4	RF + StatSensor		£278.51	9.991371002	9.97745	£199,548.91	0.00424	£84.75	4
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	13
6	RF + i-STAT + Lab		£275.84	9.991371002	9.97758	£199,551.58	0.00437	£87.42	1
7	RF + ABL800FLEX + Lab		£284.39	9.991371003	9.97715	£199,543.03	0.00394	£78.87	7
8	RF + StatSensor + Lab		£276.61	9.991371002	9.97754	£199,550.81	0.00433	£86.66	2
9	i-STAT		£286.35	9.991371002	9.97705	£199,541.07	0.00385	£76.91	10
10	ABL800FLEX		£290.99	9.991371003	9.97682	£199,536.43	0.00361	£72.28	12
11	StatSensor		£285.13	9.991371002	9.97711	£199,542.29	0.00391	£78.13	8
12	i-STAT+ Lab		£280.08	9.991371002	9.97737	£199,547.34	0.00416	£83.18	6
13	ABL800FLEX+ Lab		£286.70	9.991371003	9.97704	£199,540.72	0.00383	£76.56	11
14	StatSensor + Lab		£279.62	9.991371002	9.97739	£199,547.80	0.00418	£83.65	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 77 Cost effectiveness results – Scenario 2: CKD-EPI equation studies

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	14
2	RF+ i-STAT		£277.73	9.991371001	9.97748	£199,549.69	0.00428	£85.54	3
3	RF + ABL800FLEX		£286.05	9.991371001	9.97707	£199,541.37	0.00386	£77.21	9
4	RF + StatSensor		£278.67	9.991370989	9.97744	£199,548.75	0.00423	£84.60	4
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	13
6	RF + i-STAT + Lab		£275.72	9.991371001	9.97758	£199,551.70	0.00438	£87.54	2
7	RF + ABL800FLEX + Lab		£284.26	9.991371001	9.97716	£199,543.16	0.00395	£79.01	7
8	RF + StatSensor + Lab		£275.68	9.991370989	9.97759	£199,551.74	0.00438	£87.59	1
9	i-STAT		£285.70	9.991371001	9.97709	£199,541.72	0.00388	£77.57	8
10	ABL800FLEX		£291.85	9.991371001	9.97678	£199,535.57	0.00357	£71.41	12
11	StatSensor		£287.65	9.991370989	9.97699	£199,539.77	0.00378	£75.61	11
12	i-STAT+ Lab		£279.90	9.991371001	9.97738	£199,547.52	0.00417	£83.36	6
13	ABL800FLEX+ Lab		£286.67	9.991371001	9.97704	£199,540.75	0.00383	£76.59	10
14	StatSensor + Lab		£279.03	9.991370989	9.97742	£199,548.39	0.00421	£84.23	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 78 Cost effectiveness results – Scenario 3: Alternative risk factor questionnaire

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	14
2	RF+ i-STAT		£280.52	9.991370997	9.97734	£199,546.90	0.00414	£82.74	6
3	RF + ABL800FLEX		£287.38	9.991370998	9.97700	£199,540.04	0.00379	£75.89	11
4	RF + StatSensor		£279.71	9.991370993	9.97739	£199,547.71	0.00418	£83.55	4
5	RF + Lab		£322.14	9.991371004	9.97526	£199,505.28	0.00206	£41.12	13
6	RF + i-STAT + Lab		£277.09	9.991370997	9.97752	£199,550.33	0.00431	£86.18	2
7	RF + ABL800FLEX + Lab		£285.03	9.991370998	9.97712	£199,542.39	0.00391	£78.23	8
8	RF + StatSensor + Lab		£277.05	9.991370993	9.97752	£199,550.37	0.00431	£86.22	1
9	i-STAT		£286.35	9.991371002	9.97705	£199,541.07	0.00385	£76.91	9
10	ABL800FLEX		£290.99	9.991371003	9.97682	£199,536.43	0.00361	£72.28	12
11	StatSensor		£283.96	9.991370997	9.97717	£199,543.46	0.00396	£79.30	7
12	i-STAT+ Lab		£280.08	9.991371002	9.97737	£199,547.34	0.00416	£83.18	5
13	ABL800FLEX+ Lab		£286.70	9.991371003	9.97704	£199,540.72	0.00383	£76.56	10
14	StatSensor + Lab		£279.09	9.991370997	9.97742	£199,548.33	0.00421	£84.17	3

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 79 Cost effectiveness results – Scenario 4: eGFR distribution - Harris subgroup without prior eGFR

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£361.06	9.991371782	9.97332	£199,466.38	0.00000	£0.00	14
2	RF+ i-STAT		£275.59	9.991371778	9.97759	£199,551.85	0.00427	£85.47	3
3	RF + ABL800FLEX		£283.62	9.991371779	9.97719	£199,543.81	0.00387	£77.44	10
4	RF + StatSensor		£275.65	9.991371776	9.97759	£199,551.78	0.00427	£85.41	4
5	RF + Lab		£301.65	9.991371782	9.97629	£199,525.78	0.00297	£59.41	13
6	RF + i-STAT + Lab		£273.62	9.991371778	9.97769	£199,553.82	0.00437	£87.44	1
7	RF + ABL800FLEX + Lab		£282.16	9.991371779	9.97726	£199,545.28	0.00395	£78.90	8
8	RF + StatSensor + Lab		£274.16	9.991371776	9.97766	£199,553.27	0.00434	£86.90	2
9	i-STAT		£283.47	9.991371778	9.97720	£199,543.96	0.00388	£77.59	9
10	ABL800FLEX		£288.69	9.991371779	9.97694	£199,538.74	0.00362	£72.37	12
11	StatSensor		£281.34	9.991371776	9.97730	£199,546.10	0.00399	£79.72	7
12	i-STAT+ Lab		£277.80	9.991371778	9.97748	£199,549.63	0.00416	£83.26	6
13	ABL800FLEX+ Lab		£284.47	9.991371779	9.97715	£199,542.96	0.00383	£76.59	11
14	StatSensor + Lab		£277.05	9.991371776	9.97752	£199,550.39	0.00420	£84.01	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 80 Cost effectiveness results – Scenario 5: eGFR distribution - GSTT audit data population

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£460.78	9.991336844	9.96830	£199,365.95	0.00000	£0.00	14
2	RF+ i-STAT		£374.98	9.991336644	9.97259	£199,451.76	0.00429	£85.80	6
3	RF + ABL800FLEX		£384.19	9.991336669	9.97213	£199,442.54	0.00383	£76.59	10
4	RF + StatSensor		£364.55	9.991336515	9.97311	£199,462.18	0.00481	£96.23	2
5	RF + Lab		£410.83	9.991336844	9.97080	£199,415.90	0.00250	£49.95	13
6	RF + i-STAT + Lab		£372.81	9.991336644	9.97270	£199,453.93	0.00440	£87.97	5
7	RF + ABL800FLEX + Lab		£383.05	9.991336669	9.97218	£199,443.69	0.00389	£77.73	8
8	RF + StatSensor + Lab		£362.79	9.991336515	9.97320	£199,463.94	0.00490	£97.98	1
9	i-STAT		£383.53	9.991336644	9.97216	£199,443.20	0.00386	£77.25	9
10	ABL800FLEX		£389.08	9.991336669	9.97188	£199,437.66	0.00359	£71.70	12
11	StatSensor		£371.11	9.991336515	9.97278	£199,455.62	0.00448	£89.67	4
12	i-STAT+ Lab		£376.46	9.991336644	9.97251	£199,450.27	0.00422	£84.32	7
13	ABL800FLEX+ Lab		£384.94	9.991336669	9.97209	£199,441.79	0.00379	£75.84	11
14	StatSensor + Lab		£365.34	9.991336515	9.97307	£199,461.39	0.00477	£95.44	3

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 81 Cost effectiveness results – Scenario 6.1: Throughput – 12.7% without a prior eGFR

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£361.06	9.991371782	9.97332	£199,466.38	0.00000	£0.00	14
2	RF+ i-STAT		£278.41	9.991371778	9.97745	£199,549.02	0.00413	£82.65	2
3	RF + ABL800FLEX		£302.33	9.991371779	9.97626	£199,525.11	0.00294	£58.73	11
4	RF + StatSensor		£280.85	9.991371776	9.97733	£199,546.58	0.00401	£80.21	5
5	RF + Lab		£301.65	9.991371782	9.97629	£199,525.78	0.00297	£59.41	10
6	RF + i-STAT + Lab		£276.44	9.991371778	9.97755	£199,550.99	0.00423	£84.62	1
7	RF + ABL800FLEX + Lab		£300.87	9.991371779	9.97633	£199,526.57	0.00301	£60.19	9
8	RF + StatSensor + Lab		£279.36	9.991371776	9.97740	£199,548.07	0.00408	£81.70	3
9	i-STAT		£286.30	9.991371778	9.97706	£199,541.14	0.00374	£74.76	7
10	ABL800FLEX		£307.40	9.991371779	9.97600	£199,520.04	0.00268	£53.66	13
11	StatSensor		£286.54	9.991371776	9.97704	£199,540.90	0.00373	£74.52	8
12	i-STAT+ Lab		£280.62	9.991371778	9.97734	£199,546.81	0.00402	£80.44	4
13	ABL800FLEX+ Lab		£303.18	9.991371779	9.97621	£199,524.25	0.00289	£57.88	12
14	StatSensor + Lab		£282.25	9.991371776	9.97726	£199,545.19	0.00394	£78.81	6

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit

Table 82 Cost effectiveness results – Scenario 6.2: Throughput - 50% lower than base-case

	Identification	Management	Total costs	Total QALYs	NHB *** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	14
2	RF+ i-STAT		£279.71	9.991371002	9.97739	£199,547.71	0.00418	£83.56	3
3	RF + ABL800FLEX		£297.07	9.991371003	9.97652	£199,530.35	0.00331	£66.20	10
4	RF + StatSensor		£280.95	9.991370997	9.97732	£199,546.47	0.00412	£82.31	4
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	13
6	RF + i-STAT + Lab		£277.53	9.991371002	9.97749	£199,549.89	0.00429	£85.73	1
7	RF + ABL800FLEX + Lab		£295.59	9.991371003	9.97659	£199,531.83	0.00338	£67.67	9
8	RF + StatSensor + Lab		£279.27	9.991370997	9.97741	£199,548.15	0.00420	£84.00	2
9	i-STAT		£288.04	9.991371002	9.97697	£199,539.38	0.00376	£75.22	8
10	ABL800FLEX		£302.18	9.991371003	9.97626	£199,525.24	0.00305	£61.08	12
11	StatSensor		£287.07	9.991370997	9.97702	£199,540.35	0.00381	£76.19	7
12	i-STAT+ Lab		£281.77	9.991371002	9.97728	£199,545.65	0.00407	£81.49	5
13	ABL800FLEX+ Lab		£297.90	9.991371003	9.97648	£199,529.52	0.00327	£65.36	11
14	StatSensor + Lab		£282.21	9.991370997	9.97726	£199,545.21	0.00405	£81.06	6

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 83 Cost effectiveness results – Scenario 6.3: Throughput - 50% higher than base-case

	Identification	Management	Total costs	Total QALYs	NHB *** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	14
2	RF+ i-STAT		£277.45	9.991371002	9.97750	£199,549.97	0.00429	£85.81	4
3	RF + ABL800FLEX		£282.14	9.991371003	9.97726	£199,545.28	0.00406	£81.12	8
4	RF + StatSensor		£276.80	9.991370997	9.97753	£199,550.62	0.00432	£86.46	3
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	13
6	RF + i-STAT + Lab		£275.28	9.991371002	9.97761	£199,552.14	0.00440	£87.98	2
7	RF + ABL800FLEX + Lab		£280.66	9.991371003	9.97734	£199,546.76	0.00413	£82.60	7
8	RF + StatSensor + Lab		£275.12	9.991370997	9.97762	£199,552.30	0.00441	£88.14	1
9	i-STAT		£285.79	9.991371002	9.97708	£199,541.63	0.00387	£77.47	11
10	ABL800FLEX		£287.25	9.991371003	9.97701	£199,540.17	0.00380	£76.01	12
11	StatSensor		£282.93	9.991370997	9.97722	£199,544.49	0.00402	£80.34	9
12	i-STAT+ Lab		£279.52	9.991371002	9.97740	£199,547.90	0.00419	£83.75	6
13	ABL800FLEX+ Lab		£282.97	9.991371003	9.97722	£199,544.45	0.00401	£80.29	10
14	StatSensor + Lab		£278.06	9.991370997	9.97747	£199,549.36	0.00426	£85.21	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 84 Cost effectiveness results – Scenario 7.1: Proportion of cancelled CT scans (0%)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£273.51	9.991371010	9.97770	£199,553.91	0.00000	£0.00	2
2	RF+ i-STAT		£277.20	9.991371002	9.97751	£199,550.22	-0.00018	-£3.69	6
3	RF + ABL800FLEX		£285.15	9.991371003	9.97711	£199,542.27	-0.00058	-£11.64	12
4	RF + StatSensor		£277.16	9.991370997	9.97751	£199,550.26	-0.00018	-£3.64	5
5	RF + Lab		£272.48	9.991371010	9.97775	£199,554.94	0.00005	£1.03	1
6	RF + i-STAT + Lab		£275.03	9.991371002	9.97762	£199,552.39	-0.00008	-£1.51	3
7	RF + ABL800FLEX + Lab		£283.67	9.991371003	9.97719	£199,543.75	-0.00051	-£10.16	10
8	RF + StatSensor + Lab		£275.47	9.991370997	9.97760	£199,551.95	-0.00010	-£1.96	4
9	i-STAT		£284.87	9.991371002	9.97713	£199,542.55	-0.00057	-£11.36	11
10	ABL800FLEX		£289.82	9.991371003	9.97688	£199,537.60	-0.00082	-£16.30	14
11	StatSensor		£282.77	9.991370997	9.97723	£199,544.65	-0.00046	-£9.25	9
12	i-STAT+ Lab		£278.60	9.991371002	9.97744	£199,548.82	-0.00025	-£5.09	8
13	ABL800FLEX+ Lab		£285.54	9.991371003	9.97709	£199,541.88	-0.00060	-£12.02	13
14	StatSensor + Lab		£277.90	9.991370997	9.97748	£199,549.52	-0.00022	-£4.39	7

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit

Table 85 Cost effectiveness results – Scenario 7.1: Proportion of cancelled CT scans (25%)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£295.95	9.991371010	9.97657	£199,531.47	0.00000	£0.00	14
2	RF+ i-STAT		£277.40	9.991371002	9.97750	£199,550.02	0.00093	£18.55	4
3	RF + ABL800FLEX		£285.33	9.991371003	9.97710	£199,542.09	0.00053	£10.62	11
4	RF + StatSensor		£277.33	9.991370997	9.97750	£199,550.09	0.00093	£18.62	3
5	RF + Lab		£280.37	9.991371010	9.97735	£199,547.05	0.00078	£15.58	7
6	RF + i-STAT + Lab		£275.23	9.991371002	9.97761	£199,552.19	0.00104	£20.72	1
7	RF + ABL800FLEX + Lab		£283.85	9.991371003	9.97718	£199,543.57	0.00060	£12.10	9
8	RF + StatSensor + Lab		£275.64	9.991370997	9.97759	£199,551.78	0.00102	£20.31	2
9	i-STAT		£285.24	9.991371002	9.97711	£199,542.18	0.00054	£10.71	10
10	ABL800FLEX		£290.11	9.991371003	9.97687	£199,537.31	0.00029	£5.84	13
11	StatSensor		£283.07	9.991370997	9.97722	£199,544.35	0.00064	£12.88	8
12	i-STAT+ Lab		£278.97	9.991371002	9.97742	£199,548.45	0.00085	£16.98	6
13	ABL800FLEX+ Lab		£285.83	9.991371003	9.97708	£199,541.59	0.00051	£10.12	12
14	StatSensor + Lab		£278.20	9.991370997	9.97746	£199,549.22	0.00089	£17.75	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 86 Cost effectiveness results – Scenario 7.3: Proportion of cancelled CT scans (50%)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£318.39	9.991371010	9.97545	£199,509.03	0.00000	£0.00	14
2	RF+ i-STAT		£277.61	9.991371002	9.97749	£199,549.81	0.00204	£40.78	4
3	RF + ABL800FLEX		£285.51	9.991371003	9.97710	£199,541.91	0.00164	£32.88	9
4	RF + StatSensor		£277.50	9.991370997	9.97750	£199,549.92	0.00204	£40.89	3
5	RF + Lab		£288.27	9.991371010	9.97696	£199,539.15	0.00151	£30.12	12
6	RF + i-STAT + Lab		£275.44	9.991371002	9.97760	£199,551.98	0.00215	£42.95	1
7	RF + ABL800FLEX + Lab		£284.03	9.991371003	9.97717	£199,543.39	0.00172	£34.35	8
8	RF + StatSensor + Lab		£275.81	9.991370997	9.97758	£199,551.61	0.00213	£42.57	2
9	i-STAT		£285.61	9.991371002	9.97709	£199,541.81	0.00164	£32.77	10
10	ABL800FLEX		£290.40	9.991371003	9.97685	£199,537.02	0.00140	£27.99	13
11	StatSensor		£283.36	9.991370997	9.97720	£199,544.06	0.00175	£35.02	7
12	i-STAT+ Lab		£279.34	9.991371002	9.97740	£199,548.08	0.00195	£39.05	6
13	ABL800FLEX+ Lab		£286.12	9.991371003	9.97706	£199,541.30	0.00161	£32.27	11
14	StatSensor + Lab		£278.50	9.991370997	9.97745	£199,548.92	0.00199	£39.89	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 87 Cost effectiveness results – Scenario 7.4: Proportion of cancelled CT scans (75%)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£340.83	9.991371010	9.97433	£199,486.60	0.00000	£0.00	14
2	RF+ i-STAT		£277.81	9.991371002	9.97748	£199,549.61	0.00315	£63.01	4
3	RF + ABL800FLEX		£285.69	9.991371003	9.97709	£199,541.73	0.00276	£55.13	9
4	RF + StatSensor		£277.67	9.991370997	9.97749	£199,549.75	0.00316	£63.16	3
5	RF + Lab		£296.17	9.991371010	9.97656	£199,531.25	0.00223	£44.66	13
6	RF + i-STAT + Lab		£275.64	9.991371002	9.97759	£199,551.78	0.00326	£65.18	1
7	RF + ABL800FLEX + Lab		£284.21	9.991371003	9.97716	£199,543.21	0.00283	£56.61	8
8	RF + StatSensor + Lab		£275.98	9.991370997	9.97757	£199,551.44	0.00324	£64.84	2
9	i-STAT		£285.98	9.991371002	9.97707	£199,541.44	0.00274	£54.84	10
10	ABL800FLEX		£290.69	9.991371003	9.97684	£199,536.73	0.00251	£50.13	12
11	StatSensor		£283.66	9.991370997	9.97719	£199,543.76	0.00286	£57.16	7
12	i-STAT+ Lab		£279.71	9.991371002	9.97739	£199,547.71	0.00306	£61.12	6
13	ABL800FLEX+ Lab		£286.41	9.991371003	9.97705	£199,541.01	0.00272	£54.41	11
14	StatSensor + Lab		£278.79	9.991370997	9.97743	£199,548.63	0.00310	£62.03	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 88 Scenario cost effectiveness results – Scenario 8: Anxiety from delay

	Identification	Management	Total costs	Total QALYs	NHB *** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.982325151	9.96416	£199,283.24	0.00000	£0.00	14
2	RF+ i-STAT		£278.02	9.991288549	9.97739	£199,547.75	0.01323	£264.51	4
3	RF + ABL800FLEX		£285.87	9.991298687	9.97701	£199,540.10	0.01284	£256.86	9
4	RF + StatSensor		£277.84	9.991302192	9.97741	£199,548.20	0.01325	£264.96	3
5	RF + Lab		£304.06	9.988187660	9.97298	£199,459.69	0.00882	£176.45	13
6	RF + i-STAT + Lab		£275.84	9.991288549	9.97750	£199,549.93	0.01333	£266.69	1
7	RF + ABL800FLEX + Lab		£284.39	9.991298687	9.97708	£199,541.58	0.01292	£258.34	7
8	RF + StatSensor + Lab		£276.15	9.991302192	9.97749	£199,549.89	0.01333	£266.65	2
9	i-STAT		£286.35	9.991221895	9.97690	£199,538.08	0.01274	£254.84	11
10	ABL800FLEX		£290.99	9.991253148	9.97670	£199,534.08	0.01254	£250.84	12
11	StatSensor		£283.96	9.991250450	9.97705	£199,541.05	0.01289	£257.81	8
12	i-STAT+ Lab		£280.08	9.991221895	9.97722	£199,544.36	0.01306	£261.12	6
13	ABL800FLEX+ Lab		£286.70	9.991253148	9.97692	£199,538.36	0.01276	£255.12	10
14	StatSensor + Lab		£279.09	9.991250450	9.97730	£199,545.92	0.01313	£262.67	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit.

Table 89 Cost effectiveness results – Scenario 9: Effect of IV hydration (PC-AKI risk)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - IVH + Contrast enhanced CT scan	£363.26	9.991371010	9.97321	£199,464.16	0.00000	£0.00	14
2	RF+ i-STAT		£278.09	9.991370798	9.97747	£199,549.33	0.00426	£85.17	4
3	RF + ABL800FLEX		£285.93	9.991370825	9.97707	£199,541.48	0.00387	£77.33	9
4	RF + StatSensor		£277.96	9.991370662	9.97747	£199,549.46	0.00426	£85.30	3
5	RF + Lab		£304.06	9.991371010	9.97617	£199,523.36	0.00296	£59.20	13
6	RF + i-STAT + Lab		£275.92	9.991370798	9.97757	£199,551.50	0.00437	£87.34	1
7	RF + ABL800FLEX + Lab		£284.46	9.991370825	9.97715	£199,542.96	0.00394	£78.80	8
8	RF + StatSensor + Lab		£276.27	9.991370662	9.97756	£199,551.14	0.00435	£86.98	2
9	i-STAT		£286.43	9.991370798	9.97705	£199,540.99	0.00384	£76.83	10
10	ABL800FLEX		£291.05	9.991370825	9.97682	£199,536.37	0.00361	£72.21	12
11	StatSensor		£284.08	9.991370662	9.97717	£199,543.33	0.00396	£79.17	7
12	i-STAT+ Lab		£280.15	9.991370798	9.97736	£199,547.26	0.00416	£83.11	6
13	ABL800FLEX+ Lab		£286.77	9.991370825	9.97703	£199,540.65	0.00382	£76.49	11
14	StatSensor + Lab		£279.21	9.991370662	9.97741	£199,548.20	0.00420	£84.04	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit

Table 90 Cost effectiveness results – Scenario10.1: Management approach for test positives (50% IV hydration + contrast CT scan, 50% no contrast CT scan)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - 50% IVH + Contrast enhanced CT scan - 50% unenhanced contrast CT scan	£362.04	9.991370986	9.97327	£199,465.38	0.00000	£0.00	14
2	RF+ i-STAT		£276.20	9.991370982	9.97756	£199,551.22	0.00429	£85.84	3
3	RF + ABL800FLEX		£284.28	9.991370982	9.97716	£199,543.14	0.00389	£77.76	10
4	RF + StatSensor		£276.33	9.991370979	9.97755	£199,551.09	0.00429	£85.71	4
5	RF + Lab		£302.84	9.991370986	9.97623	£199,524.58	0.00296	£59.20	13
6	RF + i-STAT + Lab		£274.82	9.991370982	9.97763	£199,552.60	0.00436	£87.22	1
7	RF + ABL800FLEX + Lab		£283.34	9.991370982	9.97720	£199,544.08	0.00394	£78.70	9
8	RF + StatSensor + Lab		£275.25	9.991370979	9.97761	£199,552.17	0.00434	£86.79	2
9	i-STAT		£283.07	9.991370982	9.97722	£199,544.35	0.00395	£78.97	8
10	ABL800FLEX		£288.39	9.991370982	9.97695	£199,539.03	0.00368	£73.65	12
11	StatSensor		£281.31	9.991370979	9.97731	£199,546.11	0.00404	£80.73	7
12	i-STAT+ Lab		£279.05	9.991370982	9.97742	£199,548.37	0.00415	£82.99	6
13	ABL800FLEX+ Lab		£285.65	9.991370982	9.97709	£199,541.77	0.00382	£76.39	11
14	StatSensor + Lab		£278.19	9.991370979	9.97746	£199,549.23	0.00419	£83.85	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit

Table 91 Cost effectiveness results – Scenario analysis 10.2: Management approach for test positives (1/3rd IV hydration + contrast CT scan, 1/3rd no contrast CT scan+1/3rd MRI)

	Identification	Management	Total costs	Total QALYs	NHB*** (QALYs)	NMB***	INHB*** (QALYs)	INMB***	NB rank
1	Lab	Test negative* - Contrast enhanced CT scan Test positive** - 33.3% IVH + Contrast enhanced CT scan - 33.3% unenhanced contrast CT scan - 33.3% MRI	£361.77	9.991370978	9.97328	£199,465.65	0.00000	£0.00	14
2	RF+ i-STAT		£275.80	9.991370975	9.97758	£199,551.62	0.00430	£85.97	3
3	RF + ABL800FLEX		£283.93	9.991370975	9.97717	£199,543.49	0.00389	£77.84	10
4	RF + StatSensor		£275.99	9.991370973	9.97757	£199,551.43	0.00429	£85.78	4
5	RF + Lab		£302.57	9.991370978	9.97624	£199,524.85	0.00296	£59.20	13
6	RF + i-STAT + Lab		£274.59	9.991370975	9.97764	£199,552.83	0.00436	£87.18	1
7	RF + ABL800FLEX + Lab		£283.11	9.991370975	9.97722	£199,544.31	0.00393	£78.66	9
8	RF + StatSensor + Lab		£275.05	9.991370973	9.97762	£199,552.37	0.00434	£86.72	2
9	i-STAT		£282.34	9.991370975	9.97725	£199,545.08	0.00397	£79.43	8
10	ABL800FLEX		£287.81	9.991370975	9.97698	£199,539.60	0.00370	£73.95	12
11	StatSensor		£280.72	9.991370973	9.97734	£199,546.70	0.00405	£81.05	7
12	i-STAT+ Lab		£278.82	9.991370975	9.97743	£199,548.60	0.00415	£82.95	6
13	ABL800FLEX+ Lab		£285.42	9.991370975	9.97710	£199,542.00	0.00382	£76.35	11
14	StatSensor + Lab		£277.99	9.991370973	9.97747	£199,549.43	0.00419	£83.78	5

*According to any test in the testing sequence **According to last test in the testing sequence ***At £20,000 per QALY; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NB, net benefit; NHB, net health benefit; INMB, net monetary benefit